

試験番号

B10-0093

## 最 終 報 告 書

遺伝子発現量解析のための  
Phenolphthalein のラットにおける 28 日間反復経口投与毒性試験

2012 年 3 月

一般財団法人 化学物質評価研究機構

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本文書は正本を正確に転写したものです。

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2012 年 3 月 26 日

試験責任者 審 珠 山 五 月

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## 1. 表 題

遺伝子発現量解析のための Phenolphthalein のラットにおける 28 日間反復経口投与毒性試験

## 2. 試験委託者

名 称 一般財団法人化学物質評価研究機構 安全性評価技術研究所  
研究第一部  
所在地 〒345-0043 埼玉県北葛飾郡杉戸町下高野 1600 番地

## 3. 試験施設

名 称 一般財団法人化学物質評価研究機構 日田事業所  
所在地 〒877-0061 大分県日田市石井町 3 丁目 822 番地

## 4. 試験目的

Phenolphthalein をラットに 28 日間毎日反復経口投与したときに現れる生体の機能及び形態の変化を観察することにより、Phenolphthalein の毒性を明らかにすることを目的とする。また、遺伝子発現量解析のための試料を採取する。

## 5. 試験法

以下の試験法を参考に実施した。

- a) 「新規化学物質等に係る試験の方法について」（平成 23 年 3 月 31 日、薬食発 0331 第 7 号、平成 23・03・29 製局第 5 号、環保企発第 110331009 号）に定める「哺乳類を用いる 28 日間の反復投与毒性試験」
- b) OECD Guidelines for the Testing of Chemicals, No. 407, October 3, 2008, “Repeated Dose 28-day Oral Toxicity Study in Rodents”

## 6. GLP 基準

適用しなかった。

## 7. 動物愛護

LABORATORY ANIMAL SCIENCE (1987) by the American Association for Laboratory Animal Science を参考に当試験施設が作成した「日田事業所動物実験に関する指針」及び「ヘルシンキ宣言」(2008 年ソウル改訂) の主旨に沿って試験を行った。

## 8. 試験日程

|            |               |
|------------|---------------|
| 試験開始日      | 2011年 10月 27日 |
| 動物入荷日      | 2011年 11月 1日  |
| 投与開始日      | 2011年 11月 10日 |
| 1回投与後解剖日   | 2011年 11月 11日 |
| 7日間投与後解剖日  | 2011年 11月 17日 |
| 14日間投与後解剖日 | 2011年 11月 24日 |
| 28日間投与後解剖日 | 2011年 12月 8日  |
| 試験終了日      | 2012年 3月 26日  |

## 9. 試験責任者

寶珠山 五月 (所属 試験第二課)

## 10. 試験関係者及び業務分担

試験担当者 後藤純平

(動物の検疫・馴化及び飼育管理、被験物質液の調製、投与、一般状態観察、体重測定、摂餌量測定、詳細な一般状態観察及び機能検査についての動物試験業務に対して責任を持つ)

病理検査責任者 大嶋 浩

(剖検、組織採取、器官重量測定及び病理組織学的検査についての病理検査業務に対して責任を持つ)

臨床検査責任者 室井貴子

(尿検査、血液学的検査及び血液生化学的検査についての臨床検査業務に対して責任を持つ)

## 11. 試資料の保管

試験計画書（正本）、最終報告書（正本）、生データ、その他の記録、標本及び被験物質は当試験施設に保管する。

保管期間は試験終了後 10 年間とする。なお、保管期間中の被験物質の安定性は確認しない。

保管期間終了後の処置（継続保管、廃棄又は返却）は、試験委託者と協議の上決定する。

## 12. 最終報告書の承認

2012年 3月 26日

試験責任者

寶珠山五月

### 13. 要 約

Phenolphthalein の生物学的な影響及び遺伝子発現に及ぼす影響について検討する目的で、化審法テストガイドライン及びOECD テストガイドライン 407 を参考に 28 日間反復経口投与毒性試験を実施した。

5 週齢の雄の Crl:CD(SD)ラットにコーン油に懸濁させた Phenolphthalein を 1、7、14 又は 28 日間毎日強制経口投与した。投与用量は 0 (コーン油)、200 及び 1000 mg/kg/day とし、1、7 及び 14 日間投与後に解剖するサテライト群には 1 群あたり 4 匹、28 日間投与群には 1 群あたり 5 匹を使用した。投与期間中は全例について一般状態観察、体重測定及び摂餌量測定を行い、各投与期間終了後に CO<sub>2</sub>/O<sub>2</sub> 混合ガス麻酔下で血液を採取した後解剖して、血液検査、病理学的検査及び遺伝子発現量解析のための試料採取を実施した。加えて、28 日間投与群については、投与期間中に詳細な一般状態観察及び機能検査を行い、最終投与日の翌日に尿を採取して尿検査を行った。

200 及び 1000 mg/kg 群において投与期間の後半に摂餌量の低値並びに体重の低値又は低値傾向がみられたが用量との関連性は明確でなかった。

病理学的検査では、200 及び 1000 mg/kg 群で 1 回投与後に肝臓の相対重量の高値、1000 mg/kg 群で 7 日間投与後に肝臓の相対重量の高値及び腫大がみられたが、14 日間投与後には異常は認められなかった。28 日間投与後には 1000 mg/kg 群で甲状腺の相対重量の高値がみられた。病理組織学的検査ではいずれの解剖時にも被験物質投与に関係した変化は認められなかった。

一般状態観察、詳細な一般状態観察、機能検査、尿検査、血液学的検査及び血液生化学的検査では被験物質投与による影響はみられなかった。

以上のとおり、本試験条件下において、Phenolphthalein の投与による毒性影響は認められなかった。

## 14. 試験材料

## 14.1 被験物質

## a) 名称等

名 称 Phenolphthalein

CAS 番号 77-09-8

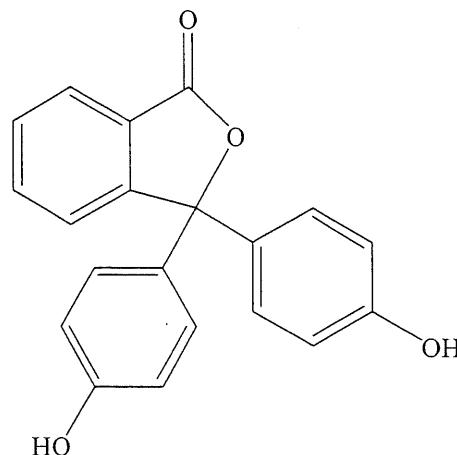
## b) 製造元及びロット番号

製造元 和光純薬工業

ロット番号 DCL2577

## c) 構造式等

## 構造式

分子式 C<sub>20</sub>H<sub>14</sub>O<sub>4</sub>

分子量 318.32

## d) 純度等

純 度 99.8%

被験物質は純度 100% として取り扱った。

## e) 物理化学的性状

対水溶解度 不溶

融 点 約 262°C

常温における性状 白色、結晶性粉末

## f) 保管条件

遮光した気密容器に入れ、被験物質保管室のキャビネットにて室温保管した。

保管温度の実測値 18.7~21.2°C (許容範囲 10~30°C)

保管場所及び期間 キャビネット 5、2011年10月24日及び

2011年10月26日~2011年10月27日

キャビネット 1、2011年10月24日~2011年11月28日

## g) 被験物質の同一性及び保管条件下における安定性の確認

当試験施設で実施した「Phenolphthalein の安定性、被験物質液の均一性、安定性及び濃度確認試験」（試験番号 X02-0249、非 GLP 試験）において確認した。

被験物質の同一性については、独立行政法人産業技術総合研究所の有機化合物のスペ

クトルデータベース (Spectral Database for Organic Compounds: SDBS) から入手したスペクトルと当試験施設において測定したデータを比較することにより確認した。投与開始前に測定した赤外吸収スペクトルは SDBS から入手したスペクトルと同様であった。

また、投与開始前及び投与期間終了後の赤外吸収スペクトルを比較することにより、保管条件下における被験物質の安定性を確認した。投与開始前と比較して投与期間終了後のスペクトルに変化は認められなかったことから、被験物質は保管期間中安定であったと判断した。

#### h) 取扱い上の注意

被験物質の取扱い時は、皮膚及び目への接触並びに吸入をさけるため、手袋、マスク、帽子、保護めがね及び白衣を着用した。

### 14.2 媒体

#### a) 名称

コーン油

#### b) 選択理由

被験物質は水に不溶との情報があることから、コーン油を用いた調製法を検討した。その結果、被験物質は 20 w/v% の濃度でコーン油に均一に懸濁した。また、被験物質液は調製後 7 日間で色調の変化等の異常がみられなかったことから、コーン油を媒体として選択した。

#### c) 製造元、グレード及びロット番号

|       |         |
|-------|---------|
| 製造元   | ナカライトスク |
| グレード  | 化学用     |
| ロット番号 | V1P6999 |

#### d) 保管

|      |       |
|------|-------|
| 保管場所 | 試薬保管室 |
| 保管温度 | 室温    |

### 14.3 使用動物

実験動物として確立された動物であり、一般毒性試験に汎用され、当試験施設においても背景データを保有している Crl:CD(SD)ラット (SPF) を日本チャールス・リバ一日野飼育センターから入手した。

4 週齢の雄ラットを 55 匹入手し、1 ケージあたり 5 匹の群飼育で入荷 6 日後まで検疫・馴化を行った。さらに、投与開始 1 日前の入荷 8 日後まで馴化し、すべての動物に異常がみられなかったため、当日測定した体重を用いて体重層別無作為抽出法で群分けし、51 匹を試験に使用した。群分け後は投与開始まで個別飼育で馴化した。群分けにより外れた動物は試験から除外した。また、受入れから投与開始までは、一般状態及び排泄物を毎日 1 回以上観察した。

動物は、群分け前は尾部へ油性インクを塗布し、群分け後は耳鉗を付けて識別した。ケージにはラベルを付け、ラックは試験番号を表示してそれぞれ識別した。

投与開始時の動物の週齢は 5 週齢、体重範囲は 137.1～161.9 g であり、全例の体重が全體の平均体重±20% の範囲内であることを確認した。

#### 14.4 飼育環境

動物は、検疫・馴化期間中を含む全飼育期間を通して、温度 21～25°C、相対湿度 40～70%、換気回数 10～15 回/時間、明暗サイクル 12 時間間隔（7 時点灯、19 時消灯）に設定したバリアーシステムの飼育室（検疫期間中は検疫室 1、検疫終了後は飼育室 1）に収容した。温度及び相対湿度の実測値は、それぞれ 22.5～23.3°C 及び 51.6～61.1% であった。

ケージは、群分け前はステンレス製金網床ケージ（W260×D380×H180 mm）、群分け後はステンレス製金網床ケージ（W165×D300×H150 mm）を使用した。

トレイは、検疫期間終了時及び群分け時に交換し、群分け後は週 2 回の頻度で交換した。さらに、動物を飼育室から解剖室に搬出する際にも交換した。給餌器、ケージ及びラックは、群分け時に交換した。また、サテライト群（1、7 及び 14 日間投与群）については解剖室に搬出する際にもラックを交換した。

飼料は固型飼料 MF（ロット番号 110705 及び 110906、オリエンタル酵母工業）を、飲料水は日田市上水道水に給水末端での塩素濃度が 3～5 ppm となるように次亜塩素酸ナトリウム（ピューラックス）を添加した水を、それぞれ自由摂取させた。飼料及び飼育用器材はオートクレーブ滅菌（121°C、30 分間）したものをそれぞれ使用した。

飼料は、製造元から混入物の分析データ入手し、米国環境保護庁有害物質規制法の「飼料及び媒体の汚染物質限度」（1979）を参考に、当試験施設で定めた基準値内であることを確認したロットを使用した。

飲料水については、厚生労働省の「水質基準に関する省令」（厚生労働省令第 101 号）に準拠した水質検査を年 2 回の頻度で実施しており、動物入荷前に入手した検査結果及び最終報告書作成までに入手した検査結果が、同省令の基準を満たしていることを確認した。

### 15. 試験方法

#### 15.1 被験物質の設定用量

用量設定試験として、当試験施設で「Phenolphthalein のラットにおける 7 日間反復経口投与毒性試験」（試験番号 P12-0093、非 GLP 試験）を実施した。用量設定試験ではコーン油で調製した被験物質液を、各群 3 匹の 5 週齢の Crl:CD(SD)雄ラットに 0、100、300 及び 1000 mg/kg/day の用量で 7 日間毎日投与した。投与期間中は一般状態観察及び体重測定を行い、最終投与 1 日後に剖検及び器官重量測定を行った。その結果、1000 mg/kg 群で肝臓の相対重量の高値及び腫大が認められたが、軽度な変化であったことから、1000 mg/kg/day を 28 日間反復投与しても瀕死や死亡等の重篤な毒性影響は発現しないと推測した。

したがって、本試験では 1000 mg/kg/day を高用量とし、低用量として 200 mg/kg/day を設定した。

#### 15.2 群構成

被験物質投与群として 2 用量群を設け、さらに媒体のみを投与する媒体対照群を設定した。また、媒体対照群及び各用量群に、1、7 及び 14 日間投与後に解剖するサテライト群を設けた。以下、媒体対照群は対照群と記載する。

サテライト群の投与期間中の観察及び測定データは、28 日間投与群に含めて取り扱った。

| 試験群           | 投与用量<br>(mg/kg/day) | 投与容量<br>(mL/kg) | 被験物質液<br>濃度(w/v%) | 動物数<br>(動物番号) |
|---------------|---------------------|-----------------|-------------------|---------------|
| 媒体対照 (1回投与)   | 0                   | 5               | 0                 | 4(1 - 4)      |
| 媒体対照 (7日間投与)  | 0                   | 5               | 0                 | 4(5 - 8)      |
| 媒体対照 (14日間投与) | 0                   | 5               | 0                 | 4(9 - 12)     |
| 媒体対照 (28日間投与) | 0                   | 5               | 0                 | 5(13 - 17)    |
| 被験物質          | 低用量 (1回投与)          | 200             | 5                 | 4(18 - 21)    |
|               | 低用量 (7日間投与)         | 200             | 5                 | 4(22 - 25)    |
|               | 低用量 (14日間投与)        | 200             | 5                 | 4(26 - 29)    |
|               | 低用量 (28日間投与)        | 200             | 5                 | 5(30 - 34)    |
|               | 高用量 (1回投与)          | 1000            | 5                 | 20.0          |
|               | 高用量 (7日間投与)         | 1000            | 5                 | 20.0          |
|               | 高用量 (14日間投与)        | 1000            | 5                 | 20.0          |
|               | 高用量 (28日間投与)        | 1000            | 5                 | 20.0          |

### 15.3 投与液

#### a) 被験物質液の調製及び保管

被験物質を秤量後、乳鉢内で粉碎し、コーン油を少量ずつ加えて懸濁させた。その後、コーン油を加えて定容し 20.0 w/v% の被験物質液を調製した。さらに、20.0 w/v% の被験物質液をマグネチックスターラーで攪拌しながら一部を採取し、コーン油を加えて希釈し、4.00 w/v% の被験物質液を調製した。調製は被験物質液の安定性確認の結果から 9 ~11 日間に 1 回の頻度で行った。

調製した各濃度の被験物質液及び投与に用いる媒体はガラス製瓶にそれぞれ小分けし、被験物質調製室の保冷庫 7 にて冷所（実測値 3~9°C、許容範囲 1~10°C）で保管し、調製後 11 日以内に使用した。

小分け保管した各濃度の被験物質液及び媒体は、各投与日に投与に必要な個数を保管場所から取り出し、飼育室まで室温で運搬し投与に用いた。

#### b) 被験物質液の均一性及び安定性の確認

当試験施設で実施した「Phenolphthalein の安定性、被験物質液の均一性、安定性及び濃度確認試験」（試験番号 X02-0249、非 GLP 試験）で、20.0 及び 0.200 w/v% の被験物質液の均一性及び冷所保管での安定性を高速液体クロマトグラフィー (HPLC) を用いて確認した。

均一性については、調製直後に測定した被験物質液の上、中及び下層の被験物質濃度の変動係数 (CV) が 5% 以内であったことから、20.0 及び 0.200 w/v% の被験物質液は均一と判断した。

$$CV(\%) = \frac{\text{各層の測定濃度の標準偏差}}{\text{各層の測定濃度の平均値}} \times 100$$

### 被験物質液の均一性確認結果

| 設定濃度<br>(w/v%) | 測定濃度(w/v%) |       |       |       |       |
|----------------|------------|-------|-------|-------|-------|
|                | 上層         | 中層    | 下層    | 平均    | 標準偏差  |
| 20.0           | 20.6       | 20.8  | 20.5  | 20.6  | 0.15  |
| 0.200          | 0.216      | 0.212 | 0.203 | 0.210 | 0.007 |

安定性については、調製 13 日後に測定した被験物質液の中層の被験物質濃度が、調製直後の測定濃度に対し  $100\pm10\%$  以内であったことから、20.0 及び 0.200 w/v% の被験物質液は冷所保管で 12 日間安定であることが確認された。

### 被験物質液の冷所保管での安定性の確認結果

| 設定濃度(w/v%) | 調製直後<br>平均測定濃度(w/v%) | 調製 13 日後<br>中層測定濃度(w/v%) | 対調製直後<br>(%) |
|------------|----------------------|--------------------------|--------------|
|            |                      |                          | (%)          |
| 20.0       | 20.6                 | 20.0                     | 97.1         |
| 0.200      | 0.210                | 0.208                    | 99.0         |

#### c) 投与に用いる被験物質液の濃度確認

初回に調製した 20.0 及び 4.00 w/v% の被験物質液について、当試験施設で実施した試験（試験番号 X02-0249）で、調製直後の被験物質濃度を測定した。

被験物質液をマグネチックスターラーで攪拌しながら一部を採取して分析試料を調製し、HPLC を用いて被験物質濃度を測定した。測定した被験物質濃度が設定値に対し  $100\pm10\%$  以内であったため、適切に調製できたと判定して投与に用いた。

### 初回に調製した被験物質液の被験物質濃度確認結果

| 設定濃度 (w/v%) | 調製直後<br>測定濃度 (w/v%) | 対設定値 (%) |
|-------------|---------------------|----------|
| 20.0        | 19.4                | 97.0     |
| 4.00        | 3.99                | 99.8     |

## 15.4 投与

1、7、14 又は 28 日間毎日 1 回、強制経口投与した。投与は 13:18～14:50 に行った。

投与にはネラトンカテーテル（テルモ）を取り付けた注射筒（テルモ）を用い、測定した最新の体重を基に、5 mL/kg で投与した。被験物質液はマグネチックスターラーで攪拌しながら注射筒に採取した。

## 15.5 一般状態観察

投与期間中は毎日 3 回（投与前、投与直後～1 時間後、投与 2～6 時間後）、生死を含む一般状態を観察した。

## 15.6 詳細な一般状態観察

28 日間投与群について、投与開始前に 1 回、投与開始後は週 1 回の頻度で次表の項目を観察した。投与開始後の観察は動物に乱数（検査動物番号）を割付け、動物の並び替えを行った後、試験群が判別できない状態（盲検法）で行った。

|               |  |
|---------------|--|
| ケージから取り出す際の反応 | ケージに手を入れてから、動物をケージ外に取り出すまでの反応（出し易さ及び発声）を、スコアリング法で評価  |
| 手にとっての詳細な観察   | 筋緊張及び体温低下の有無、被毛の状態（立毛、毛の汚れ及び被毛粗剛）、皮膚及び粘膜の色（蒼白、発赤及びチアノーゼ）、眼の異常（流涙、眼球突出及び瞳孔径）、流涎及び分泌物の有無を観察                                |
| アリーナ内での行動の観察  | 動物を 90 cm×60 cm の観察台上に 1 分間以上（5 分以内）置き、姿勢、活動性、呼吸、歩行の状態、眼瞼閉鎖、振戦・攣縮・痙攣、常同行動及び異常行動の有無を観察<br>1 分間の排糞回数（糞の数）及び排尿回数（尿のプール数）を測定 |

### 15.7 機能検査

28 日間投与群について、投与 4 週目（投与 26 日目）に 1 回、次表の項目を検査した。反応性及び握力は詳細な一般状態観察と同様に試験群が判別できない状態で検査した。

|       |   |   |
|-------|---|---|
| 反応性   | 視 覚   | 顔面前約 3 cm にボールペンの鞘を近づけ、4 秒間保持したときの反応をスコアリング法で評価 |
|       | 聴 覚   | 頭上で指を鳴らしたときの反応をスコアリング法で評価                       |
|       | 痛 覚   | 洗濯バサミで尾の 1/3 尾根部側を挟んだときの反応を観察                   |
|       | 瞳孔反射  | 眼を手で覆った後、瞳孔に光を当てたときの反応の有無を観察                    |
|       | 空中正向反射  | 約 30 cm の高さから、動物の腹部を上にした状態で落としたときの異常反応の有無を観察    |
| 握 力   | 握力メータ FGC-2（メイティス）を用い、前肢及び後肢の握力を 2 回測定し、平均値で評価  |   |
| 自発運動量 | ラット用運動量測定装置 ACTIMO-10（シンテクノ）を用い、動物の運動量を 1 時間（10 分間隔で 6 回）測定し、赤外線（42.6 cm×26.5 cm の範囲を縦横 5 cm 間隔で発生）を横切った回数で評価 |   |

### 15.8 体重測定

全例について、電子上皿天秤（ザルトリウス）を用い、下記の日に体重を測定した。

- ・ 群分け日
- ・ 投与 1、3、7、14、21 及び 28 日目
- ・ 各試験群の解剖日（飼育室からの搬出前、絶食状態）

### 15.9 摂餌量測定

7、14 及び 28 日間投与群について、電子上皿天秤（ザルトリウス）を用い、下記の日に餌重量を測定した。

- ・ 群分け日の給餌量
- ・ 投与 1、3、7、14、21 及び 28 日目の残餌量

投与 7、14 及び 21 日目には残餌量測定後に餌を補充し、補充後の給餌量を測定した。

測定した給餌量と残餌量から各測定日間での 1 日平均摂餌量を求めた。

## 15.10 尿検査

### a) 採尿

28日間投与群について、投与28日目の夜にW 150×D 200×H 263 mmの個体別代謝ケージに動物を収容し、自由飲水及び絶食状態で翌日までの約15時間の蓄積尿を採取した。

### b) 検査項目及び方法

採取した蓄積尿を用い次表の項目を測定した。尿沈渣は対照群及び高用量群を検査した結果、高用量群で被験物質の投与に関連した変化は認められなかったため、低用量群については検査を行わなかった。

| 項目                     | 方法                       | 機器 |
|------------------------|--------------------------|----|
| 尿量 (Urine volume)      | メスシリンダーによる計量             | —  |
| 色調 (Color)             | 肉眼観察                     | —  |
| 濁り (Turbidity)         |                          | —  |
| 尿浸透圧 (Uosm)            | 氷点降下法                    | A  |
| pH                     |                          |    |
| 蛋白 (Protein)           | 試験紙法                     |    |
| ケトン体 (Ketones)         | (試験紙にはラブスティックス(シームス)を使用) | —  |
| 糖 (Glucose)            |                          |    |
| 潜血 (Occult blood)      |                          |    |
| 尿沈渣 (Urinary sediment) | Sternheimer 変法           | B  |

使用機器 A: 自動浸透圧計 OM-6040 (アーフレイ)

B: システム生物顕微鏡 BX41 (オリンパス)

## 15.11 血液検査

### a) 採血及び検査試料

各試験群について最終投与日の夜から絶食し、翌日(絶食開始16~20時間後)、CO<sub>2</sub>/O<sub>2</sub>混合ガス(CO<sub>2</sub>:O<sub>2</sub>混合比=4:1)下で腹部大動脈から次表のとおり採血し、検査試料を作製した。サテライト群については血漿の試料作製は行わなかった。

| 検査試料 | 作製方法   |
|------|--|
| 全 血  | EDTA-2K 添加採血びん SB-41 (ロット番号 G9059、シスメックス) で採血した血液  |
| 血 漿  | くえん酸三ナトリウム二水和物(ロット番号 STP5940、和光純薬工業)の3.2 w/v%水溶液を100 μL添加したガラス製試験管で採血し、遠心分離(3000 r.p.m.×10 mins)して得た血漿 |
| 血 清  | ガラス製試験管で採血し遠心分離(3000 r.p.m.×10 mins)して得た血清   |

## b) 血液学的検査

全血及び血漿を用い次表の項目を測定した。サテライト群についてはプロトロンビン時間及び活性化部分トロンボプラスチン時間の測定は行わなかった。また、すべての項目について機器測定できたため、全血を用いた塗抹標本は作製しなかった。

| 項目   | 方法                                      | 機器 |
|--|---|----|
| 赤血球数 (RBC)   | 暗視野板法                                   | C  |
| ヘモグロビン濃度 (Hb)  | シアンメトヘモグロビン法                            |    |
| ヘマトクリット値 (Ht)  | $\frac{RBC \times MCV}{10^3}$           |    |
| 平均赤血球容積 (MCV)  | 暗視野板法                                   |    |
| 平均赤血球ヘモグロビン量 (MCH)   | $\frac{Hb}{RBC} \times 10^3$            |    |
| 平均赤血球ヘモグロビン濃度 (MCHC)   | $\frac{Hb}{RBC \times MCV} \times 10^5$ |    |
| 血小板数 (Platelet)  | 暗視野板法                                   |    |
| 網状赤血球数比率 (Reticulo)  | RNA 染色法                                 |    |
| 白血球数 (WBC)   | フローサイトメトリー法                             |    |
| 白血球百分率 (Differentiation of leukocyte)<br>好中球 (Neutro) 、 リンパ球 (Lymph)<br>好酸球 (Eosino) 、 好塩基球 (Baso)<br>单球 (Mono) 、 大型非染色球 (LUC) | フローサイトメトリー法                             |    |
| プロトロンビン時間 (PT)   | 粘度変化感知方式                                | D  |
| 活性化部分トロンボプラスチン時間 (APTT)  | 粘度変化感知方式                                |    |

検査試料 C には全血、D には血漿を使用

使用機器 C: 総合血液学検査装置 ADVIA 120 (シーメンス)

D: 全自動血液凝固線溶測定装置 STA Compact (ロシュ・ダイアグノスティックス)

## c) 血液生化学的検査

血清を用いて次表の項目を測定した。サテライト群についてはアスパラギン酸アミノトランスフェラーゼ、アラニンアミノトランスフェラーゼ、アルカリ性 fospha ターゼ、尿素窒素、クレアチニン及び総ビリルビンを測定し、その他の項目は測定しなかつた。

| 項目                        | 方 法                                     | 機器 |
|---------------------------|---|----|
| アスパラギン酸アミノトランスフェラーゼ (AST) | UV 法 JSCC 標準化対応法                        | E  |
| アラニンアミノトランスフェラーゼ (ALT)    | UV 法 JSCC 標準化対応法                        |    |
| アルカリ性 fospha ターゼ (ALP)    | p-Nitrophenyl phosphate 法               |    |
| コリンエステラーゼ (ChE)           | Butyrylthiocholine iodide 法             |    |
| γ-グルタミルトランスペプチダーゼ (γ-GTP) | L-γ-glutamyl-3-carboxy-4-nitroanilide 法 |    |
| 総コレステロール (T-Chol)         | COD·ESPAS 法                             |    |
| トリグリセリド (TG)              | GPO·ESPAS グリセロール消去法                     |    |
| 尿素窒素 (BUN)                | Urease · GIDH 法                         |    |
| クレアチニン (Creatinine)       | Creatininase · F-DAOS 法                 |    |
| 総蛋白 (T-Protein)           | Biuret 法                                |    |
| アルブミン (Albumin)           | Bromocresol green 法                     |    |
| A/G 比 (A/G ratio)         | Albumin<br>T - Protein – Albumin        | —  |
| 血糖 (Glucose)              | Hexokinase · G-6-PDH 法                  | E  |
| 総ビリルビン (T-Bil)            | 酵素法                                     |    |
| 総胆汁酸 (TBA)                | 酵素サイクリング法                               |    |
| 無機リン (IP)                 | Fiske-Subbarow 法                        |    |
| カルシウム (Ca)                | OCPC 法                                  |    |
| ナトリウム (Na)                | Crown-Ether 膜電極法                        | F  |
| カリウム (K)                  | Crown-Ether 膜電極法                        |    |
| 塩素 (Cl)                   | MO 膜法                                   |    |

使用機器 E: 生化学自動分析装置 7170 形 (日立製作所)

F: 電解質分析装置 PVA-EX II (A&T)

## 15.12 病理学的検査

## a) 剖 検

各試験群について最終投与日の翌日のいずれも採血後に、動物を腹部大動脈から放血して安樂死させ、体表、開孔部、皮下、頭蓋腔、胸腔、腹腔及び骨盤腔とその内容について肉眼的観察を行った。

## b) 組織採取及び器官重量測定

## (a) サテライト群

1、7及び14日間投与群について、剖検時に次表の器官・組織を採取した。

| 分類    | 器官・組織                |
|-------|----------------------|
| 消化器系  | 肝臓                   |
| 心・血管系 | 心臓                   |
| 泌尿器系  | 腎臓                   |
| 生殖器系  | 精巣、精巣上体、腹葉前立腺、背側葉前立腺 |
| 神経系   | 脳（大脳、小脳及び橋を含む）       |
| 造血器系  | 骨髓（大腿骨）脾臓、胸腺         |
| 内分泌系  | 下垂体、甲状腺（上皮小体を含む）、副腎  |

採取した器官のうち、肝臓、心臓、腎臓、精巣、精巣上体、腹葉前立腺、背側葉前立腺、脳、脾臓、胸腺、下垂体及び副腎は固定液又は保存液に浸漬する前に、甲状腺は固定液に浸漬した後に電子天秤（ザルトリウス）で重量を測定した。腎臓、精巣及び精巣上体は左右を別々に測定した。副腎は左右をまとめて測定した。背側葉前立腺は尿道の一部を含めて測定した。甲状腺は上皮小体を含めて気管から分離せずに10%中性緩衝ホルマリン液に浸漬し、翌日、左右の葉を気管から分離して重量を測定した。また、解剖日に測定した体重を基に相対重量も算出した。

## (b) 28日間投与群

剖検時に次表の器官・組織を採取した。

| 分類     | 器官・組織                            |
|--------|----------------------------------|
| 呼吸器系   | 気管、肺                             |
| 消化器系   | 顎下腺、胃、腸（十二指腸から直腸、パイエル板を含む）、脾臓、肝臓 |
| 心・血管系  | 心臓                               |
| 泌尿器系   | 腎臓、膀胱                            |
| 生殖器系   | 精巣、精巣上体、腹葉前立腺、背側葉前立腺、精嚢（凝固腺を含む）  |
| 神経系    | 脳（大脳、小脳及び橋を含む）、脊髄、坐骨神経           |
| 造血器系   | 骨髓（大腿骨）、腋窩リンパ節、腸間膜リンパ節、脾臓、胸腺     |
| 内分泌系   | 下垂体、甲状腺（上皮小体を含む）、副腎              |
| 感覚器    | 眼球                               |
| 筋・骨髄系  | 骨格筋（大腿部）、骨（大腿骨）                  |
| 皮膚・付属器 | 乳腺                               |

気管、肺及び膀胱は10%中性緩衝ホルマリン液を注入後に採取し、胃及び腸は10%中性緩衝ホルマリン液を注入して同液に浸漬した後、内容物を水洗除去した。

採取した器官のうち、肝臓、心臓、腎臓、精巣、精巣上体、腹葉前立腺、背側葉前立腺、精嚢、脳、脾臓、胸腺、下垂体及び副腎は固定液又は保存液に浸漬する前に、甲状腺は固定液に浸漬した後に電子天秤（ザルトリウス）で重量を測定した。腎臓、精巣及び精巣上体は左右を別々に測定した。副腎は左右をまとめて測定した。背側葉前立腺は尿道の一部を含めて測定した。精嚢は凝固腺を含めて起始部を糸で結紮して採取し、重量を測定した。甲状腺は上皮小体を含めて気管から分離せずに10%中性緩衝ホルマリン液に浸漬し、翌日、左右の葉を気管から分離して重量を測定した。また、解剖日に測定した体重を基に相対重量も算出した。

### c) 組織の固定及び保存

採取した器官・組織は、以下のように固定及び保存した。

肝臓は、重量を測定後、外側左葉の中央部から（門脈側とその反対側を結ぶ対角線に沿って）2~3 mm幅の組織片4枚を採取し、遺伝子発現量解析用に供した。2枚ずつの重量が1.5 g以下であることを確認後、それぞれ重量の5倍量以上のRNAlater<sup>®</sup>(Ambion, Inc.)に浸漬させた。右葉は氷冷後、-80°Cで保存した。外側左葉の遺伝子発現量解析用部位の採取後の残り部分及び残りの葉を10%中性緩衝ホルマリン液で固定した。

腎臓は、左右別々に重量を測定後、右側の中央部から乳頭を含むように横断で4~5 mm幅の組織片を採取し、組織片から被膜を取り除いた後、正中で二分した。半分を幅3 mm以内に細切りRNAlaterに浸漬した。残りの半分から乳頭、髓質内帯、髓質外帯及び皮質を分けてサンプリングし、それぞれRNAlaterに浸漬した。残りの部分は氷冷後、-80°Cで保存した。左側は10%中性緩衝ホルマリン液で固定した。

精巣は、左右別々に重量を測定後、右側を4分割し、組織片の半分をRNAlaterに浸漬した。残りの半分は氷冷後、-80°Cで保存した。左側は変法デビットゾン液で固定した。

精巣上体は、重量を測定後、左右とも変法デビットゾン液で固定した。

腹葉前立腺は、重量測定後、正中で二分し、一方をRNAlaterに浸漬した。残りは10%中性緩衝ホルマリン液で固定した。

脳は、重量を測定後、氷冷したメタカーン液（メタノール：クロロホルム：酢酸混合比=6:3:1）に浸漬した。その後、氷冷下で5時間振とうし無水エタノールに交換した。さらに氷冷下で振とうしながら、1時間おきに2回、無水エタノールを交換した。氷冷下で一晩振とうした後、無水エタノールを再度交換し4°Cで保存した。保存した試料は保冷剤を同封して東京農工大学に送付した。

大腿骨は、左側を膝関節から大腿骨頭付近まで採取した。両端を切除し、RPMI1640(Invitrogen)5 mLで骨髄を洗い出し、70 μmのメッシュを通してコニカルチューブに回収した。4°Cで遠心(1100 rpm、5分間)後、上清を除いた。さらに5 mLのRPMI1640に再懸濁し、4°Cで遠心(1100 rpm、5分間)後、上清を除いた。残渣を5 mLのRNAlaterに再浮遊させた。右側は膝関節を含むように採取し、10%中性緩衝ホルマリン液で固定した。

脾臓は、重量を測定後、中央部から横断で幅1~2 mmの組織片を1枚採取し、RNAlaterに浸漬した。残りは10%中性緩衝ホルマリン液で固定した。

胸腺は、重量を測定後、正中で二分し、一方を *RNAlater* に浸漬した。残りは 10% 中性緩衝ホルマリン液で固定した。

下垂体は、重量を測定後、*RNAlater* に浸漬した。

*RNAlater* に浸漬した各組織は *RNAlater* を組織に浸潤させるため、脾臓は 4°C で 72 時間、その他の組織は 4°C で 24 時間放置した後、*RNAlater* に浸漬させたまま -80°C で凍結し、ドライアイスを同封して安全性評価技術研究所に送付した。-80°C 凍結保存した組織についてもドライアイスを同封して安全性評価技術研究所に送付した。

その他の器官・組織は、10% 中性緩衝ホルマリン液で固定した。

#### d) 病理組織学的検査

##### (a) サテライト群

1、7 及び 14 日間投与群の対照群及び高用量群について、肝臓、腎臓、精巢、前立腺、骨髓（大腿骨）、脾臓、胸腺のパラフィン包埋薄切切片を作製し、ヘマトキシリソ・エオジン（HE）染色後、光学顕微鏡的に検査した。骨髓（大腿骨）は切り出し前に 10% 蟻酸・ホルマリン液による脱灰を行った。

なお、1、7 及び 14 日間投与群の高用量群で被験物質の投与に関連した変化が認められなかったため、低用量群については検査を行わなかった。

##### (b) 28 日間投与群

対照群及び高用量群について、脳及び下垂体を除いて採取したすべての器官又は組織のパラフィン包埋薄切切片を作製し、HE 染色後、光学顕微鏡的に検査した。骨及び骨髓（大腿骨）は切り出し前に 10% 蟻酸・ホルマリン液による脱灰を行った。

なお、高用量群で被験物質の投与に関連した変化が認められなかったため、低用量群については検査を行わなかった。

#### 15.13 統計学的方法

体重、摂餌量、握力、自発運動量、血液学的検査、血液生化学的検査、尿量、尿浸透圧及び器官重量の成績については、Bartlett 法による等分散検定を行い、5%有意水準で等分散が認められた場合は、Dunnett 法による検定を行った。等分散が認められない場合はノンパラメトリックの Dunnett 法による検定を行った。排糞回数（糞の数）及び排尿回数（尿のプール数）はノンパラメトリックの Dunnett 法による検定を行った。

#### 16. 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及び試験計画書からの逸脱

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及び試験計画書からの逸脱は認められなかった。

## 17. 試験成績

### 17.1 一般状態 (Table 1、Appendix 1)

投与期間中、すべての被験物質投与群及び対照群に異常は認められなかった。

### 17.2 詳細な一般状態 (Table 2、Appendix 2)

被験物質投与群で排糞回数及び排尿回数に有意な変動は認められず、他の詳細観察項目においても被験物質投与群及び対照群に異常は認められなかった。

### 17.3 機能検査 (Table 3、4 及び 5、Appendix 3、4 及び 5)

200 mg/kg 群で測定 0~10 分の時間帯に自発運動量の有意な高値がみられたが、用量依存性のない変動であった。握力では被験物質投与群に有意な変動は認められず、反応性検査においても被験物質投与群及び対照群に異常は認められなかった。

### 17.4 体 重 (Fig. 1、Table 6、Appendix 6)

200 mg/kg 群で投与 21 及び 28 日目に有意な低値（対照群の 93.4% 及び 92.0%）がみられた。1000 mg/kg 群では有意な変動は認められなかつたが、投与 21 及び 28 日目に低値傾向（対照群の 94.0% 及び 93.6%）がみられた。

### 17.5 摂餌量 (Fig. 2、Table 7、Appendix 7)

200 mg/kg 群で投与 21 及び 28 日目に有意な低値（対照群の 85.0% 及び 83.3%）、1000 mg/kg 群で投与 14、21 及び 28 日目に有意な低値（対照群の 92.2%、87.8% 及び 89.1%）がみられた。

### 17.6 尿検査 (Table 8、Appendix 8)

被験物質投与群で尿量及び尿浸透圧に有意な変動は認められず、他の検査項目においても被験物質投与群及び対照群に異常は認められなかった。

### 17.7 血液検査

#### a) 血液学的検査 (Table 9、Appendix 9)

1 回投与群において、200 及び 1000 mg/kg 群で網状赤血球数比率の有意な高値、1000 mg/kg 群で平均赤血球ヘモグロビン濃度の有意な低値がみられた。

7 日間投与群において、200 及び 1000 mg/kg 群で赤血球数の有意な高値及び好酸球比率の有意な低値がみられた。

14 日間投与群では被験物質投与群に有意な変動は認められなかつた。

28 日間投与群において、1000 mg/kg 群で平均赤血球ヘモグロビン量の有意な高値及び白血球数の有意な低値がみられた。なお、同群の 1 例 (No. 51) で血小板数が低値を示したが、出血傾向はみられず、1 例のみでの異常値であること並びにその他の検査項目には異常が認められなかつたことから、被験物質投与とは関係のない変化と考えた。

200 mg/kg 群では有意な変動は認められなかつた。

#### b) 血液生化学的検査 (Table 10、Appendix 10)

1、7 及び 14 日間投与群では被験物質投与群に有意な変動は認められなかつた。

28 日間投与群において、1000 mg/kg 群で総胆汁酸の有意な低値がみられた。200 mg/kg 群では有意な変動は認められなかつた。

## 17.8 病理学的検査

### a) 器官重量 (Table 11 及び 12、Appendix 11 及び 12)

1回投与群において、200 及び 1000 mg/kg 群で肝臓の相対重量の有意な高値（対照群の 105.6% 及び 108.4%）がみられた。このほか、1000 mg/kg 群で左側精巣の相対重量の有意な高値がみられたが、片側のみの変動であったことから被験物質投与とは関係のない変化と考えた。

7 日間投与群において、1000 mg/kg 群で肝臓の相対重量の有意な高値（対照群の 110.6%）がみられた。200 mg/kg 群では有意な変動は認められなかった。

14 日間投与群において、200 mg/kg 群で左側精巣上体の相対重量の有意な低値がみられたが、片側のみでの変動であり用量との関連性も認められないことから被験物質投与とは関係のない変化と考えた。1000 mg/kg 群では有意な変動は認められなかった。

28 日間投与群において、1000 mg/kg 群で甲状腺の相対重量の有意な高値（対照群の 138.4%）がみられた。このほか、200 及び 1000 mg/kg 群で脳の相対重量の有意な高値、200 mg/kg 群で左側精巣上体の相対重量の有意な高値、1000 mg/kg 群で左右精巣の相対重量の有意な高値がみられ、200 及び 1000 mg/kg 群で解剖日体重が有意な低値（対照群の 91.4% 及び 92.2%）を示した。200 mg/kg 群で心臓及び右側腎臓の絶対重量の有意な低値がみられたが、用量との関連性が認められないことから被験物質投与とは関係のない変化と考えた。

### b) 剖 検 (Table 13、Appendix 13)

7 日間投与群において、1000 mg/kg 群で肝臓の腫大が 4 例中 1 例に認められたが、その他の投与群では対照群を含めて異常は認められなかった。

### c) 病理組織学的検査 (Table 14、Appendix 13)

1回投与群では、相対重量の有意な高値を示した 1000 mg/kg 群の肝臓を含め、1000 mg/kg 群及び対照群で異常は認められなかった。

7 日間投与群において、対照群の 1 例で腎臓に髓質の囊胞がみられた。1000 mg/kg 群では、肉眼的に腫大がみられ相対重量も有意な高値を示した肝臓を含めて検査を行ったすべての器官・組織に異常は認められなかった。

14 日間投与群では 1000 mg/kg 群及び対照群に異常は認められなかった。

28 日間投与群において、1000 mg/kg 群で精巣の限局性の精細管萎縮が 5 例中 1 例にみられたが、1 例のみでの発現であり軽度な変化であったことから、被験物質投与とは関係のない偶発的所見と考えた。相対重量の有意な高値がみられた甲状腺では異常は認められなかった。対照群では腹嚢前立腺のリンパ球浸潤が 1 例みられた。

## 18. 考 察

被験物質は酸塩基指示薬として広く用いられる有機化合物であり、国際がん研究機関（International Agency for Research on Cancer, IARC）の発がん性評価ではグループ2B（ヒトに対して発がん性がある可能性がある）に分類されている。実験動物を用いた混餌投与による発がん性試験では、ラットの雌雄において副腎腫瘍（良性又は悪性褐色細胞腫）、ラットの雄において腎臓腫瘍（尿細管腺腫又はがん）、マウスの雌雄において組織球性肉腫及び悪性リンパ腫、マウスの雌において卵巣腫瘍（良性性索間質腫瘍）の発生率が増加したことが報告されているが、用量設定試験として実施されたラットの14日間混餌投与試験及び13週間混餌投与試験では被験物質投与と関連した病変の発現は認められていない（NTP, 1996）。本試験においても被験物質投与による明らかな毒性影響は認められなかった。

200及び1000 mg/kg群において投与期間の後半に摂餌量の低値並びに体重の低値又は低値傾向がみられ、28日間投与群の解剖日体重が低値を示したが、用量との関連性が明らかでなく、同時期の他の検査項目において体重及び摂餌量の低値に関連すると考えられる異常が認められなかつたことから、これらの変化の毒性学的な意義は低いと判断した。

血液学的検査において、1回投与群では1000 mg/kg群で平均赤血球ヘモグロビン濃度の低値、200及び1000 mg/kg群で造血亢進を示す網状赤血球数比率の高値がみられ、7日間投与群では200及び1000 mg/kg群で赤血球数の高値がみられたことから、投与期間の初期に貧血が発現しその代償性変化として造血が亢進した可能性が考えられた。しかしながら、前赤芽球から成熟赤血球の形成には4日間を要するとされており（伊東, 1994）、1回投与した翌日に造血亢進が確認されることはないと考えられた。すなわち、これらの変化は被験物質投与とは関係のない生理的変動と考えられた。また、28日間投与群においてみられた1000 mg/kg群の平均赤血球ヘモグロビン量の高値及び白血球数の低値も、他の赤血球指数（平均赤血球容積及び平均赤血球ヘモグロビン濃度）には異常がみられなかつたこと並びに病理組織学的検査において造血器に異常が認められなかつたことから、被験物質投与とは関係のない偶発的変化と判断した。

血液生化学的検査において、28日間投与群で1000 mg/kg群に総胆汁酸の低値がみられたが、肝障害を示す高値変化ではなく、肝機能に関連する他の検査項目には異常が認められなかつたことから被験物質投与とは関係のない変化と判断した。

病理学的検査において、1回投与群では200及び1000 mg/kg群で肝臓の相対重量の高値、7日間投与群では1000 mg/kg群で肝臓の相対重量の高値及び腫大がみられたが、変動の程度及び発現頻度が低く、血液生化学的検査及び病理組織学的検査において異常が認められなかつたことから、毒性学的意義の低い変化と考えた。また、28日間投与群において1000 mg/kg群でみられた甲状腺の相対重量の高値についても甲状腺及び肝臓に器質的変化が認められないことから毒性学的意義は低いと考えた。このほか、200及び1000 mg/kg群で脳の相対重量の高値、200 mg/kg群で左側精巣上体の相対重量の高値、1000 mg/kg群で左右精巣の相対重量の高値がみられたが、いずれも週齢によって重量が一定の範囲を示す器官であることから、前述の体重及び摂餌量の低値に起因した変動と考えた。

以上のとおり、本試験では、呼吸器系、消化器系、心・血管系、泌尿器系、生殖器系、神経系、造血器系、内分泌系、感覺器、筋・骨格系、乳腺を含むいずれの器官・組織にも被験

物質投与による毒性影響は認められなかった。

#### 19. 参考文献

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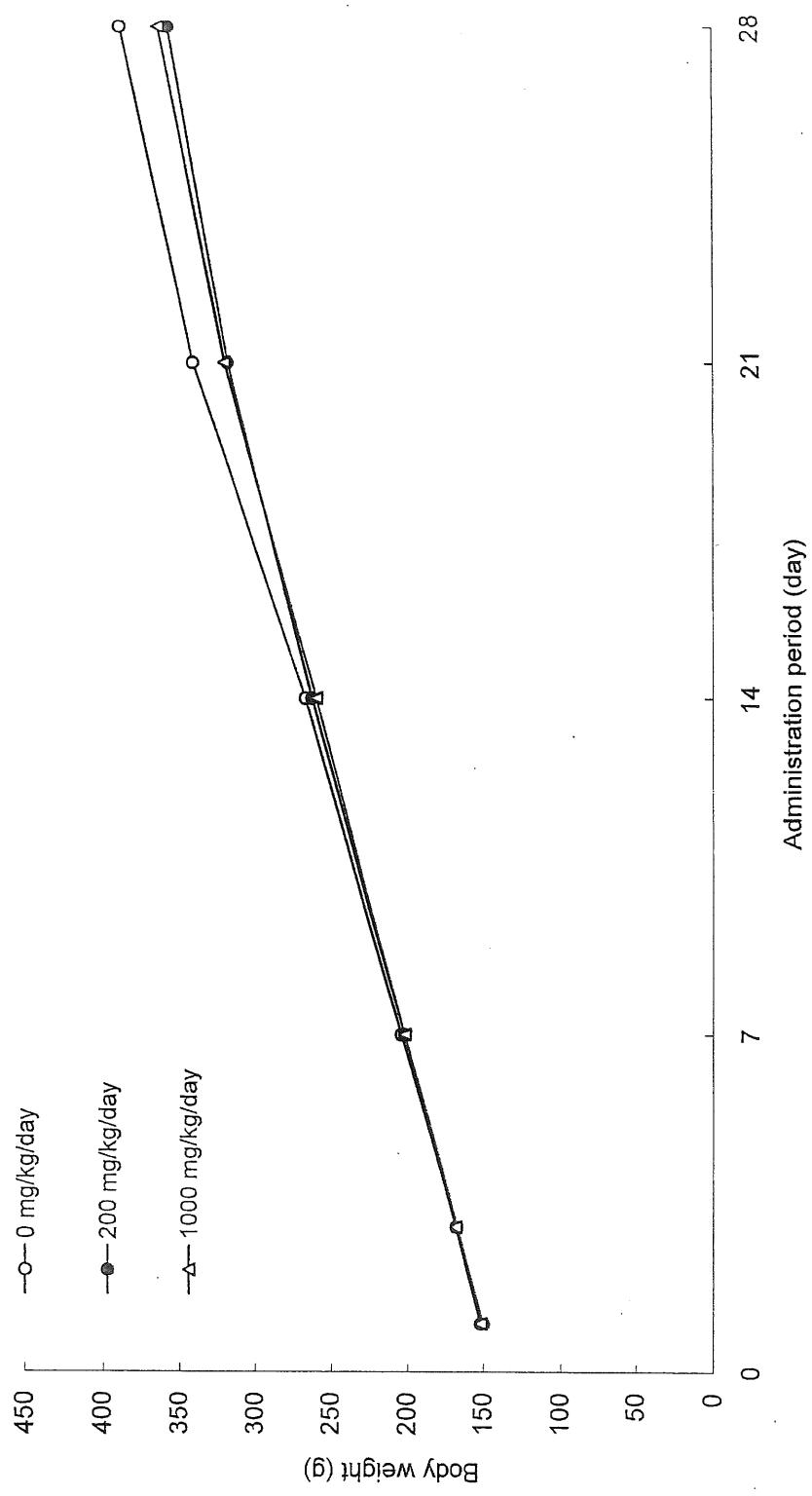


Fig. 1

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights: Male

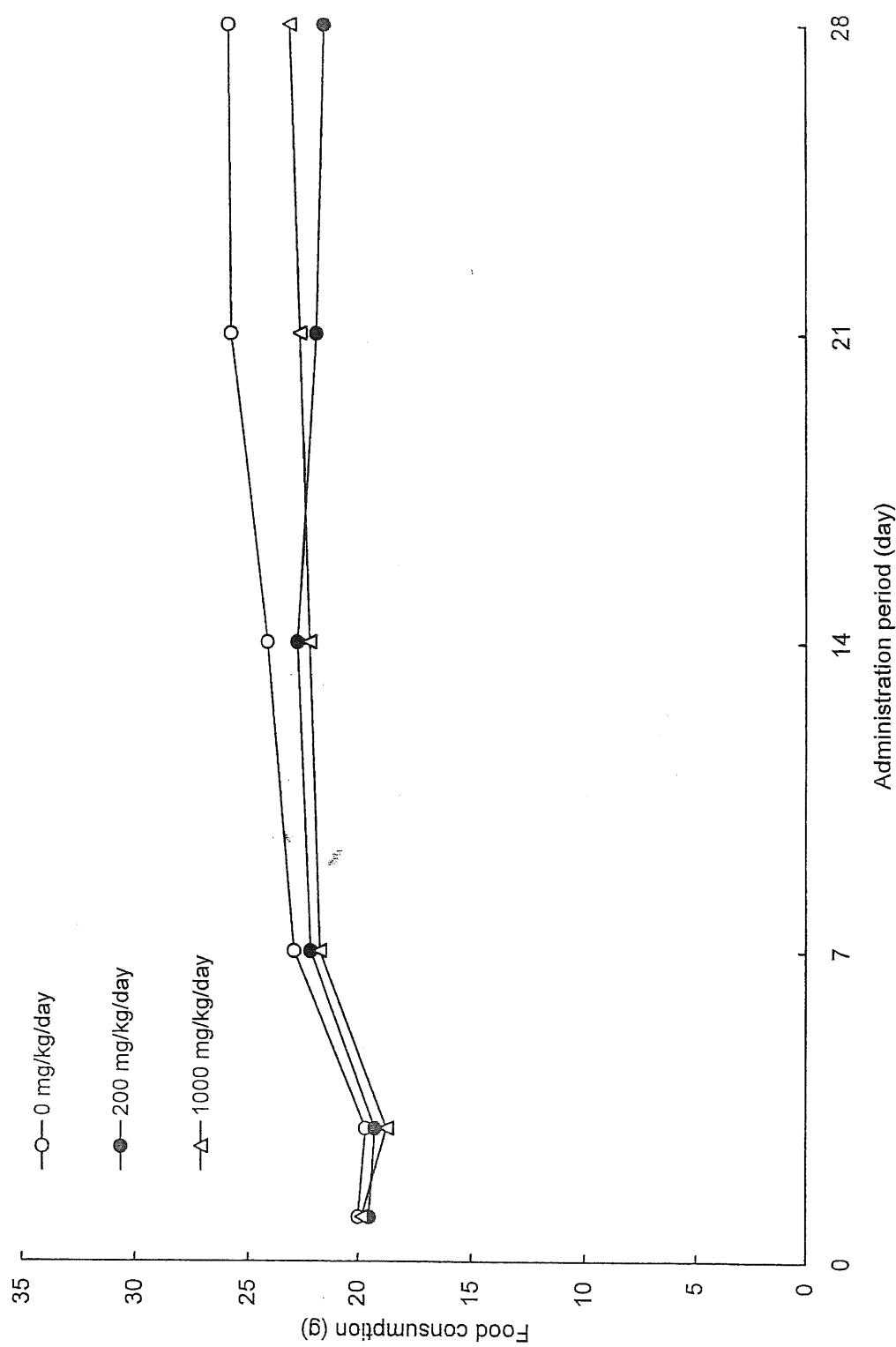


Fig. 2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Food consumption: Male

Table 1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of clinical signs

| Sex  | Signs                     | Administration period  |          |          |          |
|------|---------------------------|------------------------|----------|----------|----------|
|      |                           | mg/kg/day              | 0        | 200      | 1000     |
| Male |                           | ss<br>17 <sup>a)</sup> | ss<br>17 | ss<br>17 | ss<br>17 |
|      | No abnormalities detected |                        | 17       | 17       | 17       |

ss, scheduled sacrifice animal.

a) Number of animals examined.

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

| REMOVAL FROM CAGE     |                              |
|-----------------------|------------------------------|
| Ease of removal       |                              |
| -2                    | No reaction                  |
| -1                    | Very easy                    |
| 0                     | Easy (slight resistance)     |
| +1                    | Difficult                    |
| +2                    | Very difficult               |
| Vocalization          |                              |
| 0                     | None                         |
| +1                    | Vocalization during handling |
| +2                    | Continuous vocalization      |
| HANDLING OBSERVATIONS |                              |
| Muscle tone           |                              |
| -1                    | Decreased                    |
| 0                     | Normal                       |
| +1                    | Increased                    |
| Subnormal temperature |                              |
| -                     | Absent                       |
| +                     | Present                      |
| Piloerection          |                              |
| -                     | Absent                       |
| +                     | Present                      |
| Staining hair         |                              |
| -                     | Absent                       |
| +                     | Present                      |
| Unkempt hair          |                              |
| -                     | Absent                       |
| +                     | Present                      |
| Paleness              |                              |
| -                     | Absent                       |
| +                     | Present                      |
| Reddening             |                              |
| -                     | Absent                       |
| +                     | Present                      |
| Cyanosis              |                              |
| -                     | Absent                       |
| +                     | Present                      |
| Lacrimation           |                              |
| -                     | Absent                       |
| +                     | Present                      |

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

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HANDLING OBSERVATIONS-continued

## Exophthalmos

|   |         |
|---|---------|
| - | Absent  |
| + | Present |

## Pupillary size

|    |           |
|----|-----------|
| -1 | Miosis    |
| 0  | Normal    |
| +1 | Mydriasis |

## Salivation

|   |         |
|---|---------|
| - | Absent  |
| + | Present |

## Secretion

|   |         |
|---|---------|
| - | Absent  |
| + | Present |

---

OBSERVATIONS IN ARENA

## Posture

|    |  |
|----|--|
| 0  | Normal                                   |
| +1 | Crouching position or hunchback position |
| +2 | Prone position or lateral position       |

## Motor activity

|    |                         |
|----|-------------------------|
| -2 | Significantly decreased |
| -1 | Decreased               |
| 0  | Normal                  |
| +1 | Increased               |
| +2 | Significantly increased |

## Respiration

|    |                          |
|----|--------------------------|
| 0  | Normal                   |
| +1 | Slightly insufficiency   |
| +2 | Moderately insufficiency |
| +3 | Severely insufficiency   |

## Lid closure

|   |         |
|---|---------|
| - | Absent  |
| + | Present |

## Gait

|    |                            |
|----|----------------------------|
| -  | Normal                     |
| S  | Staggering gait            |
| T  | Tip toe gait               |
| P  | Shuffling (paralytic) gait |
| GD | Gait disturbance           |

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Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

## OBSERVATIONS IN ARENA-continued

## Tremor/twitch/convulsion

|    |   |
|----|---|
| 0  | None  |
| +1 | Tremor  |
| +2 | Twitch or convulsion  |
| +3 | Systematic tonic convulsion (opisthotonus or episthotonus etc.) |

## Stereotypic behavior

|   |              |
|---|--------------|
| - | None         |
| C | Circling     |
| G | Grooming     |
| S | Sniffing     |
| H | Head bobbing |

## Abnormal behavior

|    |                       |
|----|-----------------------|
| -  | None                  |
| S  | Self-biting           |
| B  | Backing               |
| C  | Circling              |
| R  | Rolling               |
| W  | Writhing              |
| V  | Vocalization          |
| ST | Straub tail           |
| T  | Tail lashing behavior |

Table 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Ease of removal |    |   |    |    | Removal from cage |    |    |
|------|-----------|---------------------|----------------------|-----------------|----|---|----|----|-------------------|----|----|
|      |           |                     |                      | -2              | -1 | 0 | +1 | +2 | 0                 | +1 | +2 |
| Male | Predosing | 0                   | 5                    | 0               | 0  | 5 | 0  | 0  | 4                 | 1  | 0  |
|      |           | 200                 | 5                    | 0               | 0  | 5 | 0  | 0  | 5                 | 0  | 0  |
|      |           | 1000                | 5                    | 0               | 0  | 5 | 0  | 0  | 4                 | 1  | 0  |
|      | week 1    | 0                   | 5                    | 0               | 1  | 4 | 0  | 0  | 5                 | 0  | 0  |
|      |           | 200                 | 5                    | 0               | 0  | 5 | 0  | 0  | 4                 | 1  | 0  |
|      |           | 1000                | 5                    | 0               | 1  | 4 | 0  | 0  | 5                 | 0  | 0  |
|      | week 2    | 0                   | 5                    | 0               | 0  | 5 | 0  | 0  | 4                 | 1  | 0  |
|      |           | 200                 | 5                    | 0               | 0  | 5 | 0  | 0  | 5                 | 0  | 0  |
|      |           | 1000                | 5                    | 0               | 0  | 5 | 0  | 0  | 5                 | 0  | 0  |
|      | week 3    | 0                   | 5                    | 0               | 0  | 5 | 0  | 0  | 4                 | 1  | 0  |
|      |           | 200                 | 5                    | 0               | 0  | 5 | 0  | 0  | 3                 | 2  | 0  |
|      |           | 1000                | 5                    | 0               | 0  | 5 | 0  | 0  | 3                 | 2  | 0  |
|      | week 4    | 0                   | 5                    | 0               | 0  | 5 | 0  | 0  | 3                 | 2  | 0  |
|      |           | 200                 | 5                    | 0               | 0  | 5 | 0  | 0  | 4                 | 1  | 0  |
|      |           | 1000                | 5                    | 0               | 0  | 5 | 0  | 0  | 4                 | 1  | 0  |

Table 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Handling observations |   |    |                       |   |              |   |  |
|------|-----------|---------------------|----------------------|-----------------------|---|----|-----------------------|---|--------------|---|--|
|      |           |                     |                      | Muscle tone           |   |    | Subnormal temperature |   | Piloerection |   |  |
|      |           |                     |                      | -1                    | 0 | +1 | -                     | + | -            | + |  |
| Male | Predosing | 0                   | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 200                 | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 1000                | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      | week 1    | 0                   | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 200                 | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 1000                | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      | week 2    | 0                   | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 200                 | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 1000                | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      | week 3    | 0                   | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 200                 | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 1000                | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      | week 4    | 0                   | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 200                 | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |
|      |           | 1000                | 5                    | 0                     | 5 | 0  | 5                     | 0 | 5            | 0 |  |

Table 2-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Handling observations |   |              |   |          |   |           |   |
|------|-----------|---------------------|----------------------|-----------------------|---|--------------|---|----------|---|-----------|---|
|      |           |                     |                      | Staining hair         |   | Unkempt hair |   | Paleness |   | Reddening |   |
|      |           |                     |                      | -                     | + | -            | + | -        | + | -         | + |
| Male | Predosing | 0                   | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      | week 1    | 0                   | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      | week 2    | 0                   | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      | week 3    | 0                   | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      | week 4    | 0                   | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5            | 0 | 5        | 0 | 5         | 0 |

Table 2-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Handling observations |   |             |   |
|------|-----------|---------------------|----------------------|-----------------------|---|-------------|---|
|      |           |                     |                      | Cyanosis              |   | Lacrimation |   |
|      |           |                     |                      | -                     | + | -           | + |
| Male | Predosing | 0                   | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5           | 0 |
|      | week 1    | 0                   | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5           | 0 |
|      | week 2    | 0                   | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5           | 0 |
|      | week 3    | 0                   | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5           | 0 |
|      | week 4    | 0                   | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 5           | 0 |

Table 2-5 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex       | Period | Dose<br>(mg/kg/day) | Number of<br>animals | Handling observations |   |    |            |   |           |   |  |
|-----------|--------|---------------------|----------------------|-----------------------|---|----|------------|---|-----------|---|--|
|           |        |                     |                      | Pupillary size        |   |    | Salivation |   | Secretion |   |  |
|           |        |                     |                      | -1                    | 0 | +1 | -          | + | -         | + |  |
| Predosing | 0      | 5                   | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           | 200    | 5                   | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           | 1000   | 5                   | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
| Male      | 0      | 5                   | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           | week 1 | 200                 | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           |        | 1000                | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           | 0      | 5                   | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           | week 2 | 200                 | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           |        | 1000                | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
| week 3    | 0      | 5                   | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           | 200    | 5                   | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           |        | 1000                | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
| week 4    | 0      | 5                   | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           | 200    | 5                   | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |
|           |        | 1000                | 5                    | 0                     | 5 | 0  | 5          | 0 | 5         | 0 |  |

Table 2-6 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Observations in arena |    |    |                |    |   |    |    |
|------|-----------|---------------------|----------------------|-----------------------|----|----|----------------|----|---|----|----|
|      |           |                     |                      | Posture               |    |    | Motor activity |    |   |    |    |
|      |           |                     |                      | 0                     | +1 | +2 | -2             | -1 | 0 | +1 | +2 |
| Male | Predosing | 0                   | 5                    | 5                     | 0  | 0  | 0              | 0  | 4 | 1  | 0  |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0              | 0  | 4 | 1  | 0  |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      | week 1    | 0                   | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0              | 0  | 4 | 1  | 0  |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      | week 2    | 0                   | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      | week 3    | 0                   | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      | week 4    | 0                   | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0              | 0  | 5 | 0  | 0  |

Table 2-7 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Observations in arena |    |    |    |             |   |
|------|-----------|---------------------|----------------------|-----------------------|----|----|----|-------------|---|
|      |           |                     |                      | Respiration           |    |    |    | Lid closure |   |
|      |           |                     |                      | 0                     | +1 | +2 | +3 | -           | + |
| Male | Predosing | 0                   | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      | week 1    | 0                   | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      | week 2    | 0                   | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      | week 3    | 0                   | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      | week 4    | 0                   | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 5           | 0 |

Table 2-8 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Observations in arena |   |   |   |    |
|------|-----------|---------------------|----------------------|-----------------------|---|---|---|----|
|      |           |                     |                      | -                     | S | T | P | GD |
| Male | Predosing | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      | week 1    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      | week 2    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      | week 3    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      | week 4    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0  |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0  |

Table 2-9 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Observations in arena |    |    |    | Defecation<br>(count/min) <sup>a)</sup> | Urination<br>(count/min) <sup>a)</sup> |
|------|-----------|---------------------|----------------------|-----------------------|----|----|----|---|--|
|      |           |                     |                      | 0                     | +1 | +2 | +3 |   |  |
| Male | Predosing | 0                   | 5                    | 5                     | 0  | 0  | 0  | 0.0 ±0.00                               | 0.8 ±1.10                              |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 0.4 ±0.55                               | 1.0 ±1.41                              |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 0.2 ±0.45                               | 0.6 ±0.89                              |
|      | week 1    | 0                   | 5                    | 5                     | 0  | 0  | 0  | 0.6 ±1.34                               | 0.4 ±0.89                              |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 0.6 ±0.89                               | 1.0 ±1.41                              |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 0.4 ±0.89                               | 1.4 ±2.19                              |
|      | week 2    | 0                   | 5                    | 5                     | 0  | 0  | 0  | 0.2 ±0.45                               | 0.4 ±0.89                              |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 0.2 ±0.45                               | 0.4 ±0.55                              |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 0.8 ±1.10                               | 1.4 ±2.61                              |
|      | week 3    | 0                   | 5                    | 5                     | 0  | 0  | 0  | 0.4 ±0.89                               | 2.8 ±3.83                              |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 0.2 ±0.45                               | 0.4 ±0.89                              |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 0.4 ±0.55                               | 2.0 ±2.35                              |
|      | week 4    | 0                   | 5                    | 5                     | 0  | 0  | 0  | 0.2 ±0.45                               | 0.2 ±0.45                              |
|      |           | 200                 | 5                    | 5                     | 0  | 0  | 0  | 0.2 ±0.45                               | 0.0 ±0.00                              |
|      |           | 1000                | 5                    | 5                     | 0  | 0  | 0  | 0.4 ±0.55                               | 1.0 ±1.41                              |

a) Mean ±S.D.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 2-10 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Observations in arena |   |   |   |   |
|------|-----------|---------------------|----------------------|-----------------------|---|---|---|---|
|      |           |                     |                      | -                     | C | G | S | H |
| Male | Predosing | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      | week 1    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      | week 2    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      | week 3    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      | week 4    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 |

Table 2-11 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of detailed clinical observations

| Sex  | Period    | Dose<br>(mg/kg/day) | Number of<br>animals | Observations in arena |   |   |   |   |   |   |    |   |
|------|-----------|---------------------|----------------------|-----------------------|---|---|---|---|---|---|----|---|
|      |           |                     |                      | -                     | S | B | C | R | W | V | ST | T |
| Male | Predosing | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      | week 1    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      | week 2    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      | week 3    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      | week 4    | 0                   | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 200                 | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |
|      |           | 1000                | 5                    | 5                     | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0 |

Table 3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of reflex (scoring scale for reflex)

| SENSORIMOTOR FUNCTION           |                   |
|---------------------------------|-------------------|
| Approach contact/touch response |                   |
| -1                              | No reaction       |
| 0                               | Normal            |
| +1                              | Hyper reaction    |
| Pinna response                  |                   |
| -1                              | No reaction       |
| 0                               | Normal            |
| +1                              | Hyper reaction    |
| Pain response (tail pinch)      |                   |
| -1                              | No reaction       |
| 0                               | Normal            |
| +1                              | Hyper reaction    |
| Pupillary reflex                |                   |
| +                               | Normal            |
| -                               | Abnormal reaction |
| Air righting reflex             |                   |
| +                               | Normal            |
| -                               | Abnormal reaction |

Table 3-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of reflex

| Sex  | Period | Dose<br>(mg/kg/day) | Number of<br>animals | Sensorimotor function               |   |    |                |   |    |
|------|--------|---------------------|----------------------|-------------------------------------|---|----|----------------|---|----|
|      |        |                     |                      | Approach contact/<br>touch response |   |    | Pinna response |   |    |
|      |        |                     |                      | -1                                  | 0 | +1 | -1             | 0 | +1 |
| Male | week 4 | 0                   | 5                    | 0                                   | 5 | 0  | 0              | 5 | 0  |
|      |        | 200                 | 5                    | 0                                   | 5 | 0  | 0              | 5 | 0  |
|      |        | 1000                | 5                    | 0                                   | 5 | 0  | 0              | 5 | 0  |

Table 3-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of reflex

| Sex  | Period | Dose<br>(mg/kg/day) | Number of<br>animals | Sensorimotor function      |   |    |                  |   |                     |   |
|------|--------|---------------------|----------------------|----------------------------|---|----|------------------|---|---------------------|---|
|      |        |                     |                      | Pain response (tail pinch) |   |    | Pupillary reflex |   | Air righting reflex |   |
|      |        |                     |                      | -1                         | 0 | +1 | +                | - | +                   | - |
| Male | week 4 | 0                   | 5                    | 0                          | 5 | 0  | 5                | 0 | 5                   | 0 |
|      |        | 200                 | 5                    | 0                          | 5 | 0  | 5                | 0 | 5                   | 0 |
|      |        | 1000                | 5                    | 0                          | 5 | 0  | 5                | 0 | 5                   | 0 |

Table 4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of grip strength

| Sex  | Period | Dose<br>(mg/kg/day) | Number of<br>animals | Forelimb<br>(g) | Hindlimb<br>(g) |
|------|--------|---------------------|----------------------|-----------------|-----------------|
| Male | week 4 | 0                   | 5                    | 456 ±37         | 442 ±22         |
|      |        | 200                 | 5                    | 467 ±27         | 432 ±31         |
|      |        | 1000                | 5                    | 443 ±60         | 455 ±29         |

Mean ±S.D.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 5 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of motor activity

| Sex  | Period | Dose<br>(mg/kg/day) | Number of<br>animals | Interval (min) |       |       |       |       |       |       |
|------|--------|---------------------|----------------------|----------------|-------|-------|-------|-------|-------|-------|
|      |        |                     |                      | 0-10           | 10-20 | 20-30 | 30-40 | 40-50 | 50-60 | Total |
| Male | week 4 | 0                   | 5                    | 130            | 97    | 79    | 64    | 51    | 17    | 437   |
|      |        |                     |                      | ±32            | ±35   | ±40   | ±30   | ±18   | ±18   | ±109  |
| Male | week 4 | 200                 | 5                    | 191 *          | 112   | 109   | 56    | 40    | 18    | 526   |
|      |        |                     |                      | ±25            | ±36   | ±46   | ±43   | ±40   | ±33   | ±147  |
| Male | week 4 | 1000                | 5                    | 145            | 81    | 48    | 46    | 24    | 13    | 356   |
|      |        |                     |                      | ±35            | ±24   | ±32   | ±43   | ±36   | ±15   | ±78   |

Mean ±S.D.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 6 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of body weights (g) : Male

| Administration period | Dose<br>(mg/kg/day) | Dose                 |                        |                      |
|-----------------------|---------------------|----------------------|------------------------|----------------------|
|                       |                     | 0                    | 200                    | 1000                 |
| 1                     |                     | 151.48<br>±6.72 (17) | 150.05<br>±5.57 (17)   | 151.64<br>±5.61 (17) |
| 3                     |                     | 168.34<br>±6.43 (13) | 167.22<br>±6.49 (13)   | 168.03<br>±5.50 (13) |
| 7                     |                     | 204.02<br>±8.41 (13) | 202.01<br>±9.01 (13)   | 201.89<br>±6.90 (13) |
| 14                    |                     | 266.79<br>±16.33 (9) | 262.73<br>±9.91 (9)    | 259.59<br>±10.55 (9) |
| 21                    |                     | 340.86<br>±9.44 (5)  | 318.28 *<br>±12.00 (5) | 320.52<br>±18.58 (5) |
| 28                    |                     | 388.38<br>±13.34 (5) | 357.18 *<br>±12.10 (5) | 363.40<br>±23.82 (5) |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 7      Twenty-eight-day repeated-dose oral toxicity study in rats      B10-0093  
 Summary of food consumption (g/rat/day) : male

| Sex                   | Dose<br>(mg/kg/day) | 0                    | 200                    | 1000                   |
|-----------------------|---------------------|----------------------|------------------------|------------------------|
| Administration period | 1                   | 20.00<br>± 1.60 (13) | 19.51<br>± 1.78 (13)   | 19.85<br>± 1.23 (13)   |
|                       | 3                   | 19.68<br>± 1.65 (13) | 19.26<br>± 1.75 (13)   | 18.75<br>± 0.75 (13)   |
|                       | 7                   | 22.90<br>± 1.28 (13) | 22.16<br>± 1.84 (13)   | 21.74<br>± 1.24 (13)   |
|                       | 14                  | 24.13<br>± 1.85 (9)  | 22.77<br>± 1.62 (9)    | 22.24 *<br>± 1.14 (9)  |
|                       | 21                  | 25.82<br>± 1.12 (5)  | 21.95 **<br>± 0.99 (5) | 22.67 **<br>± 1.42 (5) |
|                       | 28                  | 25.93<br>± 1.02 (5)  | 21.59 **<br>± 0.65 (5) | 23.11 *<br>± 1.96 (5)  |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 8-1      Twenty-eight-day repeated-dose oral toxicity study in rats  
 Summary of urinalyses:Male

| Items                | Dose<br>(mg/kg/day) | Twenty-eight-day treatment |                     |                     |
|----------------------|---------------------|----------------------------|---------------------|---------------------|
|                      |                     | 0                          | 200                 | 1000                |
| Urine volume<br>(mL) |                     | 12.0<br>±6.2 (5)           | 11.4<br>±5.9 (5)    | 13.0<br>±7.5 (5)    |
| Uosm<br>(mOsm/L)     |                     | 985.2<br>±558.1 (5)        | 795.6<br>±352.0 (5) | 902.6<br>±515.7 (5) |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 8-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of urinalyses: Male

| Items               | Group | Twenty-eight-day treatment |   |     |      |
|---------------------|-------|----------------------------|---|-----|------|
|                     |       | Dose (mg/kg/day)           | 0 | 200 | 1000 |
| No. of animals      |       |                            | 5 | 5   | 5    |
| <b>Color</b>        |       |                            |   |     |      |
| SY                  |       | 3                          | 2 | 2   |      |
| Y                   |       | 0                          | 3 | 2   |      |
| YB                  |       | 2                          | 0 | 1   |      |
| <b>Turbidity</b>    |       |                            |   |     |      |
| Clear               |       | 5                          | 5 | 5   |      |
| <b>pH</b>           |       |                            |   |     |      |
| 6.0                 |       | 1                          | 1 | 1   |      |
| 6.5                 |       | 3                          | 0 | 1   |      |
| 7.0                 |       | 1                          | 4 | 3   |      |
| <b>Protein</b>      |       |                            |   |     |      |
| -                   |       | 2                          | 1 | 1   |      |
| ±                   |       | 2                          | 4 | 2   |      |
| 1+                  |       | 1                          | 0 | 2   |      |
| <b>Glucose</b>      |       |                            |   |     |      |
| -                   |       | 5                          | 5 | 5   |      |
| <b>Ketones</b>      |       |                            |   |     |      |
| -                   |       | 1                          | 1 | 0   |      |
| ±                   |       | 3                          | 2 | 3   |      |
| 1+                  |       | 1                          | 2 | 2   |      |
| <b>Occult blood</b> |       |                            |   |     |      |
| -                   |       | 4                          | 5 | 5   |      |
| ±                   |       | 1                          | 0 | 0   |      |

Color: SY: Slightly yellow, Y: Yellow, YB:Yellow-brown.

Table 8-3      Twenty-eight-day repeated-dose oral toxicity study in rats      B1D-0093  
 Summary of urinalyses: Male

| Items                           | Group          | Twenty-eight-day treatment |   |     |
|---------------------------------|----------------|----------------------------|---|-----|
|                                 |                | Dose (mg/kg/day)           | 0 | 200 |
|                                 | No. of animals | 5                          | 0 | 5   |
| <b>Urinaly sediment</b>         |                |                            |   |     |
| Red blood cells <sup>a)</sup>   | 0              | 5                          | — | 5   |
| White blood cells <sup>a)</sup> | 0              | 5                          | — | 5   |
| Epithelial cells <sup>a)</sup>  | 0              | 5                          | — | 5   |
| Casts <sup>b)</sup>             | 0              | 5                          | — | 5   |
| Crystals <sup>c)</sup>          | -              | 1                          | — | 0   |
|                                 | ±              | 1                          | — | 2   |
|                                 | 1+             | 2                          | — | 1   |
|                                 | 2+             | 1                          | — | 2   |

<sup>a)</sup>: Number of cells/10views( $\times 400$ ).

<sup>b)</sup>: Number of casts/ $18 \times 18 \text{ mm}^2$ .

<sup>c)</sup>: Incidence of crystals/ $18 \times 18 \text{ mm}^2$ .

—:Not examined.

Table 9-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of hematological examinations:Male

| Items                               | Dose<br>(mg/kg/day)           | One-day treatment         |                           |                           |
|-------------------------------------|-------------------------------|---------------------------|---------------------------|---------------------------|
|                                     |                               | 0                         | 200                       | 1000                      |
| RBC                                 | ( $\times 10^4/\mu\text{L}$ ) | 735.8<br>$\pm 23.6$ (4)   | 722.5<br>$\pm 38.4$ (4)   | 700.3<br>$\pm 23.8$ (4)   |
| Hb                                  | (g/dL)                        | 15.80<br>$\pm 0.67$ (4)   | 15.13<br>$\pm 0.80$ (4)   | 14.80<br>$\pm 0.63$ (4)   |
| Ht                                  | (%)                           | 49.63<br>$\pm 2.58$ (4)   | 48.53<br>$\pm 1.99$ (4)   | 48.10<br>$\pm 2.10$ (4)   |
| MCV                                 | (fL)                          | 67.45<br>$\pm 1.89$ (4)   | 67.20<br>$\pm 2.02$ (4)   | 68.68<br>$\pm 2.06$ (4)   |
| MCH                                 | (pg)                          | 21.53<br>$\pm 0.38$ (4)   | 20.95<br>$\pm 0.83$ (4)   | 21.15<br>$\pm 0.75$ (4)   |
| MCHC                                | (g/dL)                        | 31.88<br>$\pm 0.53$ (4)   | 31.20<br>$\pm 0.48$ (4)   | 30.78 *<br>$\pm 0.22$ (4) |
| Platelet                            | ( $\times 10^4/\mu\text{L}$ ) | 138.03<br>$\pm 13.30$ (4) | 140.63<br>$\pm 22.00$ (4) | 118.35<br>$\pm 12.73$ (4) |
| Reticulo                            | (%)                           | 10.13<br>$\pm 0.41$ (4)   | 11.90 *<br>$\pm 0.57$ (4) | 11.88 *<br>$\pm 1.17$ (4) |
| WBC                                 | ( $\times 10^2/\mu\text{L}$ ) | 122.83<br>$\pm 21.34$ (4) | 134.40<br>$\pm 27.52$ (4) | 130.40<br>$\pm 11.13$ (4) |
| <b>Differentiation of leukocyte</b> |                               |                           |                           |                           |
| Neutro                              | (%)                           | 9.13<br>$\pm 2.76$ (4)    | 9.60<br>$\pm 1.71$ (4)    | 9.73<br>$\pm 0.97$ (4)    |
| Lymph                               | (%)                           | 86.03<br>$\pm 2.59$ (4)   | 85.55<br>$\pm 1.30$ (4)   | 85.53<br>$\pm 1.00$ (4)   |
| Eosino                              | (%)                           | 0.63<br>$\pm 0.13$ (4)    | 0.40<br>$\pm 0.14$ (4)    | 0.45<br>$\pm 0.19$ (4)    |
| Baso                                | (%)                           | 0.95<br>$\pm 0.33$ (4)    | 0.88<br>$\pm 0.50$ (4)    | 0.83<br>$\pm 0.29$ (4)    |
| Mono                                | (%)                           | 2.23<br>$\pm 0.67$ (4)    | 2.60<br>$\pm 1.25$ (4)    | 2.18<br>$\pm 0.50$ (4)    |
| LUC                                 | (%)                           | 1.00<br>$\pm 0.14$ (4)    | 0.98<br>$\pm 0.25$ (4)    | 1.33<br>$\pm 0.43$ (4)    |

Values are shown as Mean  $\pm$  S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 9-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of hematological examinations:Male

| Items                                     | Dose<br>(mg/kg/day) | Seven-day treatment       |                           |                           |
|---|---------------------|---------------------------|---------------------------|---------------------------|
|   |                     | 0                         | 200                       | 1000                      |
| RBC<br>( $\times 10^4/\mu\text{L}$ )      |                     | 709.0<br>$\pm 11.7$ (4)   | 742.8 *<br>$\pm 10.7$ (4) | 746.3 *<br>$\pm 25.1$ (4) |
| Hb<br>(g/dL)                              |                     | 14.58<br>$\pm 0.24$ (4)   | 15.05<br>$\pm 0.54$ (4)   | 15.23<br>$\pm 0.74$ (4)   |
| Ht<br>(%)                                 |                     | 47.45<br>$\pm 0.82$ (4)   | 49.35<br>$\pm 1.95$ (4)   | 49.85<br>$\pm 2.37$ (4)   |
| MCV<br>(fL)                               |                     | 66.95<br>$\pm 0.91$ (4)   | 66.43<br>$\pm 3.08$ (4)   | 66.83<br>$\pm 2.08$ (4)   |
| MCH<br>(pg)                               |                     | 20.55<br>$\pm 0.40$ (4)   | 20.33<br>$\pm 0.79$ (4)   | 20.38<br>$\pm 0.64$ (4)   |
| MCHC<br>(g/dL)                            |                     | 30.68<br>$\pm 0.44$ (4)   | 30.58<br>$\pm 0.48$ (4)   | 30.53<br>$\pm 0.46$ (4)   |
| Platelet<br>( $\times 10^4/\mu\text{L}$ ) |                     | 124.73<br>$\pm 11.29$ (4) | 116.73<br>$\pm 17.75$ (4) | 119.75<br>$\pm 10.27$ (4) |
| Reticulo<br>(%)                           |                     | 8.43<br>$\pm 0.29$ (4)    | 8.53<br>$\pm 1.49$ (4)    | 8.65<br>$\pm 0.68$ (4)    |
| WBC<br>( $\times 10^2/\mu\text{L}$ )      |                     | 127.05<br>$\pm 28.60$ (4) | 144.23<br>$\pm 45.52$ (4) | 122.30<br>$\pm 25.08$ (4) |
| <b>Differentiation of leukocyte</b>       |                     |                           |                           |                           |
| Neutro<br>(%)                             |                     | 16.78<br>$\pm 2.19$ (4)   | 13.58<br>$\pm 1.26$ (4)   | 14.35<br>$\pm 4.53$ (4)   |
| Lymph<br>(%)                              |                     | 77.53<br>$\pm 2.88$ (4)   | 82.18<br>$\pm 0.93$ (4)   | 81.53<br>$\pm 5.85$ (4)   |
| Eosino<br>(%)                             |                     | 0.53<br>$\pm 0.13$ (4)    | 0.23 **<br>$\pm 0.13$ (4) | 0.25 *<br>$\pm 0.06$ (4)  |
| Baso<br>(%)                               |                     | 0.68<br>$\pm 0.13$ (4)    | 0.78<br>$\pm 0.30$ (4)    | 0.53<br>$\pm 0.05$ (4)    |
| Mono<br>(%)                               |                     | 2.63<br>$\pm 1.37$ (4)    | 1.85<br>$\pm 0.44$ (4)    | 1.75<br>$\pm 0.76$ (4)    |
| LUC<br>(%)                                |                     | 1.83<br>$\pm 1.02$ (4)    | 1.30<br>$\pm 0.24$ (4)    | 1.55<br>$\pm 0.83$ (4)    |

Values are shown as Mean  $\pm$  S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 9-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of hematological examinations:Male

| Items                               | Dose<br>(mg/kg/day)           | Fourteen-day treatment    |                           |                           |
|-------------------------------------|-------------------------------|---------------------------|---------------------------|---------------------------|
|                                     |                               | 0                         | 200                       | 1000                      |
| RBC                                 | ( $\times 10^4/\mu\text{L}$ ) | 757.3<br>$\pm 23.4$ (4)   | 748.3<br>$\pm 46.8$ (4)   | 783.5<br>$\pm 7.3$ (4)    |
| Hb                                  | (g/dL)                        | 15.10<br>$\pm 0.62$ (4)   | 15.18<br>$\pm 0.79$ (4)   | 15.43<br>$\pm 0.32$ (4)   |
| Ht                                  | (%)                           | 49.65<br>$\pm 1.69$ (4)   | 49.28<br>$\pm 2.66$ (4)   | 50.03<br>$\pm 1.17$ (4)   |
| MCV                                 | (fL)                          | 65.60<br>$\pm 1.60$ (4)   | 65.85<br>$\pm 1.34$ (4)   | 63.88<br>$\pm 1.53$ (4)   |
| MCH                                 | (pg)                          | 19.95<br>$\pm 0.45$ (4)   | 20.30<br>$\pm 0.63$ (4)   | 19.68<br>$\pm 0.41$ (4)   |
| MCHC                                | (g/dL)                        | 30.38<br>$\pm 0.28$ (4)   | 30.83<br>$\pm 0.43$ (4)   | 30.78<br>$\pm 0.15$ (4)   |
| Platelet                            | ( $\times 10^4/\mu\text{L}$ ) | 127.58<br>$\pm 12.33$ (4) | 113.85<br>$\pm 13.72$ (4) | 133.60<br>$\pm 9.40$ (4)  |
| Reticulo                            | (%)                           | 4.65<br>$\pm 0.85$ (4)    | 4.58<br>$\pm 0.51$ (4)    | 4.15<br>$\pm 0.17$ (4)    |
| WBC                                 | ( $\times 10^2/\mu\text{L}$ ) | 151.43<br>$\pm 5.39$ (4)  | 122.25<br>$\pm 35.52$ (4) | 137.80<br>$\pm 11.31$ (4) |
| <b>Differentiation of leukocyte</b> |                               |                           |                           |                           |
| Neutro                              | (%)                           | 19.30<br>$\pm 8.53$ (4)   | 12.15<br>$\pm 3.70$ (4)   | 12.63<br>$\pm 1.24$ (4)   |
| Lymph                               | (%)                           | 74.03<br>$\pm 8.47$ (4)   | 82.80<br>$\pm 4.00$ (4)   | 81.60<br>$\pm 1.59$ (4)   |
| Eosino                              | (%)                           | 0.55<br>$\pm 0.17$ (4)    | 0.50<br>$\pm 0.14$ (4)    | 0.50<br>$\pm 0.08$ (4)    |
| Baso                                | (%)                           | 2.80<br>$\pm 1.22$ (4)    | 1.33<br>$\pm 0.65$ (4)    | 1.95<br>$\pm 0.83$ (4)    |
| Mono                                | (%)                           | 2.18<br>$\pm 0.59$ (4)    | 1.85<br>$\pm 0.42$ (4)    | 1.93<br>$\pm 0.61$ (4)    |
| LUC                                 | (%)                           | 1.18<br>$\pm 0.22$ (4)    | 1.38<br>$\pm 0.34$ (4)    | 1.35<br>$\pm 0.66$ (4)    |

Values are shown as Mean  $\pm$  S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 9-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of hematological examinations:Male

| Items                                     | Dose<br>(mg/kg/day) | Twenty-eight-day treatment |                           |                             |
|---|---------------------|----------------------------|---------------------------|-----------------------------|
|   |                     | 0                          | 200                       | 1000                        |
| RBC<br>( $\times 10^4/\mu\text{L}$ )      |                     | 791.2<br>$\pm 30.9$ (5)    | 818.6<br>$\pm 64.4$ (5)   | 780.2<br>$\pm 46.5$ (5)     |
| Hb<br>(g/dL)                              |                     | 15.08<br>$\pm 0.62$ (5)    | 15.66<br>$\pm 1.11$ (5)   | 15.54<br>$\pm 0.94$ (5)     |
| Ht<br>(%)                                 |                     | 48.74<br>$\pm 2.33$ (5)    | 49.94<br>$\pm 3.82$ (5)   | 49.58<br>$\pm 3.49$ (5)     |
| MCV<br>(fL)                               |                     | 61.58<br>$\pm 1.18$ (5)    | 61.06<br>$\pm 1.64$ (5)   | 63.56<br>$\pm 2.06$ (5)     |
| MCH<br>(pg)                               |                     | 19.04<br>$\pm 0.23$ (5)    | 19.12<br>$\pm 0.54$ (5)   | 19.94 *<br>$\pm 0.55$ (5)   |
| MCHC<br>(g/dL)                            |                     | 30.96<br>$\pm 0.40$ (5)    | 31.36<br>$\pm 0.40$ (5)   | 31.34<br>$\pm 0.36$ (5)     |
| Platelet<br>( $\times 10^4/\mu\text{L}$ ) |                     | 119.72<br>$\pm 9.85$ (5)   | 105.58<br>$\pm 16.89$ (5) | 88.18<br>$\pm 45.94$ (5)    |
| Reticulo<br>(%)                           |                     | 3.18<br>$\pm 0.33$ (5)     | 2.86<br>$\pm 0.30$ (5)    | 3.08<br>$\pm 0.32$ (5)      |
| WBC<br>( $\times 10^2/\mu\text{L}$ )      |                     | 145.06<br>$\pm 22.39$ (5)  | 143.02<br>$\pm 32.19$ (5) | 103.70 *<br>$\pm 11.34$ (5) |
| <b>Differentiation of leukocyte</b>       |                     |                            |                           |                             |
| Neutro<br>(%)                             |                     | 12.94<br>$\pm 6.17$ (5)    | 16.30<br>$\pm 3.70$ (5)   | 19.86<br>$\pm 6.76$ (5)     |
| Lymph<br>(%)                              |                     | 81.74<br>$\pm 7.17$ (5)    | 78.86<br>$\pm 3.32$ (5)   | 75.76<br>$\pm 7.07$ (5)     |
| Eosino<br>(%)                             |                     | 0.68<br>$\pm 0.19$ (5)     | 0.54<br>$\pm 0.15$ (5)    | 0.44<br>$\pm 0.18$ (5)      |
| Baso<br>(%)                               |                     | 1.02<br>$\pm 0.65$ (5)     | 0.94<br>$\pm 0.36$ (5)    | 0.80<br>$\pm 0.88$ (5)      |
| Mono<br>(%)                               |                     | 2.32<br>$\pm 0.71$ (5)     | 1.82<br>$\pm 0.60$ (5)    | 1.86<br>$\pm 0.55$ (5)      |
| LUC<br>(%)                                |                     | 1.26<br>$\pm 0.32$ (5)     | 1.48<br>$\pm 0.42$ (5)    | 1.28<br>$\pm 0.20$ (5)      |
| PT<br>(sec)                               |                     | 17.12<br>$\pm 2.47$ (5)    | 21.68<br>$\pm 6.27$ (5)   | 19.62<br>$\pm 3.93$ (5)     |
| APTT<br>(sec)                             |                     | 19.66<br>$\pm 2.42$ (5)    | 24.18<br>$\pm 6.68$ (5)   | 25.04<br>$\pm 2.56$ (5)     |

Values are shown as Mean  $\pm$  S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 10-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of blood chemical examinations:Male

| Items      | Dose<br>(mg/kg/day) | One-day treatment   |                     |                     |
|------------|---------------------|---------------------|---------------------|---------------------|
|            |                     | 0                   | 200                 | 1000                |
| AST        | (IU/L)              | 83.0<br>±7.5 (4)    | 82.3<br>±4.3 (4)    | 90.5<br>±5.3 (4)    |
| ALT        | (IU/L)              | 26.5<br>±3.9 (4)    | 30.5<br>±3.7 (4)    | 34.5<br>±7.3 (4)    |
| ALP        | (IU/L)              | 851.0<br>±73.9 (4)  | 921.3<br>±110.3 (4) | 968.8<br>±140.9 (4) |
| BUN        | (mg/dL)             | 11.53<br>±2.13 (4)  | 12.98<br>±0.65 (4)  | 12.23<br>±1.04 (4)  |
| Creatinine | (mg/dL)             | 0.128<br>±0.022 (4) | 0.128<br>±0.010 (4) | 0.128<br>±0.010 (4) |
| T-Bil      | (mg/dL)             | 0.080<br>±0.014 (4) | 0.068<br>±0.005 (4) | 0.073<br>±0.019 (4) |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 10-2      Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of blood chemical examinations:Male

| Items      | Dose<br>(mg/kg/day) | Seven-day treatment |                     |                     |
|------------|---------------------|---------------------|---------------------|---------------------|
|            |                     | 0                   | 200                 | 1000                |
| AST        | (IU/L)              | 83.3<br>±3.0 (4)    | 81.0<br>±7.7 (4)    | 86.3<br>±6.1 (4)    |
| ALT        | (IU/L)              | 27.8<br>±4.6 (4)    | 33.0<br>±4.1 (4)    | 33.5<br>±2.6 (4)    |
| ALP        | (IU/L)              | 833.8<br>±103.7 (4) | 872.5<br>±31.5 (4)  | 748.8<br>±135.7 (4) |
| BUN        | (mg/dL)             | 11.08<br>±1.39 (4)  | 11.10<br>±1.00 (4)  | 11.40<br>±2.08 (4)  |
| Creatinine | (mg/dL)             | 0.133<br>±0.010 (4) | 0.145<br>±0.013 (4) | 0.143<br>±0.010 (4) |
| T-Bil      | (mg/dL)             | 0.070<br>±0.012 (4) | 0.065<br>±0.013 (4) | 0.060<br>±0.014 (4) |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 10-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of blood chemical examinations:Male

| Items      | Dose<br>(mg/kg/day) | Fourteen-day treatment |                     |                     |
|------------|---------------------|------------------------|---------------------|---------------------|
|            |                     | 0                      | 200                 | 1000                |
| AST        | (IU/L)              | 80.0<br>±20.0 (4)      | 69.8<br>±8.7 (4)    | 72.5<br>±6.6 (4)    |
| ALT        | (IU/L)              | 28.5<br>±14.3 (4)      | 24.3<br>±4.2 (4)    | 25.8<br>±4.9 (4)    |
| ALP        | (IU/L)              | 749.3<br>±254.6 (4)    | 673.3<br>±176.0 (4) | 701.8<br>±164.1 (4) |
| BUN        | (mg/dL)             | 10.00<br>±1.54 (4)     | 10.98<br>±2.54 (4)  | 12.08<br>±1.98 (4)  |
| Creatinine | (mg/dL)             | 0.165<br>±0.010 (4)    | 0.158<br>±0.021 (4) | 0.168<br>±0.022 (4) |
| T-Bil      | (mg/dL)             | 0.043<br>±0.013 (4)    | 0.038<br>±0.017 (4) | 0.035<br>±0.017 (4) |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 10-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of blood chemical examinations:Male

| Items      | Dose<br>(mg/kg/day) | Twenty-eight-day treatment |                     |                     |
|------------|---------------------|----------------------------|---------------------|---------------------|
|            |                     | 0                          | 200                 | 1000                |
| AST        | (IU/L)              | 60.2<br>±6.8 (5)           | 57.2<br>±10.4 (5)   | 51.2<br>±6.0 (5)    |
| ALT        | (IU/L)              | 21.4<br>±3.6 (5)           | 22.6<br>±5.1 (5)    | 21.2<br>±3.6 (5)    |
| ALP        | (IU/L)              | 586.0<br>±166.8 (5)        | 493.8<br>±96.2 (5)  | 455.8<br>±136.4 (5) |
| ChE        | (IU/L)              | 61.8<br>±25.9 (5)          | 60.2<br>±20.8 (5)   | 46.4<br>±6.3 (5)    |
| γ-GTP      | (IU/L)              | 0.46<br>±0.28 (5)          | 0.40<br>±0.12 (5)   | 0.46<br>±0.18 (5)   |
| T-Chol     | (mg/dL)             | 59.2<br>±13.2 (5)          | 68.0<br>±15.5 (5)   | 60.0<br>±12.8 (5)   |
| TG         | (mg/dL)             | 60.0<br>±16.4 (5)          | 54.0<br>±21.9 (5)   | 60.4<br>±26.5 (5)   |
| BUN        | (mg/dL)             | 12.48<br>±1.36 (5)         | 12.22<br>±2.17 (5)  | 11.26<br>±2.12 (5)  |
| Creatinine | (mg/dL)             | 0.220<br>±0.042 (5)        | 0.218<br>±0.015 (5) | 0.198<br>±0.028 (5) |
| T-Protein  | (g/dL)              | 5.62<br>±0.90 (5)          | 6.18<br>±0.98 (5)   | 5.44<br>±0.64 (5)   |
| Albumin    | (g/dL)              | 2.64<br>±0.36 (5)          | 2.84<br>±0.43 (5)   | 2.56<br>±0.31 (5)   |
| A/G ratio  | (-)                 | 0.892<br>±0.062 (5)        | 0.854<br>±0.036 (5) | 0.892<br>±0.056 (5) |
| Glucose    | (mg/dL)             | 169.8<br>±26.4 (5)         | 152.4<br>±44.6 (5)  | 153.6<br>±44.5 (5)  |
| T-Bil      | (mg/dL)             | 0.054<br>±0.005 (5)        | 0.054<br>±0.013 (5) | 0.050<br>±0.012 (5) |
| TBA        | (μmol/L)            | 20.12<br>±6.97 (5)         | 15.32<br>±6.77 (5)  | 9.12 *<br>±2.37 (5) |
| IP         | (mg/dL)             | 10.98<br>±1.03 (5)         | 11.54<br>±1.15 (5)  | 11.10<br>±1.22 (5)  |
| Ca         | (mg/dL)             | 10.98<br>±1.15 (5)         | 11.72<br>±1.43 (5)  | 10.72<br>±0.75 (5)  |
| Na         | (mEq/L)             | 146.6<br>±1.7 (5)          | 146.0<br>±1.0 (5)   | 145.6<br>±1.1 (5)   |
| K          | (mEq/L)             | 6.74<br>±0.64 (5)          | 6.86<br>±0.11 (5)   | 6.74<br>±1.03 (5)   |
| Cl         | (mEq/L)             | 101.50<br>±1.58 (5)        | 99.82<br>±1.14 (5)  | 100.30<br>±1.24 (5) |

Values are shown as Mean ± S.D.

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 11-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of absolute organ weights:Male

| Items                 | Dose<br>(mg/kg/day) | One-day treatment    |                      |                      |
|-----------------------|---------------------|----------------------|----------------------|----------------------|
|                       |                     | 0                    | 200                  | 1000                 |
| Liver                 | (g)                 | 4.510<br>±0.244 (4)  | 4.725<br>±0.162 (4)  | 4.925<br>±0.350 (4)  |
| Heart                 | (g)                 | 0.663<br>±0.036 (4)  | 0.655<br>±0.047 (4)  | 0.640<br>±0.037 (4)  |
| Kidney(R)             | (g)                 | 0.655<br>±0.058 (4)  | 0.663<br>±0.029 (4)  | 0.720<br>±0.061 (4)  |
| Kidney(L)             | (g)                 | 0.633<br>±0.061 (4)  | 0.653<br>±0.021 (4)  | 0.703<br>±0.044 (4)  |
| Testis(R)             | (g)                 | 0.680<br>±0.094 (4)  | 0.690<br>±0.080 (4)  | 0.778<br>±0.067 (4)  |
| Testis(L)             | (g)                 | 0.663<br>±0.085 (4)  | 0.683<br>±0.070 (4)  | 0.783<br>±0.039 (4)  |
| Epididymis(R)         | (g)                 | 0.070<br>±0.012 (4)  | 0.078<br>±0.005 (4)  | 0.080<br>±0.020 (4)  |
| Epididymis(L)         | (g)                 | 0.070<br>±0.008 (4)  | 0.078<br>±0.010 (4)  | 0.083<br>±0.005 (4)  |
| Ventral prostate      | (g)                 | 0.065<br>±0.006 (4)  | 0.058<br>±0.026 (4)  | 0.078<br>±0.013 (4)  |
| Dorsolateral prostate | (g)                 | 0.075<br>±0.024 (4)  | 0.075<br>±0.026 (4)  | 0.078<br>±0.017 (4)  |
| Brain                 | (g)                 | 1.785<br>±0.054 (4)  | 1.790<br>±0.080 (4)  | 1.690<br>±0.061 (4)  |
| Spleen                | (g)                 | 0.383<br>±0.051 (4)  | 0.378<br>±0.050 (4)  | 0.395<br>±0.019 (4)  |
| Thymus                | (mg)                | 471.98<br>±23.07 (4) | 428.75<br>±65.97 (4) | 463.03<br>±85.99 (4) |
| Pituitary gland       | (mg)                | 5.35<br>±0.57 (4)    | 5.65<br>±0.37 (4)    | 5.50<br>±0.36 (4)    |
| Thyroid               | (mg)                | 7.78<br>±1.05 (4)    | 8.48<br>±1.36 (4)    | 9.45<br>±2.19 (4)    |
| Adrenals              | (mg)                | 34.68<br>±4.12 (4)   | 31.58<br>±2.79 (4)   | 32.15<br>±3.05 (4)   |
| Final body weight     | (g)                 | 132.45<br>±6.43 (4)  | 131.58<br>±4.47 (4)  | 133.38<br>±5.18 (4)  |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 11-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of absolute organ weights:Male

| Items                 | Dose<br>(mg/kg/day) | Seven-day treatment  |                      |                      |
|-----------------------|---------------------|----------------------|----------------------|----------------------|
|                       |                     | 0                    | 200                  | 1000                 |
| Liver                 | (g)                 | 6.373<br>±0.114 (4)  | 6.848<br>±0.744 (4)  | 7.205<br>±0.659 (4)  |
| Heart                 | (g)                 | 0.835<br>±0.030 (4)  | 0.813<br>±0.093 (4)  | 0.825<br>±0.042 (4)  |
| Kidney(R)             | (g)                 | 0.858<br>±0.038 (4)  | 0.818<br>±0.106 (4)  | 0.848<br>±0.030 (4)  |
| Kidney(L)             | (g)                 | 0.830<br>±0.059 (4)  | 0.805<br>±0.113 (4)  | 0.823<br>±0.022 (4)  |
| Testis(R)             | (g)                 | 0.910<br>±0.071 (4)  | 1.008<br>±0.095 (4)  | 1.020<br>±0.070 (4)  |
| Testis(L)             | (g)                 | 0.893<br>±0.088 (4)  | 0.988<br>±0.112 (4)  | 0.983<br>±0.040 (4)  |
| Epididymis(R)         | (g)                 | 0.120<br>±0.014 (4)  | 0.110<br>±0.012 (4)  | 0.128<br>±0.010 (4)  |
| Epididymis(L)         | (g)                 | 0.115<br>±0.019 (4)  | 0.113<br>±0.010 (4)  | 0.128<br>±0.015 (4)  |
| Ventral prostate      | (g)                 | 0.115<br>±0.010 (4)  | 0.118<br>±0.017 (4)  | 0.133<br>±0.033 (4)  |
| Dorsolateral prostate | (g)                 | 0.100<br>±0.037 (4)  | 0.108<br>±0.028 (4)  | 0.080<br>±0.012 (4)  |
| Brain                 | (g)                 | 1.813<br>±0.022 (4)  | 1.865<br>±0.070 (4)  | 1.830<br>±0.053 (4)  |
| Spleen                | (g)                 | 0.520<br>±0.050 (4)  | 0.468<br>±0.098 (4)  | 0.423<br>±0.058 (4)  |
| Thymus                | (mg)                | 516.63<br>±58.77 (4) | 434.98<br>±99.36 (4) | 472.10<br>±74.86 (4) |
| Pituitary gland       | (mg)                | 6.53<br>±0.76 (4)    | 6.98<br>±0.63 (4)    | 6.70<br>±0.54 (4)    |
| Thyroid               | (mg)                | 11.85<br>±1.06 (4)   | 10.15<br>±1.76 (4)   | 12.40<br>±2.35 (4)   |
| Adrenals              | (mg)                | 45.35<br>±10.83 (4)  | 37.95<br>±0.54 (4)   | 39.15<br>±4.04 (4)   |
| Final body weight     | (g)                 | 177.28<br>±4.47 (4)  | 177.73<br>±10.70 (4) | 181.08<br>±8.39 (4)  |

Values are shown as Mean ± S.D.

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 11-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of absolute organ weights:Male

| Items                 | Dose<br>(mg/kg/day) | Fourteen-day treatment |                       |                      |
|-----------------------|---------------------|------------------------|-----------------------|----------------------|
|                       |                     | 0                      | 200                   | 1000                 |
| Liver                 | (g)                 | 8.708<br>±0.664 (4)    | 9.223<br>±0.929 (4)   | 8.820<br>±0.588 (4)  |
| Heart                 | (g)                 | 1.025<br>±0.082 (4)    | 1.025<br>±0.066 (4)   | 0.988<br>±0.035 (4)  |
| Kidney(R)             | (g)                 | 1.010<br>±0.080 (4)    | 1.013<br>±0.074 (4)   | 1.030<br>±0.078 (4)  |
| Kidney(L)             | (g)                 | 1.003<br>±0.043 (4)    | 1.003<br>±0.072 (4)   | 1.015<br>±0.060 (4)  |
| Testis(R)             | (g)                 | 1.285<br>±0.045 (4)    | 1.338<br>±0.075 (4)   | 1.375<br>±0.084 (4)  |
| Testis(L)             | (g)                 | 1.280<br>±0.052 (4)    | 1.313<br>±0.091 (4)   | 1.363<br>±0.085 (4)  |
| Epididymis(R)         | (g)                 | 0.188<br>±0.031 (4)    | 0.193<br>±0.019 (4)   | 0.195<br>±0.017 (4)  |
| Epididymis(L)         | (g)                 | 0.183<br>±0.015 (4)    | 0.170<br>±0.008 (4)   | 0.198<br>±0.015 (4)  |
| Ventral prostate      | (g)                 | 0.240<br>±0.047 (4)    | 0.230<br>±0.014 (4)   | 0.203<br>±0.028 (4)  |
| Dorsolateral prostate | (g)                 | 0.195<br>±0.010 (4)    | 0.198<br>±0.017 (4)   | 0.163<br>±0.030 (4)  |
| Brain                 | (g)                 | 1.885<br>±0.050 (4)    | 1.895<br>±0.067 (4)   | 1.868<br>±0.104 (4)  |
| Spleen                | (g)                 | 0.653<br>±0.115 (4)    | 0.620<br>±0.063 (4)   | 0.563<br>±0.056 (4)  |
| Thymus                | (mg)                | 593.03<br>±92.99 (4)   | 599.55<br>±131.35 (4) | 595.65<br>±72.33 (4) |
| Pituitary gland       | (mg)                | 7.93<br>±0.49 (4)      | 8.08<br>±0.72 (4)     | 8.25<br>±0.49 (4)    |
| Thyroid               | (mg)                | 19.55<br>±4.74 (4)     | 20.18<br>±2.55 (4)    | 17.38<br>±2.22 (4)   |
| Adrenals              | (mg)                | 43.65<br>±6.06 (4)     | 43.78<br>±4.41 (4)    | 45.70<br>±2.42 (4)   |
| Final body weight     | (g)                 | 238.35<br>±20.80 (4)   | 242.50<br>±6.72 (4)   | 235.40<br>±7.07 (4)  |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 11-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of absolute organ weights:Male

| Items                 | Dose<br>(mg/kg/day) | Twenty-eight-day treatment |                        |                        |
|-----------------------|---------------------|----------------------------|------------------------|------------------------|
|                       |                     | 0                          | 200                    | 1000                   |
| Liver                 | (g)                 | 12.150<br>±0.598 (5)       | 11.772<br>±1.350 (5)   | 11.762<br>±1.193 (5)   |
| Heart                 | (g)                 | 1.368<br>±0.055 (5)        | 1.188 *<br>±0.050 (5)  | 1.316<br>±0.136 (5)    |
| Kidney(R)             | (g)                 | 1.382<br>±0.084 (5)        | 1.252 *<br>±0.060 (5)  | 1.282<br>±0.077 (5)    |
| Kidney(L)             | (g)                 | 1.350<br>±0.045 (5)        | 1.238<br>±0.086 (5)    | 1.284<br>±0.080 (5)    |
| Testis(R)             | (g)                 | 1.568<br>±0.121 (5)        | 1.538<br>±0.061 (5)    | 1.662<br>±0.157 (5)    |
| Testis(L)             | (g)                 | 1.570<br>±0.119 (5)        | 1.532<br>±0.054 (5)    | 1.640<br>±0.122 (5)    |
| Epididymis(R)         | (g)                 | 0.354<br>±0.011 (5)        | 0.356<br>±0.019 (5)    | 0.362<br>±0.041 (5)    |
| Epididymis(L)         | (g)                 | 0.344<br>±0.017 (5)        | 0.368<br>±0.022 (5)    | 0.362<br>±0.043 (5)    |
| Ventral prostate      | (g)                 | 0.412<br>±0.111 (5)        | 0.358<br>±0.079 (5)    | 0.358<br>±0.031 (5)    |
| Dorsolateral prostate | (g)                 | 0.318<br>±0.061 (5)        | 0.296<br>±0.038 (5)    | 0.320<br>±0.041 (5)    |
| Seminal vesicle       | (g)                 | 0.930<br>±0.139 (5)        | 0.856<br>±0.119 (5)    | 0.918<br>±0.127 (5)    |
| Brain                 | (g)                 | 1.996<br>±0.107 (5)        | 2.008<br>±0.050 (5)    | 2.064<br>±0.078 (5)    |
| Spleen                | (g)                 | 0.722<br>±0.033 (5)        | 0.772<br>±0.102 (5)    | 0.622<br>±0.099 (5)    |
| Thymus                | (mg)                | 552.00<br>±58.88 (5)       | 552.86<br>±54.61 (5)   | 521.68<br>±104.68 (5)  |
| Pituitary gland       | (mg)                | 11.58<br>±0.98 (5)         | 11.28<br>±1.27 (5)     | 10.26<br>±1.44 (5)     |
| Thyroid               | (mg)                | 14.90<br>±2.44 (5)         | 16.12<br>±2.88 (5)     | 19.18<br>±4.69 (5)     |
| Adrenals              | (mg)                | 55.46<br>±4.52 (5)         | 50.18<br>±11.38 (5)    | 59.28<br>±5.19 (5)     |
| Final body weight     | (g)                 | 367.24<br>±11.33 (5)       | 335.84 *<br>±11.58 (5) | 338.54 *<br>±21.12 (5) |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 12-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of relative organ weights:Male

| Items                 | Dose<br>(mg/kg/day) | One-day treatment    |                       |                        |
|-----------------------|---------------------|----------------------|-----------------------|------------------------|
|                       |                     | 0                    | 200                   | 1000                   |
| Liver                 | (g/100g)            | 3.403<br>±0.080 (4)  | 3.595 *<br>±0.051 (4) | 3.690 **<br>±0.119 (4) |
| Heart                 | (g/100g)            | 0.498<br>±0.010 (4)  | 0.498<br>±0.024 (4)   | 0.478<br>±0.028 (4)    |
| Kidney(R)             | (g/100g)            | 0.493<br>±0.029 (4)  | 0.505<br>±0.030 (4)   | 0.538<br>±0.030 (4)    |
| Kidney(L)             | (g/100g)            | 0.478<br>±0.034 (4)  | 0.498<br>±0.029 (4)   | 0.525<br>±0.013 (4)    |
| Testis(R)             | (g/100g)            | 0.515<br>±0.049 (4)  | 0.525<br>±0.073 (4)   | 0.583<br>±0.036 (4)    |
| Testis(L)             | (g/100g)            | 0.498<br>±0.045 (4)  | 0.520<br>±0.065 (4)   | 0.585 *<br>±0.021 (4)  |
| Epididymis(R)         | (g/100g)            | 0.055<br>±0.006 (4)  | 0.058<br>±0.005 (4)   | 0.063<br>±0.015 (4)    |
| Epididymis(L)         | (g/100g)            | 0.053<br>±0.005 (4)  | 0.060<br>±0.008 (4)   | 0.063<br>±0.005 (4)    |
| Ventral prostate      | (g/100g)            | 0.050<br>±0.000 (4)  | 0.043<br>±0.017 (4)   | 0.058<br>±0.013 (4)    |
| Dorsolateral prostate | (g/100g)            | 0.058<br>±0.021 (4)  | 0.060<br>±0.022 (4)   | 0.058<br>±0.010 (4)    |
| Brain                 | (g/100g)            | 1.350<br>±0.098 (4)  | 1.363<br>±0.095 (4)   | 1.270<br>±0.041 (4)    |
| Spleen                | (g/100g)            | 0.288<br>±0.033 (4)  | 0.288<br>±0.042 (4)   | 0.298<br>±0.017 (4)    |
| Thymus                | (mg/100g)           | 356.93<br>±23.94 (4) | 327.18<br>±59.74 (4)  | 347.60<br>±66.98 (4)   |
| Pituitary gland       | (mg/100g)           | 4.08<br>±0.46 (4)    | 4.30<br>±0.29 (4)     | 4.13<br>±0.22 (4)      |
| Thyroid               | (mg/100g)           | 5.90<br>±1.01 (4)    | 6.45<br>±0.82 (4)     | 7.08<br>±1.40 (4)      |
| Adrenals              | (mg/100g)           | 26.13<br>±2.04 (4)   | 24.05<br>±2.59 (4)    | 24.08<br>±1.77 (4)     |
| Final body weight     | (g)                 | 132.45<br>±6.43 (4)  | 131.58<br>±4.47 (4)   | 133.38<br>±5.18 (4)    |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 12-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of relative organ weights:Male

| Items                 | Dose<br>(mg/kg/day) | Seven-day treatment  |                      |                       |
|-----------------------|---------------------|----------------------|----------------------|-----------------------|
|                       |                     | 0                    | 200                  | 1000                  |
| Liver                 | (g/100g)            | 3.595<br>±0.035 (4)  | 3.848<br>±0.293 (4)  | 3.975 *<br>±0.195 (4) |
| Heart                 | (g/100g)            | 0.473<br>±0.024 (4)  | 0.455<br>±0.037 (4)  | 0.458<br>±0.021 (4)   |
| Kidney(R)             | (g/100g)            | 0.485<br>±0.013 (4)  | 0.460<br>±0.035 (4)  | 0.468<br>±0.017 (4)   |
| Kidney(L)             | (g/100g)            | 0.468<br>±0.026 (4)  | 0.453<br>±0.039 (4)  | 0.458<br>±0.029 (4)   |
| Testis(R)             | (g/100g)            | 0.513<br>±0.046 (4)  | 0.570<br>±0.075 (4)  | 0.565<br>±0.039 (4)   |
| Testis(L)             | (g/100g)            | 0.503<br>±0.051 (4)  | 0.558<br>±0.081 (4)  | 0.545<br>±0.034 (4)   |
| Epididymis(R)         | (g/100g)            | 0.068<br>±0.010 (4)  | 0.063<br>±0.005 (4)  | 0.070<br>±0.008 (4)   |
| Epididymis(L)         | (g/100g)            | 0.068<br>±0.010 (4)  | 0.065<br>±0.006 (4)  | 0.068<br>±0.010 (4)   |
| Ventral prostate      | (g/100g)            | 0.065<br>±0.010 (4)  | 0.065<br>±0.010 (4)  | 0.075<br>±0.017 (4)   |
| Dorsolateral prostate | (g/100g)            | 0.058<br>±0.022 (4)  | 0.060<br>±0.018 (4)  | 0.045<br>±0.006 (4)   |
| Brain                 | (g/100g)            | 1.025<br>±0.026 (4)  | 1.053<br>±0.078 (4)  | 1.015<br>±0.073 (4)   |
| Spleen                | (g/100g)            | 0.290<br>±0.024 (4)  | 0.260<br>±0.047 (4)  | 0.233<br>±0.025 (4)   |
| Thymus                | (mg/100g)           | 291.10<br>±28.55 (4) | 243.03<br>±42.72 (4) | 261.88<br>±48.65 (4)  |
| Pituitary gland       | (mg/100g)           | 3.68<br>±0.36 (4)    | 3.95<br>±0.31 (4)    | 3.70<br>±0.14 (4)     |
| Thyroid               | (mg/100g)           | 6.70<br>±0.59 (4)    | 5.70<br>±0.88 (4)    | 6.85<br>±1.32 (4)     |
| Adrenals              | (mg/100g)           | 25.55<br>±5.89 (4)   | 21.40<br>±1.25 (4)   | 21.58<br>±1.53 (4)    |
| Final body weight     | (g)                 | 177.28<br>±4.47 (4)  | 177.73<br>±10.70 (4) | 181.08<br>±8.39 (4)   |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 12-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of relative organ weights:Male

| Items                 | Dose<br>(mg/kg/day) | Fourteen-day treatment |                       |                      |
|-----------------------|---------------------|------------------------|-----------------------|----------------------|
|                       |                     | 0                      | 200                   | 1000                 |
| Liver                 | (g/100g)            | 3.658<br>±0.093 (4)    | 3.800<br>±0.302 (4)   | 3.748<br>±0.230 (4)  |
| Heart                 | (g/100g)            | 0.430<br>±0.022 (4)    | 0.423<br>±0.022 (4)   | 0.420<br>±0.008 (4)  |
| Kidney(R)             | (g/100g)            | 0.423<br>±0.005 (4)    | 0.418<br>±0.022 (4)   | 0.435<br>±0.033 (4)  |
| Kidney(L)             | (g/100g)            | 0.423<br>±0.021 (4)    | 0.413<br>±0.021 (4)   | 0.433<br>±0.022 (4)  |
| Testis(R)             | (g/100g)            | 0.543<br>±0.046 (4)    | 0.553<br>±0.038 (4)   | 0.585<br>±0.047 (4)  |
| Testis(L)             | (g/100g)            | 0.540<br>±0.042 (4)    | 0.543<br>±0.046 (4)   | 0.578<br>±0.043 (4)  |
| Epididymis(R)         | (g/100g)            | 0.080<br>±0.008 (4)    | 0.078<br>±0.010 (4)   | 0.085<br>±0.010 (4)  |
| Epididymis(L)         | (g/100g)            | 0.078<br>±0.005 (4)    | 0.068 *<br>±0.005 (4) | 0.085<br>±0.006 (4)  |
| Ventral prostate      | (g/100g)            | 0.100<br>±0.014 (4)    | 0.095<br>±0.006 (4)   | 0.088<br>±0.015 (4)  |
| Dorsolateral prostate | (g/100g)            | 0.083<br>±0.005 (4)    | 0.080<br>±0.008 (4)   | 0.068<br>±0.013 (4)  |
| Brain                 | (g/100g)            | 0.793<br>±0.063 (4)    | 0.783<br>±0.031 (4)   | 0.795<br>±0.066 (4)  |
| Spleen                | (g/100g)            | 0.275<br>±0.026 (4)    | 0.255<br>±0.021 (4)   | 0.240<br>±0.027 (4)  |
| Thymus                | (mg/100g)           | 250.33<br>±45.07 (4)   | 247.65<br>±55.98 (4)  | 253.03<br>±30.13 (4) |
| Pituitary gland       | (mg/100g)           | 3.33<br>±0.26 (4)      | 3.33<br>±0.22 (4)     | 3.53<br>±0.15 (4)    |
| Thyroid               | (mg/100g)           | 8.35<br>±2.66 (4)      | 8.33<br>±0.87 (4)     | 7.38<br>±0.92 (4)    |
| Adrenals              | (mg/100g)           | 18.35<br>±2.52 (4)     | 18.03<br>±1.38 (4)    | 19.43<br>±1.24 (4)   |
| Final body weight     | (g)                 | 238.35<br>±20.80 (4)   | 242.50<br>±6.72 (4)   | 235.40<br>±7.07 (4)  |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 12-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of relative organ weights:Male

| Items                 | Dose<br>(mg/kg/day) | Twenty-eight-day treatment |                        |                        |
|-----------------------|---------------------|----------------------------|------------------------|------------------------|
|                       |                     | 0                          | 200                    | 1000                   |
| Liver                 | (g/100g)            | 3.306<br>±0.098 (5)        | 3.506<br>±0.388 (5)    | 3.468<br>±0.157 (5)    |
| Heart                 | (g/100g)            | 0.374<br>±0.011 (5)        | 0.354<br>±0.015 (5)    | 0.388<br>±0.023 (5)    |
| Kidney(R)             | (g/100g)            | 0.378<br>±0.029 (5)        | 0.372<br>±0.013 (5)    | 0.376<br>±0.015 (5)    |
| Kidney(L)             | (g/100g)            | 0.368<br>±0.016 (5)        | 0.368<br>±0.029 (5)    | 0.380<br>±0.020 (5)    |
| Testis(R)             | (g/100g)            | 0.428<br>±0.038 (5)        | 0.458<br>±0.018 (5)    | 0.490 *<br>±0.037 (5)  |
| Testis(L)             | (g/100g)            | 0.428<br>±0.037 (5)        | 0.456<br>±0.009 (5)    | 0.486 *<br>±0.035 (5)  |
| Epididymis(R)         | (g/100g)            | 0.098<br>±0.004 (5)        | 0.106<br>±0.009 (5)    | 0.106<br>±0.005 (5)    |
| Epididymis(L)         | (g/100g)            | 0.094<br>±0.009 (5)        | 0.110 *<br>±0.007 (5)  | 0.106<br>±0.011 (5)    |
| Ventral prostate      | (g/100g)            | 0.110<br>±0.028 (5)        | 0.106<br>±0.024 (5)    | 0.106<br>±0.009 (5)    |
| Dorsolateral prostate | (g/100g)            | 0.086<br>±0.017 (5)        | 0.088<br>±0.011 (5)    | 0.094<br>±0.009 (5)    |
| Seminal vesicle       | (g/100g)            | 0.252<br>±0.033 (5)        | 0.256<br>±0.034 (5)    | 0.274<br>±0.047 (5)    |
| Brain                 | (g/100g)            | 0.542<br>±0.034 (5)        | 0.598 *<br>±0.028 (5)  | 0.610 **<br>±0.028 (5) |
| Spleen                | (g/100g)            | 0.196<br>±0.009 (5)        | 0.230<br>±0.026 (5)    | 0.184<br>±0.027 (5)    |
| Thymus                | (mg/100g)           | 150.38<br>±16.27 (5)       | 164.68<br>±16.32 (5)   | 155.66<br>±39.52 (5)   |
| Pituitary gland       | (mg/100g)           | 3.14<br>±0.27 (5)          | 3.38<br>±0.45 (5)      | 3.04<br>±0.30 (5)      |
| Thyroid               | (mg/100g)           | 4.06<br>±0.73 (5)          | 4.80<br>±0.82 (5)      | 5.62 *<br>±1.23 (5)    |
| Adrenals              | (mg/100g)           | 15.12<br>±1.39 (5)         | 14.92<br>±3.26 (5)     | 17.50<br>±0.97 (5)     |
| Final body weight     | (g)                 | 367.24<br>±11.33 (5)       | 335.84 *<br>±11.58 (5) | 338.54 *<br>±21.12 (5) |

Values are shown as Mean ± S.D..

Figure(s) in parentheses indicate number of animals used for the statistical analysis.

\* Significantly different from vehicle control at P<0.05.

\*\* Significantly different from vehicle control at P<0.01.

Table 13-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of macroscopic examinations: One-day treatment

| Findings                  | Male            |     |      |
|---------------------------|-----------------|-----|------|
|                           | 0               | 200 | 1000 |
|                           | (mg/kg/day)     | ss  | ss   |
|                           | 4 <sup>a)</sup> | 4   | 4    |
| No abnormalities detected | 4               | 4   | 4    |

ss, scheduled sacrifice animal.

a) Number of animals examined.

Table 13-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Summary of macroscopic examinations: Seven-day treatment

| Findings                  | Male            |     |      |
|---------------------------|-----------------|-----|------|
|                           | 0               | 200 | 1000 |
|                           | (mg/kg/day)     | ss  | ss   |
|                           | 4 <sup>a)</sup> | 4   | 4    |
| No abnormalities detected | 4               | 4   | 3    |
| Liver                     |                 |     |      |
| Enlargement               | 0               | 0   | 1    |

ss, scheduled sacrifice animal.

a) Number of animals examined.

Table 13-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of macroscopic examinations: Fourteen-day treatment

| Findings                  | Male            |     |      |
|---------------------------|-----------------|-----|------|
|                           | 0               | 200 | 1000 |
|                           | (mg/kg/day)     | ss  | ss   |
|                           | 4 <sup>a)</sup> | 4   | 4    |
| No abnormalities detected | 4               | 4   | 4    |

ss, scheduled sacrifice animal.

a) Number of animals examined.

Table 13-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of macroscopic examinations: Twenty-eight-day treatment

| Findings                  | Male        |     |      |
|---------------------------|-------------|-----|------|
|                           | 0           | 200 | 1000 |
|                           | (mg/kg/day) | ss  | ss   |
| 5 <sup>a)</sup>           | 5           | 5   | 5    |
| No abnormalities detected | 5           | 5   | 5    |

ss, scheduled sacrifice animal.

a) Number of animals examined.

Table 14-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of histopathological examinations: One-day treatment

| Findings                  | Grade | Male              |     |      |
|---------------------------|-------|-------------------|-----|------|
|                           |       | 0                 | 200 | 1000 |
|                           |       | ss                | ss  | ss   |
|                           |       | 4 <sup>a)</sup>   | 4   | 4    |
| Liver                     |       |                   |     |      |
| No abnormalities detected |       | 4/4 <sup>b)</sup> | --- | 4/4  |
| Kidney                    |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Testis                    |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Ventral prostate          |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Dorsolateral prostate     |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Bone marrow               |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Spleen                    |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Thymus                    |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |

ss, scheduled sacrifice animal.

a) Number of animals autopsied.

b) Number of animals affected / Number of animals examined.

---, Not examined.

Table 14-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of histopathological examinations: Seven-day treatment

| Findings                  | Grade | Male              |                 |      |
|---------------------------|-------|-------------------|-----------------|------|
|                           |       | 0                 | 200             | 1000 |
|                           |       | (mg/kg/day)       | ss              | ss   |
|                           |       |                   | 4 <sup>a)</sup> | 4    |
| Liver                     |       |                   |                 |      |
| No abnormalities detected |       | 4/4 <sup>b)</sup> | ---             | 4/4  |
| Kidney                    |       |                   |                 |      |
| No abnormalities detected |       | 3/4               | ---             | 4/4  |
| Cyst/Medulla              | +     | 1/4               | ---             | 0/4  |
| Testis                    |       |                   |                 |      |
| No abnormalities detected |       | 4/4               | ---             | 4/4  |
| Ventral prostate          |       |                   |                 |      |
| No abnormalities detected |       | 4/4               | ---             | 4/4  |
| Dorsolateral prostate     |       |                   |                 |      |
| No abnormalities detected |       | 4/4               | ---             | 4/4  |
| Bone marrow               |       |                   |                 |      |
| No abnormalities detected |       | 4/4               | ---             | 4/4  |
| Spleen                    |       |                   |                 |      |
| No abnormalities detected |       | 4/4               | ---             | 4/4  |
| Thymus                    |       |                   |                 |      |
| No abnormalities detected |       | 4/4               | ---             | 4/4  |

ss, scheduled sacrifice animal.

a) Number of animals autopsied.

b) Number of animals affected / Number of animals examined.

--, Not examined.

+, slight.

Table 14-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Summary of histopathological examinations: Fourteen-day treatment

| Findings                  | Grade | Male              |     |      |
|---------------------------|-------|-------------------|-----|------|
|                           |       | 0                 | 200 | 1000 |
|                           |       | ss                | ss  | ss   |
|                           |       | 4 <sup>a)</sup>   | 4   | 4    |
| Liver                     |       |                   |     |      |
| No abnormalities detected |       | 4/4 <sup>b)</sup> | --- | 4/4  |
| Kidney                    |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Testis                    |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Ventral prostate          |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Dorsolateral prostate     |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Bone marrow               |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Spleen                    |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |
| Thymus                    |       |                   |     |      |
| No abnormalities detected |       | 4/4               | --- | 4/4  |

ss, scheduled sacrifice animal.

a) Number of animals autopsied.

b) Number of animals affected / Number of animals examined.

--, Not examined.

Table 14-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of histopathological examinations: Twenty-eight-day treatment

| Findings                  | Grade | Male              |     |      |
|---------------------------|-------|-------------------|-----|------|
|                           |       | 0                 | 200 | 1000 |
|                           |       | ss                | ss  | ss   |
|                           |       | 5 <sup>a)</sup>   | 5   | 5    |
| Trachea                   |       |                   |     |      |
| No abnormalities detected |       | 5/5 <sup>b)</sup> | --- | 5/5  |
| Lung                      |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Submandibular gland       |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Forestomach               |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Glandular stomach         |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Duodenum                  |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Jejunum                   |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Ileum                     |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Cecum                     |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Colon                     |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Rectum                    |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Pancreas                  |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Liver                     |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Heart                     |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Kidney                    |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Urinary bladder           |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |
| Testis                    |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 4/5  |
| Atrophy, tubular/Focal    | +     | 0/5               | --- | 1/5  |
| Epididymis                |       |                   |     |      |
| No abnormalities detected |       | 5/5               | --- | 5/5  |

ss, scheduled sacrifice animal.

a) Number of animals autopsied.

b) Number of animals affected / Number of animals examined.

--, Not examined.

+, slight.

Table 14-5 Twenty-eight-day repeated-dose oral toxicity study in rats  
Summary of histopathological examinations: Twenty-eight-day treatment

| Findings                  | Grade | Male              |     |      | (mg/kg/day) |
|---------------------------|-------|-------------------|-----|------|-------------|
|                           |       | 0                 | 200 | 1000 |             |
|                           |       | ss                | ss  | ss   |             |
|                           |       | 5 <sup>a)</sup>   | 5   | 5    |             |
| Ventral prostate          |       |                   |     |      |             |
| No abnormalities detected |       | 4/5 <sup>b)</sup> | --- | 5/5  |             |
| Cellular infiltration     | +     | 1/5               | --- | 0/5  |             |
| Dorsolateral prostate     |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Coagulating gland         |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Seminal vesicle           |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Spinal cord               |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Sciatic nerve             |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Bone marrow               |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Axillary lymph node       |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Mesenteric lymph node     |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Spleen                    |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Thymus                    |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Thyroid                   |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Parathyroid               |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Adrenal                   |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Eye ball                  |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Skeletal muscle           |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Bone                      |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |
| Mammary gland             |       |                   |     |      |             |
| No abnormalities detected |       | 5/5               | --- | 5/5  |             |

ss, scheduled sacrifice animal.

a) Number of animals autopsied.

b) Number of animals affected / Number of animals examined.

---, Not examined.

+, slight.

Appendix 1-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Clinical signs of individual animals  
 0 mg/kg/day

| Signs                     | Sex  | Administration period  |  |   |                       |                       |
|---------------------------|------|--|--|---|-----------------------|-----------------------|
|                           |      | 1  | 2-7  | 8-14                                    | 15-21                 | 22-28 (day)           |
| No abnormalities detected | Male | 1 <sup>a)</sup> 2, 3, 4,<br>5, 6, 7, 8,<br>9, 10, 11,<br>12, 13, 14,<br>15, 16, 17 | 5, 6, 7, 8,<br>9, 10, 11,<br>12, 13, 14,<br>15, 16, 17 | 9, 10, 11,<br>12, 13, 14,<br>15, 16, 17 | 13, 14, 15,<br>16, 17 | 13, 14, 15,<br>16, 17 |

a) Animal number.

Appendix 1-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Clinical signs of individual animals  
 200 mg/kg/day

| Signs                     | Sex  | Administration period   |  |  |                       |                       |
|---------------------------|------|---|--|--|-----------------------|-----------------------|
|                           |      | 1   | 2-7  | 8-14                                     | 15-21                 | 22-28 (day)           |
| No abnormalities detected | Male | 18, <sup>a)</sup> 19, 20,<br>21, 22, 23,<br>24, 25, 26,<br>27, 28, 29,<br>30, 31, 32,<br>33, 34 | 22, 23, 24,<br>25, 26, 27,<br>28, 29, 30,<br>31, 32, 33,<br>34 | 26, 27, 28,<br>29, 30, 31,<br>32, 33, 34 | 30, 31, 32,<br>33, 34 | 30, 31, 32,<br>33, 34 |

a) Animal number.

Appendix 1-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Clinical signs of individual animals  
 1000 mg/kg/day

| Signs                     | Sex  | Administration period   |  |  |                       |                       | (day) |
|---------------------------|------|---|--|--|-----------------------|-----------------------|-------|
|                           |      | 1   | 2-7  | 8-14                                     | 15-21                 | 22-28                 |       |
| No abnormalities detected | Male | 35, a)<br>36, 37,<br>38, 39, 40,<br>41, 42, 43,<br>44, 45, 46,<br>47, 48, 49,<br>50, 51 | 39, 40, 41,<br>42, 43, 44,<br>45, 46, 47,<br>48, 49, 50,<br>51 | 43, 44, 45,<br>46, 47, 48,<br>49, 50, 51 | 47, 48, 49,<br>50, 51 | 47, 48, 49,<br>50, 51 |       |

a) Animal number.

Appendix 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (Predosing)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Removal from cage |              |
|------|---------------------|------------|-------------------|--------------|
|      |                     |            | Ease of removal   | Vocalization |
| Male | 0                   | 13         | 0                 | 0            |
|      |                     | 14         | 0                 | 0            |
|      |                     | 15         | 0                 | 0            |
|      |                     | 16         | 0                 | 0            |
|      |                     | 17         | 0                 | +1           |
|      | 200                 | 30         | 0                 | 0            |
|      |                     | 31         | 0                 | 0            |
|      |                     | 32         | 0                 | 0            |
|      |                     | 33         | 0                 | 0            |
|      |                     | 34         | 0                 | 0            |
| 1000 | 1000                | 47         | 0                 | +1           |
|      |                     | 48         | 0                 | 0            |
|      |                     | 49         | 0                 | 0            |
|      |                     | 50         | 0                 | 0            |
|      |                     | 51         | 0                 | 0            |

## Appendix 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats

## Detailed clinical observations of individual animals (week 1)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Removal from cage |              |
|------|---------------------|------------|-------------------|--------------|
|      |                     |            | Ease of removal   | Vocalization |
| Male | 0                   | 13         | -1                | 0            |
|      |                     | 14         | 0                 | 0            |
|      |                     | 15         | 0                 | 0            |
|      |                     | 16         | 0                 | 0            |
|      |                     | 17         | 0                 | 0            |
|      | 200                 | 30         | 0                 | 0            |
|      |                     | 31         | 0                 | 0            |
|      |                     | 32         | 0                 | 0            |
|      |                     | 33         | 0                 | +1           |
|      |                     | 34         | 0                 | 0            |
|      | 1000                | 47         | 0                 | 0            |
|      |                     | 48         | 0                 | 0            |
|      |                     | 49         | 0                 | 0            |
|      |                     | 50         | -1                | 0            |
|      |                     | 51         | 0                 | 0            |

Appendix 2-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 2)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Removal from cage |              |
|------|---------------------|------------|-------------------|--------------|
|      |                     |            | Ease of removal   | Vocalization |
| Male | 0                   | 13         | 0                 | +1           |
|      |                     | 14         | 0                 | 0            |
|      |                     | 15         | 0                 | 0            |
|      |                     | 16         | 0                 | 0            |
|      |                     | 17         | 0                 | 0            |
|      | 200                 | 30         | 0                 | 0            |
|      |                     | 31         | 0                 | 0            |
|      |                     | 32         | 0                 | 0            |
|      |                     | 33         | 0                 | 0            |
|      |                     | 34         | 0                 | 0            |
| 1000 | 47                  | 47         | 0                 | 0            |
|      |                     | 48         | 0                 | 0            |
|      |                     | 49         | 0                 | 0            |
|      |                     | 50         | 0                 | 0            |
|      |                     | 51         | 0                 | 0            |

Appendix 2-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 3)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Removal from cage |              |
|------|---------------------|------------|-------------------|--------------|
|      |                     |            | Ease of removal   | Vocalization |
| Male | 0                   | 13         | 0                 | +1           |
|      |                     | 14         | 0                 | 0            |
|      |                     | 15         | 0                 | 0            |
|      |                     | 16         | 0                 | 0            |
|      |                     | 17         | 0                 | 0            |
|      | 200                 | 30         | 0                 | +1           |
|      |                     | 31         | 0                 | 0            |
|      |                     | 32         | 0                 | 0            |
|      |                     | 33         | 0                 | 0            |
|      |                     | 34         | 0                 | +1           |
|      | 1000                | 47         | 0                 | 0            |
|      |                     | 48         | 0                 | +1           |
|      |                     | 49         | 0                 | 0            |
|      |                     | 50         | 0                 | +1           |
|      |                     | 51         | 0                 | 0            |

Appendix 2-5 Twenty-eight-day repeated-dose oral toxicity study in rats  
Detailed clinical observations of individual animals (week 4)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Removal from cage |              |
|------|---------------------|------------|-------------------|--------------|
|      |                     |            | Ease of removal   | Vocalization |
| Male | 0                   | 13         | 0                 | +1           |
|      |                     | 14         | 0                 | 0            |
|      |                     | 15         | 0                 | 0            |
|      |                     | 16         | 0                 | +1           |
|      |                     | 17         | 0                 | 0            |
|      | 200                 | 30         | 0                 | 0            |
|      |                     | 31         | 0                 | 0            |
|      |                     | 32         | 0                 | 0            |
|      |                     | 33         | 0                 | +1           |
|      |                     | 34         | 0                 | 0            |
|      | 1000                | 47         | 0                 | 0            |
|      |                     | 48         | 0                 | 0            |
|      |                     | 49         | 0                 | 0            |
|      |                     | 50         | 0                 | +1           |
|      |                     | 51         | 0                 | 0            |

Appendix 2-6 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (Predosing)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |                       |              |               |              |          |           |
|------|---------------------|------------|-----------------------|-----------------------|--------------|---------------|--------------|----------|-----------|
|      |                     |            | Muscle tone           | Subnormal temperature | Piloerection | Staining hair | Unkempt hair | Paleness | Reddening |
| Male | 0                   | 13         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 14         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 15         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 16         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 17         | 0                     | -                     | -            | -             | -            | -        | -         |
|      | 200                 | 30         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 31         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 32         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 33         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 34         | 0                     | -                     | -            | -             | -            | -        | -         |
|      | 1000                | 47         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 48         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 49         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 50         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 51         | 0                     | -                     | -            | -             | -            | -        | -         |

Appendix 2-7 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 1)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |                       |              |               |              |          |
|------|---------------------|------------|-----------------------|-----------------------|--------------|---------------|--------------|----------|
|      |                     |            | Muscle tone           | Subnormal temperature | Piloerection | Staining hair | Unkempt hair | Paleness |
| Male | 0                   | 13         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 14         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 15         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 16         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 17         | 0                     | -                     | -            | -             | -            | -        |
|      | 200                 | 30         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 31         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 32         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 33         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 34         | 0                     | -                     | -            | -             | -            | -        |
| 1000 | 1000                | 47         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 48         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 49         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 50         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 51         | 0                     | -                     | -            | -             | -            | -        |

Appendix 2-8 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 2)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |                       |              |               |              |          |           |
|------|---------------------|------------|-----------------------|-----------------------|--------------|---------------|--------------|----------|-----------|
|      |                     |            | Muscle tone           | Subnormal temperature | Piloerection | Staining hair | Unkempt hair | Paleness | Reddening |
| Male | 0                   | 13         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 14         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 15         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 16         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 17         | 0                     | -                     | -            | -             | -            | -        | -         |
|      | 200                 | 30         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 31         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 32         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 33         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 34         | 0                     | -                     | -            | -             | -            | -        | -         |
| 1000 | 1000                | 47         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 48         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 49         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 50         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 51         | 0                     | -                     | -            | -             | -            | -        | -         |

Appendix 2-9 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 3)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |                       |              |               |              |          |           |
|------|---------------------|------------|-----------------------|-----------------------|--------------|---------------|--------------|----------|-----------|
|      |                     |            | Muscle tone           | Subnormal temperature | Piloerection | Staining hair | Unkempt hair | Paleness | Reddening |
| Male | 0                   | 13         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 14         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 15         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 16         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 17         | 0                     | -                     | -            | -             | -            | -        | -         |
|      | 200                 | 30         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 31         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 32         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 33         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 34         | 0                     | -                     | -            | -             | -            | -        | -         |
| 1000 | 1000                | 47         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 48         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 49         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 50         | 0                     | -                     | -            | -             | -            | -        | -         |
|      |                     | 51         | 0                     | -                     | -            | -             | -            | -        | -         |

Appendix 2-10 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 4)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |                       |              |               |              |          |
|------|---------------------|------------|-----------------------|-----------------------|--------------|---------------|--------------|----------|
|      |                     |            | Muscle tone           | Subnormal temperature | Piloerection | Staining hair | Unkempt hair | Paleness |
| Male | 0                   | 13         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 14         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 15         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 16         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 17         | 0                     | -                     | -            | -             | -            | -        |
|      | 200                 | 30         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 31         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 32         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 33         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 34         | 0                     | -                     | -            | -             | -            | -        |
| 1000 | 1000                | 47         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 48         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 49         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 50         | 0                     | -                     | -            | -             | -            | -        |
|      |                     | 51         | 0                     | -                     | -            | -             | -            | -        |

Appendix 2-11 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (Predosing)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |             |              |                |            |
|------|---------------------|------------|-----------------------|-------------|--------------|----------------|------------|
|      |                     |            | Cyanosis              | Lacrimation | Exophthalmos | Pupillary size | Salivation |
| Male | 0                   | 13         | -                     | -           | -            | 0              | -          |
|      |                     | 14         | -                     | -           | -            | 0              | -          |
|      |                     | 15         | -                     | -           | -            | 0              | -          |
|      |                     | 16         | -                     | -           | -            | 0              | -          |
|      |                     | 17         | -                     | -           | -            | 0              | -          |
|      | 200                 | 30         | -                     | -           | -            | 0              | -          |
|      |                     | 31         | -                     | -           | -            | 0              | -          |
|      |                     | 32         | -                     | -           | -            | 0              | -          |
|      |                     | 33         | -                     | -           | -            | 0              | -          |
|      |                     | 34         | -                     | -           | -            | 0              | -          |
| 1000 | 1000                | 47         | -                     | -           | -            | 0              | -          |
|      |                     | 48         | -                     | -           | -            | 0              | -          |
|      |                     | 49         | -                     | -           | -            | 0              | -          |
|      |                     | 50         | -                     | -           | -            | 0              | -          |
|      |                     | 51         | -                     | -           | -            | 0              | -          |

Appendix 2-12 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 1)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |             |              |                |            |           |
|------|---------------------|------------|-----------------------|-------------|--------------|----------------|------------|-----------|
|      |                     |            | Cyanosis              | Lacrimation | Exophthalmos | Pupillary size | Salivation | Secretion |
| Male | 0                   | 13         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 14         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 15         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 16         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 17         | -                     | -           | -            | 0              | -          | -         |
|      | 200                 | 30         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 31         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 32         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 33         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 34         | -                     | -           | -            | 0              | -          | -         |
|      | 1000                | 47         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 48         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 49         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 50         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 51         | -                     | -           | -            | 0              | -          | -         |

Appendix 2-13 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 2)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |             |              |                |            |
|------|---------------------|------------|-----------------------|-------------|--------------|----------------|------------|
|      |                     |            | Cyanosis              | Lacrimation | Exophthalmos | Pupillary size | Salivation |
| Male | 0                   | 13         | -                     | -           | -            | 0              | -          |
|      |                     | 14         | -                     | -           | -            | 0              | -          |
|      |                     | 15         | -                     | -           | -            | 0              | -          |
|      |                     | 16         | -                     | -           | -            | 0              | -          |
|      |                     | 17         | -                     | -           | -            | 0              | -          |
|      | 200                 | 30         | -                     | -           | -            | 0              | -          |
|      |                     | 31         | -                     | -           | -            | 0              | -          |
|      |                     | 32         | -                     | -           | -            | 0              | -          |
|      |                     | 33         | -                     | -           | -            | 0              | -          |
|      |                     | 34         | -                     | -           | -            | 0              | -          |
| 1000 | 1000                | 47         | -                     | -           | -            | 0              | -          |
|      |                     | 48         | -                     | -           | -            | 0              | -          |
|      |                     | 49         | -                     | -           | -            | 0              | -          |
|      |                     | 50         | -                     | -           | -            | 0              | -          |
|      |                     | 51         | -                     | -           | -            | 0              | -          |

Appendix 2-14 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 3)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |             |              |                |            |           |
|------|---------------------|------------|-----------------------|-------------|--------------|----------------|------------|-----------|
|      |                     |            | Cyanosis              | Lacrimation | Exophthalmos | Pupillary size | Salivation | Secretion |
| Male | 0                   | 13         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 14         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 15         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 16         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 17         | -                     | -           | -            | 0              | -          | -         |
|      | 200                 | 30         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 31         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 32         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 33         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 34         | -                     | -           | -            | 0              | -          | -         |
|      | 1000                | 47         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 48         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 49         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 50         | -                     | -           | -            | 0              | -          | -         |
|      |                     | 51         | -                     | -           | -            | 0              | -          | -         |

Appendix 2-15 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 4)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Handling observations |             |              |                |            |
|------|---------------------|------------|-----------------------|-------------|--------------|----------------|------------|
|      |                     |            | Cyanosis              | Lacrimation | Exophthalmos | Pupillary size | Salivation |
| Male | 0                   | 13         | -                     | -           | -            | 0              | -          |
|      |                     | 14         | -                     | -           | -            | 0              | -          |
|      |                     | 15         | -                     | -           | -            | 0              | -          |
|      |                     | 16         | -                     | -           | -            | 0              | -          |
|      |                     | 17         | -                     | -           | -            | 0              | -          |
|      | 200                 | 30         | -                     | -           | -            | 0              | -          |
|      |                     | 31         | -                     | -           | -            | 0              | -          |
|      |                     | 32         | -                     | -           | -            | 0              | -          |
|      |                     | 33         | -                     | -           | -            | 0              | -          |
|      |                     | 34         | -                     | -           | -            | 0              | -          |
| 1000 | 1000                | 47         | -                     | -           | -            | 0              | -          |
|      |                     | 48         | -                     | -           | -            | 0              | -          |
|      |                     | 49         | -                     | -           | -            | 0              | -          |
|      |                     | 50         | -                     | -           | -            | 0              | -          |
|      |                     | 51         | -                     | -           | -            | 0              | -          |

Appendix 2-16 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (Predosing)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena |                |             |             |      |
|------|---------------------|------------|-----------------------|----------------|-------------|-------------|------|
|      |                     |            | Posture               | Motor activity | Respiration | Lid closure | Gait |
| Male | 0                   | 13         | 0                     | 0              | 0           | -           | -    |
|      |                     | 14         | 0                     | +1             | 0           | -           | -    |
|      |                     | 15         | 0                     | 0              | 0           | -           | -    |
|      |                     | 16         | 0                     | 0              | 0           | -           | -    |
|      |                     | 17         | 0                     | 0              | 0           | -           | -    |
|      | 200                 | 30         | 0                     | 0              | 0           | -           | -    |
|      |                     | 31         | 0                     | +1             | 0           | -           | -    |
|      |                     | 32         | 0                     | 0              | 0           | -           | -    |
|      |                     | 33         | 0                     | 0              | 0           | -           | -    |
|      |                     | 34         | 0                     | 0              | 0           | -           | -    |
| 1000 | 1000                | 47         | 0                     | 0              | 0           | -           | -    |
|      |                     | 48         | 0                     | 0              | 0           | -           | -    |
|      |                     | 49         | 0                     | 0              | 0           | -           | -    |
|      |                     | 50         | 0                     | 0              | 0           | -           | -    |
|      |                     | 51         | 0                     | 0              | 0           | -           | -    |

Appendix 2-17 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 1)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena |                |             |             |
|------|---------------------|------------|-----------------------|----------------|-------------|-------------|
|      |                     |            | Posture               | Motor activity | Respiration | Lid closure |
| Male | 0                   | 13         | 0                     | 0              | 0           | -           |
|      |                     | 14         | 0                     | 0              | 0           | -           |
|      |                     | 15         | 0                     | 0              | 0           | -           |
|      |                     | 16         | 0                     | 0              | 0           | -           |
|      |                     | 17         | 0                     | 0              | 0           | -           |
|      | 200                 | 30         | 0                     | 0              | 0           | -           |
|      |                     | 31         | 0                     | +1             | 0           | -           |
|      |                     | 32         | 0                     | 0              | 0           | -           |
|      |                     | 33         | 0                     | 0              | 0           | -           |
|      |                     | 34         | 0                     | 0              | 0           | -           |
| 1000 | 1000                | 47         | 0                     | 0              | 0           | -           |
|      |                     | 48         | 0                     | 0              | 0           | -           |
|      |                     | 49         | 0                     | 0              | 0           | -           |
|      |                     | 50         | 0                     | 0              | 0           | -           |
|      |                     | 51         | 0                     | 0              | 0           | -           |

Appendix 2-18 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 2)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena |                |             |             |
|------|---------------------|------------|-----------------------|----------------|-------------|-------------|
|      |                     |            | Posture               | Motor activity | Respiration | Lid closure |
| Male | 0                   | 13         | 0                     | 0              | 0           | -           |
|      |                     | 14         | 0                     | 0              | 0           | -           |
|      |                     | 15         | 0                     | 0              | 0           | -           |
|      |                     | 16         | 0                     | 0              | 0           | -           |
|      |                     | 17         | 0                     | 0              | 0           | -           |
|      | 200                 | 30         | 0                     | 0              | 0           | -           |
|      |                     | 31         | 0                     | 0              | 0           | -           |
|      |                     | 32         | 0                     | 0              | 0           | -           |
|      |                     | 33         | 0                     | 0              | 0           | -           |
|      |                     | 34         | 0                     | 0              | 0           | -           |
| 1000 | 1000                | 47         | 0                     | 0              | 0           | -           |
|      |                     | 48         | 0                     | 0              | 0           | -           |
|      |                     | 49         | 0                     | 0              | 0           | -           |
|      |                     | 50         | 0                     | 0              | 0           | -           |
|      |                     | 51         | 0                     | 0              | 0           | -           |

Appendix 2-19 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 3)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena |                   |             |                |
|------|---------------------|------------|-----------------------|-------------------|-------------|----------------|
|      |                     |            | Posture               | Motor<br>activity | Respiration | Lid<br>closure |
| Male | 0                   | 13         | 0                     | 0                 | 0           | -              |
|      |                     | 14         | 0                     | 0                 | 0           | -              |
|      |                     | 15         | 0                     | 0                 | 0           | -              |
|      |                     | 16         | 0                     | 0                 | 0           | -              |
|      |                     | 17         | 0                     | 0                 | 0           | -              |
|      | 200                 | 30         | 0                     | 0                 | 0           | -              |
|      |                     | 31         | 0                     | 0                 | 0           | -              |
|      |                     | 32         | 0                     | 0                 | 0           | -              |
|      |                     | 33         | 0                     | 0                 | 0           | -              |
|      |                     | 34         | 0                     | 0                 | 0           | -              |
| 1000 | 1000                | 47         | 0                     | 0                 | 0           | -              |
|      |                     | 48         | 0                     | 0                 | 0           | -              |
|      |                     | 49         | 0                     | 0                 | 0           | -              |
|      |                     | 50         | 0                     | 0                 | 0           | -              |
|      |                     | 51         | 0                     | 0                 | 0           | -              |

Appendix 2-20 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 4)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena |                |             |             |   |
|------|---------------------|------------|-----------------------|----------------|-------------|-------------|---|
|      |                     |            | Posture               | Motor activity | Respiration | Lid closure |   |
| Male | 0                   | 13         | 0                     | 0              | 0           | -           | - |
|      |                     | 14         | 0                     | 0              | 0           | -           | - |
|      |                     | 15         | 0                     | 0              | 0           | -           | - |
|      |                     | 16         | 0                     | 0              | 0           | -           | - |
|      |                     | 17         | 0                     | 0              | 0           | -           | - |
|      | 200                 | 30         | 0                     | 0              | 0           | -           | - |
|      |                     | 31         | 0                     | 0              | 0           | -           | - |
|      |                     | 32         | 0                     | 0              | 0           | -           | - |
|      |                     | 33         | 0                     | 0              | 0           | -           | - |
|      | 1000                | 34         | 0                     | 0              | 0           | -           | - |
|      |                     | 47         | 0                     | 0              | 0           | -           | - |
|      |                     | 48         | 0                     | 0              | 0           | -           | - |
|      |                     | 49         | 0                     | 0              | 0           | -           | - |
|      |                     | 50         | 0                     | 0              | 0           | -           | - |
|      |                     | 51         | 0                     | 0              | 0           | -           | - |

Appendix 2-21 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (Predosing)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena        |                           |                          |                         |
|------|---------------------|------------|------------------------------|---------------------------|--------------------------|-------------------------|
|      |                     |            | Tremor/twitch/<br>convulsion | Defecation<br>(count/min) | Urination<br>(count/min) | Stereotypic<br>behavior |
| Male | 0                   | 13         | 0                            | 0                         | 2                        | -                       |
|      |                     | 14         | 0                            | 0                         | 2                        | -                       |
|      |                     | 15         | 0                            | 0                         | 0                        | -                       |
|      |                     | 16         | 0                            | 0                         | 0                        | -                       |
|      |                     | 17         | 0                            | 0                         | 0                        | -                       |
|      | 200                 | 30         | 0                            | 1                         | 3                        | -                       |
|      |                     | 31         | 0                            | 1                         | 2                        | -                       |
|      |                     | 32         | 0                            | 0                         | 0                        | -                       |
|      |                     | 33         | 0                            | 0                         | 0                        | -                       |
|      |                     | 34         | 0                            | 0                         | 0                        | -                       |
| 1000 | 1000                | 47         | 0                            | 0                         | 1                        | -                       |
|      |                     | 48         | 0                            | 0                         | 0                        | -                       |
|      |                     | 49         | 0                            | 1                         | 2                        | -                       |
|      |                     | 50         | 0                            | 0                         | 0                        | -                       |
|      |                     | 51         | 0                            | 0                         | 0                        | -                       |

Appendix 2-22 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 1)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena        |                           |                          |                         |
|------|---------------------|------------|------------------------------|---------------------------|--------------------------|-------------------------|
|      |                     |            | Tremor/twitch/<br>convulsion | Defecation<br>(count/min) | Urination<br>(count/min) | Stereotypic<br>behavior |
| Male | 200                 | 13         | 0                            | 0                         | 2                        | -                       |
|      |                     | 14         | 0                            | 3                         | 0                        | -                       |
|      |                     | 0          | 15                           | 0                         | 0                        | -                       |
|      |                     | 16         | 0                            | 0                         | 0                        | -                       |
|      |                     | 17         | 0                            | 0                         | 0                        | -                       |
|      | 1000                | 30         | 0                            | 1                         | 2                        | -                       |
|      |                     | 31         | 0                            | 2                         | 3                        | -                       |
|      |                     | 32         | 0                            | 0                         | 0                        | -                       |
|      |                     | 33         | 0                            | 0                         | 0                        | -                       |
|      |                     | 34         | 0                            | 0                         | 0                        | -                       |
|      |                     | 47         | 0                            | 0                         | 5                        | -                       |
|      |                     | 48         | 0                            | 0                         | 0                        | -                       |
|      |                     | 49         | 0                            | 2                         | 2                        | -                       |
|      |                     | 50         | 0                            | 0                         | 0                        | -                       |
|      |                     | 51         | 0                            | 0                         | 0                        | -                       |

Appendix 2-23 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 2)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena        |                           |                          |                         |
|------|---------------------|------------|------------------------------|---------------------------|--------------------------|-------------------------|
|      |                     |            | Tremor/twitch/<br>convulsion | Defecation<br>(count/min) | Urination<br>(count/min) | Stereotypic<br>behavior |
| Male | 0                   | 13         | 0                            | 0                         | 0                        | -                       |
|      |                     | 14         | 0                            | 1                         | 2                        | -                       |
|      |                     | 15         | 0                            | 0                         | 0                        | -                       |
|      |                     | 16         | 0                            | 0                         | 0                        | -                       |
|      |                     | 17         | 0                            | 0                         | 0                        | -                       |
|      | 200                 | 30         | 0                            | 0                         | 0                        | -                       |
|      |                     | 31         | 0                            | 1                         | 1                        | -                       |
|      |                     | 32         | 0                            | 0                         | 0                        | -                       |
|      |                     | 33         | 0                            | 0                         | 1                        | -                       |
|      |                     | 34         | 0                            | 0                         | 0                        | -                       |
| 1000 | 1000                | 47         | 0                            | 2                         | 1                        | -                       |
|      |                     | 48         | 0                            | 0                         | 0                        | -                       |
|      |                     | 49         | 0                            | 2                         | 6                        | -                       |
|      |                     | 50         | 0                            | 0                         | 0                        | -                       |
|      |                     | 51         | 0                            | 0                         | 0                        | -                       |

Appendix 2-24 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 3)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena        |                           |                          |                         |
|------|---------------------|------------|------------------------------|---------------------------|--------------------------|-------------------------|
|      |                     |            | Tremor/twitch/<br>convulsion | Defecation<br>(count/min) | Urination<br>(count/min) | Stereotypic<br>behavior |
| Male | 0                   | 13         | 0                            | 0                         | 7                        | -                       |
|      |                     | 14         | 0                            | 2                         | 7                        | -                       |
|      |                     | 15         | 0                            | 0                         | 0                        | -                       |
|      |                     | 16         | 0                            | 0                         | 0                        | -                       |
|      |                     | 17         | 0                            | 0                         | 0                        | -                       |
|      | 200                 | 30         | 0                            | 0                         | 0                        | -                       |
|      |                     | 31         | 0                            | 1                         | 2                        | -                       |
|      |                     | 32         | 0                            | 0                         | 0                        | -                       |
|      |                     | 33         | 0                            | 0                         | 0                        | -                       |
|      |                     | 34         | 0                            | 0                         | 0                        | -                       |
| 1000 | 1000                | 47         | 0                            | 1                         | 4                        | -                       |
|      |                     | 48         | 0                            | 0                         | 0                        | -                       |
|      |                     | 49         | 0                            | 1                         | 5                        | -                       |
|      |                     | 50         | 0                            | 0                         | 1                        | -                       |
|      |                     | 51         | 0                            | 0                         | 0                        | -                       |

Appendix 2-25 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Detailed clinical observations of individual animals (week 4)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Observations in arena        |                           |                          |                         |
|------|---------------------|------------|------------------------------|---------------------------|--------------------------|-------------------------|
|      |                     |            | Tremor/twitch/<br>convulsion | Defecation<br>(count/min) | Urination<br>(count/min) | Stereotypic<br>behavior |
| Male | 0                   | 13         | 0                            | 0                         | 0                        | -                       |
|      |                     | 14         | 0                            | 1                         | 1                        | -                       |
|      |                     | 15         | 0                            | 0                         | 0                        | -                       |
|      |                     | 16         | 0                            | 0                         | 0                        | -                       |
|      |                     | 17         | 0                            | 0                         | 0                        | -                       |
|      | 200                 | 30         | 0                            | 0                         | 0                        | -                       |
|      |                     | 31         | 0                            | 1                         | 0                        | -                       |
|      |                     | 32         | 0                            | 0                         | 0                        | -                       |
|      |                     | 33         | 0                            | 0                         | 0                        | -                       |
|      |                     | 34         | 0                            | 0                         | 0                        | -                       |
| 1000 | 1000                | 47         | 0                            | 1                         | 3                        | -                       |
|      |                     | 48         | 0                            | 0                         | 0                        | -                       |
|      |                     | 49         | 0                            | 1                         | 2                        | -                       |
|      |                     | 50         | 0                            | 0                         | 0                        | -                       |
|      |                     | 51         | 0                            | 0                         | 0                        | -                       |

Appendix 3      Twenty-eight-day repeated-dose oral toxicity study in rats  
 Reflex of individual animals (week 4)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Sensorimotor function               |                   |                               |                     |                        |
|------|---------------------|------------|-------------------------------------|-------------------|-------------------------------|---------------------|------------------------|
|      |                     |            | Approach contact/<br>touch response | Pinna<br>response | Pain response<br>(tail pinch) | Pupillary<br>reflex | Air righting<br>reflex |
| Male | 0                   | 13         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 14         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 15         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 16         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 17         | 0                                   | 0                 | 0                             | +                   | +                      |
|      | 200                 | 30         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 31         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 32         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 33         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 34         | 0                                   | 0                 | 0                             | +                   | +                      |
|      | 1000                | 47         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 48         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 49         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 50         | 0                                   | 0                 | 0                             | +                   | +                      |
|      |                     | 51         | 0                                   | 0                 | 0                             | +                   | +                      |

Appendix 4      Twenty-eight-day repeated-dose oral toxicity study in rats  
 Grip strength of individual animals (week 4)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Forelimb (g) |         |      | Hindlimb (g) |         |      |
|------|---------------------|------------|--------------|---------|------|--------------|---------|------|
|      |                     |            | Trial 1      | Trial 2 | Mean | Trial 1      | Trial 2 | Mean |
| Male | 0                   | 13         | 525          | 466     | 496  | 447          | 470     | 459  |
|      |                     | 14         | 500          | 489     | 495  | 472          | 410     | 441  |
|      |                     | 15         | 401          | 435     | 418  | 416          | 421     | 419  |
|      |                     | 16         | 444          | 411     | 428  | 461          | 479     | 470  |
|      |                     | 17         | 447          | 436     | 442  | 373          | 473     | 423  |
|      | 200                 | 30         | 478          | 485     | 482  | 472          | 390     | 431  |
|      |                     | 31         | 523          | 464     | 494  | 459          | 439     | 449  |
|      |                     | 32         | 395          | 471     | 433  | 400          | 368     | 384  |
|      |                     | 33         | 491          | 395     | 443  | 488          | 443     | 466  |
|      |                     | 34         | 491          | 473     | 482  | 440          | 424     | 432  |
| 1000 | 1000                | 47         | 405          | 458     | 432  | 500          | 449     | 475  |
|      |                     | 48         | 383          | 483     | 433  | 428          | 443     | 436  |
|      |                     | 49         | 353          | 361     | 357  | 425          | 420     | 423  |
|      |                     | 50         | 489          | 470     | 480  | 541          | 444     | 493  |
|      |                     | 51         | 496          | 533     | 515  | 459          | 432     | 446  |

Appendix 5      Twenty-eight-day repeated-dose oral toxicity study in rats  
 Motor activity of individual animals (week 4)

| Sex  | Dose<br>(mg/kg/day) | Animal No. | Interval (min) |       |       |       |       |       | Total |
|------|---------------------|------------|----------------|-------|-------|-------|-------|-------|-------|
|      |                     |            | 0-10           | 10-20 | 20-30 | 30-40 | 40-50 | 50-60 |       |
| Male | 0                   | 13         | 97             | 91    | 55    | 114   | 23    | 1     | 381   |
|      |                     | 14         | 152            | 93    | 62    | 40    | 45    | 31    | 423   |
|      |                     | 15         | 118            | 123   | 123   | 64    | 53    | 0     | 481   |
|      |                     | 16         | 108            | 43    | 35    | 44    | 61    | 15    | 306   |
|      |                     | 17         | 174            | 134   | 120   | 56    | 72    | 40    | 596   |
|      | 200                 | 30         | 158            | 141   | 169   | 83    | 71    | 77    | 699   |
|      |                     | 31         | 222            | 60    | 45    | 26    | 18    | 0     | 371   |
|      |                     | 32         | 179            | 144   | 89    | 39    | 5     | 12    | 468   |
|      |                     | 33         | 208            | 124   | 123   | 117   | 94    | 0     | 666   |
|      |                     | 34         | 190            | 89    | 121   | 16    | 10    | 0     | 426   |
| 1000 | 1000                | 47         | 134            | 73    | 42    | 80    | 28    | 0     | 357   |
|      |                     | 48         | 178            | 80    | 0     | 14    | 2     | 7     | 281   |
|      |                     | 49         | 148            | 111   | 47    | 5     | 1     | 1     | 313   |
|      |                     | 50         | 175            | 96    | 88    | 103   | 2     | 21    | 485   |
|      |                     | 51         | 91             | 47    | 62    | 26    | 85    | 35    | 346   |

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Appendix 6-1

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Group                 |            | One-day treatment |       |       |       |
|-----------------------|------------|-------------------|-------|-------|-------|
| Dose (mg/kg/day)      |            | 0                 |       |       |       |
|                       | Animal No. | 1                 | 2     | 3     | 4     |
| Administration period | 1          | 137.1             | 147.3 | 157.3 | 157.5 |
|                       | 3          | --                | --    | --    | --    |
|                       | 7          | --                | --    | --    | --    |
|                       | 14         | --                | --    | --    | --    |
|                       | 21         | --                | --    | --    | --    |
|                       | 28         | --                | --    | --    | --    |

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Appendix 6-2

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Group                 |            | Seven-day treatment |       |       |       |
|-----------------------|------------|---------------------|-------|-------|-------|
| Dose (mg/kg/day)      |            | 0                   |       |       |       |
|                       | Animal No. | 5                   | 6     | 7     | 8     |
| Administration period | 1          | 146.4               | 148.4 | 150.6 | 151.9 |
|                       | 3          | 164.4               | 163.3 | 168.6 | 163.9 |
|                       | 7          | 199.8               | 196.1 | 206.4 | 197.6 |
|                       | 14         | --                  | --    | --    | --    |
|                       | 21         | --                  | --    | --    | --    |
|                       | 28         | --                  | --    | --    | --    |

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## Appendix 6-3

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Administration period | Animal No. | Fourteen-day treatment |       |       |       |
|-----------------------|------------|------------------------|-------|-------|-------|
|                       |            | 0                      | 9     | 10    | 11    |
|                       | 1          | 139.5                  | 150.7 | 154.5 | 159.9 |
|                       | 3          | 155.6                  | 164.5 | 175.5 | 175.0 |
|                       | 7          | 186.3                  | 198.6 | 208.7 | 214.8 |
|                       | 14         | 235.7                  | 250.2 | 263.9 | 285.8 |
|                       | 21         | —                      | —     | —     | —     |
|                       | 28         | —                      | —     | —     | —     |

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## Appendix 6-4

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Group                 |            | Twenty-eight-day treatment |       |       |       |       |
|-----------------------|------------|----------------------------|-------|-------|-------|-------|
| Dose (mg/kg/day)      |            | 0                          |       |       |       |       |
|                       | Animal No. | 13                         | 14    | 15    | 16    | 17    |
| Administration period | 1          | 148.6                      | 151.0 | 154.8 | 157.7 | 161.9 |
|                       | 3          | 165.1                      | 168.3 | 170.5 | 175.6 | 178.1 |
|                       | 7          | 205.6                      | 200.6 | 213.5 | 210.6 | 213.6 |
|                       | 14         | 266.0                      | 261.7 | 282.4 | 280.2 | 275.2 |
|                       | 21         | 339.0                      | 329.1 | 353.3 | 346.9 | 336.0 |
|                       | 28         | 383.8                      | 381.5 | 412.1 | 384.0 | 380.5 |

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Appendix 6-5

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Group                 |            | One-day treatment |       |       |       |
|-----------------------|------------|-------------------|-------|-------|-------|
| Dose (mg/kg/day)      |            | 200               |       |       |       |
|                       | Animal No. | 18                | 19    | 20    | 21    |
| Administration period | 1          | 146.5             | 146.0 | 150.7 | 153.8 |
|                       | 3          | --                | --    | --    | --    |
|                       | 7          | --                | --    | --    | --    |
|                       | 14         | --                | --    | --    | --    |
|                       | 21         | --                | --    | --    | --    |
|                       | 28         | --                | --    | --    | --    |

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## Appendix 6-6

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Group                 |            | Seven-day treatment |       |       |       |
|-----------------------|------------|---------------------|-------|-------|-------|
| Dose (mg/kg/day)      |            | 200                 |       |       |       |
|                       | Animal No. | 22                  | 23    | 24    | 25    |
| Administration period | 1          | 144.0               | 142.9 | 154.0 | 155.3 |
|                       | 3          | 156.2               | 159.0 | 169.0 | 171.5 |
|                       | 7          | 183.4               | 193.7 | 210.6 | 203.9 |
|                       | 14         | --                  | --    | --    | --    |
|                       | 21         | --                  | --    | --    | --    |
|                       | 28         | --                  | --    | --    | --    |

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## Appendix 6-7

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

|                       | Group            | Fourteen-day treatment |       |       |       |       |
|-----------------------|------------------|------------------------|-------|-------|-------|-------|
|                       |                  | 200                    |       |       |       |       |
|                       | Dose (mg/kg/day) | Animal No.             | 26    | 27    | 28    | 29    |
| Administration period | 1                |                        | 145.7 | 149.7 | 151.4 | 155.9 |
|                       | 3                |                        | 165.4 | 166.5 | 169.1 | 173.8 |
|                       | 7                |                        | 202.7 | 205.7 | 204.5 | 202.8 |
|                       | 14               |                        | 260.5 | 260.4 | 274.6 | 257.0 |
|                       | 21               |                        | —     | —     | —     | —     |
|                       | 28               |                        | —     | —     | —     | —     |

## Appendix 6-8

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

|                       | Group      | Twenty-eight-day treatment |       |       |       |       |
|-----------------------|------------|----------------------------|-------|-------|-------|-------|
|                       |            | Dose (mg/kg/day)           | 200   |       |       |       |
|                       | Animal No. | 30                         | 31    | 32    | 33    | 34    |
| Administration period | 1          | 140.1                      | 147.0 | 154.7 | 151.5 | 161.7 |
|                       | 3          | 157.5                      | 165.0 | 170.8 | 172.8 | 177.3 |
|                       | 7          | 189.4                      | 196.3 | 207.0 | 213.5 | 212.6 |
|                       | 14         | 249.1                      | 251.5 | 262.2 | 273.0 | 276.3 |
|                       | 21         | 302.1                      | 309.2 | 325.7 | 324.2 | 330.2 |
|                       | 28         | 344.1                      | 350.3 | 371.1 | 351.4 | 369.0 |

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Appendix 6-9

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Group                 |            | One-day treatment |       |       |       |
|-----------------------|------------|-------------------|-------|-------|-------|
| Dose (mg/kg/day)      |            | 1000              |       |       |       |
|                       | Animal No. | 35                | 36    | 37    | 38    |
| Administration period | 1          | 143.6             | 146.4 | 152.2 | 160.5 |
|                       | 3          | --                | --    | --    | --    |
|                       | 7          | --                | --    | --    | --    |
|                       | 14         | --                | --    | --    | --    |
|                       | 21         | --                | --    | --    | --    |
|                       | 28         | --                | --    | --    | --    |

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Appendix 6-10

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Group                 |            | Seven-day treatment |       |       |       |
|-----------------------|------------|---------------------|-------|-------|-------|
| Dose (mg/kg/day)      |            | 1000                |       |       |       |
|                       | Animal No. | 39                  | 40    | 41    | 42    |
| Administration period | 1          | 147.6               | 149.1 | 154.3 | 158.5 |
|                       | 3          | 161.7               | 165.5 | 167.9 | 170.7 |
|                       | 7          | 192.7               | 199.8 | 204.2 | 207.9 |
|                       | 14         | —                   | —     | —     | —     |
|                       | 21         | —                   | —     | —     | —     |
|                       | 28         | —                   | —     | —     | —     |

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## Appendix 6-11

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Group                 |            | Fourteen-day treatment |       |       |       |
|-----------------------|------------|------------------------|-------|-------|-------|
| Dose (mg/kg/day)      |            | 1000                   |       |       |       |
|                       | Animal No. | 43                     | 44    | 45    | 46    |
| Administration period | 1          | 143.8                  | 149.2 | 152.4 | 155.9 |
|                       | 3          | 161.4                  | 166.4 | 167.8 | 174.8 |
|                       | 7          | 190.8                  | 197.3 | 202.5 | 208.8 |
|                       | 14         | 254.3                  | 249.3 | 252.8 | 261.3 |
|                       | 21         | —                      | —     | —     | —     |
|                       | 28         | —                      | —     | —     | —     |

## Appendix 6-12

Twenty-eight-day repeated-dose oral toxicity study in rats  
Body weights of individual animals (g) : Male

| Group                 |            | Twenty-eight-day treatment |       |       |       |       |
|-----------------------|------------|----------------------------|-------|-------|-------|-------|
| Dose (mg/kg/day)      |            | 1000                       |       |       |       |       |
|                       | Animal No. | 47                         | 48    | 49    | 50    | 51    |
| Administration period | 1          | 146.0                      | 147.5 | 152.2 | 158.6 | 160.1 |
|                       | 3          | 162.1                      | 167.9 | 164.2 | 175.2 | 178.8 |
|                       | 7          | 199.3                      | 201.7 | 195.7 | 211.0 | 212.9 |
|                       | 14         | 260.9                      | 261.3 | 245.5 | 276.3 | 274.6 |
|                       | 21         | 314.1                      | 315.0 | 295.5 | 338.5 | 339.5 |
|                       | 28         | 361.4                      | 353.8 | 329.6 | 386.2 | 386.0 |

## Appendix 7

Twenty-eight-day repeated-dose oral toxicity study in rats  
Food consumption of individual animals (g/rat/day)

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| Sex  | Dose<br>(mg/kg/day) | Animal No. | Administration period |       |       |       |           |
|------|---------------------|------------|-----------------------|-------|-------|-------|-----------|
|      |                     |            | 1                     | 3     | 7     | 14    | 28 (days) |
| Male | 0                   | 5          | 20.45                 | 20.61 | 22.58 | -     | -         |
|      |                     | 6          | 18.29                 | 17.27 | 21.16 | -     | -         |
|      |                     | 7          | 19.11                 | 20.46 | 23.37 | -     | -         |
|      |                     | 8          | 18.09                 | 17.84 | 21.80 | -     | -         |
|      |                     | 9          | 16.78                 | 18.23 | 20.79 | 20.78 | -         |
|      |                     | 10         | 22.01                 | 20.39 | 22.80 | 22.88 | -         |
|      |                     | 11         | 21.99                 | 21.92 | 23.79 | 24.01 | -         |
|      |                     | 12         | 21.55                 | 19.39 | 24.01 | 26.00 | -         |
|      |                     | 13         | 19.54                 | 17.52 | 22.48 | 22.98 | 25.16     |
|      |                     | 14         | 20.16                 | 19.10 | 21.74 | 23.08 | 24.34     |
|      |                     | 15         | 19.99                 | 19.59 | 23.90 | 25.65 | 25.81     |
|      |                     | 16         | 20.93                 | 21.37 | 24.60 | 26.12 | 26.65     |
|      |                     | 17         | 21.05                 | 22.18 | 24.68 | 25.67 | 27.13     |
|      |                     | 22         | 18.80                 | 17.45 | 18.75 | -     | -         |
|      |                     | 23         | 16.25                 | 16.30 | 20.37 | -     | -         |
|      |                     | 24         | 20.37                 | 19.45 | 24.33 | -     | -         |
|      |                     | 25         | 19.69                 | 20.70 | 23.06 | -     | -         |
| Male | 200                 | 26         | 19.78                 | 20.39 | 22.69 | 22.98 | -         |
|      |                     | 27         | 20.34                 | 19.65 | 21.85 | 21.34 | -         |
|      |                     | 28         | 19.51                 | 19.47 | 22.40 | 24.72 | -         |
|      |                     | 29         | 21.39                 | 21.85 | 22.28 | 22.59 | -         |
|      |                     | 30         | 16.48                 | 16.67 | 20.54 | 21.14 | 21.63     |
|      |                     | 31         | 17.80                 | 17.30 | 19.96 | 21.08 | 20.98     |
|      |                     | 32         | 22.02                 | 20.16 | 23.68 | 21.80 | 21.99     |
|      |                     | 33         | 19.86                 | 20.69 | 25.25 | 25.53 | 23.59     |
|      |                     | 34         | 21.36                 | 20.30 | 22.90 | 23.73 | 21.55     |
|      |                     | 39         | 19.36                 | 18.85 | 20.42 | -     | -         |
|      |                     | 40         | 20.06                 | 17.78 | 22.10 | -     | -         |
|      |                     | 41         | 21.14                 | 19.12 | 23.14 | -     | -         |
|      |                     | 42         | 21.91                 | 17.80 | 22.38 | -     | -         |
|      |                     | 43         | 18.27                 | 18.45 | 20.01 | 22.25 | -         |
|      |                     | 44         | 17.99                 | 17.69 | 19.47 | 20.10 | -         |
|      |                     | 45         | 20.33                 | 19.68 | 22.79 | 22.20 | -         |
|      |                     | 46         | 18.32                 | 19.59 | 22.45 | 21.90 | -         |
| Male | 1000                | 47         | 19.26                 | 19.19 | 21.79 | 23.14 | 22.21     |
|      |                     | 48         | 19.96                 | 19.36 | 22.54 | 23.34 | 21.71     |
|      |                     | 49         | 20.16                 | 18.55 | 20.51 | 20.88 | 21.20     |
|      |                     | 50         | 19.70                 | 18.07 | 21.86 | 23.29 | 23.63     |
|      |                     | 51         | 21.55                 | 19.68 | 23.22 | 23.04 | 24.62     |
|      |                     |            |                       |       |       |       | 25.40     |

Appendix 8-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Urinalytic data of individual animals:Male

| Group            |            | Twenty-eight-day treatment |       |       |       |       |
|------------------|------------|----------------------------|-------|-------|-------|-------|
| Dose (mg/kg/day) |            | 0                          |       |       |       |       |
| Items            | Animal No. | 13 ss                      | 14 ss | 15 ss | 16 ss | 17 ss |
| Urine volume     | (mL)       | 19                         | 5     | 16    | 6     | 14    |
| Uosm             | (mOsm/L)   | 509                        | 1502  | 640   | 1679  | 596   |

ss: scheduled sacrifice animal.

Appendix 8-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Urinalytic data of individual animals:Male

| Group             |            | Twenty-eight-day treatment |       |       |       |       |
|-------------------|------------|----------------------------|-------|-------|-------|-------|
| Dose (mg/kg/day)  |            | 200                        |       |       |       |       |
| Items             | Animal No. | 30 ss                      | 31 ss | 32 ss | 33 ss | 34 ss |
| Urine volume (mL) |            | 19                         | 5     | 12    | 6     | 15    |
| Uosm (mOsm/L)     |            | 504                        | 1317  | 664   | 988   | 505   |

ss: scheduled sacrifice animal.

Appendix 8-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Urinalytic data of individual animals: Male

| Group            |            | Twenty-eight-day treatment |       |       |       |       |
|------------------|------------|----------------------------|-------|-------|-------|-------|
| Dose (mg/kg/day) |            | 1000                       |       |       |       |       |
| Items            | Animal No. | 47 ss                      | 48 ss | 49 ss | 50 ss | 51 ss |
| Urine volume     | (mL)       | 17                         | 9     | 5     | 24    | 10    |
| Uosm             | (mOsm/L)   | 528                        | 1132  | 1630  | 318   | 905   |

ss: scheduled sacrifice animal.

## Appendix 8-4

Twenty-eight-day repeated-dose oral toxicity study in rats  
Urinalytic data of individual animals:Male

| Items                           | Animal No. | Twenty-eight-day treatment |    |       |    |       |    |       |    |       |    |
|---------------------------------|------------|----------------------------|----|-------|----|-------|----|-------|----|-------|----|
|                                 |            | 13                         | ss | 14    | ss | 15    | ss | 16    | ss | 17    | ss |
| Color                           |            | SY                         |    | YB    |    | SY    |    | YB    |    | SY    |    |
| Turbidity                       |            | Clear                      |    | Clear |    | Clear |    | Clear |    | Clear |    |
| pH                              |            | 6.5                        |    | 6.5   |    | 6.5   |    | 6.0   |    | 7.0   |    |
| Protein                         |            | ±                          |    | ±     |    | -     |    | 1+    |    | -     |    |
| Glucose                         |            | -                          |    | -     |    | -     |    | -     |    | -     |    |
| Ketones                         |            | ±                          |    | ±     |    | ±     |    | -     |    | 1+    |    |
| Occult blood                    |            | ±                          |    | -     |    | -     |    | -     |    | -     |    |
| Urinalytic sediment             |            |                            |    |       |    |       |    |       |    |       |    |
| Red blood cells <sup>a)</sup>   |            | 0                          |    | 0     |    | 0     |    | 0     |    | 0     |    |
| White blood cells <sup>a)</sup> |            | 0                          |    | 0     |    | 0     |    | 0     |    | 0     |    |
| Epithelial cells <sup>a)</sup>  |            | 0                          |    | 0     |    | 0     |    | 0     |    | 0     |    |
| Casts <sup>b)</sup>             |            | 0                          |    | 0     |    | 0     |    | 0     |    | 0     |    |
| Crystals <sup>c)</sup>          |            | ±                          |    | 2+    |    | -     |    | 1+    |    | 1+    |    |

ss:scheduled sacrifice animal.

Color: SY: Slightly yellow, YB: Yellow-brown.

<sup>a)</sup>:Number of cells/10views(×400).<sup>b)</sup>:Number of casts/18×18 mm<sup>2</sup>.<sup>c)</sup>:Incidence of crystals/18×18 mm<sup>2</sup>.

## Appendix 8-5

Twenty-eight-day repeated-dose oral toxicity study in rats  
Urinalytic data of individual animals:Male

| Items                           | Animal No. | Twenty-eight-day treatment |    |       |    |       |    |       |    |       |    |
|---------------------------------|------------|----------------------------|----|-------|----|-------|----|-------|----|-------|----|
|                                 |            | 30                         | ss | 31    | ss | 32    | ss | 33    | ss | 34    | ss |
| Color                           |            | SY                         |    | Y     |    | Y     |    | Y     |    | SY    |    |
| Turbidity                       |            | Clear                      |    | Clear |    | Clear |    | Clear |    | Clear |    |
| pH                              |            | 7.0                        |    | 7.0   |    | 7.0   |    | 6.0   |    | 7.0   |    |
| Protein                         |            | -                          |    | ±     |    | ±     |    | ±     |    | ±     |    |
| Glucose                         |            | -                          |    | -     |    | -     |    | -     |    | -     |    |
| Ketones                         |            | ±                          |    | -     |    | ±     |    | 1+    |    | 1+    |    |
| Occult blood                    |            | -                          |    | -     |    | -     |    | -     |    | -     |    |
| Urinalytic sediment             |            |                            |    |       |    |       |    |       |    |       |    |
| Red blood cells <sup>a)</sup>   |            | --                         |    | --    |    | --    |    | --    |    | --    |    |
| White blood cells <sup>a)</sup> |            | --                         |    | --    |    | --    |    | --    |    | --    |    |
| Epithelial cells <sup>a)</sup>  |            | --                         |    | --    |    | --    |    | --    |    | --    |    |
| Casts <sup>b)</sup>             |            | --                         |    | --    |    | --    |    | --    |    | --    |    |
| Crystals <sup>c)</sup>          |            | --                         |    | --    |    | --    |    | --    |    | --    |    |

ss:scheduled sacrifice animal.

Color: SY: Slightly yellow, Y: Yellow.

<sup>a)</sup>: Number of cells/10views(×400).

<sup>b)</sup>: Number of casts/18×18 mm<sup>2</sup>.

<sup>c)</sup>: Incidence of crystals/18×18 mm<sup>2</sup>.

## Appendix 8-6

Twenty-eight-day repeated-dose oral toxicity study in rats  
Urinalytic data of individual animals:Male

| Items                           | Animal No. | Twenty-eight-day treatment |    |       |    |       |    |       |    |       |    |
|---------------------------------|------------|----------------------------|----|-------|----|-------|----|-------|----|-------|----|
|                                 |            | 47                         | ss | 48    | ss | 49    | ss | 50    | ss | 51    | ss |
| Color                           |            | SY                         |    | Y     |    | YB    |    | SY    |    | Y     |    |
| Turbidity                       |            | Clear                      |    | Clear |    | Clear |    | Clear |    | Clear |    |
| pH                              |            | 7.0                        |    | 7.0   |    | 6.0   |    | 6.5   |    | 7.0   |    |
| Protein                         |            | ±                          |    | 1+    |    | 1+    |    | -     |    | ±     |    |
| Glucose                         |            | -                          |    | -     |    | -     |    | -     |    | -     |    |
| Ketones                         |            | ±                          |    | 1+    |    | 1+    |    | ±     |    | ±     |    |
| Occult blood                    |            | -                          |    | -     |    | -     |    | -     |    | -     |    |
| Urinalytic sediment             |            |                            |    |       |    |       |    |       |    |       |    |
| Red blood cells <sup>a)</sup>   |            | 0                          |    | 0     |    | 0     |    | 0     |    | 0     |    |
| White blood cells <sup>a)</sup> |            | 0                          |    | 0     |    | 0     |    | 0     |    | 0     |    |
| Epithelial cells <sup>a)</sup>  |            | 0                          |    | 0     |    | 0     |    | 0     |    | 0     |    |
| Casts <sup>b)</sup>             |            | 0                          |    | 0     |    | 0     |    | 0     |    | 0     |    |
| Crystals <sup>c)</sup>          |            | 2+                         |    | 2+    |    | ±     |    | ±     |    | 1+    |    |

ss:scheduled sacrifice animal.

Color: SY: Slightly yellow, Y: Yellow, YB: Yellow-brown.

<sup>a)</sup>:Number of cells/10views(×400).<sup>b)</sup>:Number of casts/18×18 mm<sup>2</sup>.<sup>c)</sup>:Incidence of crystals/18×18 mm<sup>2</sup>.

Appendix 9-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | One-day treatment |       |       |       |
|------------------------------|-------------------------------|-------------------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 0                 |       |       |       |
| Items                        | Animal No.                    | 1 ss              | 2 ss  | 3 ss  | 4 ss  |
| RBC                          | ( $\times 10^4/\mu\text{L}$ ) | 709               | 738   | 730   | 766   |
| Hb                           | (g/dL)                        | 14.9              | 16.2  | 15.7  | 16.4  |
| Ht                           | (%)                           | 45.9              | 50.7  | 50.1  | 51.8  |
| MCV                          | (fL)                          | 64.7              | 68.7  | 68.7  | 67.7  |
| MCH                          | (pg)                          | 21.1              | 22.0  | 21.6  | 21.4  |
| MCHC                         | (g/dL)                        | 32.6              | 31.9  | 31.4  | 31.6  |
| Platelet                     | ( $\times 10^4/\mu\text{L}$ ) | 141.7             | 134.6 | 122.0 | 153.8 |
| Reticulo                     | (%)                           | 10.6              | 9.6   | 10.1  | 10.2  |
| WBC                          | ( $\times 10^2/\mu\text{L}$ ) | 96.7              | 139.8 | 140.7 | 114.1 |
| Differentiation of leukocyte |                               |                   |       |       |       |
| Neutro                       | (%)                           | 8.8               | 6.9   | 13.1  | 7.7   |
| Lymph                        | (%)                           | 87.5              | 86.7  | 82.2  | 87.7  |
| Eosino                       | (%)                           | 0.6               | 0.6   | 0.5   | 0.8   |
| Baso                         | (%)                           | 0.5               | 1.3   | 1.0   | 1.0   |
| Mono                         | (%)                           | 1.7               | 3.2   | 2.1   | 1.9   |
| LUC                          | (%)                           | 0.9               | 1.2   | 1.0   | 0.9   |

ss: scheduled sacrifice animal.

Appendix 9-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | Seven-day treatment |       |       |       |
|------------------------------|-------------------------------|---------------------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 0                   |       |       |       |
| Items                        | Animal No.                    | 5 ss                | 6 ss  | 7 ss  | 8 ss  |
| RBC                          | ( $\times 10^6/\mu\text{L}$ ) | 715                 | 692   | 711   | 718   |
| Hb                           | (g/dL)                        | 14.9                | 14.4  | 14.6  | 14.4  |
| Ht                           | (%)                           | 48.0                | 46.4  | 48.2  | 47.2  |
| MCV                          | (fL)                          | 67.1                | 67.1  | 67.9  | 65.7  |
| MCH                          | (pg)                          | 20.8                | 20.9  | 20.5  | 20.0  |
| MCHC                         | (g/dL)                        | 31.0                | 31.1  | 30.2  | 30.4  |
| Platelet                     | ( $\times 10^4/\mu\text{L}$ ) | 127.0               | 110.3 | 137.7 | 123.9 |
| Reticulo                     | (%)                           | 8.6                 | 8.6   | 8.5   | 8.0   |
| WBC                          | ( $\times 10^2/\mu\text{L}$ ) | 164.7               | 96.0  | 128.8 | 118.7 |
| Differentiation of leukocyte |                               |                     |       |       |       |
| Neutro                       | (%)                           | 15.7                | 20.0  | 15.2  | 16.2  |
| Lymph                        | (%)                           | 79.9                | 74.3  | 75.9  | 80.0  |
| Eosino                       | (%)                           | 0.5                 | 0.4   | 0.5   | 0.7   |
| Baso                         | (%)                           | 0.8                 | 0.5   | 0.7   | 0.7   |
| Mono                         | (%)                           | 2.0                 | 2.7   | 4.5   | 1.3   |
| LUC                          | (%)                           | 1.0                 | 2.2   | 3.1   | 1.0   |

ss: scheduled sacrifice animal.

Appendix 9-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                                     |            | Fourteen-day treatment |       |       |       |
|---|------------|------------------------|-------|-------|-------|
| Dose(mg/kg/day)                           |            | 0                      |       |       |       |
| Items                                     | Animal No. | 9 ss                   | 10 ss | 11 ss | 12 ss |
| RBC<br>( $\times 10^4/\mu\text{L}$ )      |            | 792                    | 744   | 750   | 743   |
| Hb<br>(g/dL)                              |            | 15.8                   | 14.3  | 15.2  | 15.1  |
| Ht<br>(%)                                 |            | 51.5                   | 47.4  | 49.7  | 50.0  |
| MCV<br>(fL)                               |            | 65.0                   | 63.7  | 66.3  | 67.4  |
| MCH<br>(pg)                               |            | 20.0                   | 19.3  | 20.2  | 20.3  |
| MCHC<br>(g/dL)                            |            | 30.7                   | 30.2  | 30.5  | 30.1  |
| Platelet<br>( $\times 10^4/\mu\text{L}$ ) |            | 142.9                  | 129.3 | 125.1 | 113.0 |
| Reticulo<br>(%)                           |            | 4.0                    | 4.4   | 4.3   | 5.9   |
| WBC<br>( $\times 10^2/\mu\text{L}$ )      |            | 157.1                  | 145.5 | 154.7 | 148.4 |
| Differentiation of leukocyte              |            |                        |       |       |       |
| Neutro<br>(%)                             |            | 21.7                   | 11.0  | 14.3  | 30.2  |
| Lymph<br>(%)                              |            | 70.5                   | 81.1  | 80.8  | 63.7  |
| Eosino<br>(%)                             |            | 0.5                    | 0.5   | 0.4   | 0.8   |
| Baso<br>(%)                               |            | 4.0                    | 3.7   | 1.8   | 1.7   |
| Mono<br>(%)                               |            | 2.4                    | 2.6   | 1.3   | 2.4   |
| LUC<br>(%)                                |            | 0.9                    | 1.1   | 1.4   | 1.3   |

ss: scheduled sacrifice animal.

Appendix 9-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

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| Group                                     |            | Twenty-eight-day treatment |       |       |       |       |
|---|------------|----------------------------|-------|-------|-------|-------|
| Dose(mg/kg/day)                           |            | 0                          |       |       |       |       |
| Items                                     | Animal No. | 13 ss                      | 14 ss | 15 ss | 16 ss | 17 ss |
| RBC<br>( $\times 10^6/\mu\text{L}$ )      | 811        | 802                        | 752   | 766   | 825   |       |
| Hb<br>(g/dL)                              | 15.7       | 15.3                       | 14.2  | 14.7  | 15.5  |       |
| Ht<br>(%)                                 | 50.9       | 50.4                       | 45.5  | 47.1  | 49.8  |       |
| MCV<br>(fL)                               | 62.7       | 62.9                       | 60.5  | 61.4  | 60.4  |       |
| MCH<br>(pg)                               | 19.4       | 19.0                       | 18.9  | 19.1  | 18.8  |       |
| MCHC<br>(g/dL)                            | 30.9       | 30.3                       | 31.3  | 31.2  | 31.1  |       |
| Platelet<br>( $\times 10^4/\mu\text{L}$ ) | 127.8      | 111.4                      | 131.7 | 118.4 | 109.3 |       |
| Reticulo<br>(%)                           | 3.4        | 3.6                        | 3.2   | 2.9   | 2.8   |       |
| WBC<br>( $\times 10^2/\mu\text{L}$ )      | 176.2      | 121.2                      | 128.2 | 141.6 | 158.1 |       |
| Differentiation of leukocyte              |            |                            |       |       |       |       |
| Neutro<br>(%)                             | 11.1       | 23.1                       | 10.0  | 6.9   | 13.6  |       |
| Lymph<br>(%)                              | 82.0       | 70.1                       | 84.8  | 89.5  | 82.3  |       |
| Eosino<br>(%)                             | 0.7        | 0.9                        | 0.6   | 0.4   | 0.8   |       |
| Baso<br>(%)                               | 1.6        | 1.8                        | 0.8   | 0.6   | 0.3   |       |
| Mono<br>(%)                               | 2.9        | 2.7                        | 2.9   | 1.5   | 1.6   |       |
| LUC<br>(%)                                | 1.7        | 1.4                        | 0.9   | 1.0   | 1.3   |       |
| PT<br>(sec)                               | 20.5       | 14.4                       | 16.8  | 15.3  | 18.6  |       |
| APTT<br>(sec)                             | 20.3       | 17.2                       | 18.3  | 19.0  | 23.5  |       |

ss: scheduled sacrifice animal.

Appendix 9-5 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | One-day treatment |       |       |       |
|------------------------------|-------------------------------|-------------------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 200               |       |       |       |
| Items                        | Animal No.                    | 18 ss             | 19 ss | 20 ss | 21 ss |
| RBC                          | ( $\times 10^4/\mu\text{L}$ ) | 670               | 733   | 725   | 762   |
| Hb                           | (g/dL)                        | 14.0              | 15.7  | 15.7  | 15.1  |
| Ht                           | (%)                           | 45.6              | 49.5  | 50.0  | 49.0  |
| MCV                          | (fL)                          | 68.1              | 67.5  | 68.9  | 64.3  |
| MCH                          | (pg)                          | 20.9              | 21.4  | 21.7  | 19.8  |
| MCHC                         | (g/dL)                        | 30.7              | 31.7  | 31.5  | 30.9  |
| Platelet                     | ( $\times 10^4/\mu\text{L}$ ) | 141.8             | 134.7 | 116.5 | 169.5 |
| Reticulo                     | (%)                           | 11.6              | 12.1  | 12.6  | 11.3  |
| WBC                          | ( $\times 10^2/\mu\text{L}$ ) | 117.1             | 167.5 | 107.1 | 145.9 |
| Differentiation of leukocyte |                               |                   |       |       |       |
| Neutro                       | (%)                           | 11.1              | 7.2   | 10.5  | 9.6   |
| Lymph                        | (%)                           | 83.7              | 85.7  | 86.1  | 86.7  |
| Eosino                       | (%)                           | 0.3               | 0.4   | 0.6   | 0.3   |
| Baso                         | (%)                           | 0.8               | 1.6   | 0.5   | 0.6   |
| Mono                         | (%)                           | 2.8               | 4.2   | 1.2   | 2.2   |
| LUC                          | (%)                           | 1.3               | 0.9   | 1.0   | 0.7   |

ss: scheduled sacrifice animal.

Appendix 9-6 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | Seven-day treatment |       |       |       |
|------------------------------|-------------------------------|---------------------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 200                 |       |       |       |
| Items                        | Animal No.                    | 22 ss               | 23 ss | 24 ss | 25 ss |
| RBC                          | ( $\times 10^4/\mu\text{L}$ ) | 752                 | 728   | 742   | 749   |
| Hb                           | (g/dL)                        | 14.6                | 14.7  | 15.8  | 15.1  |
| Ht                           | (%)                           | 47.6                | 49.2  | 52.1  | 48.5  |
| MCV                          | (fL)                          | 63.2                | 67.5  | 70.2  | 64.8  |
| MCH                          | (pg)                          | 19.5                | 20.2  | 21.4  | 20.2  |
| MCHC                         | (g/dL)                        | 30.8                | 30.0  | 30.4  | 31.1  |
| Platelet                     | ( $\times 10^4/\mu\text{L}$ ) | 132.4               | 131.7 | 103.0 | 99.8  |
| Reticulo                     | (%)                           | 7.1                 | 9.6   | 10.0  | 7.4   |
| WBC                          | ( $\times 10^2/\mu\text{L}$ ) | 207.8               | 136.0 | 133.5 | 99.6  |
| Differentiation of leukocyte |                               |                     |       |       |       |
| Neutro                       | (%)                           | 14.9                | 12.6  | 12.4  | 14.4  |
| Lymph                        | (%)                           | 81.1                | 83.0  | 82.9  | 81.7  |
| Eosino                       | (%)                           | 0.2                 | 0.1   | 0.4   | 0.2   |
| Baso                         | (%)                           | 0.7                 | 1.2   | 0.7   | 0.5   |
| Mono                         | (%)                           | 1.5                 | 1.7   | 2.5   | 1.7   |
| LUC                          | (%)                           | 1.6                 | 1.3   | 1.0   | 1.3   |

ss: scheduled sacrifice animal.

Appendix 9-7 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | Fourteen-day treatment |       |       |       |
|------------------------------|-------------------------------|------------------------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 200                    |       |       |       |
| Items                        | Animal No.                    | 26 ss                  | 27 ss | 28 ss | 29 ss |
| RBC                          | ( $\times 10^4/\mu\text{L}$ ) | 694                    | 725   | 781   | 793   |
| Hb                           | (g/dL)                        | 14.5                   | 14.6  | 16.2  | 15.4  |
| Ht                           | (%)                           | 46.8                   | 47.2  | 52.0  | 51.1  |
| MCV                          | (fL)                          | 67.4                   | 65.0  | 66.5  | 64.5  |
| MCH                          | (pg)                          | 20.9                   | 20.1  | 20.7  | 19.5  |
| MCHC                         | (g/dL)                        | 31.0                   | 30.9  | 31.2  | 30.2  |
| Platelet                     | ( $\times 10^4/\mu\text{L}$ ) | 102.9                  | 101.4 | 122.7 | 128.4 |
| Reticulo                     | (%)                           | 4.4                    | 4.1   | 5.3   | 4.5   |
| WBC                          | ( $\times 10^2/\mu\text{L}$ ) | 128.1                  | 86.1  | 105.9 | 168.9 |
| Differentiation of leukocyte |                               |                        |       |       |       |
| Neutro                       | (%)                           | 7.7                    | 16.2  | 10.8  | 13.9  |
| Lymph                        | (%)                           | 87.0                   | 77.9  | 84.9  | 81.4  |
| Eosino                       | (%)                           | 0.4                    | 0.5   | 0.4   | 0.7   |
| Baso                         | (%)                           | 2.2                    | 1.4   | 0.7   | 1.0   |
| Mono                         | (%)                           | 1.4                    | 2.3   | 1.6   | 2.1   |
| LUC                          | (%)                           | 1.4                    | 1.7   | 1.5   | 0.9   |

ss: scheduled sacrifice animal.

Appendix 9-8 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | Twenty-eight-day treatment |       |       |       |       |
|------------------------------|-------------------------------|----------------------------|-------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 200                        |       |       |       |       |
| Items                        | Animal No.                    | 30 ss                      | 31 ss | 32 ss | 33 ss | 34 ss |
| RBC                          | ( $\times 10^4/\mu\text{L}$ ) | 794                        | 762   | 915   | 770   | 852   |
| Hb                           | (g/dL)                        | 15.6                       | 15.0  | 17.5  | 14.6  | 15.6  |
| Ht                           | (%)                           | 49.0                       | 48.1  | 56.2  | 46.1  | 50.3  |
| MCV                          | (fL)                          | 61.7                       | 63.2  | 61.5  | 59.9  | 59.0  |
| MCH                          | (pg)                          | 19.6                       | 19.6  | 19.1  | 19.0  | 18.3  |
| MCHC                         | (g/dL)                        | 31.8                       | 31.1  | 31.1  | 31.8  | 31.0  |
| Platelet                     | ( $\times 10^4/\mu\text{L}$ ) | 116.3                      | 106.3 | 76.4  | 117.3 | 111.6 |
| Reticulo                     | (%)                           | 2.7                        | 3.1   | 3.0   | 2.4   | 3.1   |
| WBC                          | ( $\times 10^2/\mu\text{L}$ ) | 102.2                      | 184.7 | 122.3 | 145.4 | 160.5 |
| Differentiation of leukocyte |                               |                            |       |       |       |       |
| Neutro                       | (%)                           | 22.1                       | 13.5  | 12.7  | 16.7  | 16.5  |
| Lymph                        | (%)                           | 73.1                       | 81.3  | 80.9  | 79.4  | 79.6  |
| Eosino                       | (%)                           | 0.4                        | 0.7   | 0.7   | 0.5   | 0.4   |
| Baso                         | (%)                           | 0.8                        | 1.0   | 1.2   | 0.4   | 1.3   |
| Mono                         | (%)                           | 2.3                        | 2.0   | 2.4   | 1.4   | 1.0   |
| LUC                          | (%)                           | 1.2                        | 1.5   | 2.1   | 1.6   | 1.0   |
| PT                           | (sec)                         | 22.8                       | 19.0  | 16.6  | 32.1  | 17.9  |
| APTT                         | (sec)                         | 27.6                       | 23.1  | 14.3  | 32.4  | 23.5  |

ss: scheduled sacrifice animal.

Appendix 9-9 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | One-day treatment |       |       |       |
|------------------------------|-------------------------------|-------------------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 1000              |       |       |       |
| Items                        | Animal No.                    | 35 ss             | 36 ss | 37 ss | 38 ss |
| RBC                          | ( $\times 10^4/\mu\text{L}$ ) | 697               | 715   | 721   | 668   |
| Hb                           | (g/dL)                        | 15.3              | 15.3  | 14.6  | 14.0  |
| Ht                           | (%)                           | 49.6              | 49.7  | 47.9  | 45.2  |
| MCV                          | (fL)                          | 71.1              | 69.5  | 66.4  | 67.7  |
| MCH                          | (pg)                          | 22.0              | 21.4  | 20.2  | 21.0  |
| MCHC                         | (g/dL)                        | 30.9              | 30.7  | 30.5  | 31.0  |
| Platelet                     | ( $\times 10^4/\mu\text{L}$ ) | 118.3             | 136.0 | 106.4 | 112.7 |
| Reticulo                     | (%)                           | 10.6              | 11.2  | 12.6  | 13.1  |
| WBC                          | ( $\times 10^2/\mu\text{L}$ ) | 143.0             | 117.2 | 126.3 | 135.1 |
| Differentiation of leukocyte |                               |                   |       |       |       |
| Neutro                       | (%)                           | 9.3               | 8.6   | 10.2  | 10.8  |
| Lymph                        | (%)                           | 86.7              | 85.8  | 85.3  | 84.3  |
| Eosino                       | (%)                           | 0.4               | 0.6   | 0.6   | 0.2   |
| Baso                         | (%)                           | 1.0               | 0.9   | 1.0   | 0.4   |
| Mono                         | (%)                           | 1.5               | 2.6   | 2.1   | 2.5   |
| LUC                          | (%)                           | 1.2               | 1.5   | 0.8   | 1.8   |

ss: scheduled sacrifice animal.

Appendix 9-10 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | Seven-day treatment |       |       |       |
|------------------------------|-------------------------------|---------------------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 1000                |       |       |       |
| Items                        | Animal No.                    | 39 ss               | 40 ss | 41 ss | 42 ss |
| RBC                          | ( $\times 10^4/\mu\text{L}$ ) | 769                 | 744   | 760   | 712   |
| Hb                           | (g/dL)                        | 15.2                | 15.3  | 16.1  | 14.3  |
| Ht                           | (%)                           | 50.1                | 48.9  | 53.0  | 47.4  |
| MCV                          | (fL)                          | 65.1                | 65.8  | 69.8  | 66.6  |
| MCH                          | (pg)                          | 19.7                | 20.5  | 21.2  | 20.1  |
| MCHC                         | (g/dL)                        | 30.3                | 31.2  | 30.4  | 30.2  |
| Platelet                     | ( $\times 10^4/\mu\text{L}$ ) | 110.1               | 125.0 | 112.3 | 131.6 |
| Reticulo                     | (%)                           | 7.7                 | 8.8   | 9.3   | 8.8   |
| WBC                          | ( $\times 10^3/\mu\text{L}$ ) | 120.7               | 132.0 | 88.6  | 147.9 |
| Differentiation of leukocyte |                               |                     |       |       |       |
| Neutro                       | (%)                           | 10.3                | 16.5  | 19.7  | 10.9  |
| Lymph                        | (%)                           | 86.4                | 79.6  | 74.1  | 86.0  |
| Eosino                       | (%)                           | 0.2                 | 0.3   | 0.3   | 0.2   |
| Baso                         | (%)                           | 0.6                 | 0.5   | 0.5   | 0.5   |
| Mono                         | (%)                           | 1.1                 | 1.3   | 2.8   | 1.8   |
| LUC                          | (%)                           | 1.3                 | 1.7   | 2.6   | 0.6   |

ss: scheduled sacrifice animal.

Appendix 9-11 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | Fourteen-day treatment |       |       |       |
|------------------------------|-------------------------------|------------------------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 1000                   |       |       |       |
| Items                        | Animal No.                    | 43 ss                  | 44 ss | 45 ss | 46 ss |
| RBC                          | ( $\times 10^4/\mu\text{L}$ ) | 779                    | 776   | 787   | 792   |
| Hb                           | (g/dL)                        | 15.1                   | 15.7  | 15.2  | 15.7  |
| Ht                           | (%)                           | 48.7                   | 51.2  | 49.4  | 50.8  |
| MCV                          | (fL)                          | 62.6                   | 65.9  | 62.8  | 64.2  |
| MCH                          | (pg)                          | 19.4                   | 20.2  | 19.3  | 19.8  |
| MCHC                         | (g/dL)                        | 30.9                   | 30.6  | 30.7  | 30.9  |
| Platelet                     | ( $\times 10^4/\mu\text{L}$ ) | 124.4                  | 127.2 | 144.4 | 138.4 |
| Reticulo                     | (%)                           | 3.9                    | 4.2   | 4.3   | 4.2   |
| WBC                          | ( $\times 10^2/\mu\text{L}$ ) | 124.5                  | 149.1 | 145.0 | 132.6 |
| Differentiation of leukocyte |                               |                        |       |       |       |
| Neutro                       | (%)                           | 11.5                   | 14.1  | 13.2  | 11.7  |
| Lymph                        | (%)                           | 83.2                   | 79.4  | 81.8  | 82.0  |
| Eosino                       | (%)                           | 0.6                    | 0.4   | 0.5   | 0.5   |
| Baso                         | (%)                           | 2.8                    | 2.5   | 1.4   | 1.1   |
| Mono                         | (%)                           | 1.3                    | 2.5   | 1.5   | 2.4   |
| LUC                          | (%)                           | 0.7                    | 1.0   | 1.5   | 2.2   |

ss: scheduled sacrifice animal.

Appendix 9-12 Twenty-eight-day repeated-dose oral toxicity study in rats  
Hematological data of individual animals:Male

| Group                        |                               | Twenty-eight-day treatment |       |       |       |       |
|------------------------------|-------------------------------|----------------------------|-------|-------|-------|-------|
| Dose(mg/kg/day)              |                               | 1000                       |       |       |       |       |
| Items                        | Animal No.                    | 47 ss                      | 48 ss | 49 ss | 50 ss | 51 ss |
| RBC                          | ( $\times 10^4/\mu\text{L}$ ) | 838                        | 820   | 760   | 729   | 754   |
| Hb                           | (g/dL)                        | 17.1                       | 15.7  | 15.2  | 14.9  | 14.8  |
| Ht                           | (%)                           | 55.5                       | 50.0  | 47.8  | 47.3  | 47.3  |
| MCV                          | (fL)                          | 66.3                       | 61.0  | 62.8  | 64.9  | 62.8  |
| MCH                          | (pg)                          | 20.4                       | 19.2  | 20.0  | 20.5  | 19.6  |
| MCHC                         | (g/dL)                        | 30.8                       | 31.4  | 31.7  | 31.6  | 31.2  |
| Platelet                     | ( $\times 10^3/\mu\text{L}$ ) | 115.4                      | 96.5  | 119.2 | 102.1 | 7.7   |
| Reticulo                     | (%)                           | 3.5                        | 2.9   | 2.7   | 3.3   | 3.0   |
| WBC                          | ( $\times 10^3/\mu\text{L}$ ) | 118.0                      | 104.1 | 111.0 | 90.0  | 95.4  |
| Differentiation of leukocyte |                               |                            |       |       |       |       |
| Neutro                       | (%)                           | 19.4                       | 22.1  | 29.1  | 18.3  | 10.4  |
| Lymph                        | (%)                           | 74.2                       | 72.6  | 67.4  | 78.3  | 86.3  |
| Eosino                       | (%)                           | 0.6                        | 0.5   | 0.6   | 0.3   | 0.2   |
| Baso                         | (%)                           | 2.3                        | 0.9   | 0.2   | 0.3   | 0.3   |
| Mono                         | (%)                           | 2.4                        | 2.4   | 1.1   | 1.8   | 1.6   |
| LUC                          | (%)                           | 1.1                        | 1.5   | 1.5   | 1.1   | 1.2   |
| PT                           | (sec)                         | 24.4                       | 15.5  | 15.7  | 20.5  | 22.0  |
| APTT                         | (sec)                         | 27.8                       | 21.9  | 23.3  | 24.8  | 27.4  |

ss: scheduled sacrifice animal.

Appendix 10-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Blood chemical data of individual animals:Male

| Group           |            | One-day treatment |      |      |      |
|-----------------|------------|-------------------|------|------|------|
| Dose(mg/kg/day) |            | 0                 |      |      |      |
| Items           | Animal No. | 1 ss              | 2 ss | 3 ss | 4 ss |
| AST             | (IU/L)     | 86                | 75   | 79   | 92   |
| ALT             | (IU/L)     | 26                | 23   | 25   | 32   |
| ALP             | (IU/L)     | 842               | 947  | 848  | 767  |
| BUN             | (mg/dL)    | 12.4              | 13.8 | 8.8  | 11.1 |
| Creatinine      | (mg/dL)    | 0.12              | 0.16 | 0.12 | 0.11 |
| T-Bil           | (mg/dL)    | 0.10              | 0.08 | 0.07 | 0.07 |

ss: scheduled sacrifice animal.

Appendix 10-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Blood chemical data of individual animals:Male

| Group           |            | Seven-day treatment |      |      |      |
|-----------------|------------|---------------------|------|------|------|
| Dose(mg/kg/day) |            | 0                   |      |      |      |
| Items           | Animal No. | 5 ss                | 6 ss | 7 ss | 8 ss |
| AST             | (IU/L)     | 84                  | 82   | 87   | 80   |
| ALT             | (IU/L)     | 29                  | 30   | 31   | 21   |
| ALP             | (IU/L)     | 869                 | 956  | 712  | 798  |
| BUN             | (mg/dL)    | 10.2                | 12.9 | 11.4 | 9.8  |
| Creatinine      | (mg/dL)    | 0.12                | 0.14 | 0.14 | 0.13 |
| T-Bil           | (mg/dL)    | 0.08                | 0.08 | 0.06 | 0.06 |

ss: scheduled sacrifice animal.

Appendix 10-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Blood chemical data of individual animals:Male

| Group           |            | Fourteen-day treatment |       |       |       |
|-----------------|------------|------------------------|-------|-------|-------|
| Dose(mg/kg/day) |            | 0                      |       |       |       |
| Items           | Animal No. | 9 ss                   | 10 ss | 11 ss | 12 ss |
| AST             | (IU/L)     | 109                    | 77    | 64    | 70    |
| ALT             | (IU/L)     | 49                     | 27    | 17    | 21    |
| ALP             | (IU/L)     | 565                    | 651   | 655   | 1126  |
| BUN             | (mg/dL)    | 12.1                   | 8.5   | 9.3   | 10.1  |
| Creatinine      | (mg/dL)    | 0.15                   | 0.17  | 0.17  | 0.17  |
| T-Bil           | (mg/dL)    | 0.04                   | 0.06  | 0.03  | 0.04  |

ss: scheduled sacrifice animal.

Appendix 10-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Blood chemical data of individual animals:Male

| Group              |            | Twenty-eight-day treatment |       |       |       |       |
|--------------------|------------|----------------------------|-------|-------|-------|-------|
| Dose(mg/kg/day)    |            | 0                          |       |       |       |       |
| Items              | Animal No. | 13 ss                      | 14 ss | 15 ss | 16 ss | 17 ss |
| AST (IU/L)         |            | 66                         | 67    | 62    | 53    | 53    |
| ALT (IU/L)         |            | 23                         | 27    | 18    | 20    | 19    |
| ALP (IU/L)         |            | 759                        | 748   | 533   | 524   | 366   |
| ChE (IU/L)         |            | 84                         | 54    | 94    | 40    | 37    |
| γ-GTP (IU/L)       |            | 0.7                        | 0.4   | 0.2   | 0.8   | 0.2   |
| T-Chol (mg/dL)     |            | 67                         | 77    | 59    | 46    | 47    |
| TG (mg/dL)         |            | 87                         | 64    | 52    | 50    | 47    |
| BUN (mg/dL)        |            | 12.3                       | 13.4  | 13.8  | 10.3  | 12.6  |
| Creatinine (mg/dL) |            | 0.25                       | 0.26  | 0.24  | 0.17  | 0.18  |
| T-Protein (g/dL)   |            | 6.3                        | 6.2   | 6.3   | 4.9   | 4.4   |
| Albumin (g/dL)     |            | 2.9                        | 2.9   | 2.9   | 2.3   | 2.2   |
| A/G ratio (-)      |            | 0.85                       | 0.88  | 0.85  | 0.88  | 1.00  |
| Glucose (mg/dL)    |            | 183                        | 199   | 168   | 128   | 171   |
| T-Bil (mg/dL)      |            | 0.06                       | 0.06  | 0.05  | 0.05  | 0.05  |
| TBA (μmol/L)       |            | 30.3                       | 20.7  | 18.9  | 10.7  | 20.0  |
| IP (mg/dL)         |            | 11.5                       | 12.4  | 10.9  | 10.4  | 9.7   |
| Ca (mg/dL)         |            | 11.8                       | 12.0  | 11.5  | 10.3  | 9.3   |
| Na (mEq/L)         |            | 148                        | 148   | 146   | 144   | 147   |
| K (mEq/L)          |            | 6.4                        | 7.0   | 6.8   | 7.6   | 5.9   |
| Cl (mEq/L)         |            | 100.9                      | 104.0 | 99.8  | 100.9 | 101.9 |

ss: scheduled sacrifice animal.

Appendix 10-5 Twenty-eight-day repeated-dose oral toxicity study in rats  
Blood chemical data of individual animals:Male

| Group           |            | One-day treatment |       |       |       |
|-----------------|------------|-------------------|-------|-------|-------|
| Dose(mg/kg/day) |            | 200               |       |       |       |
| Items           | Animal No. | 18 ss             | 19 ss | 20 ss | 21 ss |
| AST             | (IU/L)     | 88                | 80    | 83    | 78    |
| ALT             | (IU/L)     | 35                | 31    | 30    | 26    |
| ALP             | (IU/L)     | 975               | 787   | 883   | 1040  |
| BUN             | (mg/dL)    | 12.9              | 13.9  | 12.7  | 12.4  |
| Creatinine      | (mg/dL)    | 0.14              | 0.12  | 0.12  | 0.13  |
| T-Bil           | (mg/dL)    | 0.07              | 0.06  | 0.07  | 0.07  |

ss: scheduled sacrifice animal.

Appendix 10-6 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Blood chemical data of individual animals:Male

| Group           |            | Seven-day treatment |       |       |       |
|-----------------|------------|---------------------|-------|-------|-------|
| Dose(mg/kg/day) |            | 200                 |       |       |       |
| Items           | Animal No. | 22 ss               | 23 ss | 24 ss | 25 ss |
| AST             | (IU/L)     | 79                  | 88    | 86    | 71    |
| ALT             | (IU/L)     | 34                  | 36    | 35    | 27    |
| ALP             | (IU/L)     | 867                 | 869   | 915   | 839   |
| BUN             | (mg/dL)    | 11.2                | 12.4  | 10.8  | 10.0  |
| Creatinine      | (mg/dL)    | 0.14                | 0.16  | 0.13  | 0.15  |
| T-Bil           | (mg/dL)    | 0.06                | 0.05  | 0.07  | 0.06  |

ss: scheduled sacrifice animal.

Appendix 10-7 Twenty-eight-day repeated-dose oral toxicity study in rats  
Blood chemical data of individual animals:Male

| Group           |            | Fourteen-day treatment |       |       |       |
|-----------------|------------|------------------------|-------|-------|-------|
| Dose(mg/kg/day) |            | 200                    |       |       |       |
| Items           | Animal No. | 26 ss                  | 27 ss | 28 ss | 29 ss |
| AST             | (IU/L)     | 82                     | 66    | 62    | 69    |
| ALT             | (IU/L)     | 30                     | 20    | 24    | 23    |
| ALP             | (IU/L)     | 858                    | 494   | 555   | 786   |
| BUN             | (mg/dL)    | 14.2                   | 9.2   | 8.7   | 11.8  |
| Creatinine      | (mg/dL)    | 0.18                   | 0.17  | 0.14  | 0.14  |
| T-Bil           | (mg/dL)    | 0.04                   | 0.03  | 0.02  | 0.06  |

ss: scheduled sacrifice animal.

Appendix 10-8 Twenty-eight-day repeated-dose oral toxicity study in rats  
Blood chemical data of individual animals:Male

| Group              |            | Twenty-eight-day treatment |       |       |       |       |
|--------------------|------------|----------------------------|-------|-------|-------|-------|
| Dose(mg/kg/day)    |            | 200                        |       |       |       |       |
| Items              | Animal No. | 30 ss                      | 31 ss | 32 ss | 33 ss | 34 ss |
| AST (IU/L)         |            | 59                         | 41    | 67    | 54    | 65    |
| ALT (IU/L)         |            | 29                         | 16    | 20    | 22    | 26    |
| ALP (IU/L)         |            | 406                        | 456   | 591   | 413   | 603   |
| ChE (IU/L)         |            | 63                         | 28    | 76    | 54    | 80    |
| γ-GTP (IU/L)       |            | 0.4                        | 0.2   | 0.5   | 0.4   | 0.5   |
| T-Chol (mg/dL)     |            | 61                         | 55    | 75    | 57    | 92    |
| TG (mg/dL)         |            | 41                         | 45    | 89    | 34    | 61    |
| BUN (mg/dL)        |            | 15.0                       | 14.1  | 10.2  | 10.8  | 11.0  |
| Creatinine (mg/dL) |            | 0.24                       | 0.21  | 0.20  | 0.22  | 0.22  |
| T-Protein (g/dL)   |            | 6.5                        | 4.5   | 6.4   | 6.4   | 7.1   |
| Albumin (g/dL)     |            | 2.9                        | 2.1   | 3.0   | 3.0   | 3.2   |
| A/G ratio (-)      |            | 0.81                       | 0.88  | 0.88  | 0.88  | 0.82  |
| Glucose (mg/dL)    |            | 128                        | 90    | 160   | 180   | 204   |
| T-Bil (mg/dL)      |            | 0.06                       | 0.07  | 0.06  | 0.04  | 0.04  |
| TBA (μmol/L)       |            | 20.1                       | 21.8  | 18.2  | 6.0   | 10.5  |
| IP (mg/dL)         |            | 11.2                       | 9.7   | 12.6  | 11.9  | 12.3  |
| Ca (mg/dL)         |            | 12.0                       | 9.2   | 12.2  | 12.5  | 12.7  |
| Na (mEq/L)         |            | 147                        | 147   | 145   | 146   | 145   |
| K (mEq/L)          |            | 6.7                        | 6.9   | 6.9   | 6.8   | 7.0   |
| Cl (mEq/L)         |            | 99.4                       | 101.4 | 100.6 | 98.8  | 98.9  |

ss: scheduled sacrifice animal.

Appendix 10-9 Twenty-eight-day repeated-dose oral toxicity study in rats  
Blood chemical data of individual animals:Male

| Group           |            | One-day treatment |       |       |       |
|-----------------|------------|-------------------|-------|-------|-------|
| Dose(mg/kg/day) |            | 1000              |       |       |       |
| Items           | Animal No. | 35 ss             | 36 ss | 37 ss | 38 ss |
| AST             | (IU/L)     | 87                | 96    | 94    | 85    |
| ALT             | (IU/L)     | 25                | 42    | 33    | 38    |
| ALP             | (IU/L)     | 1042              | 1058  | 1016  | 759   |
| BUN             | (mg/dL)    | 12.4              | 11.7  | 13.6  | 11.2  |
| Creatinine      | (mg/dL)    | 0.13              | 0.12  | 0.12  | 0.14  |
| T-Bil           | (mg/dL)    | 0.10              | 0.07  | 0.06  | 0.06  |

ss: scheduled sacrifice animal.

Appendix 10-10 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Blood chemical data of individual animals:Male

| Group           |            | Seven-day treatment |       |       |       |
|-----------------|------------|---------------------|-------|-------|-------|
| Dose(mg/kg/day) |            | 1000                |       |       |       |
| Items           | Animal No. | 39 ss               | 40 ss | 41 ss | 42 ss |
| AST             | (IU/L)     | 93                  | 89    | 84    | 79    |
| ALT             | (IU/L)     | 32                  | 37    | 34    | 31    |
| ALP             | (IU/L)     | 640                 | 782   | 646   | 927   |
| BUN             | (mg/dL)    | 9.4                 | 13.7  | 9.9   | 12.6  |
| Creatinine      | (mg/dL)    | 0.13                | 0.15  | 0.14  | 0.15  |
| T-Bil           | (mg/dL)    | 0.05                | 0.08  | 0.06  | 0.05  |

ss: scheduled sacrifice animal.

Appendix 10-11 Twenty-eight-day repeated-dose oral toxicity study in rats  
Blood chemical data of individual animals:Male

| Group           |            | Fourteen-day treatment |       |       |       |
|-----------------|------------|------------------------|-------|-------|-------|
| Dose(mg/kg/day) |            | 1000                   |       |       |       |
| Items           | Animal No. | 43 ss                  | 44 ss | 45 ss | 46 ss |
| AST             | (IU/L)     | 79                     | 76    | 71    | 64    |
| ALT             | (IU/L)     | 32                     | 25    | 26    | 20    |
| ALP             | (IU/L)     | 691                    | 798   | 475   | 843   |
| BUN             | (mg/dL)    | 11.3                   | 15.0  | 11.4  | 10.6  |
| Creatinine      | (mg/dL)    | 0.18                   | 0.19  | 0.14  | 0.16  |
| T-Bil           | (mg/dL)    | 0.03                   | 0.06  | 0.02  | 0.03  |

ss: scheduled sacrifice animal.

Appendix 10-12 Twenty-eight-day repeated-dose oral toxicity study in rats  
Blood chemical data of individual animals:Male

| Group           |            | Twenty-eight-day treatment |       |       |       |       |
|-----------------|------------|----------------------------|-------|-------|-------|-------|
| Dose(mg/kg/day) |            | 1000                       |       |       |       |       |
| Items           | Animal No. | 47 ss                      | 48 ss | 49 ss | 50 ss | 51 ss |
| AST             | (IU/L)     | 46                         | 58    | 55    | 44    | 53    |
| ALT             | (IU/L)     | 18                         | 25    | 25    | 18    | 20    |
| ALP             | (IU/L)     | 492                        | 461   | 660   | 308   | 358   |
| ChE             | (IU/L)     | 50                         | 40    | 52    | 39    | 51    |
| γ-GTP           | (IU/L)     | 0.4                        | 0.6   | 0.3   | 0.7   | 0.3   |
| T-Chol          | (mg/dL)    | 60                         | 73    | 58    | 40    | 69    |
| TG              | (mg/dL)    | 54                         | 53    | 107   | 44    | 44    |
| BUN             | (mg/dL)    | 11.4                       | 14.7  | 10.1  | 9.1   | 11.0  |
| Creatinine      | (mg/dL)    | 0.22                       | 0.23  | 0.20  | 0.17  | 0.17  |
| T-Protein       | (g/dL)     | 5.0                        | 6.2   | 6.0   | 4.7   | 5.3   |
| Albumin         | (g/dL)     | 2.3                        | 2.9   | 2.9   | 2.3   | 2.4   |
| A/G ratio       | (-)        | 0.85                       | 0.88  | 0.94  | 0.96  | 0.83  |
| Glucose         | (mg/dL)    | 193                        | 185   | 175   | 89    | 126   |
| T-Bil           | (mg/dL)    | 0.06                       | 0.05  | 0.03  | 0.05  | 0.06  |
| TBA             | (μmol/L)   | 7.7                        | 11.5  | 9.6   | 11.0  | 5.8   |
| IP              | (mg/dL)    | 11.8                       | 12.4  | 11.5  | 10.5  | 9.3   |
| Ca              | (mg/dL)    | 10.7                       | 11.7  | 11.2  | 10.0  | 10.0  |
| Na              | (mEq/L)    | 145                        | 144   | 146   | 147   | 146   |
| K               | (mEq/L)    | 7.8                        | 7.3   | 5.9   | 7.3   | 5.4   |
| Cl              | (mEq/L)    | 101.1                      | 98.9  | 101.1 | 99.0  | 101.4 |

ss: scheduled sacrifice animal.

Appendix 11-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Absolute organ weights of individual animals:Male

| Group                 |             | One-day treatment |       |       |       |
|-----------------------|-------------|-------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 0                 |       |       |       |
| Items                 | Animal No.  | 1 ss              | 2 ss  | 3 ss  | 4 ss  |
| Liver                 | (g)         | 4.31              | 4.33  | 4.83  | 4.57  |
| Heart                 | (g)         | 0.63              | 0.64  | 0.71  | 0.67  |
| Kidney(R)             | (g)         | 0.64              | 0.58  | 0.71  | 0.69  |
| Kidney(L)             | (g)         | 0.61              | 0.56  | 0.66  | 0.70  |
| Testis(R)             | (g)         | 0.61              | 0.59  | 0.74  | 0.78  |
| Testis(L)             | (g)         | 0.58              | 0.60  | 0.72  | 0.75  |
| Epididymis(R)         | (g)         | 0.06              | 0.06  | 0.08  | 0.08  |
| Epididymis(L)         | (g)         | 0.06              | 0.07  | 0.08  | 0.07  |
| Ventral prostate      | (g)         | 0.06              | 0.06  | 0.07  | 0.07  |
| Dorsolateral prostate | (g)         | 0.05              | 0.10  | 0.06  | 0.09  |
| Brain                 | (g)         | 1.86              | 1.74  | 1.75  | 1.79  |
| Spleen                | (g)         | 0.31              | 0.43  | 0.40  | 0.39  |
| Thymus                | (mg)        | 488.5             | 438.7 | 474.2 | 486.5 |
| Pituitary gland       | (mg)        | 5.7               | 4.5   | 5.5   | 5.7   |
| Thyroid               | (mg)        | 8.3               | 8.7   | 7.8   | 6.3   |
| Adrenals              | (mg)        | 29.2              | 34.6  | 39.1  | 35.8  |
| Final body weight     | (g)         | 124.8             | 129.5 | 138.3 | 137.2 |

ss: scheduled sacrifice animal.

Appendix 11-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Absolute organ weights of individual animals:Male

| Group                 |             | Seven-day treatment |       |       |       |
|-----------------------|-------------|---------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 0                   |       |       |       |
| Items                 | Animal No.  | 5 ss                | 6 ss  | 7 ss  | 8 ss  |
| Liver                 | (g)         | 6.37                | 6.26  | 6.53  | 6.33  |
| Heart                 | (g)         | 0.87                | 0.81  | 0.81  | 0.85  |
| Kidney(R)             | (g)         | 0.89                | 0.82  | 0.89  | 0.83  |
| Kidney(L)             | (g)         | 0.88                | 0.75  | 0.87  | 0.82  |
| Testis(R)             | (g)         | 0.86                | 1.01  | 0.91  | 0.86  |
| Testis(L)             | (g)         | 0.80                | 0.99  | 0.94  | 0.84  |
| Epididymis(R)         | (g)         | 0.11                | 0.14  | 0.12  | 0.11  |
| Epididymis(L)         | (g)         | 0.10                | 0.14  | 0.12  | 0.10  |
| Ventral prostate      | (g)         | 0.11                | 0.13  | 0.11  | 0.11  |
| Dorsolateral prostate | (g)         | 0.06                | 0.14  | 0.12  | 0.08  |
| Brain                 | (g)         | 1.80                | 1.84  | 1.82  | 1.79  |
| Spleen                | (g)         | 0.58                | 0.51  | 0.53  | 0.46  |
| Thymus                | (mg)        | 591.6               | 474.0 | 535.1 | 465.8 |
| Pituitary gland       | (mg)        | 7.6                 | 6.1   | 6.5   | 5.9   |
| Thyroid               | (mg)        | 11.9                | 10.5  | 11.9  | 13.1  |
| Adrenals              | (mg)        | 61.1                | 40.7  | 43.0  | 36.6  |
| Final body weight     | (g)         | 178.9               | 172.9 | 182.8 | 174.5 |

ss: scheduled sacrifice animal.

Appendix 11-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Absolute organ weights of individual animals:Male

| Group                 |             | Fourteen-day treatment |       |       |       |
|-----------------------|-------------|------------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 0                      |       |       |       |
| Items                 | Animal No.  | 9 ss                   | 10 ss | 11 ss | 12 ss |
| Liver                 | (g)         | 8.10                   | 8.27  | 8.90  | 9.56  |
| Heart                 | (g)         | 0.99                   | 0.95  | 1.02  | 1.14  |
| Kidney(R)             | (g)         | 0.92                   | 0.98  | 1.03  | 1.11  |
| Kidney(L)             | (g)         | 0.96                   | 0.98  | 1.01  | 1.06  |
| Testis(R)             | (g)         | 1.28                   | 1.23  | 1.34  | 1.29  |
| Testis(L)             | (g)         | 1.26                   | 1.22  | 1.34  | 1.30  |
| Epididymis(R)         | (g)         | 0.17                   | 0.16  | 0.19  | 0.23  |
| Epididymis(L)         | (g)         | 0.17                   | 0.17  | 0.19  | 0.20  |
| Ventral prostate      | (g)         | 0.18                   | 0.23  | 0.26  | 0.29  |
| Dorsolateral prostate | (g)         | 0.18                   | 0.20  | 0.20  | 0.20  |
| Brain                 | (g)         | 1.88                   | 1.82  | 1.90  | 1.94  |
| Spleen                | (g)         | 0.51                   | 0.62  | 0.70  | 0.78  |
| Thymus                | (mg)        | 515.6                  | 715.8 | 614.2 | 526.5 |
| Pituitary gland       | (mg)        | 8.0                    | 7.3   | 7.9   | 8.5   |
| Thyroid               | (mg)        | 26.4                   | 15.5  | 18.4  | 17.9  |
| Adrenals              | (mg)        | 44.3                   | 34.9  | 48.1  | 47.3  |
| Final body weight     | (g)         | 214.5                  | 232.1 | 242.5 | 264.3 |

ss: scheduled sacrifice animal.

Appendix 11-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Absolute organ weights of individual animals:Male

| Group                 |             | Twenty-eight-day treatment |       |       |       |       |
|-----------------------|-------------|----------------------------|-------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 0                          |       |       |       |       |
| Items                 | Animal No.  | 13 ss                      | 14 ss | 15 ss | 16 ss | 17 ss |
| Liver                 | (g)         | 11.62                      | 12.09 | 13.17 | 11.85 | 12.02 |
| Heart                 | (g)         | 1.43                       | 1.35  | 1.42  | 1.34  | 1.30  |
| Kidney(R)             | (g)         | 1.38                       | 1.28  | 1.32  | 1.46  | 1.47  |
| Kidney(L)             | (g)         | 1.33                       | 1.29  | 1.35  | 1.37  | 1.41  |
| Testis(R)             | (g)         | 1.54                       | 1.73  | 1.65  | 1.43  | 1.49  |
| Testis(L)             | (g)         | 1.54                       | 1.75  | 1.61  | 1.43  | 1.52  |
| Epididymis(R)         | (g)         | 0.37                       | 0.36  | 0.34  | 0.35  | 0.35  |
| Epididymis(L)         | (g)         | 0.36                       | 0.34  | 0.32  | 0.36  | 0.34  |
| Ventral prostate      | (g)         | 0.44                       | 0.22  | 0.51  | 0.44  | 0.45  |
| Dorsolateral prostate | (g)         | 0.38                       | 0.22  | 0.33  | 0.31  | 0.35  |
| Seminal vesicle       | (g)         | 0.96                       | 0.73  | 1.09  | 0.86  | 1.01  |
| Brain                 | (g)         | 2.08                       | 1.99  | 1.98  | 2.10  | 1.83  |
| Spleen                | (g)         | 0.77                       | 0.72  | 0.73  | 0.71  | 0.68  |
| Thymus                | (mg)        | 564.1                      | 556.3 | 558.0 | 622.7 | 458.9 |
| Pituitary gland       | (mg)        | 10.0                       | 12.1  | 12.5  | 11.3  | 12.0  |
| Thyroid               | (mg)        | 14.0                       | 15.0  | 11.6  | 15.6  | 18.3  |
| Adrenals              | (mg)        | 58.0                       | 50.2  | 51.0  | 60.0  | 58.1  |
| Final body weight     | (g)         | 365.1                      | 356.6 | 386.5 | 365.3 | 362.7 |

ss: scheduled sacrifice animal.

Appendix 11-5 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Absolute organ weights of individual animals:Male

| Group                 |             | One-day treatment |       |       |       |
|-----------------------|-------------|-------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 200               |       |       |       |
| Items                 | Animal No.  | 18 ss             | 19 ss | 20 ss | 21 ss |
| Liver                 | (g)         | 4.51              | 4.69  | 4.86  | 4.84  |
| Heart                 | (g)         | 0.64              | 0.61  | 0.72  | 0.65  |
| Kidney(R)             | (g)         | 0.70              | 0.63  | 0.66  | 0.66  |
| Kidney(L)             | (g)         | 0.67              | 0.64  | 0.67  | 0.63  |
| Testis(R)             | (g)         | 0.71              | 0.77  | 0.58  | 0.70  |
| Testis(L)             | (g)         | 0.69              | 0.77  | 0.60  | 0.67  |
| Epididymis(R)         | (g)         | 0.08              | 0.08  | 0.07  | 0.08  |
| Epididymis(L)         | (g)         | 0.07              | 0.09  | 0.07  | 0.08  |
| Ventral prostate      | (g)         | 0.08              | 0.02  | 0.07  | 0.06  |
| Dorsolateral prostate | (g)         | 0.06              | 0.11  | 0.05  | 0.08  |
| Brain                 | (g)         | 1.76              | 1.91  | 1.74  | 1.75  |
| Spleen                | (g)         | 0.45              | 0.34  | 0.37  | 0.35  |
| Thymus                | (mg)        | 441.9             | 516.7 | 373.8 | 382.6 |
| Pituitary gland       | (mg)        | 5.9               | 5.5   | 5.2   | 6.0   |
| Thyroid               | (mg)        | 7.2               | 7.4   | 9.8   | 9.5   |
| Adrenals              | (mg)        | 30.2              | 35.5  | 29.1  | 31.5  |
| Final body weight     | (g)         | 127.2             | 128.3 | 134.8 | 136.0 |

ss: scheduled sacrifice animal.

Appendix 11-6 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Absolute organ weights of individual animals:Male

| Group                 |             | Seven-day treatment |       |       |       |
|-----------------------|-------------|---------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 200                 |       |       |       |
| Items                 | Animal No.  | 22 ss               | 23 ss | 24 ss | 25 ss |
| Liver                 | (g)         | 6.90                | 5.98  | 7.79  | 6.72  |
| Heart                 | (g)         | 0.78                | 0.77  | 0.95  | 0.75  |
| Kidney(R)             | (g)         | 0.75                | 0.74  | 0.97  | 0.81  |
| Kidney(L)             | (g)         | 0.72                | 0.70  | 0.93  | 0.87  |
| Testis(R)             | (g)         | 0.96                | 1.11  | 0.90  | 1.06  |
| Testis(L)             | (g)         | 0.93                | 1.10  | 0.86  | 1.06  |
| Epididymis(R)         | (g)         | 0.10                | 0.10  | 0.12  | 0.12  |
| Epididymis(L)         | (g)         | 0.11                | 0.10  | 0.12  | 0.12  |
| Ventral prostate      | (g)         | 0.10                | 0.11  | 0.12  | 0.14  |
| Dorsolateral prostate | (g)         | 0.09                | 0.12  | 0.08  | 0.14  |
| Brain                 | (g)         | 1.81                | 1.92  | 1.80  | 1.93  |
| Spleen                | (g)         | 0.47                | 0.35  | 0.59  | 0.46  |
| Thymus                | (mg)        | 328.1               | 373.2 | 528.2 | 510.4 |
| Pituitary gland       | (mg)        | 6.8                 | 6.2   | 7.2   | 7.7   |
| Thyroid               | (mg)        | 7.9                 | 11.5  | 11.6  | 9.6   |
| Adrenals              | (mg)        | 38.1                | 38.0  | 38.5  | 37.2  |
| Final body weight     | (g)         | 167.8               | 170.8 | 191.4 | 180.9 |

ss: scheduled sacrifice animal.

Appendix 11-7 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Absolute organ weights of individual animals:Male

| Group                 |             | Fourteen-day treatment |       |       |       |
|-----------------------|-------------|------------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 200                    |       |       |       |
| Items                 | Animal No.  | 26 ss                  | 27 ss | 28 ss | 29 ss |
| Liver                 | (g)         | 9.02                   | 8.51  | 10.58 | 8.78  |
| Heart                 | (g)         | 1.08                   | 0.99  | 1.08  | 0.95  |
| Kidney(R)             | (g)         | 0.99                   | 0.99  | 1.12  | 0.95  |
| Kidney(L)             | (g)         | 0.98                   | 0.96  | 1.11  | 0.96  |
| Testis(R)             | (g)         | 1.23                   | 1.37  | 1.35  | 1.40  |
| Testis(L)             | (g)         | 1.20                   | 1.37  | 1.28  | 1.40  |
| Epididymis(R)         | (g)         | 0.16                   | 0.22  | 0.18  | 0.19  |
| Epididymis(L)         | (g)         | 0.17                   | 0.18  | 0.16  | 0.17  |
| Ventral prostate      | (g)         | 0.22                   | 0.25  | 0.22  | 0.23  |
| Dorsolateral prostate | (g)         | 0.19                   | 0.20  | 0.18  | 0.22  |
| Brain                 | (g)         | 1.93                   | 1.80  | 1.95  | 1.90  |
| Spleen                | (g)         | 0.63                   | 0.60  | 0.70  | 0.55  |
| Thymus                | (mg)        | 790.6                  | 574.6 | 496.0 | 537.0 |
| Pituitary gland       | (mg)        | 8.3                    | 7.5   | 9.0   | 7.5   |
| Thyroid               | (mg)        | 19.9                   | 17.9  | 23.8  | 19.1  |
| Adrenals              | (mg)        | 40.3                   | 44.8  | 49.6  | 40.4  |
| Final body weight     | (g)         | 241.2                  | 243.3 | 250.9 | 234.6 |

ss: scheduled sacrifice animal.

Appendix 11-8 Twenty-eight-day repeated-dose oral toxicity study in rats  
Absolute organ weights of individual animals:Male

| Group                 |             | Twenty-eight-day treatment |       |       |       |       |
|-----------------------|-------------|----------------------------|-------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 200                        |       |       |       |       |
| Items                 | Animal No.  | 30 ss                      | 31 ss | 32 ss | 33 ss | 34 ss |
| Liver                 | (g)         | 11.44                      | 10.58 | 10.46 | 13.09 | 13.29 |
| Heart                 | (g)         | 1.12                       | 1.22  | 1.17  | 1.25  | 1.18  |
| Kidney(R)             | (g)         | 1.16                       | 1.25  | 1.30  | 1.31  | 1.24  |
| Kidney(L)             | (g)         | 1.19                       | 1.21  | 1.25  | 1.38  | 1.16  |
| Testis(R)             | (g)         | 1.47                       | 1.57  | 1.54  | 1.49  | 1.62  |
| Testis(L)             | (g)         | 1.46                       | 1.55  | 1.55  | 1.50  | 1.60  |
| Epididymis(R)         | (g)         | 0.34                       | 0.39  | 0.35  | 0.35  | 0.35  |
| Epididymis(L)         | (g)         | 0.34                       | 0.40  | 0.36  | 0.37  | 0.37  |
| Ventral prostate      | (g)         | 0.25                       | 0.40  | 0.36  | 0.46  | 0.32  |
| Dorsolateral prostate | (g)         | 0.24                       | 0.28  | 0.34  | 0.30  | 0.32  |
| Seminal vesicle       | (g)         | 0.71                       | 0.85  | 0.86  | 1.04  | 0.82  |
| Brain                 | (g)         | 1.97                       | 2.09  | 2.02  | 1.99  | 1.97  |
| Spleen                | (g)         | 0.61                       | 0.78  | 0.83  | 0.88  | 0.76  |
| Thymus                | (mg)        | 470.4                      | 598.9 | 535.1 | 604.7 | 555.2 |
| Pituitary gland       | (mg)        | 10.6                       | 12.4  | 10.2  | 12.9  | 10.3  |
| Thyroid               | (mg)        | 11.5                       | 18.6  | 17.4  | 17.9  | 15.2  |
| Adrenals              | (mg)        | 32.8                       | 53.7  | 45.3  | 61.0  | 58.1  |
| Final body weight     | (g)         | 321.8                      | 327.6 | 348.2 | 334.9 | 346.7 |

ss: scheduled sacrifice animal.

Appendix 11-9 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Absolute organ weights of individual animals:Male

| Group                 |             | One-day treatment |       |       |       |
|-----------------------|-------------|-------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 1000              |       |       |       |
| Items                 | Animal No.  | 35 ss             | 36 ss | 37 ss | 38 ss |
| Liver                 | (g)         | 4.68              | 4.57  | 5.25  | 5.20  |
| Heart                 | (g)         | 0.60              | 0.66  | 0.62  | 0.68  |
| Kidney(R)             | (g)         | 0.69              | 0.66  | 0.80  | 0.73  |
| Kidney(L)             | (g)         | 0.66              | 0.67  | 0.75  | 0.73  |
| Testis(R)             | (g)         | 0.68              | 0.79  | 0.81  | 0.83  |
| Testis(L)             | (g)         | 0.73              | 0.78  | 0.80  | 0.82  |
| Epididymis(R)         | (g)         | 0.09              | 0.09  | 0.09  | 0.05  |
| Epididymis(L)         | (g)         | 0.08              | 0.09  | 0.08  | 0.08  |
| Ventral prostate      | (g)         | 0.08              | 0.09  | 0.06  | 0.08  |
| Dorsolateral prostate | (g)         | 0.07              | 0.06  | 0.08  | 0.10  |
| Brain                 | (g)         | 1.60              | 1.71  | 1.73  | 1.72  |
| Spleen                | (g)         | 0.42              | 0.38  | 0.38  | 0.40  |
| Thymus                | (mg)        | 555.0             | 384.5 | 395.2 | 517.4 |
| Pituitary gland       | (mg)        | 5.0               | 5.7   | 5.8   | 5.5   |
| Thyroid               | (mg)        | 8.6               | 6.8   | 10.7  | 11.7  |
| Adrenals              | (mg)        | 27.8              | 32.5  | 33.5  | 34.8  |
| Final body weight     | (g)         | 129.3             | 128.5 | 137.8 | 137.9 |

ss: scheduled sacrifice animal.

Appendix 11-10 Twenty-eight-day repeated-dose oral toxicity study in rats  
Absolute organ weights of individual animals:Male

| Group                 |             | Seven-day treatment |       |       |       |
|-----------------------|-------------|---------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 1000                |       |       |       |
| Items                 | Animal No.  | 39 ss               | 40 ss | 41 ss | 42 ss |
| Liver                 | (g)         | 6.57                | 6.71  | 7.68  | 7.86  |
| Heart                 | (g)         | 0.81                | 0.78  | 0.88  | 0.83  |
| Kidney(R)             | (g)         | 0.84                | 0.81  | 0.86  | 0.88  |
| Kidney(L)             | (g)         | 0.85                | 0.80  | 0.81  | 0.83  |
| Testis(R)             | (g)         | 0.99                | 1.01  | 1.12  | 0.96  |
| Testis(L)             | (g)         | 0.98                | 0.96  | 1.04  | 0.95  |
| Epididymis(R)         | (g)         | 0.12                | 0.14  | 0.12  | 0.13  |
| Epididymis(L)         | (g)         | 0.11                | 0.14  | 0.12  | 0.14  |
| Ventral prostate      | (g)         | 0.15                | 0.10  | 0.11  | 0.17  |
| Dorsolateral prostate | (g)         | 0.09                | 0.07  | 0.09  | 0.07  |
| Brain                 | (g)         | 1.90                | 1.80  | 1.78  | 1.84  |
| Spleen                | (g)         | 0.41                | 0.36  | 0.42  | 0.50  |
| Thymus                | (mg)        | 481.1               | 572.0 | 397.4 | 437.9 |
| Pituitary gland       | (mg)        | 6.1                 | 6.6   | 6.7   | 7.4   |
| Thyroid               | (mg)        | 12.6                | 11.6  | 15.5  | 9.9   |
| Adrenals              | (mg)        | 33.3                | 41.1  | 39.8  | 42.4  |
| Final body weight     | (g)         | 170.4               | 178.6 | 186.1 | 189.2 |

ss: scheduled sacrifice animal.

Appendix 11-11 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Absolute organ weights of individual animals:Male

| Group                 |             | Fourteen-day treatment |       |       |       |
|-----------------------|-------------|------------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 1000                   |       |       |       |
| Items                 | Animal No.  | 43 ss                  | 44 ss | 45 ss | 46 ss |
| Liver                 | (g)         | 9.40                   | 8.43  | 8.21  | 9.24  |
| Heart                 | (g)         | 0.97                   | 0.95  | 1.00  | 1.03  |
| Kidney(R)             | (g)         | 1.03                   | 0.94  | 1.13  | 1.02  |
| Kidney(L)             | (g)         | 1.02                   | 0.93  | 1.04  | 1.07  |
| Testis(R)             | (g)         | 1.50                   | 1.34  | 1.34  | 1.32  |
| Testis(L)             | (g)         | 1.48                   | 1.28  | 1.33  | 1.36  |
| Epididymis(R)         | (g)         | 0.17                   | 0.20  | 0.20  | 0.21  |
| Epididymis(L)         | (g)         | 0.19                   | 0.21  | 0.18  | 0.21  |
| Ventral prostate      | (g)         | 0.23                   | 0.22  | 0.17  | 0.19  |
| Dorsolateral prostate | (g)         | 0.19                   | 0.12  | 0.17  | 0.17  |
| Brain                 | (g)         | 1.84                   | 2.00  | 1.88  | 1.75  |
| Spleen                | (g)         | 0.58                   | 0.60  | 0.59  | 0.48  |
| Thymus                | (mg)        | 491.5                  | 656.6 | 607.3 | 627.2 |
| Pituitary gland       | (mg)        | 8.3                    | 8.3   | 7.6   | 8.8   |
| Thyroid               | (mg)        | 17.7                   | 14.5  | 19.9  | 17.4  |
| Adrenals              | (mg)        | 42.9                   | 46.2  | 48.7  | 45.0  |
| Final body weight     | (g)         | 231.7                  | 230.8 | 233.2 | 245.9 |

ss: scheduled sacrifice animal.

Appendix 11-12 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Absolute organ weights of individual animals:Male

| Group                 |             | Twenty-eight-day treatment |       |       |       |       |
|-----------------------|-------------|----------------------------|-------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 1000                       |       |       |       |       |
| Items                 | Animal No.  | 47 ss                      | 48 ss | 49 ss | 50 ss | 51 ss |
| Liver                 | (g)         | 11.88                      | 11.64 | 9.84  | 12.48 | 12.97 |
| Heart                 | (g)         | 1.35                       | 1.35  | 1.08  | 1.37  | 1.43  |
| Kidney(R)             | (g)         | 1.22                       | 1.28  | 1.20  | 1.39  | 1.32  |
| Kidney(L)             | (g)         | 1.23                       | 1.29  | 1.20  | 1.41  | 1.29  |
| Testis(R)             | (g)         | 1.52                       | 1.83  | 1.48  | 1.69  | 1.79  |
| Testis(L)             | (g)         | 1.47                       | 1.77  | 1.57  | 1.66  | 1.73  |
| Epididymis(R)         | (g)         | 0.32                       | 0.33  | 0.35  | 0.40  | 0.41  |
| Epididymis(L)         | (g)         | 0.33                       | 0.31  | 0.36  | 0.40  | 0.41  |
| Ventral prostate      | (g)         | 0.33                       | 0.41  | 0.34  | 0.36  | 0.35  |
| Dorsolateral prostate | (g)         | 0.27                       | 0.29  | 0.32  | 0.36  | 0.36  |
| Seminal vesicle       | (g)         | 0.94                       | 0.75  | 1.08  | 0.84  | 0.98  |
| Brain                 | (g)         | 2.03                       | 2.14  | 1.97  | 2.03  | 2.15  |
| Spleen                | (g)         | 0.48                       | 0.59  | 0.61  | 0.73  | 0.70  |
| Thymus                | (mg)        | 592.6                      | 405.8 | 659.5 | 507.4 | 443.1 |
| Pituitary gland       | (mg)        | 8.7                        | 9.9   | 9.2   | 12.0  | 11.5  |
| Thyroid               | (mg)        | 13.9                       | 15.8  | 18.6  | 25.5  | 22.1  |
| Adrenals              | (mg)        | 64.2                       | 58.1  | 50.9  | 60.9  | 62.3  |
| Final body weight     | (g)         | 335.6                      | 332.7 | 308.3 | 352.3 | 363.8 |

ss: scheduled sacrifice animal.

Appendix 12-1 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Dose                  | Group      | One-day treatment |       |       |       |
|-----------------------|------------|-------------------|-------|-------|-------|
|                       |            | 0                 | 1 ss  | 2 ss  | 3 ss  |
| Items                 | Animal No. |                   |       |       | 4 ss  |
| Liver                 | (g/100g)   | 3.45              | 3.34  | 3.49  | 3.33  |
| Heart                 | (g/100g)   | 0.50              | 0.49  | 0.51  | 0.49  |
| Kidney(R)             | (g/100g)   | 0.51              | 0.45  | 0.51  | 0.50  |
| Kidney(L)             | (g/100g)   | 0.49              | 0.43  | 0.48  | 0.51  |
| Testis(R)             | (g/100g)   | 0.49              | 0.46  | 0.54  | 0.57  |
| Testis(L)             | (g/100g)   | 0.46              | 0.46  | 0.52  | 0.55  |
| Epididymis(R)         | (g/100g)   | 0.05              | 0.05  | 0.06  | 0.06  |
| Epididymis(L)         | (g/100g)   | 0.05              | 0.05  | 0.06  | 0.05  |
| Ventral prostate      | (g/100g)   | 0.05              | 0.05  | 0.05  | 0.05  |
| Dorsolateral prostate | (g/100g)   | 0.04              | 0.08  | 0.04  | 0.07  |
| Brain                 | (g/100g)   | 1.49              | 1.34  | 1.27  | 1.30  |
| Spleen                | (g/100g)   | 0.25              | 0.33  | 0.29  | 0.28  |
| Thymus                | (mg/100g)  | 391.4             | 338.8 | 342.9 | 354.6 |
| Pituitary gland       | (mg/100g)  | 4.6               | 3.5   | 4.0   | 4.2   |
| Thyroid               | (mg/100g)  | 6.7               | 6.7   | 5.6   | 4.6   |
| Adrenals              | (mg/100g)  | 23.4              | 26.7  | 28.3  | 26.1  |
| Final body weight     | (g)        | 124.8             | 129.5 | 138.3 | 137.2 |

ss: scheduled sacrifice animal.

Appendix 12-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Dose                  | Group<br>(mg/kg/day) | Seven-day treatment |       |       |       |
|-----------------------|----------------------|---------------------|-------|-------|-------|
|                       |                      | 0                   | 5 ss  | 6 ss  | 7 ss  |
| Items                 | Animal No.           |                     |       |       | 8 ss  |
| Liver                 | (g/100g)             | 3.56                | 3.62  | 3.57  | 3.63  |
| Heart                 | (g/100g)             | 0.49                | 0.47  | 0.44  | 0.49  |
| Kidney(R)             | (g/100g)             | 0.50                | 0.47  | 0.49  | 0.48  |
| Kidney(L)             | (g/100g)             | 0.49                | 0.43  | 0.48  | 0.47  |
| Testis(R)             | (g/100g)             | 0.48                | 0.58  | 0.50  | 0.49  |
| Testis(L)             | (g/100g)             | 0.45                | 0.57  | 0.51  | 0.48  |
| Epididymis(R)         | (g/100g)             | 0.06                | 0.08  | 0.07  | 0.06  |
| Epididymis(L)         | (g/100g)             | 0.06                | 0.08  | 0.07  | 0.06  |
| Ventral prostate      | (g/100g)             | 0.06                | 0.08  | 0.06  | 0.06  |
| Dorsolateral prostate | (g/100g)             | 0.03                | 0.08  | 0.07  | 0.05  |
| Brain                 | (g/100g)             | 1.01                | 1.06  | 1.00  | 1.03  |
| Spleen                | (g/100g)             | 0.32                | 0.29  | 0.29  | 0.26  |
| Thymus                | (mg/100g)            | 330.7               | 274.1 | 292.7 | 266.9 |
| Pituitary gland       | (mg/100g)            | 4.2                 | 3.5   | 3.6   | 3.4   |
| Thyroid               | (mg/100g)            | 6.7                 | 6.1   | 6.5   | 7.5   |
| Adrenals              | (mg/100g)            | 34.2                | 23.5  | 23.5  | 21.0  |
| Final body weight     | (g)                  | 178.9               | 172.9 | 182.8 | 174.5 |

ss: scheduled sacrifice animal.

Appendix 12-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Group                 |             | Fourteen-day treatment |       |       |       |
|-----------------------|-------------|------------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 0                      |       |       |       |
| Items                 | Animal No.  | 9 ss                   | 10 ss | 11 ss | 12 ss |
| Liver                 | (g/100g)    | 3.78                   | 3.56  | 3.67  | 3.62  |
| Heart                 | (g/100g)    | 0.46                   | 0.41  | 0.42  | 0.43  |
| Kidney(R)             | (g/100g)    | 0.43                   | 0.42  | 0.42  | 0.42  |
| Kidney(L)             | (g/100g)    | 0.45                   | 0.42  | 0.42  | 0.40  |
| Testis(R)             | (g/100g)    | 0.60                   | 0.53  | 0.55  | 0.49  |
| Testis(L)             | (g/100g)    | 0.59                   | 0.53  | 0.55  | 0.49  |
| Epididymis(R)         | (g/100g)    | 0.08                   | 0.07  | 0.08  | 0.08  |
| Epididymis(L)         | (g/100g)    | 0.08                   | 0.07  | 0.08  | 0.08  |
| Ventral prostate      | (g/100g)    | 0.08                   | 0.10  | 0.11  | 0.11  |
| Dorsolateral prostate | (g/100g)    | 0.08                   | 0.09  | 0.08  | 0.08  |
| Brain                 | (g/100g)    | 0.88                   | 0.78  | 0.78  | 0.73  |
| Spleen                | (g/100g)    | 0.24                   | 0.27  | 0.29  | 0.30  |
| Thymus                | (mg/100g)   | 240.4                  | 308.4 | 253.3 | 199.2 |
| Pituitary gland       | (mg/100g)   | 3.7                    | 3.1   | 3.3   | 3.2   |
| Thyroid               | (mg/100g)   | 12.3                   | 6.7   | 7.6   | 6.8   |
| Adrenals              | (mg/100g)   | 20.7                   | 15.0  | 19.8  | 17.9  |
| Final body weight     | (g)         | 214.5                  | 232.1 | 242.5 | 264.3 |

ss: scheduled sacrifice animal.

Appendix 12-4 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Group                 |             | Twenty-eight-day treatment |       |       |       |       |
|-----------------------|-------------|----------------------------|-------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 0                          |       |       |       |       |
| Items                 | Animal No.  | 13 ss                      | 14 ss | 15 ss | 16 ss | 17 ss |
| Liver                 | (g/100g)    | 3.18                       | 3.39  | 3.41  | 3.24  | 3.31  |
| Heart                 | (g/100g)    | 0.39                       | 0.38  | 0.37  | 0.37  | 0.36  |
| Kidney(R)             | (g/100g)    | 0.38                       | 0.36  | 0.34  | 0.40  | 0.41  |
| Kidney(L)             | (g/100g)    | 0.36                       | 0.36  | 0.35  | 0.38  | 0.39  |
| Testis(R)             | (g/100g)    | 0.42                       | 0.49  | 0.43  | 0.39  | 0.41  |
| Testis(L)             | (g/100g)    | 0.42                       | 0.49  | 0.42  | 0.39  | 0.42  |
| Epididymis(R)         | (g/100g)    | 0.10                       | 0.10  | 0.09  | 0.10  | 0.10  |
| Epididymis(L)         | (g/100g)    | 0.10                       | 0.10  | 0.08  | 0.10  | 0.09  |
| Ventral prostate      | (g/100g)    | 0.12                       | 0.06  | 0.13  | 0.12  | 0.12  |
| Dorsolateral prostate | (g/100g)    | 0.10                       | 0.06  | 0.09  | 0.08  | 0.10  |
| Seminal vesicle       | (g/100g)    | 0.26                       | 0.20  | 0.28  | 0.24  | 0.28  |
| Brain                 | (g/100g)    | 0.57                       | 0.56  | 0.51  | 0.57  | 0.50  |
| Spleen                | (g/100g)    | 0.21                       | 0.20  | 0.19  | 0.19  | 0.19  |
| Thymus                | (mg/100g)   | 154.5                      | 156.0 | 144.4 | 170.5 | 126.5 |
| Pituitary gland       | (mg/100g)   | 2.7                        | 3.4   | 3.2   | 3.1   | 3.3   |
| Thyroid               | (mg/100g)   | 3.8                        | 4.2   | 3.0   | 4.3   | 5.0   |
| Adrenals              | (mg/100g)   | 15.9                       | 14.1  | 13.2  | 16.4  | 16.0  |
| Final body weight     | (g)         | 365.1                      | 356.6 | 386.5 | 365.3 | 362.7 |

ss: scheduled sacrifice animal.

Appendix 12-5 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Group                 |             | One-day treatment |       |       |       |
|-----------------------|-------------|-------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 200               |       |       |       |
| Items                 | Animal No.  | 18 ss             | 19 ss | 20 ss | 21 ss |
| Liver                 | (g/100g)    | 3.55              | 3.66  | 3.61  | 3.56  |
| Heart                 | (g/100g)    | 0.50              | 0.48  | 0.53  | 0.48  |
| Kidney(R)             | (g/100g)    | 0.55              | 0.49  | 0.49  | 0.49  |
| Kidney(L)             | (g/100g)    | 0.53              | 0.50  | 0.50  | 0.46  |
| Testis(R)             | (g/100g)    | 0.56              | 0.60  | 0.43  | 0.51  |
| Testis(L)             | (g/100g)    | 0.54              | 0.60  | 0.45  | 0.49  |
| Epididymis(R)         | (g/100g)    | 0.06              | 0.06  | 0.05  | 0.06  |
| Epididymis(L)         | (g/100g)    | 0.06              | 0.07  | 0.05  | 0.06  |
| Ventral prostate      | (g/100g)    | 0.06              | 0.02  | 0.05  | 0.04  |
| Dorsolateral prostate | (g/100g)    | 0.05              | 0.09  | 0.04  | 0.06  |
| Brain                 | (g/100g)    | 1.38              | 1.49  | 1.29  | 1.29  |
| Spleen                | (g/100g)    | 0.35              | 0.27  | 0.27  | 0.26  |
| Thymus                | (mg/100g)   | 347.4             | 402.7 | 277.3 | 281.3 |
| Pituitary gland       | (mg/100g)   | 4.6               | 4.3   | 3.9   | 4.4   |
| Thyroid               | (mg/100g)   | 5.7               | 5.8   | 7.3   | 7.0   |
| Adrenals              | (mg/100g)   | 23.7              | 27.7  | 21.6  | 23.2  |
| Final body weight     | (g)         | 127.2             | 128.3 | 134.8 | 136.0 |

ss: scheduled sacrifice animal.

Appendix 12-6 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Group                 |             | Seven-day treatment |       |       |       |
|-----------------------|-------------|---------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 200                 |       |       |       |
| Items                 | Animal No.  | 22 ss               | 23 ss | 24 ss | 25 ss |
| Liver                 | (g/100g)    | 4.11                | 3.50  | 4.07  | 3.71  |
| Heart                 | (g/100g)    | 0.46                | 0.45  | 0.50  | 0.41  |
| Kidney(R)             | (g/100g)    | 0.45                | 0.43  | 0.51  | 0.45  |
| Kidney(L)             | (g/100g)    | 0.43                | 0.41  | 0.49  | 0.48  |
| Testis(R)             | (g/100g)    | 0.57                | 0.65  | 0.47  | 0.59  |
| Testis(L)             | (g/100g)    | 0.55                | 0.64  | 0.45  | 0.59  |
| Epididymis(R)         | (g/100g)    | 0.06                | 0.06  | 0.06  | 0.07  |
| Epididymis(L)         | (g/100g)    | 0.07                | 0.06  | 0.06  | 0.07  |
| Ventral prostate      | (g/100g)    | 0.06                | 0.06  | 0.06  | 0.08  |
| Dorsolateral prostate | (g/100g)    | 0.05                | 0.07  | 0.04  | 0.08  |
| Brain                 | (g/100g)    | 1.08                | 1.12  | 0.94  | 1.07  |
| Spleen                | (g/100g)    | 0.28                | 0.20  | 0.31  | 0.25  |
| Thymus                | (mg/100g)   | 195.5               | 218.5 | 276.0 | 282.1 |
| Pituitary gland       | (mg/100g)   | 4.1                 | 3.6   | 3.8   | 4.3   |
| Thyroid               | (mg/100g)   | 4.7                 | 6.7   | 6.1   | 5.3   |
| Adrenals              | (mg/100g)   | 22.7                | 22.2  | 20.1  | 20.6  |
| Final body weight     | (g)         | 167.8               | 170.8 | 191.4 | 180.9 |

ss: scheduled sacrifice animal.

Appendix 12-7 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Group                 |             | Fourteen-day treatment |       |       |       |
|-----------------------|-------------|------------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 200                    |       |       |       |
| Items                 | Animal No.  | 26 ss                  | 27 ss | 28 ss | 29 ss |
| Liver                 | (g/100g)    | 3.74                   | 3.50  | 4.22  | 3.74  |
| Heart                 | (g/100g)    | 0.45                   | 0.41  | 0.43  | 0.40  |
| Kidney(R)             | (g/100g)    | 0.41                   | 0.41  | 0.45  | 0.40  |
| Kidney(L)             | (g/100g)    | 0.41                   | 0.39  | 0.44  | 0.41  |
| Testis(R)             | (g/100g)    | 0.51                   | 0.56  | 0.54  | 0.60  |
| Testis(L)             | (g/100g)    | 0.50                   | 0.56  | 0.51  | 0.60  |
| Epididymis(R)         | (g/100g)    | 0.07                   | 0.09  | 0.07  | 0.08  |
| Epididymis(L)         | (g/100g)    | 0.07                   | 0.07  | 0.06  | 0.07  |
| Ventral prostate      | (g/100g)    | 0.09                   | 0.10  | 0.09  | 0.10  |
| Dorsolateral prostate | (g/100g)    | 0.08                   | 0.08  | 0.07  | 0.09  |
| Brain                 | (g/100g)    | 0.80                   | 0.74  | 0.78  | 0.81  |
| Spleen                | (g/100g)    | 0.26                   | 0.25  | 0.28  | 0.23  |
| Thymus                | (mg/100g)   | 327.8                  | 236.2 | 197.7 | 228.9 |
| Pituitary gland       | (mg/100g)   | 3.4                    | 3.1   | 3.6   | 3.2   |
| Thyroid               | (mg/100g)   | 8.3                    | 7.4   | 9.5   | 8.1   |
| Adrenals              | (mg/100g)   | 16.7                   | 18.4  | 19.8  | 17.2  |
| Final body weight     | (g)         | 241.2                  | 243.3 | 250.9 | 234.6 |

ss: scheduled sacrifice animal.

Appendix 12-8 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Group                 |             | Twenty-eight-day treatment |       |       |       |       |
|-----------------------|-------------|----------------------------|-------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 200                        |       |       |       |       |
| Items                 | Animal No.  | 30 ss                      | 31 ss | 32 ss | 33 ss | 34 ss |
| Liver                 | (g/100g)    | 3.56                       | 3.23  | 3.00  | 3.91  | 3.83  |
| Heart                 | (g/100g)    | 0.35                       | 0.37  | 0.34  | 0.37  | 0.34  |
| Kidney(R)             | (g/100g)    | 0.36                       | 0.38  | 0.37  | 0.39  | 0.36  |
| Kidney(L)             | (g/100g)    | 0.37                       | 0.37  | 0.36  | 0.41  | 0.33  |
| Testis(R)             | (g/100g)    | 0.46                       | 0.48  | 0.44  | 0.44  | 0.47  |
| Testis(L)             | (g/100g)    | 0.45                       | 0.47  | 0.45  | 0.45  | 0.46  |
| Epididymis(R)         | (g/100g)    | 0.11                       | 0.12  | 0.10  | 0.10  | 0.10  |
| Epididymis(L)         | (g/100g)    | 0.11                       | 0.12  | 0.10  | 0.11  | 0.11  |
| Ventral prostate      | (g/100g)    | 0.08                       | 0.12  | 0.10  | 0.14  | 0.09  |
| Dorsolateral prostate | (g/100g)    | 0.07                       | 0.09  | 0.10  | 0.09  | 0.09  |
| Seminal vesicle       | (g/100g)    | 0.22                       | 0.26  | 0.25  | 0.31  | 0.24  |
| Brain                 | (g/100g)    | 0.61                       | 0.64  | 0.58  | 0.59  | 0.57  |
| Spleen                | (g/100g)    | 0.19                       | 0.24  | 0.24  | 0.26  | 0.22  |
| Thymus                | (mg/100g)   | 146.2                      | 182.8 | 153.7 | 180.6 | 160.1 |
| Pituitary gland       | (mg/100g)   | 3.3                        | 3.8   | 2.9   | 3.9   | 3.0   |
| Thyroid               | (mg/100g)   | 3.6                        | 5.7   | 5.0   | 5.3   | 4.4   |
| Adrenals              | (mg/100g)   | 10.2                       | 16.4  | 13.0  | 18.2  | 16.8  |
| Final body weight     | (g)         | 321.8                      | 327.6 | 348.2 | 334.9 | 346.7 |

ss: scheduled sacrifice animal.

Appendix 12-9 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Dose                  | Group<br>(mg/kg/day) | One-day treatment |       |       |       |
|-----------------------|----------------------|-------------------|-------|-------|-------|
|                       |                      | 35 ss             | 36 ss | 37 ss | 38 ss |
| Liver                 | (g/100g)             | 3.62              | 3.56  | 3.81  | 3.77  |
| Heart                 | (g/100g)             | 0.46              | 0.51  | 0.45  | 0.49  |
| Kidney(R)             | (g/100g)             | 0.53              | 0.51  | 0.58  | 0.53  |
| Kidney(L)             | (g/100g)             | 0.51              | 0.52  | 0.54  | 0.53  |
| Testis(R)             | (g/100g)             | 0.53              | 0.61  | 0.59  | 0.60  |
| Testis(L)             | (g/100g)             | 0.56              | 0.61  | 0.58  | 0.59  |
| Epididymis(R)         | (g/100g)             | 0.07              | 0.07  | 0.07  | 0.04  |
| Epididymis(L)         | (g/100g)             | 0.06              | 0.07  | 0.06  | 0.06  |
| Ventral prostate      | (g/100g)             | 0.06              | 0.07  | 0.04  | 0.06  |
| Dorsolateral prostate | (g/100g)             | 0.05              | 0.05  | 0.06  | 0.07  |
| Brain                 | (g/100g)             | 1.24              | 1.33  | 1.26  | 1.25  |
| Spleen                | (g/100g)             | 0.32              | 0.30  | 0.28  | 0.29  |
| Thymus                | (mg/100g)            | 429.2             | 299.2 | 286.8 | 375.2 |
| Pituitary gland       | (mg/100g)            | 3.9               | 4.4   | 4.2   | 4.0   |
| Thyroid               | (mg/100g)            | 6.7               | 5.3   | 7.8   | 8.5   |
| Adrenals              | (mg/100g)            | 21.5              | 25.3  | 24.3  | 25.2  |
| Final body weight     | (g)                  | 129.3             | 128.5 | 137.8 | 137.9 |

ss: scheduled sacrifice animal.

Appendix 12-10 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Relative organ weights of individual animals:Male

| Group                 |             | Seven-day treatment |       |       |       |
|-----------------------|-------------|---------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 1000                |       |       |       |
| Items                 | Animal No.  | 39 ss               | 40 ss | 41 ss | 42 ss |
| Liver                 | (g/100g)    | 3.86                | 3.76  | 4.13  | 4.15  |
| Heart                 | (g/100g)    | 0.48                | 0.44  | 0.47  | 0.44  |
| Kidney(R)             | (g/100g)    | 0.49                | 0.45  | 0.46  | 0.47  |
| Kidney(L)             | (g/100g)    | 0.50                | 0.45  | 0.44  | 0.44  |
| Testis(R)             | (g/100g)    | 0.58                | 0.57  | 0.60  | 0.51  |
| Testis(L)             | (g/100g)    | 0.58                | 0.54  | 0.56  | 0.50  |
| Epididymis(R)         | (g/100g)    | 0.07                | 0.08  | 0.06  | 0.07  |
| Epididymis(L)         | (g/100g)    | 0.06                | 0.08  | 0.06  | 0.07  |
| Ventral prostate      | (g/100g)    | 0.09                | 0.06  | 0.06  | 0.09  |
| Dorsolateral prostate | (g/100g)    | 0.05                | 0.04  | 0.05  | 0.04  |
| Brain                 | (g/100g)    | 1.12                | 1.01  | 0.96  | 0.97  |
| Spleen                | (g/100g)    | 0.24                | 0.20  | 0.23  | 0.26  |
| Thymus                | (mg/100g)   | 282.3               | 320.3 | 213.5 | 231.4 |
| Pituitary gland       | (mg/100g)   | 3.6                 | 3.7   | 3.6   | 3.9   |
| Thyroid               | (mg/100g)   | 7.4                 | 6.5   | 8.3   | 5.2   |
| Adrenals              | (mg/100g)   | 19.5                | 23.0  | 21.4  | 22.4  |
| Final body weight     | (g)         | 170.4               | 178.6 | 186.1 | 189.2 |

ss: scheduled sacrifice animal.

Appendix 12-11 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Group                 |             | Fourteen-day treatment |       |       |       |
|-----------------------|-------------|------------------------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 1000                   |       |       |       |
| Items                 | Animal No.  | 43 ss                  | 44 ss | 45 ss | 46 ss |
| Liver                 | (g/100g)    | 4.06                   | 3.65  | 3.52  | 3.76  |
| Heart                 | (g/100g)    | 0.42                   | 0.41  | 0.43  | 0.42  |
| Kidney(R)             | (g/100g)    | 0.44                   | 0.41  | 0.48  | 0.41  |
| Kidney(L)             | (g/100g)    | 0.44                   | 0.40  | 0.45  | 0.44  |
| Testis(R)             | (g/100g)    | 0.65                   | 0.58  | 0.57  | 0.54  |
| Testis(L)             | (g/100g)    | 0.64                   | 0.55  | 0.57  | 0.55  |
| Epididymis(R)         | (g/100g)    | 0.07                   | 0.09  | 0.09  | 0.09  |
| Epididymis(L)         | (g/100g)    | 0.08                   | 0.09  | 0.08  | 0.09  |
| Ventral prostate      | (g/100g)    | 0.10                   | 0.10  | 0.07  | 0.08  |
| Dorsolateral prostate | (g/100g)    | 0.08                   | 0.05  | 0.07  | 0.07  |
| Brain                 | (g/100g)    | 0.79                   | 0.87  | 0.81  | 0.71  |
| Spleen                | (g/100g)    | 0.25                   | 0.26  | 0.25  | 0.20  |
| Thymus                | (mg/100g)   | 212.1                  | 284.5 | 260.4 | 255.1 |
| Pituitary gland       | (mg/100g)   | 3.6                    | 3.6   | 3.3   | 3.6   |
| Thyroid               | (mg/100g)   | 7.6                    | 6.3   | 8.5   | 7.1   |
| Adrenals              | (mg/100g)   | 18.5                   | 20.0  | 20.9  | 18.3  |
| Final body weight     | (g)         | 231.7                  | 230.8 | 233.2 | 245.9 |

ss: scheduled sacrifice animal.

Appendix 12-12 Twenty-eight-day repeated-dose oral toxicity study in rats  
Relative organ weights of individual animals:Male

| Group                 |             | Twenty-eight-day treatment |       |       |       |       |
|-----------------------|-------------|----------------------------|-------|-------|-------|-------|
| Dose                  | (mg/kg/day) | 1000                       |       |       |       |       |
| Items                 | Animal No.  | 47 ss                      | 48 ss | 49 ss | 50 ss | 51 ss |
| Liver                 | (g/100g)    | 3.54                       | 3.50  | 3.19  | 3.54  | 3.57  |
| Heart                 | (g/100g)    | 0.40                       | 0.41  | 0.35  | 0.39  | 0.39  |
| Kidney(R)             | (g/100g)    | 0.36                       | 0.38  | 0.39  | 0.39  | 0.36  |
| Kidney(L)             | (g/100g)    | 0.37                       | 0.39  | 0.39  | 0.40  | 0.35  |
| Testis(R)             | (g/100g)    | 0.45                       | 0.55  | 0.48  | 0.48  | 0.49  |
| Testis(L)             | (g/100g)    | 0.44                       | 0.53  | 0.51  | 0.47  | 0.48  |
| Epididymis(R)         | (g/100g)    | 0.10                       | 0.10  | 0.11  | 0.11  | 0.11  |
| Epididymis(L)         | (g/100g)    | 0.10                       | 0.09  | 0.12  | 0.11  | 0.11  |
| Ventral prostate      | (g/100g)    | 0.10                       | 0.12  | 0.11  | 0.10  | 0.10  |
| Dorsolateral prostate | (g/100g)    | 0.08                       | 0.09  | 0.10  | 0.10  | 0.10  |
| Seminal vesicle       | (g/100g)    | 0.28                       | 0.23  | 0.35  | 0.24  | 0.27  |
| Brain                 | (g/100g)    | 0.60                       | 0.64  | 0.64  | 0.58  | 0.59  |
| Spleen                | (g/100g)    | 0.14                       | 0.18  | 0.20  | 0.21  | 0.19  |
| Thymus                | (mg/100g)   | 176.6                      | 122.0 | 213.9 | 144.0 | 121.8 |
| Pituitary gland       | (mg/100g)   | 2.6                        | 3.0   | 3.0   | 3.4   | 3.2   |
| Thyroid               | (mg/100g)   | 4.1                        | 4.7   | 6.0   | 7.2   | 6.1   |
| Adrenals              | (mg/100g)   | 19.1                       | 17.5  | 16.5  | 17.3  | 17.1  |
| Final body weight     | (g)         | 335.6                      | 332.7 | 308.3 | 352.3 | 363.8 |

ss: scheduled sacrifice animal.

**Appendix 13-1 Twenty-eight-day repeated-dose oral toxicity study in rats**  
**Pathological findings of individual animals: One-day treatment**

| Sex  | Dose<br>(mg/kg/day) | Animal<br>No. | Fate | Macroscopic findings      | Histopathological findings <sup>a)</sup> |
|------|---------------------|---------------|------|---------------------------|--|
| Male | 0                   | 1             | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 2             | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 3             | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 4             | ss   | No abnormalities detected | No abnormalities detected                |
|      | 200                 | 18            | ss   | No abnormalities detected | Not examined                             |
|      |                     | 19            | ss   | No abnormalities detected | Not examined                             |
|      |                     | 20            | ss   | No abnormalities detected | Not examined                             |
|      |                     | 21            | ss   | No abnormalities detected | Not examined                             |
|      | 1000                | 35            | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 36            | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 37            | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 38            | ss   | No abnormalities detected | No abnormalities detected                |

a) Organs/tissues examined as follows for the 0 and 1000 mg/kg/day groups: liver, kidney, testis, ventral prostate, dorsolateral prostate, bone marrow, spleen and thymus.

ss, scheduled sacrifice animal.

Appendix 13-2 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Pathological findings of individual animals: Seven-day treatment

| Sex  | Dose<br>(mg/kg/day) | Animal<br>No. | Fate | Macroscopic findings      | Histopathological findings <sup>a)</sup>                        |
|------|---------------------|---------------|------|---------------------------|---|
| Male | 0                   | 5             | ss   | No abnormalities detected | No abnormalities detected                                       |
|      |                     | 6             | ss   | No abnormalities detected | No abnormalities detected                                       |
|      |                     | 7             | ss   | No abnormalities detected | Kidney<br>Cyst/Medulla +  |
|      |                     | 8             | ss   | No abnormalities detected | No abnormalities detected                                       |
|      |                     | 22            | ss   | No abnormalities detected | Not examined  |
|      |                     | 23            | ss   | No abnormalities detected | Not examined  |
|      |                     | 24            | ss   | No abnormalities detected | Not examined  |
|      | 200                 | 25            | ss   | No abnormalities detected | Not examined  |
|      |                     | 39            | ss   | No abnormalities detected | No abnormalities detected                                       |
|      |                     | 40            | ss   | No abnormalities detected | No abnormalities detected                                       |
|      | 1000                | 41            | ss   | Liver<br>Enlargement      | No abnormalities detected<br>Liver<br>No abnormalities detected |
|      |                     | 42            | ss   | No abnormalities detected | No abnormalities detected                                       |

a) Organs/tissues examined as follows for the 0 and 1000 mg/kg/day groups: liver, kidney, testis, ventral prostate, dorsolateral prostate, bone marrow, spleen and thymus.

ss, scheduled sacrifice animal.

+, slight.

Appendix 13-3 Twenty-eight-day repeated-dose oral toxicity study in rats  
 Pathological findings of individual animals: Fourteen-day treatment

| Sex  | Dose<br>(mg/kg/day) | Animal<br>No. | Fate | Macroscopic findings      | Histopathological findings <sup>a)</sup> |
|------|---------------------|---------------|------|---------------------------|--|
| Male | 0                   | 9             | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 10            | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 11            | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 12            | ss   | No abnormalities detected | No abnormalities detected                |
|      | 200                 | 26            | ss   | No abnormalities detected | Not examined                             |
|      |                     | 27            | ss   | No abnormalities detected | Not examined                             |
|      |                     | 28            | ss   | No abnormalities detected | Not examined                             |
|      |                     | 29            | ss   | No abnormalities detected | Not examined                             |
|      | 1000                | 43            | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 44            | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 45            | ss   | No abnormalities detected | No abnormalities detected                |
|      |                     | 46            | ss   | No abnormalities detected | No abnormalities detected                |

a) Organs/tissues examined as follows for the 0 and 1000 mg/kg/day groups: liver, kidney, testis, ventral prostate, dorsolateral prostate, bone marrow, spleen and thymus.

ss, scheduled sacrifice animal.

## Appendix 13-4 Twenty-eight-day repeated-dose oral toxicity study in rats

## Pathological findings of individual animals: Twenty-eight-day treatment

| Sex  | Dose<br>(mg/kg/day) | Animal<br>No. | Fate | Macroscopic findings      | Histopathological findings <sup>a)</sup>    |
|------|---------------------|---------------|------|---------------------------|---|
| Male | 0                   | 13            | ss   | No abnormalities detected | No abnormalities detected                   |
|      |                     | 14            | ss   | No abnormalities detected | No abnormalities detected                   |
|      |                     | 15            | ss   | No abnormalities detected | Ventral prostate<br>Cellular infiltration + |
|      |                     | 16            | ss   | No abnormalities detected | No abnormalities detected                   |
|      |                     | 17            | ss   | No abnormalities detected | No abnormalities detected                   |
|      | 200                 | 30            | ss   | No abnormalities detected | Not examined                                |
|      |                     | 31            | ss   | No abnormalities detected | Not examined                                |
|      |                     | 32            | ss   | No abnormalities detected | Not examined                                |
|      |                     | 33            | ss   | No abnormalities detected | Not examined                                |
|      |                     | 34            | ss   | No abnormalities detected | Not examined                                |
|      | 1000                | 47            | ss   | No abnormalities detected | Testis<br>Atrophy, tubular/Focal +          |
|      |                     | 48            | ss   | No abnormalities detected | No abnormalities detected                   |
|      |                     | 49            | ss   | No abnormalities detected | No abnormalities detected                   |
|      |                     | 50            | ss   | No abnormalities detected | No abnormalities detected                   |
|      |                     | 51            | ss   | No abnormalities detected | No abnormalities detected                   |

a) Organs/tissues examined as follows for the 0 and 1000 mg/kg/day groups: trachea, lungs, submandibular gland, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, pancreas, liver, heart, kidney, urinary bladder, testis, epididymides, ventral prostate, dorsolateral prostate, coagulating gland, seminal vesicle, spinal cord, sciatic nerve, bone marrow, axillary lymph node, mesenteric lymph node, spleen, thymus, thyroid, parathyroid, adrenals, eye ball, skeletal muscle, bone and mammary gland.

ss, scheduled sacrifice animal.

+, slight.