

修正報告書

N,N-ジメチルアニリンのラットを用いた
反復経口投与毒性・生殖発生毒性併合試験

修正報告書の作成



2011 年 7 月 8 日

試験責任者



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修正報告陳述書

本修正報告書は、平成19年度ハザードデータ評価委員会（独立行政法人製品評価技術基盤機構）で評価後、修正・加筆した。

試験責任者

2011 年 7 月 8 日

修正報告信頼性保証書

本修正報告書は、平成19年度ハザードデータ評価委員会（独立行政法人製品評価技術基盤機構）で評価後、修正・加筆されたものであり、その修正・加筆内容を確認し保証する。

信託性保証部門責任者

2011年 07月 08日

陳述書

本試験は以下の基準を遵守して実施した。

記

「OECD Principles of Good Laboratory Practice」(November 26, 1997)

以 上

試験責任者 _____

2007 年 / 月 31 日

信頼性保証書

試験番号：5300-1

試験表題：N,N-ジメチルアニリンのラットを用いた反復経口投与毒性/生殖発生
毒性併合試験上記試験について信頼性保証部門が調査を行った日付及び運営管理者並びに
試験責任者への報告日は以下のとおりである。

調査の段階	調査日	報告日
試験計画書	2006年 8月 8日	2006年 8月 8日
群分け	2006年 8月 14日	2006年 8月 16日
調製	2006年 8月 15日	2006年 8月 16日
投与条件下の被験物質濃度の確認	2006年 8月 15日	2006年 8月 16日
試験計画書（委託者承認）	2006年 9月 1日	2006年 9月 1日
投与	2006年 9月 4日	2006年 9月 4日
一般状態観察	2006年 9月 4日	2006年 9月 4日
分娩処置・出生日の観察	2006年 9月 21日	2006年 9月 21日
哺育状態観察	2006年 9月 21日	2006年 9月 21日
哺乳児体重測定	2006年 9月 21日	2006年 9月 21日
外表異常観察	2006年 9月 21日	2006年 9月 21日
採血	2006年 9月 27日	2006年 9月 28日
血液学的検査	2006年 9月 27日	2006年 9月 28日
血液化学的検査	2006年 9月 27日	2006年 9月 28日
剖検	2006年 9月 27日	2006年 9月 28日
臓器重量測定	2006年 9月 27日	2006年 9月 28日
最終報告書草案（図表）	2007年 1月 10日～ 2007年 1月 15日	2007年 1月 16日
最終報告書草案（図表）（再調査）	2007年 1月 22日～ 2007年 1月 23日	2007年 1月 23日
最終報告書草案	2007年 1月 22日～ 2007年 1月 26日	2007年 1月 26日
最終報告書草案（再調査）	2007年 1月 31日	2007年 1月 31日
試験計画変更書（5300-1）	2007年 1月 31日	2007年 1月 31日
生データ	2007年 1月 31日	2007年 1月 31日
最終報告書	2007年 1月 31日	2007年 1月 31日

なお、以下の試験操作については、本試験以外の調査にて信頼性を確認した。

調査の段階	調査日	試験番号等
個体識別	2006 年 6 月 19 日	5303
ケージ識別	2006 年 6 月 19 日	5303
ケージの配置	2006 年 6 月 19 日	5303
詳細観察	2006 年 6 月 19 日	5303
体重測定	2006 年 6 月 20 日	5303
摂餌量測定	2006 年 6 月 20 日	5303
性周期観察	2006 年 6 月 20 日	5303
交配、交尾確認	2006 年 6 月 27 日	5303
尿検査	2006 年 7 月 24 日	5303
検収・検疫（小動物）	2006 年 8 月 1 日	5515
検疫期間中の観察	2006 年 8 月 2 日	5515
パラフィン包埋	2006 年 8 月 30 日	5303
薄切	2006 年 9 月 7 日	5303

本試験は「OECD Principles of Good Laboratory Practice」(November 26, 1997)を遵守して実施されたことを保証する。

日精バイリス株式会社 滋賀研究所
信頼性保証部門責任者

2007 年 1 月 3 日



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試験実施概要

1. 試験番号

5300-1

2. 被験物質番号

C714

3. 表題

N,N-ジメチルアニリンのラットを用いた反復経口投与毒性・生殖発生毒性併合試験


4. 試験目的

N,N-ジメチルアニリンを雄ラットには交配開始 2 週間前から交配期間を通し解剖前日まで 42 日間, 雌ラットには交配開始 2 週間前から交配期間, 妊娠期間及び授乳期間を通し解剖前日(哺育 4 日)まで毎日反復経口投与し, 親動物に対する反復投与毒性及び生殖毒性, 次世代の発生・発育に及ぼす影響について検討することを目的とした。

5. 試験委託者

名称 : 財団法人 化学物質評価研究機構

所在地 : 〒877-0061 大分県日田市石井町 3 丁目 822

担当者 : 
TEL : 0973-24-7211, FAX : 0973-23-9800

6. 試験施設

名称 : 日精バイリス株式会社 滋賀研究所

所在地 : 〒528-0052 滋賀県甲賀市水口町宇川 555

TEL : 0748-62-2316, FAX : 0748-62-9062

7. 試験責任者

氏名 : 

所属 : 日精バイリス株式会社 滋賀研究所

TEL : 0748-63-5251, FAX : 0748-62-9062

8. 試験従事者 (* : 分担責任者)

被験物質管理責任者 : 

動物飼育管理責任者	:	
検疫	:	
	:	
投与	:	
	:	
一般状態観察	:	
	:	
詳細観察・機能検査	:	
体重、摂餌量測定	:	
	:	
尿検査	:	
血液・血液生化学的検査	:	
性周期・交配・分娩・哺育検査	:	
病理解剖学的検査	:	
	:	
	:	
器官重量測定	:	
	:	
病理組織標本作製	:	
	:	
病理組織標本検査	:	
被験液濃度分析	:	

9. 試験の基準

「OECD Principles of Good Laboratory Practice」(November 26, 1997) を適用した。

試験の方法は、「OECD GUIDELINE FOR TESTING OF CHEMICALS」に定める TG 422, Combined Repeated Dose Toxicology Study with the Reproduction /Developmental Toxicity Screening Test (Adopted by the Council on 22nd March 1996) に準拠した方法で実施した。

10. 動物の福祉

動物実験倫理規定（社内規定）に基づき実施した。

なお、社内の動物実験倫理規定は、以下の法律・指針・基準等に従っている。

「動物の愛護及び管理に関する法律」

(昭和 48 年 10 月 1 日法律第 105 号, 平成 11 年 12 月 14 日改正)

「実験動物の飼養及び保管等に関する基準」

（総理府告示第6号，昭和55年3月27日）

「動物実験に関する指針」

（（社）日本実験動物学会，昭和62年5月22日）

「動物の愛護及び管理に関する法律の一部を改正する法律について」

（平成17年6月22日 法律第68号）

「実験動物の飼養及び保管並びに苦痛の軽減に関する基本指針」

（平成18年4月28日 環境省告示第88号）

「動物実験の適正な実施に向けたガイドライン」

（平成18年6月1日 日本学術会議）

11. 試験期間

試験開始日	: 2006年8月7日
実験開始日	: 2006年8月15日
動物入手日	: 2006年8月7日
検疫・馴化期間	: 2006年8月7日 ~ 2006年8月14日
群分け日	: 2006年8月14日
投与期間	: 2006年8月15日 ~ 2006年9月29日
交配期間	: 2006年8月28日 ~ 2006年9月2日
分娩・哺育期間	: 2006年9月20日 ~ 2006年9月29日
投与期間終了後の雄解剖日	: 2006年9月26日
出生児の屠殺日	: 2006年9月24日 ~ 2006年9月29日
分娩雌動物解剖日	: 2006年9月25日 ~ 2006年9月30日
回復群解剖日	: 2006年10月10日
病理組織学的検査期間	: 2006年9月25日 ~ 2006年12月1日
実験終了日	: 2006年12月1日
試験終了日	: 2007年1月31日（最終報告書作成日）

12. 予見することができなかった試験の信頼性に影響を及ぼす疑いのある事態及び試験計画書に従わなかったこと

- 以下に示す期間中の動物飼育室の湿度が試験計画書に記載した規定範囲（35～75％）を逸脱していた．しかしながら，逸脱の程度は0.3％と小さく，逸脱時間も短く，逸脱の前後の動物の観察で一般状態に異常は認められていないことから試験の信頼性に及ぼす影響はないものと判断した．

2006年9月19日 20:36～20:53 湿度最低値 34.7%

- 2) 試験計画書に記載の計量値の検定方法において、2 群間の検定方法を記載していなかった。今回の試験では、2 群間の等分散性について分散比の F 検定を行い等分散 ($p = 0.05$) の場合には Student の t 検定、不等分散 ($p < 0.05$) の場合には Aspin-Welch の t 検定を行った。この検定は毒性試験で汎用される方法であり、試験における毒性評価は可能であると判断した。
- 3) 投与量の設定理由として、試験計画書には「投与量設定試験の結果、2000 mg/kg 投与群において全例が死亡した」と記載していたが、「投与量設定試験の結果、1000 mg/kg 投与群において雄全例及び雌 1/3 例が死亡した」の記載ミスであった。本試験では 100 mg/kg/day を最高用量としていることから、この記載ミスが本試験の毒性評価に影響を及ぼさなかったものと判断した。

13. 試験関係資料の保存

本試験に関する以下の試験関係資料は、試験終了後 5 年間で精バイリス株式会社滋賀研究所の資料保存施設に保存する。5 年経過後の保存については試験委託者と協議する。

- 1) 試験計画書（原本）
- 2) 被験物質に関する記録
- 3) 試験系に関する記録
- 4) 本試験で得られた全ての生データ
- 5) 病理組織学的検査標本（湿標本、パラフィンブロック及びプレパラート）
- 6) 最終報告書（原本）
- 7) 試験委託者との交信記録
- 8) その他の本試験に関する記録

要 約

N,N-ジメチルアニリンを 0, 1, 10 及び 100 mg/kg/day の用量で 1 群各 12 匹の雌雄 Crl:CD (SD) ラットを用い、OECD TG422 に準じて交配開始 2 週間前から雄は 42 日間、雌は哺育 4 日まで経口投与し、親動物に対する反復投与毒性及び生殖毒性、次世代に対する発生毒性について検討した。なお、媒体対照群及び 100 mg/kg/day 群において、雄については 12 匹中 5 匹、雌については上記の 12 匹以外に 5 匹を追加し、回復群とした。これらの回復群の設定により、投与後 14 日間の休薬期間による影響の可逆性についても検討した。雌の回復群については、ガイドラインに準じて交配を実施しなかった。

1. 反復投与毒性

雄の反復経口投与毒性

死亡及び瀕死例はいずれの群にも認められなかった。機能検査、体重、摂餌量及び尿検査には、いずれの群にも被験物質投与の影響は認められなかった。

一般状態の観察では、100 mg/kg 投与群で、投与 2 日より回復期間終了時まで皮膚の暗赤色化が全例に認められた。この皮膚の暗赤色化は詳細観察においても認められた。

血液学的検査では、100 mg/kg 投与群の投与期間終了時に赤血球数、ヘモグロビン量、ヘマトクリット値及び平均赤血球血色素濃度の低値と平均赤血球容積、平均赤血球血色素量及び白血球数の高値が認められ、回復期間終了時には平均赤血球血色素濃度の低値、平均赤血球容積及び平均赤血球血色素量の高値が認められた。

血液生化学的検査では、100 mg/kg 投与群の投与期間終了時に総蛋白及び γ -グロブリンの低値及び総ビリルビンの高値が認められた。

器官重量では、100 mg/kg 投与群の投与期間終了時の肝臓の相対重量、脾臓の絶対重量及び相対重量、腎臓の相対重量に高値が認められた。10 mg/kg 投与群でも肝臓の相対重量に高値が認められた。

剖検では、100 mg/kg 投与群の投与終了時に全例の脾臓の暗赤色及び腫大が認められ、回復期間終了時の剖検においても 4/5 例に脾臓の腫大が認められた。

病理組織学的検査では、100 mg/kg 投与群の投与期間終了時の肝臓に髄外造血の亢進及び黄褐色色素沈着が、脾臓にうっ血、白脾髄の萎縮、髄外造血の亢進及び黄褐色色素沈着が、骨髄には赤芽球系細胞の過形成が認められ、回復期間終了時の病理組織学的検査でも肝臓に黄褐色色素沈着が、脾臓にうっ血及び黄褐色色素沈着が認められた。さらに、10 mg/kg 投与群の投与期間終了時に脾臓にうっ血が認められた。

1 mg/kg 投与群では、*N,N*-ジメチルアニリン投与の影響は認められなかった。

雌の反復経口投与毒性

死亡及び瀕死例はいずれの群にも認められなかった。機能検査、摂餌量及び尿検査には、いずれの群にも被験物質投与の影響は認められなかった。

100 mg/kg 投与群では、投与 2 日より回復期間終了時まで皮膚の暗赤色化が全例に認められた。この皮膚の暗赤色化は詳細観察においても認められた。

母動物の体重推移では、100 mg/kg 投与群の投与 7 日、妊娠 17 及び 20 日に低値が認められ、交配を実施しなかった回復群の体重推移でも投与 8、22、29 及び 36 日、回復 1、3、7 及び 14 日に体重の低値が認められた。

血液学的検査では、100 mg/kg 投与群の投与期間終了時に赤血球数、ヘモグロビン量及びヘマトクリット値の低値、平均赤血球容積及び平均赤血球血色素量の高値が認められ、回復期間終了時には赤血球数の低値とヘモグロビン量、ヘマトクリット値、平均赤血球容積及び平均赤血球血色素量の高値が認められた。

血液生化学的検査では、100 mg/kg 投与群の投与期間終了時に γ -グロブリンの低値、総ビリルビン及び尿素窒素の高値が、回復期間終了時には総ビリルビン及びクレアチニンの低値が認められた。10 mg/kg 投与群の投与期間終了時には γ -グロブリンの低値が認められた。

器官重量では、100 mg/kg 投与群の投与期間終了時に心臓の相対重量及び脾臓の絶対重量及び相対重量に高値が認められ、回復期間終了時には脾臓の絶対重量及び相対重量の高値が認められた。

剖検では、100 mg/kg 投与群の投与期間終了時の全例に脾臓の暗赤色及び腫大が認められた。

病理組織学的検査では、100 mg/kg 投与群の投与期間終了時の肝臓に髄外造血の亢進及び黄褐色色素沈着が、骨髄に赤芽球系細胞の過形成が、脾臓にうっ血、白脾髄の萎縮、髄外造血の亢進及び黄褐色色素沈着が認められ、回復期間終了時の病理組織学的検査でも肝臓に黄褐色色素沈着、骨髄に赤芽球系細胞の過形成、脾臓には黄褐色色素沈着が認められた。さらに、10 mg/kg 投与群の投与期間終了時には、骨髄に赤芽球系細胞の過形成、脾臓にうっ血及び髄外造血の亢進が認められた。1 mg/kg 投与群の投与期間終了時には、骨髄に赤芽球系細胞の過形成、脾臓にうっ血が認められた。

2. 生殖発生毒性

各投与群の精巣、精巣上体、精囊、前立腺、卵巣、子宮、膣の病理組織学的検査で *N,N*-ジメチルアニリン投与に起因した変化は認められなかった。また、性周期、交尾率、交尾所要日数、受胎率、妊娠黄体数、着床数、着床率、出産率、妊娠期間、分娩状態及び哺育状態では、*N,N*-ジメチルアニリン投与に起因した変化は認められなかった。

児動物に対しては、総産児数、出産死亡児数、出產生児数、性比、新生児の外表観察、

生後4日の生存児数及び新生児の4日生存率、一般状態、体重及び剖検に *N,N*-ジメチルアニリン投与に起因した変化は認められなかった。

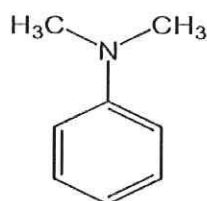
以上のように、雄に関しては10 mg/kg 投与群で肝臓の相対重量の高値及び投与期間終了時の病理組織学検査で脾臓のうっ血が認められたものの、1 mg/kg 投与群では *N,N*-ジメチルアニリン投与の影響は認められなかったことを考慮して、雄の一般毒性学的無毒性量（NOAEL）は1 mg/kg/day と推定した。一方、雌に関しては1 mg/kg 投与群の投与終了時の病理組織学検査で骨髄に赤芽球系細胞の過形成及び脾臓にうっ血が認められたことを考慮して、雌の一般毒性学的 NOAEL は1 mg/kg/day 未満と推定した。生殖発生学的な NOAEL は、いずれの投与群でも *N,N*-ジメチルアニリン投与に起因した変化は認められなかったことから、100 mg/kg/day であると推定した。

なお、*N,N*-ジメチルアニリンの一般毒性学的無影響量（NOEL）は、雄では10 mg/kg 投与群で肝臓の相対重量の高値及び投与期間終了時の病理組織学検査で脾臓のうっ血が認められたものの、1 mg/kg 投与群では *N,N*-ジメチルアニリン投与の影響は認められなかったことを考慮して1 mg/kg/day であり、雌では1 mg/kg 投与群の投与終了時の病理組織学検査で骨髄に赤芽球系細胞の過形成及び脾臓にうっ血が認められたことを考慮して1 mg/kg/day 未満と推定した。生殖発生学的な NOEL は、いずれの投与群でも *N,N*-ジメチルアニリン投与に起因した変化は認められなかったことから、100 mg/kg/day であると推定した。

1. 試験材料及び方法

1.1 被験物質

名称 : *N,N*-ジメチルアニリン



CAS 番号 : 121-69-7
 CAS 名 : *N,N*-ジメチルベンゼンアミン
 Lot No. : XXXXXXXXXX
 分子式 : C₈H₁₁N
 分子量 : 121.18
 性状 : 油状液体
 純度 : 99 %以上
 融点 : 2℃
 沸点 : 192～194℃
 引火点 : 61℃
 保管条件 : 室温
 保管場所 : 日精バイリス株式会社 被験物質保管室（室温：許容範囲 1～30℃，保管温度実測値 16～25℃）
 入手日 : 2005 年 11 月 24 日
 入手量 : 500 mL（風袋込み重量 790.70 g）
 当試験への移管日 : 2006 年 8 月 7 日（試験番号 5300 より転用）
 移管量 : 風袋込み重量 605.78g（試験番号 5300 より転用）
 供給源 : XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
 取扱い上の注意 : マスク，ゴム手袋を着用した。
 試験終了後の取扱い : 試験操作終了後の使用残分は試験委託者に返却した。

1.2 対照物質（媒体）

名称 : オリーブ油

Lot No. : XXXXXXXXXX

供給源 : XXXXXXXXXXXXXXXXXXXXXXXXXXXX

保管条件 : 室温

保管場所 : 試薬保管室

1.3 被験液の調製

調製濃度 : 0.5 , 5.0 及び 50 mg/mL

調製方法 : 50 mg/mL 液は所定量の被験物質をメスシリンダーに量り取り , オリーブ油を加えてメスアップした後 , ミキサーで攪拌した . 5.0 及び 0.5 mg/mL 液は 50 mg/mL 液をオリーブ油で希釈して調製した .

媒体の選択理由 : 被験物質は水に不溶で , 油溶性のためオリーブ油を選択した .

調製頻度 : 用時調製

被験液の安定性 : 投与開始日及び投与期間中の計 2 回 , 投与に使用した投与液中の調製後 6 時間までの安定性を確認した(添付資料) .

保存方法 : 残液は保存せず廃棄した .

被験液の濃度分析 : 投与開始日及び投与期間中の計 2 回 , 投与に使用した投与液中の被験物質濃度を測定した .

1.4 被験液の濃度分析

1.4.1 実施時期

被験液初回調製時及び投与期間中に 1 回の計 2 回

1.4.2 測定試料

N,N-ジメチルアニリン

1.4.3 調製溶液

0.5 , 5.0 , 50 mg/mL 溶液

1.4.4 測定対象物質

N,N-ジメチルアニリン

1.4.5 標準物質

N,N-ジメチルアニリン

1.4.6 主な使用機器

液体クロマトグラフ : SCL-10Avp シリーズ , 株式会社 島津製作所

検出器 : SPD-10Avp, 株式会社 島津製作所
 データ処理装置 : LC solution, 株式会社 島津製作所

1.4.7 分析方法

1.4.7.1 移動相

メタノールと水を 50 : 50 (v/v) で混ぜた。

1.4.7.2 標準原液及び検量線用標準溶液

N,N-ジメチルアニリン約 100 mg (初回調製時：濃度分析用 103.31 mg 及び調製 6 時間後の安定性試験用 104.08 mg, 投与期間中：濃度分析用 101.81 mg 及び調製 6 時間後の安定性試験用 9.48 mg) を精密に量り, イソプロパノール (IPA) を加えて溶かし, 100 mL とした (標準原液 A ; 1 mg/mL)。標準原液 A 2 mL 取り, IPA を用いて全量 20 mL にした (標準原液 B ; 100 µg/mL)。標準原液 B を以下の表に示すように IPA を用いて正確に希釈し, 検量線用標準溶液 S1 ~ S5 ; 1 ~ 50 µg/mL を調製した。

検量線用 標準溶液	標準原液 B 採取量 (mL)	全量 (mL)	濃度 (µg/mL)
S1	5	10	50
S2	2.5	10	25
S3	1	10	10
S4	1	20	5
S5	1	100	1

注意) 調製には, 褐色メスフラスコを用いた。

1.4.7.3 試料溶液

- 1) 対照物質 (オリーブ油) 1 mL を正確に取り, IPA を加えて溶かし全量 25 mL にした (25 倍希釈)。25 倍希釈した液 5 mL を正確に取り, IPA を加えて全量 10 mL にした (最終 50 倍希釈)。
- 2) 50 mg/mL 被験液 1 mL を正確に取り, IPA を加えて溶かし全量 100 mL にした (100 倍希釈)。この液 1 mL を正確に取り, IPA を加えて溶かし全量 25 mL にした (2500 倍希釈)。2500 倍希釈した液 5 mL を正確に取り, IPA を加えて全量 10 mL にした (最終 5000 倍希釈)。
- 3) 5 mg/mL 被験液 1 mL を正確に取り, IPA を加えて溶かし全量 100 mL にした (100 倍希釈)。この液 10 mL を正確に取り, IPA を加えて溶かし全量 50 mL にした (最終 500 倍希釈)。

- 4) 0.5 mg/mL 被験液 1 mL を正確に取り，IPA を加えて溶かし全量 25 mL にした（25 倍希釈）. 25 倍希釈した液 5 mL を正確に取り，IPA を加えて全量 10 mL にした（最終 50 倍希釈）.

注意）調製には，褐色メスフラスコを用いた．

対照物質の調製は調製直後の 1 回とした．

被験液の採取は撈拌しながら行い，上・中・下層からそれぞれ 1 回採取して計 3 試料を調製した．

安定性用試料溶液としての採取は中層から行い，室温保存 6 時間後に各濃度 1 試料を調製した．保存は室温，遮光条件とした．

1.4.7.4 HPLC 条件

カラム	： CAPCELL PAK C18 MG，4.6×150 mm，5 μm，資生堂
移動相	： メタノール／水混液（50：50，v/v）
流量	： 1.0 mL/min
検出器	： 紫外可視吸光光度計（測定波長：254 nm）
カラム温度	： 40.0
サンプルクーラー温度	： 5.0
試料注入量	： 10 μL

1.4.7.5 分析内容

HPLC 条件に従って操作し，次のパラメータを確認した．

1.4.7.6 システムの再現性

検量線用標準溶液 S3（10 μg/mL）を HPLC 条件に従ってそれぞれ 6 回注入し，*N,N*-ジメチルアニリンのピーク面積の変動係数（CV）を求めた．

1.4.7.7 被験液の濃度測定

被験液を用いて「1.4.7.3 試料溶液」の調製法に従って調製した試料溶液を用い，濃度分析を行った（各 1 回測定）.

被験液の濃度を測定し，その含量及び CV を算出した．濃度算出には検量線用標準溶液 S3 又は検量線用標準溶液 S1～S5 を用いた．

< 測定順序 >

- ・ 検量線用標準溶液 S1～S5
- ・ 試料溶液（被験液 0.5 mg/mL，上層）
- ・ 試料溶液（被験液 5 mg/mL，上層）

- ・ 試料溶液（被験液 50 mg/mL，上層）
- ・ 試料溶液（被験液 0.5 mg/mL，中層）
- ・ 試料溶液（被験液 5 mg/mL，中層）
- ・ 試料溶液（被験液 50 mg/mL，中層）
- ・ 試料溶液（被験液 0.5 mg/mL，下層）
- ・ 試料溶液（被験液 5 mg/mL，下層）
- ・ 試料溶液（被験液 50 mg/mL，下層）
- ・ 試料溶液（対照物質）

1.4.7.8 被験液の安定性

室温，遮光条件下で 6 時間保存しておいた被験液の中層を用い，「1.4.7.3 試料溶液」の調製法に従って試料溶液を調製し，濃度分析を行った（各 1 回測定）。

6 時間保存後の被験液の濃度を測定し，調製直後の測定濃度に対する安定性を算出した．濃度算出には検量線用標準溶液 S1～S5 を用いた．

< 測定順序 >

- ・ 検量線用標準溶液 S1～S5
- ・ 試料溶液（被験液 0.5 mg/mL，中層）
- ・ 試料溶液（被験液 5 mg/mL，中層）
- ・ 試料溶液（被験液 50 mg/mL，中層）

1.4.8 データ処理

データ処理装置でクロマトグラム及びピーク面積を記録した．得られた各ピーク面積から，次式を用いて *N,N*-ジメチルアニリンの濃度を算出した．計算は表計算ソフト Excel（Microsoft）を使用して行った．

（1）被験液の測定濃度（mg/mL）

$Y=a+bX$ より

$X=(Y-a)/b$ 又は $X=(Y-a)/b \times \text{希釈係数}/1000$

Y = 各試料溶液の *N,N*-ジメチルアニリンのピーク面積

a = y 切片

b = 傾き

希釈係数 0.5 mg/mL； 50，5 mg/mL； 500，50 mg/mL； 5000

被験液の測定濃度は，有効数字 4 桁で求めた．

(2) 被験液の含量

$$\text{被験液の含量 (\%)} = \frac{\text{被験液の測定濃度}}{\text{被験液の理論濃度}} \times 100$$

値は整数で求めた。

(3) 変動係数 (CV %)

$$\text{CV (\%)} = (\text{標準偏差} / \text{平均値}) \times 100$$

値は小数点以下 1 桁まで求めた。

(4) 被験液の残存率 (安定性, %)

$$\text{残存率 (\%)} = \frac{\text{各保存後の測定濃度}}{\text{直後の測定濃度平均値}} \times 100$$

値は整数で求めた。

1.4.9 判定基準

判定基準は以下の通りとした。

(1) システムの再現性

ピーク面積の CV (%): 3%以下

(2) 直線性

検量線の相関係数: 0.995 以上

(3) 被験液の含量及び変動係数 (CV)

含量 (設定濃度に対する百分率): 85 ~ 115%

各試料溶液濃度の CV (%): 10%以下

(4) 被験液の残存率 (安定性, %)

調製直後の測定濃度に対する残存率 (6 時間後の安定性): 90 ~ 110%

1.5 試験系

1.5.1 使用動物

種	: ラット
系統	: CrI:CD (SD)
微生物学的グレード	: SPF
性別	: 雌雄
入手動物数	: 雄 57 匹, 雌 67 匹
使用動物数	: 雄 48 匹, 雌 58 匹
入手時の週齢	: 8 週齢
投与開始時の週齢	: 9 週齢
入手時の体重範囲	: 雄 277.0 ~ 301.4 g, 雌 191.6 ~ 215.3 g

投与時の体重範囲 : 雄 336.7～381.4 g, 雌 214.9～250.5 g
 供給源 : 日本チャールス・リバー株式会社（日野飼育センター）

1.5.2 試験系選択の理由

げっ歯類の動物として毒性試験に汎用されており，背景データも豊富であるため。

1.5.3 検疫及び馴化

検疫期間 : 入手日を含めて 7 日間
 観察及び測定 : 入手時に動物の健康状態を肉眼的に確認して異常の認められない動物を飼育室に収容し，試験と同様の飼育条件及び飼育環境下で 7 日間検疫・馴化飼育した。検疫・馴化期間中は，一般状態を毎日観察し，入手日と馴化終了日に体重測定を行い，供試動物選択の指標とした。その結果，検疫，馴化期間中に全ての動物に異常は認められなかった。また，群分け後の余剰動物のうち 5 匹をモニター動物とし，試験動物の飼育期間終了後に剖検及び特定病原菌に対する微生物学的検査に供した。その結果，検査動物全例に異常は認められなかった。

1.5.4 識別方法

個体識別 : 親動物は入手時に耳パンチにより仮番号を付け，群分け後は仮番号と本番号との対応表を用いて識別した。児動物は識別しなかった。
 ケージ識別 : 試験番号，被験物質番号，試験の種類，動物種，系統，試験群，動物番号（本番号），個体識別番号（仮番号），投与・観察期間及び試験責任者を記入した色カードをケージ前面に取り付けた。

1.5.5 飼育室の環境

飼育室名 : S-101 飼育室
 温度 : 20～26℃（実測値 22.7～25.9℃）
 湿度 : 35～75%（実測値 34.7～67.6%）
 換気回数 : 15～25 回/時間
 照明時間 : 12 時間（7～19 時）/日

1.5.6 収容方法

ラック	: 鉄製可動ラック
ケージ	: 雄はアルミ製金網底ケージ (240 mm W×380 mm D×200 mm H) に収容し飼育した。雌は妊娠 17 日～授乳期間中は床敷を入れたアルミ製平底ケージ (340 mm W×460 mm D×180 mm H) に、その他の期間はアルミ製金網底ケージ (240 mm W×380 mm D×200 mm H) に収容した。
収容匹数	: 交配期間中は雌雄を、授乳期間中は母動物と出生児を同居させ、その他の期間は個別飼育とした。
ケージ交換頻度	: 2 週間に 1 回以上、高圧蒸気滅菌したものと交換した。

1.5.7 飼料

種類	: 固型飼料 F-2
供給源	: 株式会社 船橋農場
滅菌方法	: RI 滅菌 (株式会社コーガアイソトープに委託)
給餌方法	: 飼料をステンレス製給餌器に入れ自由摂取させた。給餌器は 2 週間に 1 回以上、高圧蒸気滅菌したものと交換した。
飼料の分析	: ロット毎に、株式会社 船橋農場を介して財団法人 日本食品分析センターで測定したデータを入手し、汚染物質濃度が SOP No. KA/01/02 に定めた限度値以下であることを確認した。

1.5.8 飲水

種類	: 水道水 (甲賀市)
給水方法	: 水道水を透明ポリカーボネイト製給水瓶に入れ、金属製ノズルを介して自由摂取させた。給水瓶及び給水ノズルは 1 週間に 3 回以上、高圧蒸気滅菌したものと交換した。
飲水の分析	: 水道水質基準 (平成 15 年 5 月 30 日厚生労働省令第 101 号) に従って、年 2 回の頻度で飲水の水質及び微量汚染物質の分析を株式会社 システムエイトに依頼している。飲水の最新 (2006 年 8 月 1 日) の分析結果は、水道水質基準に適合していた。

1.5.9 床敷

妊娠 17 日～授乳期間中は以下の床敷を使用した。

種類	: パルソフト（オリエンタル酵母工業株式会社）
使用方法	: オートクレーブ滅菌
床敷の分析	: 分析データを入手し，汚染物質濃度が限界値以下であることを確認した．

1.6 抽出及び群分け

投与開始前日に検疫・馴化期間中の体重増加が順調で一般状態にも異常を認めない動物から必要匹数を選別し，当日の体重を指標として層別無作為化割付法に従って群分けした．群分け後の余剰動物は試験より除外した．

1.7 試験構成

試験群	投与用量 (mg/kg/day)	雄親動物数	雌親動物数
		匹数（動物番号）	匹数（動物番号）
媒体対照群	0	7（1101-1107）	12（2101-2112）
媒体対照回復群	0	5（1121-1125）	5（2121-2125）
低用量群	1	12（1201-1212）	12（2201-2212）
中用量群	10	12（1301-1312）	12（2301-2312）
高用量群	100	7（1401-1407）	12（2401-2412）
高用量回復群	100	5（1421-1425）	5（2421-2425）

媒体対照群には媒体を投与した．

1.8 投与

投与経路	: 経口投与
投与経路の選択理由	: ヒトの暴露形態を考慮し，反復経口投与毒性・生殖発生毒性を予測するため．
投与量	: 1) 0 mg/kg（媒体投与） 2) 1 mg/kg 3) 10 mg/kg 4) 100 mg/kg
投与量の設定理由	: 14日間反復経口投与した「 <i>N,N</i> -ジメチルアニリン」のラットを用いた反復経口投与毒性・生殖発生毒性併合試験の投与量設定試験」（日精バイリス株式会社 滋賀研究所，試験番号 5298）の結果，30，100，300 及び 1000 mg/kg 投与群において投与 2 日以降メトヘモグロビン血症によるものと考えられるチアノーゼ様症状（皮膚及び眼球の暗赤色・紫色）

	が認められ、1000 mg/kg 投与群では投与 3～4 日に全例が死亡した。また、最低用量の 30 mg/kg においても脾臓の腫大が認められた。この結果から、本試験では反復投与毒性の発現が確実で、妊娠及び分娩が可能な最大用量と考えられる 100 mg/kg/day を高用量とし、以下公比 10 で 10 及び 1 mg/kg/day を設定した。これに被験物質の媒体であるオリーブ油を投与する媒体対照群を加えて計 4 群構成とした。
投与容量	: 2 mL/kg (投与液量は個体別の最新体重に基づいて算出した。)
投与容量の設定理由	: 2 mL/kg はオリーブ油をラットに反復経口投与した際に、オリーブ油投与の影響が認められない最大容量である。
投与方法	: ディスポーザブル注射筒及びラット用胃ゾンデを用いて強制投与した。
投与方法の選択理由	: ヒトの暴露形態を考慮し経口投与を選択した。
投与期間	: 投与開始日を投与 1 日とした。雄は交配開始 2 週間前から交配期間を通し解剖前日まで 42 日間、毎日 1 回反復経口投与した。雌は交配開始 2 週間前から交配期間、妊娠期間及び授乳期間を通し解剖前日(哺育 4 日)まで毎日反復経口投与した。雌の媒体対照回復群及び高用量回復群については、交配を実施せず 42 日間毎日反復経口投与した。
投与期間の選択理由	: 試験法「OECD TG 422」に準拠した。
回復期間	: 媒体対照回復群及び高用量回復群の雌雄各々 5 匹について 14 日間の回復期間を設けた。投与最終日翌日を回復 1 日、回復開始週を回復 1 週とした。

1.9 観察，測定，検査

1.9.1 反復投与毒性

1.9.1.1 一般状態

雌雄ともに、投与期間中は 1 日 2 回(投与直前及び投与後 1～4 時間)、回復期間中は 1 日 1 回の頻度で、一般状態の観察及び死亡の有無の確認を行った。

1.9.1.2 詳細観察

雌雄各群について投与開始前に 1 回と投与期間中は週 1 回(投与後約 3.5～5.5 時間後)、分娩成立の母動物についてはさらに哺育 4 日(投与後約 3.5～5.5 時間後)に実施した。

ケージから取り出す際の反応として動物を保持するために手を近づけたり、あるいは保

持するなど動物に外部刺激を与えた場合の動物の興奮性などの反応(取り出し易さ,発声)を観察した。ハンドリングによる詳細な観察として動物の筋緊張,体温低下,立毛,被毛の状態(毛の汚れ,被毛粗剛),皮膚及び粘膜の色(蒼白,発赤,チアノーゼ),眼の異常(流涙,眼球突出,瞳孔径),流涎,分泌物を観察した。その後,底面 60×90 cm,壁高 6 cm のオープンフィールドの中央に動物を静かに置き,1 分間の観察時間中の立ち上がり回数,間代性の不随意運動,強直性の不随意運動,歩調,移動性,覚醒状態,常同行動,異常行動,脱糞及び排尿を観察し記録した。各観察はブラインドで実施した。

1.9.1.3 機能検査

雄は,投与期間の最終週に 1 回,各群とも動物番号の小さい順から 5 匹を選び,投与後約 3.5～5.5 時間後に検査を実施した。

雌は,解剖前日(哺育 4 日)の絶食前に 1 回,分娩日の近い 5 匹を選び,投与後約 3.5～5.5 時間後に検査を実施した。

顔面前 3 cm に丸い棒等を近づけたときの視覚(接近・触覚)反応,頭上で指を鳴らしたときの聴覚反応,洗濯バサミで尾の 1/3 尾根部側を挟んだときの痛覚反応を記録した。さらに,光を遮った状態でペンライトの光を当てたときの瞳孔反射,動物の腹部を上に向けた状態で約 30 cm の高さから落としたときの空中正向反射を記録した。握力測定としては小動物握力測定装置(GPM-100,(有)メルクエスト)を用いて前後肢の握力を測定した。自発運動量は,ラットを個別にプラスチック製平底ケージ(215 mm(W)×320 mm(D)×130 mm(H))に入れ,15 分間の運動量を受動型赤外線センサー方式による自発運動量計測システム(Supremex,室町機械㈱)で測定した。各検査はブラインドで実施した。

1.9.1.4 体重測定

雄の体重は,投与開始日,投与 3,8,15,22,29 及び 36 日に測定し,回復期間は,1,3,7 及び 14 日に測定した。さらに,予定解剖例については,投与期間終了日の翌日あるいは回復期間終了の翌日の搬出時(絶食状態)にも体重測定を実施した。

交配実施雌の体重は,投与開始日,投与 3,7 及び 14 日に測定し,交尾成立後は妊娠 0,7,14,17 及び 20 日と哺育 0 日(分娩日)及び 4 日,さらに分娩後 5 日(搬出時・絶食状態)に測定した。媒体対照回復群及び高用量回復群の雌については,投与開始日,投与 3,8,15,22,29 及び 36 日に体重測定し,回復期間中は回復 1,3,7,14 及び 15 日(搬出時・絶食状態)に測定した。

測定には,電子天秤(BW-3200S 型,㈱島津製作所)を用いた。

1.9.1.5 摂餌量測定

雄の摂餌量は，投与開始日，投与 3，8，20，22，29 及び 36 日，さらに回復 1，3，7，14 日に測定した。

交配実施雌の摂餌量は，投与開始日，投与 7 及び 14 日，さらに交配成立後は妊娠 7，14，17 及び 20 日と哺育 4 日に測定した。媒体対照回復群及び高用量回復群の雌の摂餌量は，投与開始日，投与 3，8，15，22，29 及び 36 日，さらに回復 1，3，7 及び 14 日に測定した。

摂餌量の測定には，電子天秤（BW-3200S 型，（株）島津製作所）を用い，測定前日の給餌量から当日の摂取残量を差し引くことで 1 日当たりの摂餌量を算出した。

1.9.1.6 尿検査

媒体対照回復群及び高用量回復群を除く雄は，各群から動物番号の小さい順に 5 匹を選び，投与最終日に検査した。媒体対照回復群及び高用量回復群の雄は，回復期間終了日に全例について検査した。

分娩動物では各群とも分娩日の近い 5 匹について投与最終日に検査し，交配を実施しなかった媒体対照回復群及び高用量回復群の雌では回復 14 日に全例について検査した。

給餌，給水下で採取した新鮮尿の pH，蛋白，糖，ケトン体，ビリルビン，潜血及びウロビリノーゲンを尿検査試験紙（マルティスティックス，バイエル メディカル（株））を用いて検査した。

1.9.1.7 血液学的検査

媒体対照回復群及び高用量回復群を除く雄は各群から動物番号の小さい順に 5 匹を選び最終投与の翌日に検査した。媒体対照回復群及び高用量回復群の雄については回復期間終了日の翌日に全例について検査した。なお，いずれの動物も採血前日の夕方より 1 晩（16～20 時間）絶食処置を施した。但し，投与期間終了時の 1 mg/kg 投与群の雄 1 例については，麻酔過誤により死亡したため血液学的検査及び次項の血液生化学的検査結果を集計より除外した。

分娩動物では各群とも分娩日の近い雌 5 匹について分娩後 5 日に実施し，交配を実施しなかった回復群の雌については，回復期間終了日の翌日に全例を検査した。なお，いずれの動物も採血前日の夕方より 1 晩（16～20 時間）絶食処置を施した。

いずれの動物も，エーテル麻酔下で開腹し，後大静脈から採血した血液を用いて以下の血液学的検査を行った。

赤血球数（RBC），ヘモグロビン濃度，ヘマトクリット値，白血球数（WBC）及び血小板数（Platelet）は，EDTA-2K 添加により抗凝固処理した血液について，Sysmex 自動血球計数装置 F-800（Sysmex（株））を用いて測定し，平均赤血球容積（MCV），平均赤血球色素量（MCH）及び平均赤血球色素濃度（MCHC）を算出した。さらに，May-Giemsa 染

色の血液塗抹標本を作製し白血球型別百分率(好塩基球(Basophil),好酸球(Eosinophil),桿状核好中球(Stab neutrophil),分葉核好中球(Segmented neutrophil),リンパ球(Lymphocyte),単球(Monocyte),その他(Other))を計測した。

また,血液凝固系の検査として,3.3%クエン酸ナトリウム添加により抗凝固処理を行った後,遠心分離(4℃,3000 rpm,10 分間)して得た血漿を用いて,プロトロンビン時間(PT)及び活性化部分トロンボプラスチン時間(APTT)を Sysmex 全自動血液凝固測定装置 CA-1500 (Sysmex(株))で測定した。

1.9.1.8 血液生化学的検査

雌雄ともに,血液学的検査時に採取した血液の一部をヘパリンナトリウムにより抗凝固処理し,遠心分離(4℃,3000 rpm,10 分間)して得た血漿を用いて,以下の血液生化学的検査を実施した。

アスパラギン酸アミノ基転移酵素(AST)は UV 酵素法(JSCC 標準化対応),アラニンアミノ基転移酵素(ALT)は UV 酵素法(JSCC 標準化対応),アルカリホスファターゼ(ALP)は p-ニトロフェニルリン酸基質法,総蛋白は Biuret 法,アルブミンは BCG 法,グルコースはヘキソキナーゼ・G-6-PDH 法,総コレステロールは COD・HDAOS 法,トリグリセライドは GPO・HDAOS 法及びグリセリン消去法,総ビリルビンパナジン酸酸化法,尿素窒素はウレアーゼ・GIDH 法,クレアチニンはクレアチニナーゼ・F-DAOS 法,無機リンは PNP・XDH 法,及びカルシウムは MXB 法により日立 7170 形自動分析装置(株)日立製作所)で測定した。Na は炎光光度法,K は炎光光度法,Cl は電量滴定法により,710 形電解質自動分析装置(株)日立製作所)で測定した。蛋白分画は Cellulose acetate electrophoresis 法により平沼コンピューティングデンシトメータ HAD-501 (平沼産業(株))で測定した。

1.9.1.9 剖検及び器官重量測定

雄に関しては投与期間終了日の翌日及び回復期間終了日の翌日に当該動物の全例について,また,雌に関しては最終投与の翌日(分娩後 5 日)あるいは回復期間終了日の翌日に当該動物の全例について,さらに,不妊例については交尾 26 日後に放血致死させ病理学的手技に従って解剖し,体表,開孔部,皮下,頭蓋腔,胸腔,腹腔,骨盤腔とその内容の観察を含む肉眼的検査を実施した。

全ての動物について,脳(大脳,小脳及び橋を含む),下垂体,甲状腺(上皮小体を含む),気管及び肺,胸腺,心臓,肝臓,腎臓,脾臓,副腎,精巣,精巣上体,前立腺,精嚢,卵巣,子宮,膣,胃,小腸(十二指腸,回腸(パイエル板を含む)),大腸(結腸),盲腸,膀胱,脊髄,坐骨神経,骨髓(大腿骨)及びリンパ節(腋窩及び腸間膜リンパ節)を摘出した。なお,妊娠雌については,卵巣及び子宮摘出後に妊娠黄体数及び着床数を数えた。

これら摘出臓器のうち,脳,胸腺,心臓,肝臓,腎臓,脾臓,副腎,精巣及び精巣上体

重量を測定した。重量測定後、摘出した器官及び組織は 10%中性緩衝ホルマリン液に固定し保存した。

1.9.1.10 病理組織学的検査

雄については、投与期間終了時の高用量群と媒体対照群の動物番号の小さい順に各 5 匹から採取した全器官・組織に加え、投与期間終了時の 1 及び 10 mg/kg 投与群の動物番号の小さい順から各 5 匹と回復期間終了時の高用量群及び媒体対照群の全例から採取した肝臓、脾臓及び骨髄について、パラフィン包埋後薄切切片を作製し、ヘマトキシリン・エオジン染色した後、光学顕微鏡的に検査した。

雌については分娩日の近い雌 5 匹（血液学的検査及び血液生化学的検査を実施した動物）について、各々採取した全ての器官・組織に加え、投与期間終了時の 1、10 mg/kg 投与群の各 5 匹（血液学的検査・血液生化学的検査に用いたものと同一動物）と回復期間終了時の高用量群と媒体対照群の雌雄全例から採取した肝臓、脾臓及び骨髄について、同様の方法で検査した。

1.9.2 親動物の生殖発生に及ぼす影響

1.9.2.1 性周期検査

交配予定動物の雌全例について投与開始日から交尾が確認された日まで膣垢検査により性周期を観察した。

1.9.2.2 交配，交尾確認

14 日間投与した雌雄を同一群内で 1 対 1 に組み合わせて同居交配した。同居期間は 14 日間を限度として交尾を確認するまで連続同居交配させた。交尾確認は毎朝行い、膣栓又は膣垢中の精子を確認した雌を交尾成立としてこの日を妊娠 0 日と起算した。

1.9.2.3 分娩日の検査

妊娠動物の全例は自然分娩させた。分娩完了の確認は、午前中に営巢し、授乳を開始した状態、又は膣周囲の状態を確認し、腹部を触診することで行った。交尾が確認された日から分娩完了までの日数を妊娠期間とした。1 匹以上の生存児を出産したものを正常出産とし、出産児が全て死亡していた場合、生存児を出産したものであっても難産などの分娩異常がみられた場合及び分娩完了の確認が出来ない場合は異常出産とした。

1.9.3 出生児

1.9.3.1 出生児の観察

出生日に総産児数、出産死亡児数及び出産生児数を数え、出産生児性を算出し、出産

生児外表を観察した。

1.9.3.2 一般状態観察

出生日から屠殺日まで，毎日1回観察し，死亡の有無及び一般状態をした。

1.9.3.3 体重測定

出生日及び生後4日（屠殺日）に個体別に体重測定し，1腹の雌雄それぞれの平均値を1単位とした。

1.9.3.4 屠殺日の観察及び検査

生児数，生児外表，死亡児数及び死亡児外表を観察した。

1.10 統計学的処理

媒体対照群と各投与群との有意差検定は，The SAS System Ver.8.2 (TS2M0) for Windows (SAS Institute Inc.) に連動した生物実験データ統計解析システム (EXSAS Ver.7.10, (株)アームシステックス) を用いて行った。なお，Williams の多重比較検定及び Fisher の直接確率法は片側検定，その他の検定法では両側検定とした。有意水準は，5%及び1%とした。哺育児の成績は1腹児の値を標本単位とした。

(1) 計量値

Bartlett 検定で等分散 ($p > 0.05$) を示すデータについては，一元配置分散分析を行い，その結果，母平均が等しくない ($p < 0.05$) 場合は Dunnett の多重比較検定を行った。また，全てのデータについて，用量相関性の検定として Williams の多重比較検定を行った。

Bartlett 検定で不等分散 ($p < 0.05$) を示すデータについては，Kruskal-Wallis の順位検定を行い，その結果，母平均が等しくない ($p < 0.05$) 場合は Steel の多重比較検定を行った。但し，2群間の比較の場合には，2群間の等分散性について分散比の F 検定を行い等分散 ($p > 0.05$) の場合には Student の t 検定，不等分散 ($p < 0.05$) の場合には Aspin-Welch の t 検定を行った。

(2) 整数観測値

Kruskal-Wallis の順位検定を行い，その結果，母平均が等しくない ($p < 0.05$) 場合は Steel の多重比較を行った。

(3) 度数

媒体対照群と他の2群間で Fisher の直接確率法を行った。

2. 試験成績

2.1 被験液の分析結果

システム再現性における *N,N*-ジメチルアニリンのピーク面積の CV は 1.1% (初回調製時の分析) 及び 0.6% (投与期間中の分析) であり、いずれも基準を満たした。

初回調製時に分析した *N,N*-ジメチルアニリンの平均含量は 0.5 mg/mL 被験液で 89%、5.0 mg/mL 被験液で 95%、50 mg/mL 被験液で 96% であった。投与期間中に実施した分析では *N,N*-ジメチルアニリンの平均含量は 0.5 mg/mL 被験液で 105%、5.0 mg/mL 被験液で 106%、50 mg/mL 被験液で 99% であった。

室温遮光保存 6 時間後の被験液中の *N,N*-ジメチルアニリンの平均残存率については、初回調製時では 0.5 mg/mL 被験液で 101%、5.0 mg/mL 被験液で 100%、50 mg/mL 被験液で 99% であり、投与期間中の分析では 99%、5.0 mg/mL 被験液で 99%、50 mg/mL 被験液で 100% であった。

以上の結果より、本試験に用いた被験液は正確に調製されていると判断した。また、調製から投与終了時まで被験液は安定であったと判断した (添付資料)。

2.2 反復投与毒性

2.2.1 雄

2.2.1.1 一般状態 (Table 1)

いずれの群にも、死亡及び瀕死例は認められなかった。

投与期間中に、皮膚の暗赤色化が 100 mg/kg 投与群の 12/12 例に投与 2 日より投与期間中を通じて認められた。媒体対照群、1 及び 10 mg/kg 投与群に異常は認められなかった。

回復期間中には、皮膚の暗赤色化が 100 mg/kg 回復群の 5/5 例に終始認められた。媒体対照回復群に異常は認められなかった。

2.2.1.2 詳細観察 (Table 2)

投与 1 週目から 6 週目の観察において、100 mg/kg 投与群で全例に皮膚の暗赤色化が認められた。10 mg/kg 投与群には、投与前の排尿回数に偶発性の高値が認められた。媒体対照群、1 mg/kg 投与群には、異常は認められなかった。

2.2.1.3 機能検査 (Table 3)

被験物質投与群に有意差は認められなかった。

2.2.1.4 体重測定 (Fig. 1)

被験物質投与群に有意差は認められなかった。

2.2.1.5 摂餌量測定 (Fig. 2)

100 mg/kg 投与群で投与 36 日の摂餌量に有意な低値が認められた。また, 10 mg/kg 投与群で投与 22 日の摂餌量に有意な高値が認められた。しかしながら, いずれの変動も用量に依存しないことから偶発によるものと判断する。1 mg/kg 投与群では, 有意差は認められなかった。

2.2.1.6 尿検査 (Table 4)

投与期間終了時及び回復期間終了時に, 被験物質群の各検査項目に有意差は認められなかった。

2.2.1.7 血液学的検査 (Table 5)

投与期間終了時に, 100 mg/kg 投与群で, 赤血球数, ヘモグロビン量, ヘマトクリット値及び平均赤血球血色素濃度に有意な低値と平均赤血球容積, 平均赤血球血色素量及び白血球数に有意な高値が認められた。1 及び 10 mg/kg 投与群では, 各検査項目に有意差は認められなかった。

回復期間終了時には, 100 mg/kg 回復群で, 平均赤血球血色素濃度に有意な低値と平均赤血球容積及び平均赤血球血色素量に有意な高値が認められた。

2.2.1.8 血液生化学的検査 (Table 6)

投与期間終了時に, 100 mg/kg 投与群で, 総蛋白及び γ -グロブリンに有意な低値と総ビリルビンに有意な高値が認められた。10 及び 1 mg/kg 投与群では, 各検査項目に有意差は認められなかった。

回復期間終了時には, 100 mg/kg 回復群に有意差は認められなかった。

2.2.1.9 器官重量測定 (Table 7)

投与期間終了時に, 100 mg/kg 投与群で, 肝臓の相対重量に有意な高値, 脾臓の絶対重量及び相対重量に有意な高値, さらに腎臓の相対重量に有意な高値が認められた。10 mg/kg 投与群では, 胸腺の絶対重量及び相対重量に有意な高値, さらに肝臓の相対重量に有意な高値が認められた。1 mg/kg 投与群では, 各器官重量に有意差は認められなかった。

回復期間終了時には, 100 mg/kg 回復群で, 精巣の相対重量に有意な高値が認められた。

2.2.1.10 剖検所見 (Table 8)

投与期間終了時に, 100 mg/kg 投与群の 7/7 例に脾臓の暗赤色及び腫大が認められた。媒体対照群, 1 及び 10 mg/kg 投与群には異常は認められなかった。

回復期間終了時には, 媒体対照回復群の 1/5 例の脾臓に小結節を伴う腫大が認められ,

100 mg/kg 回復群では 4/5 例に脾臓の腫大が認められた。

2.2.1.11 病理組織学的検査 (Table 9)

1) 被験物質投与に起因した所見

投与期間終了時

100 mg/kg 投与群では、肝臓に髄外造血の亢進及び黄褐色色素沈着が各々 5/5 例、脾臓にはうっ血、白脾髄の萎縮、髄外造血の亢進及び黄褐色色素沈着が各々 5/5 例、骨髓には赤芽球系細胞の過形成が 5/5 例認められた。

10 mg/kg 投与群では、脾臓にうっ血が 1/5 例認められた。

回復期間終了時

100 mg/kg 回復群では、肝臓に黄褐色色素沈着が 4/5 例、脾臓にはうっ血が 1/5 例、黄褐色色素沈着が 5/5 例認められた。

2) 被験物質投与に起因しない所見

以下の所見はラットに自然発生的に認められる変化であり、いずれの所見も出現頻度が低いことから被験物質投与の影響ではないものと判断する。

投与期間終了時

100 mg/kg 投与群では、肝臓に限局性の出血及び小肉芽腫、精巣に限局性精細管萎縮、前立腺には間質内炎症性細胞浸潤が認められた。1 mg/kg 投与群では肝臓に出血性壊死が認められ、媒体対照群では肺動脈に石灰沈着、肺に異所性骨形成、心臓に炎症性細胞浸潤、肝臓に小肉芽腫、精巣に限局性精細管萎縮及び前立腺に間質内炎症性細胞浸潤が散見された。

回復期間終了時

100 mg/kg 回復群では、肝臓に小肉芽腫、媒体対照回復群では、肝臓に髄外造血の亢進及び肝臓と脾臓に出血性壊死及び組織球性肉腫が散見された。

2.2.2 雌

2.2.2.1 一般状態 (Table 10)

いずれの群にも、死亡及び瀕死例は認められなかった。

投与期間中に、皮膚の暗赤色化が 100 mg/kg 投与群の 17/17 例に投与 2 日より投与期間中を通じて認められた。媒体対照群、1 及び 10 mg/kg に異常は認められなかった。

回復期間中には、皮膚の暗赤色化が 100 mg/kg 回復群の 5/5 例に、終始認められた。媒体対照回復群に異常は認められなかった。

2.2.2.2 詳細観察 (Table 11)

投与 1 週目から 6 週目の観察において、100 mg/kg 投与群で全例に皮膚の暗赤色化が認

められた。なお、投与 6 週目の 100 mg/kg 回復群で、立ち上がり回数に有意な低値が認められたが、媒体対照群回復群の立ち上がり回数の高値に起因した変動であり、被験物質投与の影響はないものと判断する。媒体対照群、1 及び 10 mg/kg 投与群には、異常は認められなかった。

2.2.2.3 機能検査 (Table 12)

被験物質投与群に有意差は認められなかった。

2.2.2.4 体重測定 (Fig. 3, Fig. 5)

交配を実施した動物では、100 mg/kg 投与群で、投与 7 日、妊娠 17 日及び妊娠 20 日の体重に有意な低値が認められた。1 及び 10 mg/kg 投与群では有意差は認められなかった。

交配を実施しなかった回復群では、100 mg/kg 回復群の投与 8, 22, 29 及び 36 日、回復 1, 3, 7 及び 14 日の体重に有意な低値が認められた。

2.2.2.5 摂餌量測定 (Fig. 4, Fig. 6)

交配を実施した動物では、100 mg/kg 投与群で、投与 7 日の摂餌量に有意な低値が認められたが、媒体対照群で餌の噛みこぼし例が出現したことに起因したものと判断する。1 及び 10 mg/kg 投与群では有意差は認められなかった。

交配を実施しなかった回復群においては、100 mg/kg 回復群に有意差は認められなかった。

2.2.2.6 尿検査 (Table 13)

投与期間終了時及び回復期間終了時に、被験物質投与群の各検査項目に有意差は認められなかった。

2.2.2.7 血液学的検査 (Table 14)

投与期間終了時に、100 mg/kg 投与群で、赤血球数、ヘモグロビン量及びヘマトクリット値に有意な低値と平均赤血球容積及び平均赤血球色素量に有意な高値が認められた。1 及び 10 mg/kg 投与群では、各検査項目に有意差は認められなかった。

回復期間終了時に、100 mg/kg 回復群で、赤血球数に有意な低値とヘモグロビン量、ヘマトクリット値、平均赤血球容積及び平均赤血球色素量に有意な高値が認められた。

2.2.2.8 血液生化学的検査 (Table 15)

投与期間終了時に、100 mg/kg 投与群で、 α_1 -グロブリンに有意な低値と総ビリルビン及び尿素窒素に有意な高値が認められた。10 mg/kg 投与群では、 α_1 -グロブリンに有意な低

値が認められた．1 mg/kg 投与群の各検査項目には有意差は認められなかった．

回復期間終了時に，100 mg/kg 回復群で，総ビリルビン及びクレアチニンに有意な低値が認められた．

2.2.2.9 器官重量測定 (Table 16)

投与期間終了時に，100 mg/kg 投与群で，心臓の相対重量に有意な高値と脾臓の絶対重量及び相対重量に有意な高値が認められた．10 mg/kg 投与群では，腎臓の相対重量に有意な高値が認められた．1 mg/kg 投与群では各器官重量に有意差は認められなかった．

回復期間終了時には，100 mg/kg 回復群で，脾臓の絶対重量及び相対重量に有意な高値が認められた．なお，100 mg/kg 回復群で脳相対重量及び腎臓の相対重量に有意な高値が認められたが，病理組織学変化が認められないことから体重低値に起因した変動であり，毒性学的意義はないものと判断する．

2.2.2.10 剖検所見 (Table 17)

投与期間終了時に，100 mg/kg 投与群の 12/12 例に脾臓の暗赤色及び腫大が認められた．媒体対照群，1 及び 10 mg/kg 投与群に異常は認められなかった．

回復期間終了時に，媒体対照回復群及び 100 mg/kg 回復群に異常は認められなかった．

2.2.2.11 病理組織学的検査 (Table 18)

1) 被験物質投与に起因した所見

投与期間終了時

100 mg/kg 投与群では，肝臓に髄外造血の亢進が及び黄褐色色素沈着が各々 5/5 例，骨髓には赤芽球系細胞の過形成が 5/5 例，脾臓にはうっ血，白脾髄の萎縮，髄外造血の亢進及び黄褐色色素沈着が各々 5/5 例認められた．

10 mg/kg 投与群では，骨髓に赤芽球系細胞の過形成が 3/5 例，脾臓にはうっ血が 2/5 例及び髄外造血の亢進が 1/5 例認められた．

1 mg/kg 投与群では骨髓に赤芽球系細胞の過形成が 1/5 例，脾臓にうっ血が 2/5 例認められた．

回復期間終了時

100 mg/kg 回復群では，肝臓に黄褐色色素沈着が 3/5 例，骨髓には赤芽球系細胞の過形成が 1/5 例，脾臓には黄褐色色素沈着が 5/5 例に認められた．

2) 被験物質投与に起因しない所見

以下の所見はラットに自然発生的に認められる変化であり，いずれの所見も出現頻度が低いことから被験物質投与の影響ではないものと判断する．

投与期間終了時

1 mg/kg 投与群で肝臓に小肉芽腫が，媒体対照群で肺に肺動脈に石灰沈着及び異所性骨形成が少数例に認められた．

回復期間終了時

100 mg/kg 回復群では，肝臓に小肉芽腫が 1/5 例，媒体対照群では肝臓に出血壊死が 1/5 例及び小肉芽腫が 1/5 例に認められた．

2.3 生殖毒性試験

2.3.1 親動物の生殖発生に及ぼす影響

2.3.1.1 性周期，交尾率及び受胎率（Table 19）

被験物質投与群では，交配前 14 日間の平均性周期長，及び交尾所要日数及び受胎率に有意差は認められなかった．交配期間中に性周期の異常を示す動物はいずれの群にも認められなかった．

2.3.1.2 妊娠期間，分娩状態，妊娠黄体数，着床率及び出産率（Table 20）

被験物質投与群では，妊娠期間，妊娠黄体数，着床数及び着床率に有意差は認められなかった．

出産率はいずれの群も 100%であり，分娩状態及び哺育状態に異常例は認められなかった．

2.3.2 出生児

2.3.2.1 出生児の観察（Table 20）

被験物質投与群で，出生日における総産児数，出産死亡児数及び出產生児数に有意差は認められなかった．なお，100 mg/kg 投与群で性比に有意な低値が認められたが，妊娠黄体数，着床数，着床率，産児数，死産児数及び出產生児数に有意差が認められなかったことから，偶発によるものと判断する．

出產生児の外表観察では，いずれの群にも異常例は認められなかった．

2.3.2.2 一般状態観察（Table 20）

被験物質投与群で，生後 4 日の生存児数及び新生児の 4 日生存率に有意差は認められなかった．児動物の一般状態では，いずれの群にも異常例は認められなかった．

2.3.2.3 体重測定（Table 20）

被験物質投与群の出生日及び生後 4 日の雌雄別体重に有意差は認められなかった．

2.3.2.4 屠殺日の観察及び検査 (Table 20)

いずれの群にも異常例は認められなかった。

3. 考察

N,N-ジメチルアニリンのラットを用いた反復経口投与毒性・生殖発生毒性併合試験を行い、雌雄動物に対する毒性を検討するとともに雌雄親動物の生殖能力及び児動物の発生・発育に及ぼす影響について検討した。

反復経口投与毒性

100 mg/kg 投与群では、雌雄の一般状態の観察において投与 2 日より回復期間終了時まで皮膚の暗赤色化が全例に認められ、詳細観察においても同様の所見が認められた。*N,N*-ジメチルアニリンの生体に及ぼす影響としては、貧血、メトヘモグロビン血症が知られており¹⁾、皮膚の暗赤色変化はメトヘモグロビン血症に起因したものと推測される。体重推移については、雄では対照群との間に有意差は認められなかったものの、100 mg/kg 投与群の母動物では投与 7 日、妊娠 17 日及び 20 日に体重の低値が認められ、交配を実施しなかった雌の回復群でも投与 8, 22, 29, 36 日、回復 1, 3, 7 及び 14 日に体重の低値が認められた。100 mg/kg 投与群の血液学的検査では、投与期間終了時の雌雄に赤血球数、ヘモグロビン量及びヘマトクリット値の低値と平均赤血球容積及び平均赤血球血色素量の高値が認められ、雄では平均赤血球血色素濃度の低値及び白血球数の高値も認められた。また、雄の回復期間終了時にも血液学的検査で平均赤血球血色素濃度の低値と平均赤血球容積及び平均赤血球血色素量の高値が認められた。さらに、血液生化学的検査では、投与期間終了時の雌雄に γ -グロブリンの低値及び総ビリルビンの高値が認められ、雄では総蛋白の低値も認められた。これらの変動は、アニリンやニトロベンゼンで認められる変化と類似したものであり^{2,3)}、*N,N*-ジメチルアニリンはアニリンと同様に血色素のヘムを構成する還元型の 2 価イオンを酸化して 3 価イオンとし、メトヘモグロビン形成及び溶血性貧血を惹起したものと推察される⁴⁾。また、雌では、回復期間終了時の血液学的検査及び血液生化学的検査で投与期間終了時とは逆にヘモグロビン、ヘマトクリット値の高値及び総ビリルビンの低値が認められた。これら回復期間終了時の雌に認められた変動は、*N*-エチルアニリン投与メトヘモグロビン血症後の回復期間においても報告されており⁵⁾、この変動の機序は本試験においては明確ではないものの、*N,N*-ジメチルアニリン投与に起因した貧血による大球性の赤血球の残存と赤血球の生成によるものではないかと推測される。なお、雌では、投与期間終了時に尿素窒素の高値が、回復期間終了時にはクレアチニンの低値が認められたが、腎臓の病理組織学的検査では異常は認められなかった。100 mg/kg 投与群の剖検では、投与終了時の雌雄全例に脾臓の暗赤色及び腫大が認められ、回復期間終了時の

雄にも脾臓の腫大が認められた。また、投与期間終了時の器官重量では、雌雄に脾臓の絶対重量と相対重量の高値が認められ、雄には肝臓の相対重量及び腎臓の相対重量の高値が認められた。さらに、雌の回復期間終了時において脾臓の絶対重量及び相対重量の高値が認められた。病理組織学的検査では、雌雄ともに、投与期間終了時の肝臓には髄外造血の亢進及び黄褐色色素沈着が、脾臓にはうっ血、白脾髄の萎縮、髄外造血の亢進及び黄褐色色素沈着が、骨髄には赤芽球系細胞の過形成が認められた。また、雌雄ともに回復期間終了時の病理組織学的検査で肝臓及び脾臓に黄褐色色素沈着が認められ、さらに、雄では脾臓にうっ血が、雌では骨髄に赤芽球系細胞の過形成が認められた。これら、脾臓の腫大と脾臓重量の高値及び白脾髄の萎縮は溶血に伴う脾臓のうっ血や髄外造血巣の増加によるものであり、肝臓の相対重量の高値も髄外造血巣の増加によるものと推測される。また、骨髄における赤芽球系の過形成は貧血に対する代償性の反応と推測される。なお、雌の器官重量では、投与期間終了時に心臓の相対重量の高値が認められたが、この変動もメトヘモグロビン形成及び溶血性貧血に起因したもの、あるいは貧血に伴う代償性の反応と判断する。

10 mg/kg 投与群の雄では、投与期間終了時の病理組織学的検査で脾臓にうっ血が認められ、肝臓の相対重量にも高値が認められた。また、10 mg/kg 投与群の雌では、投与期間終了時の血液生化学的検査で γ -グロブリンの低値が認められ、投与期間終了時の病理組織学的検査で骨髄には赤芽球系細胞の過形成が、脾臓にはうっ血が認められた。10 mg/kg 投与群に認められたこれらの所見も、軽度ではあるものの、100 mg/kg 投与群と同様にメトヘモグロビン形成及び溶血性貧血が生じたものと推測される。なお、10 mg/kg 投与群の雄で投与 22 日に摂餌量の高値が、投与期間終了時には胸腺重量の高値が認められたが、いずれも用量に依存しない変化であり、偶発による変動と推測される。

1 mg/kg 投与群の雄では、病理組織学的検査で肝臓に出血性壊死及び小肉芽腫が少数例認められたが、これらはラットに自然発生的に認められる変化であることから *N,N*-ジメチルアニリン投与の影響はないものと判断する。一方、1 mg/kg 投与群の雌では、投与終了時の病理組織学的検査で、骨髄には赤芽球系細胞の過形成が、脾臓にはうっ血が認められたことから、軽度ではあるもののメトヘモグロビン形成及び溶血性貧血が推測される。

生殖発生毒性

各投与群の精巣、精巣上体、精囊、前立腺、卵巣、子宮、膣の病理組織学的検査で *N,N*-ジメチルアニリン投与に起因した変化は認められなかった。また、性周期、交尾率、交尾所要日数、受胎率、妊娠黄体数、着床数、着床率、出産率、妊娠期間、分娩状態及び哺育状態では、*N,N*-ジメチルアニリン投与に起因した変化は認められなかった。

児動物に対しては、総産児数、出産死亡児数、出産生児数、性比、生後 4 日の生存児数及び新生児の 4 日生存率、一般状態及び剖検に *N,N*-ジメチルアニリン投与に起因した変化

は認められなかった。新生児の外表観察において、*N,N*-ジメチルアニリン投与に起因した異常は認められなかった。児動物の体重では、各投与群と媒体対照群との間に有意差は認められなかった。

以上のように、雄に関しては 10 mg/kg 投与群で肝臓の相対重量の高値及び投与期間終了時の病理組織学検査で脾臓のうっ血が認められたものの、1 mg/kg 投与群では *N,N*-ジメチルアニリン投与の影響は認められなかったことを考慮して、雄の一般毒性学的 NOAEL は 1 mg/kg/day と推定した。一方、雌に関しては 1 mg/kg 投与群の投与終了時の病理組織学検査で骨髄に赤芽球系細胞の過形成及び脾臓にうっ血が認められたことを考慮して、雌の一般毒性学的 NOAEL は 1 mg/kg/day 未満と推定した。生殖発生学的な NOAEL は、いずれの投与群でも *N,N*-ジメチルアニリン投与に起因した変化は認められなかったことから、100 mg/kg/day であると推定した。

なお、*N,N*-ジメチルアニリンの一般毒性学的 NOEL は、雄では 10 mg/kg 投与群で肝臓の相対重量の高値及び投与期間終了時の病理組織学検査で脾臓のうっ血が認められたものの、1 mg/kg 投与群では *N,N*-ジメチルアニリン投与の影響は認められなかったことを考慮して 1 mg/kg/day であり、雌では 1 mg/kg 投与群の投与終了時の病理組織学検査で骨髄に赤芽球系細胞の過形成及び脾臓にうっ血が認められたことを考慮して 1 mg/kg/day 未満と推定した。生殖発生学的な NOEL は、いずれの投与群でも *N,N*-ジメチルアニリン投与に起因した変化は認められなかったことから、100 mg/kg/day であると推定した。

4. 引用文献

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添付資料

初回調製時被験液の濃度分析成績書

被験液の濃度分析を行った結果，以下の結果を得た．

測定日：2006 年 8 月 15 日

< 調製直後 >

被験液濃度 (mg/mL)	測定濃度 (mg/mL)	CV (%)	含量 (%)
0.5	0.4456	0.5	89
	0.4441		89
	0.4411		88
5	4.773	0.5	95
	4.771		95
	4.734		95
50	48.25	1.2	97
	48.13		96
	47.21		94
判定基準	-		85 ~ 115%

< 安定性（室温遮光保存 6 時間） >

被験液濃度 (mg/mL)	測定濃度 (mg/mL)	安定性 (%)
0.5	0.4485	101
5	4.756	100
50	47.33	99
判定基準	-	90 ~ 110%

以上のように，投与液は各判定基準を満たす結果が得られた．

また，媒体には交雑物は認められなかった．

投与期間中被験液の濃度分析成績書

被験液の濃度分析を行った結果、以下の結果を得た。

測定日：2006 年 9 月 12 日

< 調製直後 >

被験液濃度 (mg/mL)	測定濃度 (mg/mL)	CV (%)	含量 (%)
0.5	0.5246	0.4	105
	0.5224		104
	0.5271		105
5	5.315	0.3	106
	5.280		106
	5.292		106
50	49.59	0.6	99
	50.12		100
	49.55		99
判定基準	-		85 ~ 115%

< 安定性（室温遮光保存 6 時間） >

被験液濃度 (mg/mL)	測定濃度 (mg/mL)	安定性 (%)
0.5	0.5216	99
5	5.242	99
50	49.85	100
判定基準	-	90 ~ 110%

以上のように、投与液は各判定基準を満たす結果が得られた。
また、媒体には交雑物は認められなかった。

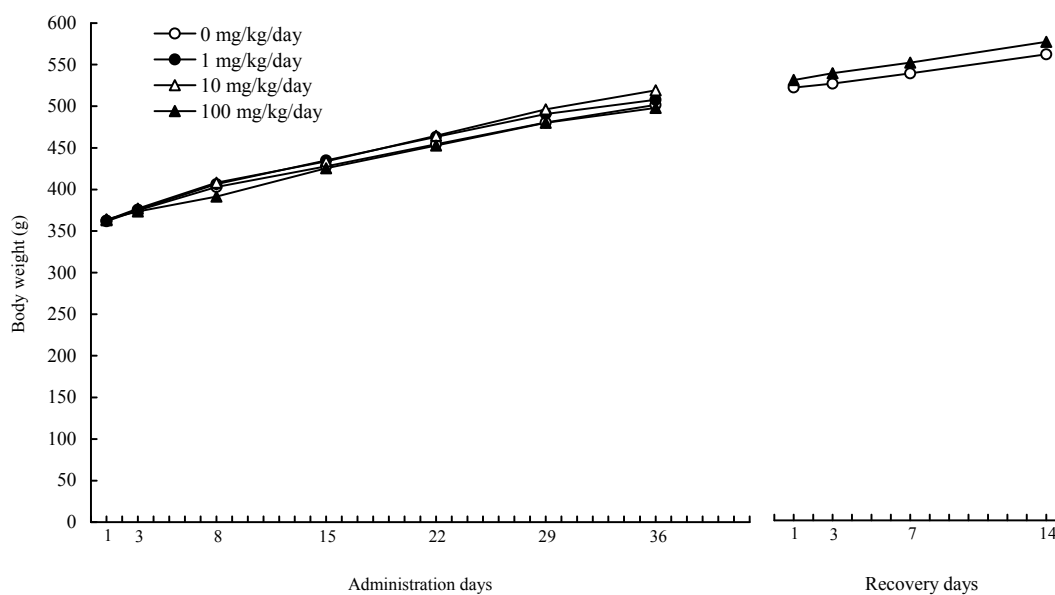


Fig. 1 Body weight changes of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

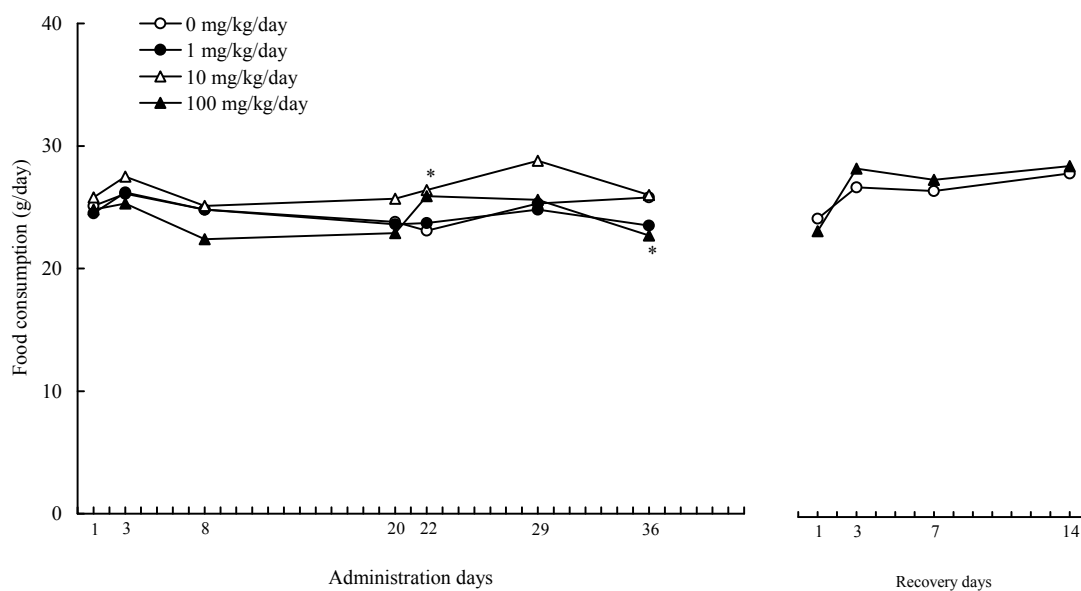


Fig. 2 Food consumption of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration
Significantly different from the control, * : $p < 0.05$ (Dunnett's test).

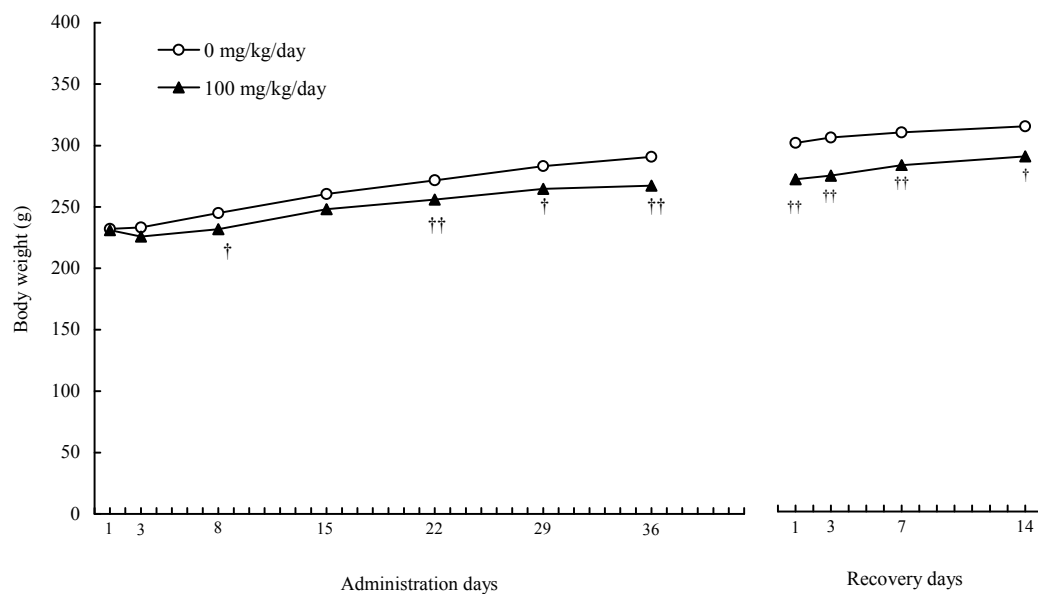


Fig. 3 Body weight changes of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration
Significantly different from the control, † : $p < 0.05$, †† : $p < 0.01$ (Student's t-test).

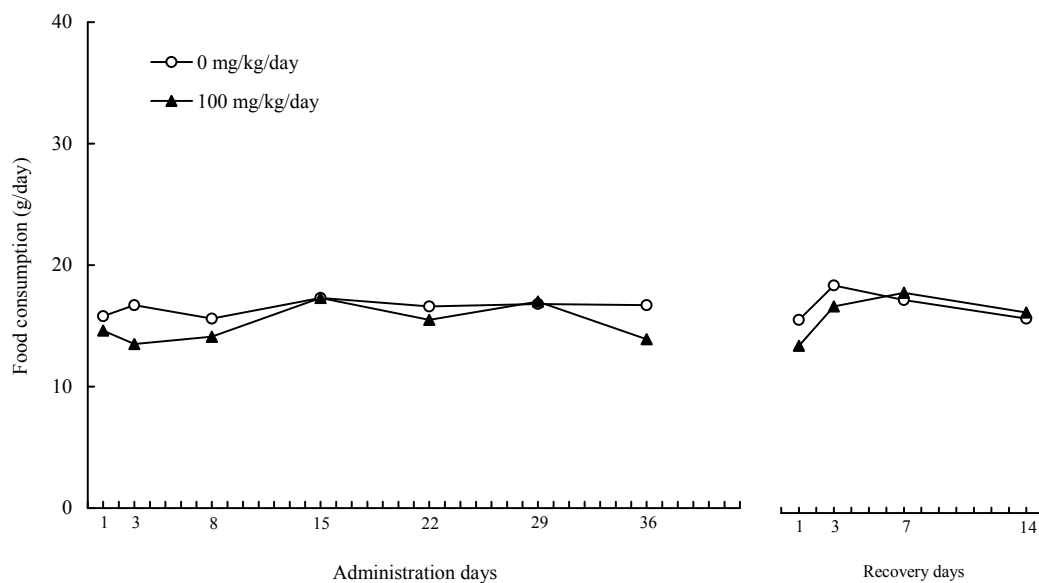


Fig. 4 Food consumption of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

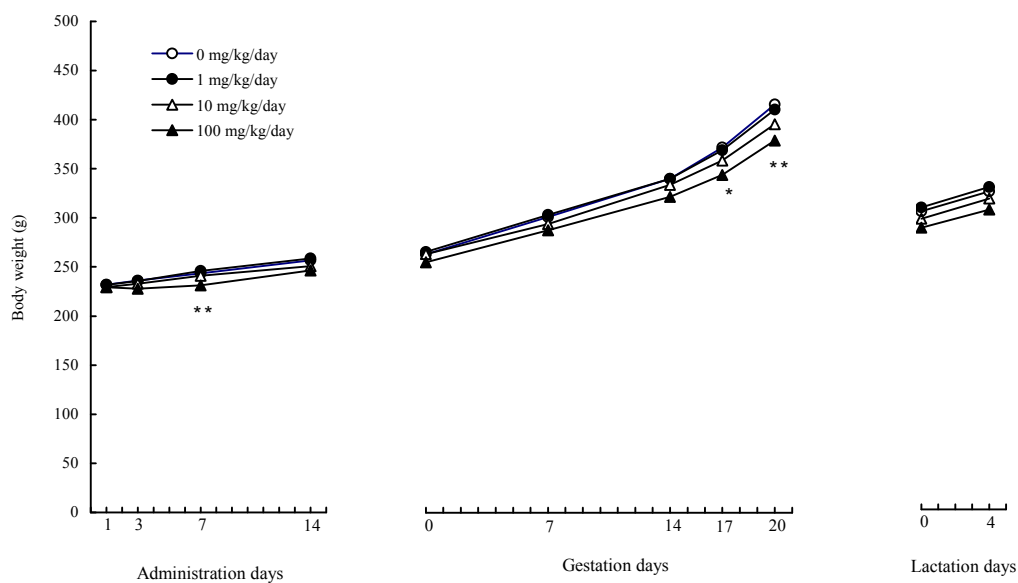


Fig. 5 Body weight changes of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration
Significantly different from the control, * : $p < 0.05$, ** : $p < 0.01$ (Dunnett's test).

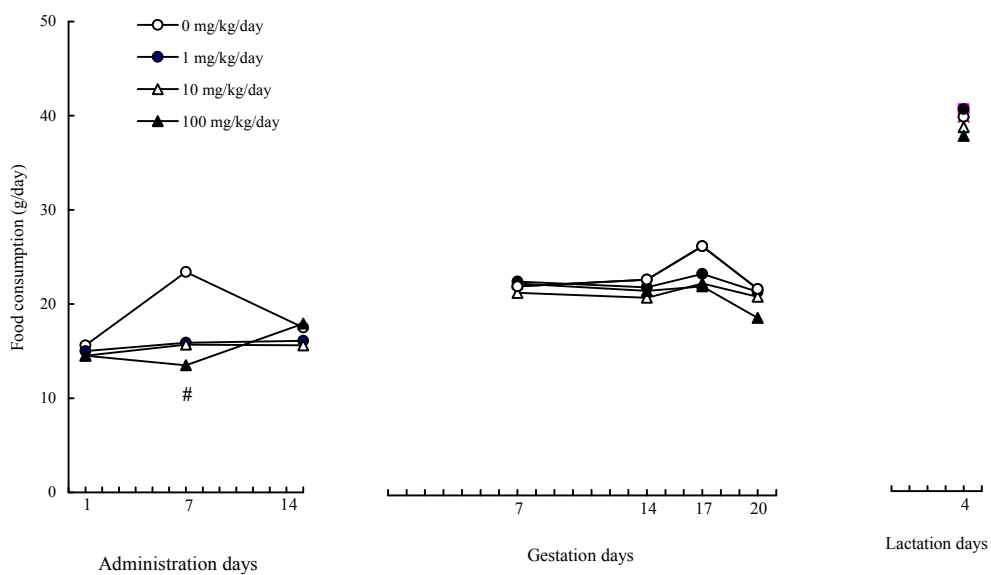


Fig. 6 Food consumption of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration
Significantly different from the control, # : $p < 0.05$ (Steel test).

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

Observation period	Administration period				Recovery period	
Dose (mg/kg/day)	0	1	10	100	0	100
Dark red discoloration of the skin	0 / 12 ^{a)}	0 / 12	0 / 12	12 / 12 ^{xx}	0 / 5	5 / 5 ^{xx}

a) : No. of animals with abnormal signs / No. of animals examined.
 Significantly different from the control, ^{xx} : p<0.01 (Fisher's exact test).

Table 2 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		0	1	10	100
Before					
No. of animals		12	12	12	12
Dark red discoloration of the skin (%) ^{a)}		0	0	0	0
Rearings	Mean ± S.D.	3.0 ± 1.5	3.3 ± 1.4	3.6 ± 2.1	3.2 ± 1.6
Defecations	Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Urinations	Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.8 ± 1.4 *	0.3 ± 0.8
1 week of administration period					
No. of animals		12	12	12	12
Dark red discoloration of the skin (%) ^{a)}		0	0	0	100 ^{xx}
Rearings	Mean ± S.D.	2.1 ± 1.7	1.5 ± 1.5	1.6 ± 1.3	1.9 ± 1.9
Defecations	Mean ± S.D.	0.3 ± 0.9	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.6
Urinations	Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.6
2 weeks of administration period					
No. of animals		12	12	12	12
Dark red discoloration of the skin (%) ^{a)}		0	0	0	100 ^{xx}
Rearings	Mean ± S.D.	1.1 ± 1.3	0.9 ± 1.0	0.3 ± 0.7	0.5 ± 0.7
Defecations	Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.6	0.0 ± 0.0
Urinations	Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
3 weeks of administration period					
No. of animals		12	12	12	12
Dark red discoloration of the skin (%) ^{a)}		0	0	0	100 ^{xx}
Rearings	Mean ± S.D.	1.6 ± 1.4	1.1 ± 1.1	1.3 ± 1.2	0.6 ± 0.8
Defecations	Mean ± S.D.	0.3 ± 1.2	0.3 ± 0.9	0.0 ± 0.0	0.0 ± 0.0
Urinations	Mean ± S.D.	0.4 ± 1.0	0.2 ± 0.6	0.1 ± 0.3	0.3 ± 0.8
4 weeks of administration period					
No. of animals		12	12	12	12
Dark red discoloration of the skin (%) ^{a)}		0	0	0	100 ^{xx}
Rearings	Mean ± S.D.	1.4 ± 0.9	1.6 ± 1.4	1.3 ± 0.8	1.0 ± 0.9
Defecations	Mean ± S.D.	0.2 ± 0.6	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Urinations	Mean ± S.D.	0.2 ± 0.6	0.2 ± 0.6	0.0 ± 0.0	0.0 ± 0.0
5 weeks of administration period					
No. of animals		12	12	12	12
Dark red discoloration of the skin (%) ^{a)}		0	0	0	100 ^{xx}
Rearings	Mean ± S.D.	1.6 ± 1.5	2.4 ± 1.5	2.2 ± 1.2	1.9 ± 1.0
Defecations	Mean ± S.D.	0.1 ± 0.3	0.0 ± 0.0	0.2 ± 0.6	0.0 ± 0.0
Urinations	Mean ± S.D.	0.1 ± 0.3	0.0 ± 0.0	0.3 ± 0.8	0.1 ± 0.3
6 weeks of administration period					
No. of animals		12	12	12	12
Dark red discoloration of the skin (%) ^{a)}		0	0	0	100 ^{xx}
Rearings	Mean ± S.D.	1.2 ± 1.5	1.5 ± 1.4	1.6 ± 1.6	1.6 ± 1.2
Defecations	Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Urinations	Mean ± S.D.	0.0 ± 0.0	0.1 ± 0.3	0.1 ± 0.3	0.0 ± 0.0

a) : (No. of animals with abnormal signs / No. of animals examined) × 100.

Significantly different from the control, ^{xx} : p<0.01 (Fisher's exact test).

Significantly different from the control, * : p<0.05 (Dunnett's test).

Table 3 Functional observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration
- 6 weeks of administration period -

Dose (mg/kg/day)	0	1	10	100
No. of animals	5	5	5	5
Responses				
Approach and/or Touch response				
No. of normal animals	5	5	5	5
Sound response				
No. of normal animals	5	5	5	5
Tail pinch response				
No. of normal animals	5	5	5	5
Pupillary reflex				
No. of normal animals	5	5	5	5
Aerial righting reflex				
No. of normal animals	5	5	5	5
Forelimb grip strength (N)				
Mean±S.D.	7.45 ± 1.02	7.07 ± 1.12	8.11 ± 1.25	8.19 ± 1.03
Hind limb grip strength (N)				
Mean±S.D.	1.44 ± 0.14	1.76 ± 0.50	1.75 ± 0.30	1.83 ± 0.33
Spontaneous locomotor activity for 15 min.				
Mean±S.D.	3715 ± 511	4279 ± 264	3693 ± 640	4075 ± 299

Table 4 Urinary findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Termination of administration period					Termination of recovery period	
Dose (mg/kg/day)	0	1	10	100	0	100
Number of animals	5	5	5	5	5	5
pH						
6.5	0 ^{b)}	1	1	1	0	0
7.0	0	0	0	0	0	0
7.5	2	1	0	4	3	1
8.0	3	1	2	0	2	3
8.5	0	2	2	0	0	1
Protein						
<30 mg/dL	0	0	0	0	0	1
30 mg/dL	3	4	4	2	2	2
100 mg/dL	2	1	0	2	3	2
300 mg/dL	0	0	1	1	0	0
Glucose						
Negative	5	5	5	5	5	5
Ketone body						
15 mg/dL	5	5	5	5	5	5
Billirubin						
Negative	5	5	5	5	5	5
Occult blood						
Negative	5	5	5	5	5	5
Urobilinogen ^{a)}						
0.1	5	5	5	5	5	5

a) : Ehrlich unit/dL.

b) : No. of animals.

Table 5 Hematological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		Termination of administration period				Termination of recovery period	
		0	1	10	100	0	100
Number of animals		5	4 ^{a)}	5	5	5	5
RBC	($\times 10^4/\mu\text{L}$)	911 \pm 45	876 \pm 23	875 \pm 60	623 \pm 51**	873 \pm 63	816 \pm 20
Hemoglobin	(g/dL)	16.9 \pm 0.6	16.3 \pm 0.2	16.2 \pm 0.7	13.5 \pm 0.7**	16.2 \pm 1.0	16.9 \pm 0.2
Hematocrit	(%)	48.1 \pm 2.2	46.9 \pm 0.4	46.9 \pm 2.6	40.7 \pm 2.3**	45.9 \pm 3.4	49.7 \pm 1.5
MCV	(fL)	52.8 \pm 2.8	53.6 \pm 1.2	53.7 \pm 1.4	65.5 \pm 1.7**	52.6 \pm 1.2	60.9 \pm 1.6 ^{††}
MCH	(pg)	18.6 \pm 0.7	18.6 \pm 0.5	18.6 \pm 0.7	21.7 \pm 0.7**	18.6 \pm 0.4	20.7 \pm 0.5 ^{††}
MCHC	(g/dL)	35.2 \pm 0.5	34.7 \pm 0.3	34.6 \pm 0.9	33.1 \pm 0.6**	35.4 \pm 0.9	34.0 \pm 1.0 [†]
WBC	($\times 10^2/\mu\text{L}$)	100 \pm 23	111 \pm 21	99 \pm 18	147 \pm 14**	109 \pm 16	113 \pm 22
Differential WBC count (%)							
Basophil		0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Eosinophil		1.2 \pm 0.8	1.0 \pm 0.8	1.0 \pm 1.4	1.8 \pm 1.5	0.4 \pm 0.5	1.4 \pm 1.1
Stab neutrophil		0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Segmented neutrophil		16.2 \pm 5.6	13.3 \pm 5.0	12.4 \pm 4.9	14.8 \pm 5.9	15.6 \pm 10.7	13.4 \pm 7.2
Lymphocyte		82.6 \pm 5.6	85.8 \pm 4.9	86.6 \pm 4.6	83.4 \pm 5.2	84.0 \pm 10.6	85.2 \pm 7.7
Monocyte		0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Other		0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Platelet	($\times 10^4/\mu\text{L}$)	95.4 \pm 12.7	101.5 \pm 16.4	111.0 \pm 18.9	113.7 \pm 14.6	111.8 \pm 19.7	109.0 \pm 5.6
PT	(second)	14.9 \pm 0.2	15.4 \pm 0.5	15.0 \pm 0.3	15.5 \pm 0.5	14.8 \pm 0.8	14.9 \pm 0.5
APTT	(second)	14.9 \pm 2.0	17.3 \pm 1.2	15.9 \pm 1.1	15.2 \pm 1.5	16.2 \pm 1.6	15.7 \pm 1.0

a) : Excluded a rat from calculation of mean value, because of the death of anesthetizing.

Each value shows mean \pm S.D.

Significantly different from the control, ** : $p < 0.01$ (Dunnett's test).

Significantly different from the control, † : $p < 0.05$, †† : $p < 0.01$ (Student's t-test).

RBC : Red blood cell .

MCV : Mean corpuscular volume.

MCH : Mean corpuscular hemoglobin level.

MCHC : Mean corpuscular hemoglobin concentration.

WBC : White blood cell .

PT : Prothrombin time.

APTT : Activated partial thromboplastin time.

Table 6 Blood biochemical findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

		Termination of administration period				Termination of recovery period	
Dose (mg/kg/day)		0	1	10	100	0	100
Number of animals		5	4 ^{a)}	5	5	5	5
AST	(IU/L)	92 ± 21	67 ± 6	69 ± 5	84 ± 17	100 ± 38	67 ± 6
ALT	(IU/L)	39 ± 17	30 ± 11	29 ± 4	36 ± 13	46 ± 24	29 ± 7
ALP	(IU/L)	268 ± 59	263 ± 40	228 ± 41	195 ± 33	235 ± 24	242 ± 52
Total protein	(g/dL)	6.4 ± 0.1	6.4 ± 0.2	6.6 ± 0.3	6.2 ± 0.0#	6.3 ± 0.2	6.5 ± 0.1
Albumin	(g/dL)	3.7 ± 0.0	3.5 ± 0.2	3.6 ± 0.2	3.5 ± 0.2	3.3 ± 0.5	3.7 ± 0.1
Plasma protein pattern (%)							
Albumin		56.3 ± 1.7	54.8 ± 1.3	55.0 ± 1.7	56.4 ± 2.0	50.3 ± 10.7	54.0 ± 1.5
α ₁ -globulin		22.5 ± 0.5	23.4 ± 1.7	22.6 ± 1.6	20.2 ± 0.9*	23.2 ± 4.1	21.1 ± 2.6
α ₂ -globulin		5.1 ± 1.2	5.0 ± 0.7	4.3 ± 0.7	5.0 ± 0.4	5.1 ± 1.0	4.9 ± 0.6
β-globulin		13.9 ± 1.5	14.4 ± 0.8	15.4 ± 1.1	15.6 ± 1.9	18.5 ± 6.2	16.2 ± 1.0
γ-globulin		2.2 ± 0.7	2.4 ± 0.2	2.7 ± 0.4	2.8 ± 0.7	2.8 ± 1.1	3.7 ± 0.8
Albumin/Globulin ratio		1.29 ± 0.09	1.21 ± 0.07	1.22 ± 0.08	1.30 ± 0.11	1.07 ± 0.35	1.17 ± 0.07
Glucose	(mg/dL)	153 ± 18	146 ± 6	157 ± 27	155 ± 14	143 ± 23	146 ± 8
Total cholesterol	(mg/dL)	74 ± 23	69 ± 12	69 ± 17	46 ± 6	64 ± 17	70 ± 8
Triglyceride	(mg/dL)	60 ± 19	67 ± 24	67 ± 32	37 ± 10	65 ± 45	72 ± 28
Total bilirubin	(mg/dL)	0.03 ± 0.02	0.04 ± 0.02	0.02 ± 0.02	0.16 ± 0.05**	0.03 ± 0.03	0.01 ± 0.01
Blood urea nitrogen	(mg/dL)	17.8 ± 2.9	15.9 ± 1.6	18.3 ± 3.5	19.5 ± 2.5	19.0 ± 1.1	20.7 ± 2.2
Creatinine	(mg/dL)	0.31 ± 0.02	0.30 ± 0.03	0.32 ± 0.06	0.30 ± 0.04	0.35 ± 0.06	0.32 ± 0.02
Inorganic phosphate	(mg/dL)	6.5 ± 0.7	6.4 ± 0.5	6.6 ± 0.9	6.9 ± 0.7	5.9 ± 0.2	6.4 ± 0.5
Calcium	(mg/dL)	10.2 ± 0.2	10.5 ± 0.2	10.4 ± 0.2	10.3 ± 0.2	10.1 ± 0.3	10.1 ± 0.1
Na	(mEq/L)	148.5 ± 0.6	148.0 ± 0.8	148.2 ± 1.2	147.3 ± 0.4	146.5 ± 1.0	146.3 ± 0.7
K	(mEq/L)	4.53 ± 0.33	4.36 ± 0.24	4.80 ± 0.66	4.63 ± 0.19	4.34 ± 0.18	4.41 ± 0.34
Cl	(mEq/L)	104.6 ± 1.0	104.8 ± 1.3	103.8 ± 1.7	104.4 ± 1.0	103.9 ± 1.0	102.6 ± 1.1

a) : Excluded a rat from calculation of mean value, because of the death of anesthetizing.

Each value shows mean ± S.D.

Significantly different from the control, * : p<0.05, ** : p<0.01 (Dunnett's test).

Significantly different from the control, # : p<0.05 (Steel test).

AST : Aspartate aminotransferase.

ALT : Alanine aminotransferase.

ALP : Alkaline phosphatase.

Na : Sodium.

K : Potassium.

Cl : Chlorine.

Table 7 Organ weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

		Termination of administration period				Termination of recovery period	
Dose (mg/kg/day)		0	1	10	100	0	100
Number of animals		7	12	12	7	5	5
Final body weight (g)		496.0 ± 31.4	496.7 ± 35.1	505.6 ± 32.2	470.6 ± 37.4	524.9 ± 45.2	539.2 ± 60.6
Brain	(g)	2.213 ± 0.072	2.210 ± 0.131	2.164 ± 0.091	2.210 ± 0.132	2.235 ± 0.139	2.209 ± 0.086
	(g%)	0.448 ± 0.033	0.447 ± 0.041	0.430 ± 0.033	0.473 ± 0.055	0.428 ± 0.036	0.414 ± 0.046
Thymus	(g)	0.348 ± 0.031	0.375 ± 0.104	0.488 ± 0.130#	0.405 ± 0.086	0.441 ± 0.108	0.440 ± 0.081
	(g%)	0.070 ± 0.007	0.075 ± 0.019	0.096 ± 0.022*	0.087 ± 0.021	0.084 ± 0.020	0.082 ± 0.017
Heart	(g)	1.562 ± 0.113	1.519 ± 0.109	1.476 ± 0.106	1.653 ± 0.295	1.563 ± 0.060	1.615 ± 0.169
	(g%)	0.315 ± 0.026	0.306 ± 0.017	0.292 ± 0.019	0.351 ± 0.056	0.300 ± 0.031	0.300 ± 0.011
Liver	(g)	12.602 ± 1.292	13.339 ± 1.100	14.194 ± 1.830	13.915 ± 2.132	14.786 ± 2.421	14.043 ± 2.333
	(g%)	2.538 ± 0.155	2.690 ± 0.197	2.800 ± 0.232*	2.944 ± 0.240**	2.817 ± 0.392	2.595 ± 0.154
Spleen	(g)	0.738 ± 0.106	0.768 ± 0.112	0.839 ± 0.095	2.259 ± 0.312##	1.023 ± 0.469	1.050 ± 0.158
	(g%)	0.150 ± 0.025	0.155 ± 0.022	0.166 ± 0.016	0.486 ± 0.097##	0.194 ± 0.088	0.195 ± 0.025
Kidneys	(g)	2.687 ± 0.214	2.957 ± 0.244	2.829 ± 0.281	3.038 ± 0.431	3.109 ± 0.197	2.999 ± 0.419
	(g%)	0.542 ± 0.031	0.596 ± 0.041	0.560 ± 0.048	0.645 ± 0.069**	0.594 ± 0.031	0.555 ± 0.024
Adrenals	(mg)	56.0 ± 9.6	62.6 ± 9.0	59.1 ± 8.6	64.4 ± 5.7	64.9 ± 8.8	61.5 ± 7.0
	(mg%)	11.3 ± 1.6	12.7 ± 2.4	11.7 ± 1.8	13.7 ± 1.4	12.3 ± 0.7	11.6 ± 2.1
Testes	(g)	3.382 ± 0.156	3.503 ± 0.281	3.327 ± 0.236	3.451 ± 0.287	3.257 ± 0.201	3.609 ± 0.327
	(g%)	0.684 ± 0.057	0.708 ± 0.073	0.660 ± 0.049	0.739 ± 0.100	0.622 ± 0.021	0.671 ± 0.037 [†]
Epididymides	(g)	1.325 ± 0.114	1.316 ± 0.122	1.323 ± 0.190	1.384 ± 0.131	1.359 ± 0.135	1.413 ± 0.109
	(g%)	0.268 ± 0.027	0.266 ± 0.032	0.263 ± 0.041	0.296 ± 0.040	0.259 ± 0.015	0.264 ± 0.025

Each value shows mean±S.D.

Significantly different from the control, * : p<0.05, ** : p<0.01 (Dunnett's test).

Significantly different from the control, # : p<0.05, ## : p<0.01 (Steel test).

Significantly different from the control, † : p<0.05 (Student's t-test).

Table 8 Gross pathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	0	1	10	100
Termination of administration period				
Spleen				
Swelling and dark red discoloration	0/7 ^{a)}	0/12	0/12	7/7 ^{xx}
Termination of recovery period				
Spleen				
Swelling and nodule	1 / 5	-	-	0/5
Swelling	0 / 5	-	-	4/5 ^x

a) : No. of animals with abnormal findings / No. of animals examined.

Significantly different from the control, ^x: p<0.05, ^{xx}: p<0.01 (Fisher's exact test).

Table 9 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)			Termination of administration period				Termination of recovery period	
			0	1	10	100	0	100
Organs	Findings	Grade						
Liver	Extramedullary hematopoiesis	+	0/5 ^{a)}	0/5	0/5	5/5] ^{xx}	0/5	0/5
	Extramedullary hematopoiesis	++	0/5	0/5	0/5	0/5	1/5	0/5
	Yellowish-brown pigmentation	+	0/5	0/5	0/5	5/5 ^{xx}	0/5	4/5 ^x
	Focal hemorrhage	+	0/5	0/5	0/5	1/5	0/5	0/5
	Focal necrosis in hepatocytes	+	0/5	0/5	0/5	0/5	1/5	0/5
	Hemorrhagic necrosis	+	0/5	1/5	0/5	0/5	0/5	0/5
	Histiocytic sarcoma	+	0/5	0/5	0/5	0/5	1/5	0/5
	Microgranuloma	+	1/5	1/5	0/5	1/5	0/5	2/5
Spleen	Congestion	+	0/5	0/5	1/5	0/5] ^{xx}	0/5	1/5
	Congestion	+++	0/5	0/5	0/5	5/5	0/5	0/5
	Atrophy of white pulp	++	0/5	0/5	0/5	5/5 ^{xx}	0/5	0/5
	Extramedullary hematopoiesis	+	0/5	0/5	0/5	2/5	0/5	0/5
	Extramedullary hematopoiesis	++	0/5	0/5	0/5	3/5] ^{xx}	0/5	0/5
	Yellowish-brown pigmentation	++	0/5	0/5	0/5	5/5 ^{xx}	0/5	5/5 ^{xx}
	Hemorrhagic necrosis	++	0/5	0/5	0/5	0/5	1/5	0/5
	Histiocytic sarcoma	+	0/5	0/5	0/5	0/5	1/5	0/5
Bone marrow (femur)	Erythroid hyperplasia	+	0/5	0/5	0/5	2/5] ^{xx}	0/5	0/5
	Erythroid hyperplasia	++	0/5	0/5	0/5	3/5	0/5	0/5
Lung	Calcification of pulmonary aorta	+	1/5	-	-	0/5	-	-
	Ectopic ossification	+	1/5	-	-	0/5	-	-
Heart	Inflammatory cell infiltration	+	1/5	-	-	0/5	-	-
Kidney	Inflammatory cell infiltration in stroma	+	0/5	-	-	1/5	-	-
	Scar formation	+	0/5	-	-	1/5	-	-
Testis	Focal atrophy of seminiferous tubules	+	1/5	-	-	1/5	-	-
Prostate	Inflammatory cell infiltration in stroma	+	2/5	-	-	1/5	-	-

Grade: + ; Slight, ++ ; moderate, +++ ; marked.

a) : No. of animals with abnormal findings / No. of animals examined.

- : Not examined.

Significantly different from the control, ^x : p<0.05, ^{xx} : p<0.01 (Fisher's exact test).

No remarkable changes were seen in the trachea, stomach, duodenum, ileum (including Peyer's patches), colon, urinary bladder, epididymis, seminal vesicle, brain (cerebrum, cerebellum and pons), spinal cord, sciatic nerve, mesenteric lymph node, axillary lymph node, thymus, pituitary, thyroid gland, parathyroid, and adrenal.

Table 10 General signs of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Observation period	Administration period				Recovery period	
Dose (mg/kg/day)	0	1	10	100	0	100
Dark red discoloration of the skin	0 / 17 ^{a)}	0 / 12	0 / 12	17 / 17 ^{xx}	0 / 5	5 / 5 ^{xx}

a) : No. of animals with abnormal signs / No. of animals examined.

Significantly different from the control, ^{xx} : $p < 0.01$ (Fisher's exact test).

Table 11 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	0	1	10	100
Before				
No. of animals	17	12	12	17
Dark red discoloration of the skin (%) ^{a)}	0	0	0	0
Rearings Mean ± S.D.	2.6 ± 1.7	2.9 ± 1.9	2.9 ± 1.5	3.2 ± 1.2
Defecations Mean ± S.D.	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0	0.1 ± 0.5
Urinations Mean ± S.D.	0.0 ± 0.0	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.2
1 week of administration period				
No. of animals	17	12	12	17
Dark red discoloration of the skin (%) ^{a)}	0	0	0	100 ^{xx}
Rearings Mean ± S.D.	3.5 ± 1.1	3.5 ± 1.8	3.2 ± 1.2	3.5 ± 1.6
Defecations Mean ± S.D.	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0	0.0 ± 0.0
Urinations Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
2 weeks of administration period				
No. of animals	17	12	12	17
Dark red discoloration of the skin (%) ^{a)}	0	0	0	100 ^{xx}
Rearings Mean ± S.D.	2.6 ± 1.6	2.8 ± 1.2	3.0 ± 1.1	3.5 ± 1.3
Defecations Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Urinations Mean ± S.D.	0.1 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
3 weeks of administration period				
No. of animals	17	12	12	17
Dark red discoloration of the skin (%) ^{a)}	0	0	0	100 ^{xx}
Rearings Mean ± S.D.	2.6 ± 1.8	2.3 ± 1.4	2.0 ± 1.4	2.9 ± 1.9
Defecations Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Urinations Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
4 weeks of administration period				
No. of animals	17	12	12	17
Dark red discoloration of the skin (%) ^{a)}	0	0	0	100 ^{xx}
Rearings Mean ± S.D.	3.4 ± 1.5	2.8 ± 1.7	3.5 ± 2.0	3.8 ± 1.6
Defecations Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Urinations Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
5 weeks of administration period				
No. of animals	17	12	12	17
Dark red discoloration of the skin (%) ^{a)}	0	0	0	100 ^{xx}
Rearings Mean ± S.D.	3.3 ± 1.7	3.5 ± 1.7	3.4 ± 2.0	3.0 ± 2.4
Defecations Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Urinations Mean ± S.D.	0.1 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
6 weeks of administration period				
No. of animals	5	-	-	5
Dark red discoloration of the skin (%) ^{a)}	0	-	-	100 ^{xx}
Rearings Mean ± S.D.	4.8 ± 1.1	-	-	2.6 ± 1.7 [†]
Defecations Mean ± S.D.	0.0 ± 0.0	-	-	0.0 ± 0.0
Urinations Mean ± S.D.	0.0 ± 0.0	-	-	0.0 ± 0.0
On day 4 postpartum				
No. of animals	12	12	12	12
Dark red discoloration of the skin (%) ^{a)}	0	0	0	100 ^{xx}
Rearings Mean ± S.D.	5.9 ± 1.4	6.1 ± 2.2	6.3 ± 2.0	5.8 ± 1.7
Defecations Mean ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0
Urinations Mean ± S.D.	0.3 ± 0.7	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.4

a) : (No. of animals with abnormal signs / No. of animals examined) × 100.

Significantly different from the control, † : p<0.05 (Student's t-test).

Significantly different from the control, ^{xx} : p<0.01 (Fisher's exact test).

Table 12 Functional observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration
- Day 4 of postpartum -

Dose (mg/kg/day)	0	1	10	100
No. of animals	5	5	5	5
Responses				
Approach and/or Touch response				
No. of normal animals	5	5	5	5
Sound response				
No. of normal animals	5	5	5	5
Tail pinch response				
No. of normal animals	5	5	5	5
Pupillary reflex				
No. of normal animals	5	5	5	5
Aerial righting reflex				
No. of normal animals	5	5	5	5
Forelimb grip strength (N)				
Mean±S.D.	6.57 ± 0.47	5.90 ± 0.16	6.05 ± 0.52	6.79 ± 0.67
Hind limb grip strength (N)				
Mean±S.D.	1.77 ± 0.25	1.76 ± 0.18	1.57 ± 0.23	1.76 ± 0.27
Spontaneous locomotor activity for 15 min.				
Mean±S.D.	3835 ± 896	3955 ± 671	3928 ± 494	3870 ± 388

Table 13 Urinary findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

	Termination of administration period				Termination of recovery period	
Dose (mg/kg/day)	0	1	10	100	0	100
Number of animals	5	5	5	5	5	5
pH						
7.0	1 ^{b)}	1	1	1	1	2
7.5	2	2	2	2	3	1
8.0	2	2	1	2	1	1
8.5	0	0	1	0	0	1
Protein						
<30 mg/dL	1	0	0	1	0	1
30 mg/dL	1	3	4	2	3	2
100 mg/dL	3	2	1	2	2	2
Glucose						
Negative	5	5	5	5	5	5
Ketone body						
Negative	5	5	5	5	5	5
Billirubin						
Negative	5	5	5	5	5	5
Occult blood						
Negative	5	5	5	5	5	5
Urobilinogen ^{a)}						
0.1	5	5	5	5	5	5

a) : Ehrlich unit/dL.

b) : No. of animals.

Table 14 Hematological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

		Termination of administration period				Termination of recovery period	
Dose (mg/kg/day)		0	1	10	100	0	100
Number of animals		5	5	5	5	4 ^{a)}	5
RBC	($\times 10^4/\mu\text{L}$)	717 \pm 20	706 \pm 22	678 \pm 56	490 \pm 32**	820 \pm 23	768 \pm 25 [†]
Hemoglobin	(g/dL)	14.5 \pm 0.2	14.6 \pm 0.7	14.1 \pm 0.9	12.4 \pm 0.4**	16.0 \pm 0.1	16.8 \pm 0.4 ^{††}
Hematocrit	(%)	41.3 \pm 1.9	41.5 \pm 2.3	40.1 \pm 1.8	37.6 \pm 1.4*	44.6 \pm 0.7	47.9 \pm 1.7 ^{††}
MCV	(fL)	57.6 \pm 2.2	58.8 \pm 3.1	59.3 \pm 2.7	77.0 \pm 4.5**	54.5 \pm 2.1	62.4 \pm 1.6 ^{††}
MCH	(pg)	20.2 \pm 0.6	20.6 \pm 0.8	20.8 \pm 1.1	25.5 \pm 1.4**	19.5 \pm 0.6	21.9 \pm 0.6 ^{††}
MCHC	(g/dL)	35.2 \pm 1.4	35.1 \pm 0.5	35.2 \pm 0.9	33.1 \pm 0.3	35.7 \pm 0.6	35.2 \pm 0.6
WBC	($\times 10^2/\mu\text{L}$)	150 \pm 43	117 \pm 38	112 \pm 30	121 \pm 29	58 \pm 12	62 \pm 12
Differential WBC count (%)							
Basophil		0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Eosinophil		0.8 \pm 1.3	0.2 \pm 0.4	0.2 \pm 0.4	0.2 \pm 0.4	1.8 \pm 1.5	0.2 \pm 0.4
Stab neutrophil		0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Segmented neutrophil		28.6 \pm 5.9	23.8 \pm 7.6	26.0 \pm 4.7	23.2 \pm 9.7	11.5 \pm 4.5	11.0 \pm 6.9
Lymphocyte		70.6 \pm 6.5	76.0 \pm 7.5	73.8 \pm 4.9	76.6 \pm 9.9	86.8 \pm 5.7	88.8 \pm 6.9
Monocyte		0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Other		0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Platelet	($\times 10^4/\mu\text{L}$)	113.2 \pm 2.5	115.2 \pm 8.9	111.1 \pm 7.5	109.3 \pm 14.9	105.5 \pm 13.3	106.0 \pm 11.3
PT	(second)	16.5 \pm 0.3	16.5 \pm 0.3	17.1 \pm 0.5	16.6 \pm 0.6	16.0 \pm 0.8	16.3 \pm 0.8
APTT	(second)	12.7 \pm 1.7	11.8 \pm 1.2	12.1 \pm 0.4	11.3 \pm 0.9	12.9 \pm 1.0	12.1 \pm 1.2

a) : Excluded a rat from calculation of mean value, because of the death of anesthetizing.

Each value shows mean \pm S.D.Significantly different from the control, * : $p < 0.05$, ** : $p < 0.01$ (Dunnett's test).Significantly different from the control, \dagger : $p < 0.05$, $\dagger\dagger$: $p < 0.01$ (Student's t-test).

RBC : Red blood cell .

MCV : Mean corpuscular volume.

MCH : Mean corpuscular hemoglobin level.

MCHC : Mean corpuscular hemoglobin concentration.

WBC : White blood cell .

PT : Prothrombin time.

APTT : Activated partial thromboplastin time.

Table 15 Blood biochemical findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

		Termination of administration period				Termination of recovery period	
Dose (mg/kg/day)		0	1	10	100	0	100
Number of animals		5	5	5	5	4 ^{a)}	5
AST	(IU/L)	74 ± 9	74 ± 7	78 ± 7	82 ± 3	76 ± 23	71 ± 31
ALT	(IU/L)	47 ± 5	41 ± 8	41 ± 5	50 ± 9	35 ± 14	25 ± 8
ALP	(IU/L)	147 ± 64	166 ± 56	154 ± 67	155 ± 52	90 ± 17	116 ± 26
Total protein	(g/dL)	6.0 ± 0.4	5.9 ± 0.3	6.0 ± 0.2	6.1 ± 0.3	7.1 ± 0.4	7.0 ± 0.5
Albumin	(g/dL)	3.5 ± 0.2	3.4 ± 0.2	3.5 ± 0.1	3.6 ± 0.3	4.6 ± 0.3	4.5 ± 0.4
Plasma protein pattern (%)							
Albumin		56.2 ± 2.4	54.8 ± 0.7	57.0 ± 2.6	58.8 ± 2.3	64.8 ± 3.2	65.3 ± 3.1
α ₁ -globulin		20.5 ± 0.3	20.7 ± 1.6	17.4 ± 1.8#	17.3 ± 1.5#	15.6 ± 1.7	15.0 ± 1.6
α ₂ -globulin		4.1 ± 0.5	4.3 ± 0.2	4.1 ± 0.1	4.1 ± 0.7	4.2 ± 0.5	4.2 ± 0.5
β-globulin		14.9 ± 1.7	16.6 ± 1.5	16.7 ± 1.0	15.6 ± 2.3	12.3 ± 1.7	12.2 ± 1.1
γ-globulin		4.2 ± 1.3	3.6 ± 0.9	4.7 ± 1.1	4.2 ± 0.8	3.2 ± 1.1	3.3 ± 0.8
Albumin/Globulin ratio		1.28 ± 0.13	1.21 ± 0.03	1.33 ± 0.14	1.43 ± 0.14	1.86 ± 0.26	1.90 ± 0.24
Glucose	(mg/dL)	130 ± 27	122 ± 17	123 ± 12	116 ± 7	137 ± 13	135 ± 9
Total cholesterol	(mg/dL)	62 ± 15	69 ± 12	62 ± 5	69 ± 13	81 ± 18	66 ± 15
Triglyceride	(mg/dL)	48 ± 17	44 ± 34	36 ± 8	34 ± 11	48 ± 29	31 ± 22
Total bilirubin	(mg/dL)	0.06 ± 0.01	0.05 ± 0.01	0.06 ± 0.02	0.22 ± 0.06#	0.08 ± 0.01	0.03 ± 0.01 ^{††}
Blood urea nitrogen	(mg/dL)	12.7 ± 2.7	16.9 ± 2.3	15.6 ± 2.7	19.5 ± 3.5**	17.5 ± 0.9	16.1 ± 1.5
Creatinine	(mg/dL)	0.31 ± 0.02	0.31 ± 0.03	0.30 ± 0.03	0.30 ± 0.05	0.36 ± 0.02	0.30 ± 0.03 [†]
Inorganic phosphate	(mg/dL)	7.9 ± 1.0	8.3 ± 1.2	7.7 ± 1.8	8.6 ± 0.8	5.4 ± 1.0	5.3 ± 0.4
Calcium	(mg/dL)	10.7 ± 0.8	10.6 ± 0.5	10.4 ± 0.5	10.4 ± 0.3	10.3 ± 0.4	10.4 ± 0.5
Na	(mEq/L)	145.5 ± 0.9	144.9 ± 1.4	144.6 ± 0.8	144.5 ± 0.6	145.5 ± 0.8	145.8 ± 1.0
K	(mEq/L)	4.59 ± 0.25	4.79 ± 0.55	4.73 ± 1.07	4.95 ± 0.34	3.65 ± 0.22	3.56 ± 0.30
Cl	(mEq/L)	102.5 ± 2.1	104.0 ± 2.2	104.3 ± 1.3	103.5 ± 0.9	104.8 ± 1.5	105.4 ± 1.9

a) : Excluded a rat from calculation of mean value, because of the death of anesthetizing.

Each value shows mean ±S.D.

Significantly different from the control, **: p<0.01 (Dunnett's test).

Significantly different from the control, # : p<0.05 (Steel test).

Significantly different from the control, † : p<0.05, ††: p<0.01 (Student's t-test).

AST : Aspartate aminotransferase.

ALT : Alanine aminotransferase.

ALP : Alkaline phosphatase.

Na : Sodium.

K : Potassium.

Cl : Chlorine.

Table 16 Organ weights of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

		Termination of administration period				Termination of recovery period	
Dose (mg/kg/day)		0	1	10	100	0	100
Number of animals		12	12	12	12	5	5
Final body weight (g)		299.4 ± 24.5	305.5 ± 22.1	290.6 ± 17.4	282.2 ± 15.6	295.5 ± 12.1	269.9 ± 9.1 ^{††}
Brain	(g)	2.029 ± 0.083	2.075 ± 0.085	2.108 ± 0.064	2.053 ± 0.073	2.028 ± 0.043	2.044 ± 0.044
	(g%)	0.681 ± 0.059	0.682 ± 0.055	0.727 ± 0.039	0.729 ± 0.046	0.688 ± 0.041	0.758 ± 0.028 [†]
Thymus	(g)	0.244 ± 0.097	0.290 ± 0.086	0.244 ± 0.045	0.260 ± 0.065	0.408 ± 0.086	0.298 ± 0.099
	(g%)	0.080 ± 0.028	0.095 ± 0.026	0.084 ± 0.017	0.092 ± 0.021	0.138 ± 0.030	0.112 ± 0.040
Heart	(g)	1.033 ± 0.105	1.062 ± 0.092	1.079 ± 0.138	1.062 ± 0.104	0.914 ± 0.086	0.927 ± 0.067
	(g%)	0.345 ± 0.016	0.348 ± 0.024	0.371 ± 0.041	0.376 ± 0.026 [#]	0.310 ± 0.038	0.343 ± 0.025
Liver	(g)	9.280 ± 0.905	9.811 ± 1.065	9.761 ± 1.731	9.501 ± 0.897	7.097 ± 0.397	6.821 ± 0.505
	(g%)	3.105 ± 0.254	3.212 ± 0.286	3.350 ± 0.494	3.364 ± 0.224	2.404 ± 0.145	2.527 ± 0.169
Spleen	(g)	0.621 ± 0.139	0.664 ± 0.106	0.774 ± 0.179	1.901 ± 0.281 ^{##}	0.499 ± 0.035	0.588 ± 0.075 [†]
	(g%)	0.208 ± 0.044	0.219 ± 0.041	0.266 ± 0.059	0.675 ± 0.104 ^{##}	0.169 ± 0.015	0.218 ± 0.028 ^{††}
Kidneys	(g)	1.855 ± 0.129	1.859 ± 0.182	1.974 ± 0.179	1.896 ± 0.155	1.594 ± 0.102	1.688 ± 0.090
	(g%)	0.622 ± 0.050	0.609 ± 0.053	0.680 ± 0.052 [*]	0.673 ± 0.052	0.540 ± 0.048	0.626 ± 0.039 [†]
Adrenals	(mg)	77.0 ± 9.5	77.0 ± 11.3	77.6 ± 11.5	78.2 ± 11.2	69.4 ± 8.2	71.9 ± 16.7
	(mg%)	25.8 ± 3.1	25.2 ± 3.7	26.8 ± 4.2	27.7 ± 3.8	23.5 ± 2.7	26.7 ± 6.4

Each value shows mean±S.D.

Significantly different from the control, * : p<0.05 (Dunnett's test).

Significantly different from the control, # : p<0.05, ## : p<0.01 (Steel test).

Significantly different from the control, † : p<0.05, †† : p<0.01 (Student's t-test).

Table 17 Gross pathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	0	1	10	100
Termination of administration period				
Spleen				
Swelling and dark red discoloration	0 / 12 ^{a)}	0/12	0/12	12/12 ^{xx}
Termination of recovery period				
Abnormal	0 / 5	-	-	0 / 5

a) : No. of animals with abnormal findings / No. of animals examined.

Significantly different from the control, ^{xx} : $p < 0.01$ (Fisher's exact test).

Table 18 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Termination of administration period				Termination of recovery period	
	0	1	10	100	0	100
Liver						
Extramedullary hematopoiesis	+	0/5 ^{a)}	0/5	0/5	5/5 ^{xx}	0/5
Yellowish-brown pigmentation	+	0/5	0/5	0/5	5/5 ^{xx}	0/5
Hemorrhagic necrosis	+	0/5	0/5	0/5	0/5	1/5
Microgranuloma	+	0/5	1/5	0/5	0/5	1/5
Bone marrow (femur)						
Erythroid hyperplasia	+	0/5	1/5	3/5	0/5 ^{xx}	0/5
Erythroid hyperplasia	++	0/5	0/5	0/5	5/5	0/5
Spleen						
Congestion	+	0/5	2/5	2/5	0/5 ^{xx}	0/5
Congestion	+++	0/5	0/5	0/5	5/5	0/5
Atrophy of white pulp	++	0/5	0/5	0/5	5/5 ^{xx}	0/5
Extramedullary hematopoiesis	+	0/5	0/5	1/5	0/5 ^{xx}	0/5
Extramedullary hematopoiesis	++	0/5	0/5	0/5	5/5	0/5
Yellowish-brown pigmentation	++	0/5	0/5	0/5	5/5 ^{xx}	0/5
Yellowish-brown pigmentation	+++	0/5	0/5	0/5	0/5	2/5 ^{xx}
Lung						
Calcification of pulmonary aorta	+	1/5	-	-	0/5	-
Ectopic ossification	+	1/5	-	-	0/5	-

Grade : + ; Slight, ++ ; moderate, +++ ; marked.

a) : No. of animals with abnormal findings / No. of animals examined.

- : Not examined.

Significantly different from the control, ^{xx} : p<0.01 (Fisher's exact test).

No remarkable changes were seen in the trachea, stomach, duodenum, ileum (including Peyer's patches), colon, heart, kidney, urinary bladder, ovary, uterus, vagina, brain (cerebrum, cerebellum and pons), spinal cord, sciatic nerve, mesenteric lymph node, axillary lymph node, thymus, pituitary, thyroid gland, parathyroid, and adrenal.

Table 19 Estrous cycle of female rats and reproductive performance of male and female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	0	1	10	100
Number of females	12	12	12	12
Length of estrous cycle before mating (14 days)				
Mean \pm S.D.	4.1 \pm 0.1	4.2 \pm 0.3	4.1 \pm 0.1	4.1 \pm 0.1
Number of females with abnormal estrous cycle before mating (14days) ^{a)}	0 / 12	0 / 12	0 / 12	0 / 12
Number of pairs in 1st mating	12	12	12	12
Number of pairs with successful copulation	12	12	12	12
Copulation index (%) ^{b)}	100	100	100	100
Number of conceiving days				
Mean \pm S.D.	2.6 \pm 1.0	2.8 \pm 1.2	3.3 \pm 1.1	2.9 \pm 1.1
Conceiving days 1-5	12	12	12	12
Conceiving days 6	0	0	0	0
Number of impregnant males	12	12	12	12
Fertility index of males (%) ^{c)}	100	100	100	100
Number of pregnant females	12	12	12	12
Fertility index of females (%) ^{d)}	100	100	100	100
Number of pregnant females with live pups	12	12	12	12

a) No. of females with abnormal estrous cycle / No. of females examined.

b) (No. of pairs with successful copulation / No. of pairs) \times 100.c) (No. of impregnant males / No. of pairs with successful copulation) \times 100.d) (No. of pregnant females / No. of pairs with successful copulation) \times 100.

Table 20 Observations of pups in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	0	1	10	100
Number of dams	12	12	12	11
Length of gestation (days)	22.5 ± 0.5	22.3 ± 0.5	22.8 ± 0.5	22.3 ± 0.5
Corpora lutea	19.1 ± 3.4	19.8 ± 4.7	19.3 ± 4.6	19.0 ± 4.1
Implantation scars	15.2 ± 1.3	14.1 ± 1.8	13.0 ± 3.3	13.8 ± 1.3
Implantation index (%) ^{a)}	81.3 ± 13.0	74.4 ± 19.1	70.7 ± 22.0	75.0 ± 12.9
Gestation index (%) ^{b)}	100	100	100	100
Pups born	14.1 ± 1.7	12.8 ± 3.1	11.5 ± 3.2	12.3 ± 1.2
Stillbirths	0.1 ± 0.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Live pups born	14.0 ± 1.8	12.8 ± 3.1	11.5 ± 3.2	12.3 ± 1.2
Delivery index (%) ^{c)}	93.1 ± 10.0	89.3 ± 13.6	88.1 ± 10.6	89.6 ± 9.9
Birth index (%) ^{d)}	92.6 ± 11.0	89.3 ± 13.6	88.1 ± 10.6	89.6 ± 9.9
Live birth index (%) ^{e)}	99.3 ± 2.4	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
Live pups on day 4 of lactation	13.8 ± 1.9	12.5 ± 3.0	11.5 ± 3.2	11.4 ± 1.7
Viability index (%) ^{f)}	98.2 ± 4.6	98.3 ± 4.1	100.0 ± 0.0	92.6 ± 10.6
External anomalies (%) ^{g)}	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Sex ratio at birth (stillbirths included) ^{h)}	87 / 169	81 / 153	81 / 138	55 / 148
Mean ± S.D.	0.52 ± 0.12	0.50 ± 0.15	0.57 ± 0.16	0.37 ± 0.09#
Sex ratio at birth (stillbirths declined) ⁱ⁾	86 / 168	81 / 153	81 / 138	55 / 148
Mean ± S.D.	0.51 ± 0.12	0.50 ± 0.15	0.57 ± 0.16	0.37 ± 0.09#
Sex ratio on day 4 of lactation ^{j)}	84 / 165	80 / 150	81 / 138	53 / 137
Mean ± S.D.	0.51 ± 0.12	0.51 ± 0.15	0.57 ± 0.16	0.37 ± 0.09#
Body weight of pups (g)				
Male Day 0	6.75 ± 0.70	6.87 ± 0.75	7.30 ± 0.86	6.56 ± 0.52
4	9.92 ± 1.85	10.58 ± 1.68	11.54 ± 1.87	10.26 ± 1.16
Female Day 0	6.36 ± 0.56	6.43 ± 0.61	6.79 ± 0.90	6.20 ± 0.45
4	9.37 ± 1.63	9.99 ± 1.47	10.87 ± 1.91	9.82 ± 1.10

Each values shows mean±S.D.

Significantly different from the control, # : p<0.05 (Steel test).

b) (No. of dams with live pups / No. of pregnant dams)×100.

d) (No. of live pups born / No. of implantation scars)×100.

f) (No. of live pups on day 4 of lactation / No. of live pups born)×100.

h) Total number of male pups born / Total number of male and female pups born. i) Total number of live males / Total number of live males and females.

j) Total number of live males on day 4 of lactation / Total number of live males and females on day 4 of lactation.

a) (No. of implantation scars / No. of corpora lutea)×100.

c) (No. of pups born / No. of implantation scars)×100.

e) (No. of live pups born / No. of pups born)×100.

g) (No. of pups with external anomalies / No. of live pups)×100.

Appendix 1-1 General signs of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Findings
0 ^{a)}	1101	No abnormality detected during administration period
	1102	No abnormality detected during administration period
	1103	No abnormality detected during administration period
	1104	No abnormality detected during administration period
	1105	No abnormality detected during administration period
	1106	No abnormality detected during administration period
	1107	No abnormality detected during administration period
	1121	No abnormality detected during administration and recovery period
	1122	No abnormality detected during administration and recovery period
	1123	No abnormality detected during administration and recovery period
	1124	No abnormality detected during administration and recovery period
	1125	No abnormality detected during administration and recovery period
	1201	No abnormality detected during administration period
	1202	No abnormality detected during administration period
	1203	No abnormality detected during administration period
1	1204	No abnormality detected during administration period
	1205	No abnormality detected during administration period
	1206	No abnormality detected during administration period
	1207	No abnormality detected during administration period
	1208	No abnormality detected during administration period
	1209	No abnormality detected during administration period
	1210	No abnormality detected during administration period
	1211	No abnormality detected during administration period
	1212	No abnormality detected during administration period
	a) : Control animals were administered olive oil orally.	

Appendix 1-2 General signs of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Findings
10	1301	No abnormality detected during administration period
	1302	No abnormality detected during administration period
	1303	No abnormality detected during administration period
	1304	No abnormality detected during administration period
	1305	No abnormality detected during administration period
	1306	No abnormality detected during administration period
	1307	No abnormality detected during administration period
	1308	No abnormality detected during administration period
	1309	No abnormality detected during administration period
	1310	No abnormality detected during administration period
	1311	No abnormality detected during administration period
	1312	No abnormality detected during administration period
100	1401	Dark red discoloration of the skin (+, Administration Day 2-42)
	1402	Dark red discoloration of the skin (+, Administration Day 2-42)
	1403	Dark red discoloration of the skin (+, Administration Day 2-42)
	1404	Dark red discoloration of the skin (+, Administration Day 2-42)
	1405	Dark red discoloration of the skin (+, Administration Day 2-42)
	1406	Dark red discoloration of the skin (+, Administration Day 2-42)
	1407	Dark red discoloration of the skin (+, Administration Day 2-42)
	1421	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)
	1422	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)
	1423	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)
	1424	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)
	1425	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)

Grade: + ; Slight

Appendix 2-1 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylamine by oral administration

Dose (mg/kg/day)			0 ^{a)}												1													
Parameters	Administration weeks		Before																									
	Animal No.		1101	1102	1103	1104	1105	1106	1107	1121	1122	1123	1124	1125	1101	1102	1103	1104	1105	1106	1107	1121	1122	1123	1124	1125		
	Normal score																											
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Behavior observations in the open field	Rearings	Counts	4	3	4	5	3	1	0	4	2	4	2	4	3	3	1	4	0	2	1	1	1	1	1	0	4	5
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a) : Control animals were administered olive oil orally.

- : no comments, N : normal.

Appendix 2-2 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		0 ^{a)}																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
Parameters	Administration weeks	2															3																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
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Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

a) : Control animals were administered olive oil orally.

- : no comments, N : normal.

Appendix 2-3

Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		0 ^{a)}																			
Parameters		Administration weeks		4										5							
		Animal No.																			
			Normal score																		
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Detailed clinical observations by the handling	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rearings	Counts	1	1	2	0	2	3	2	2	1	0	1	2	2	1	0	3	2	5	3
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Behavior observations in the open field	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0	0
Urinations	Counts	0	2	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	

a) : Control animals were administered olive oil orally.

- : no comments, N : normal.

Appendix 2-4 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylalanine by oral administration

Dose (mg/kg/day)		0 ^{a)}													
		6													
		Administration weeks													
Parameters		Animal No.													
		Normal score													
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Rearings	Counts	0	0	1	5	2	1	1	1	2	0	0	2	0
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0

a) : Control animals were administered olive oil orally.

- : no comments, N : normal.

Appendix 2-5 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		1												
Parameters	Administration weeks		Before											
	Animal No.		1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212
	Normal score													
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1
Detailed clinical observations by the handler	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rearings	Counts	5	4	3	5	2	4	2	0	4	3	3	4
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1
no comments, N : normal	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-
no comments, N : normal	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0

- : no comments, N : normal.

Appendix 2-6 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylamine by oral administration

Dose (mg/kg/day)		1												2												3													
Parameters		Administration weeks																																					
		Animal No.																																					
		Normal score																																					
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Behavior observations in the open field	Rearings	Counts	2	0	1	0	0	0	2	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	0	3	0	0	1	0	1	1	3	1	1		
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4		
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	

- : no comments, N : normal.

Appendix 2-7 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylamine by oral administration

Dose (mg/kg/day)		1																							
		4												5											
Administration weeks																									
Parameters																									
Animal No.																									
Normal score																									
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Detailed clinical observations by the handling	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Counts	1	3	3	0	1	4	1	0	1	3	2	0	2	4	3	0	0	2	4	1	3	4	2	4
	Rearings	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: no comments, N : normal.																								

- : no comments, N : normal.

Appendix 2-8 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		1											
		6											
		Administration weeks											
Parameters		Animal No.											
		Normal score											
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Rearings	Counts	4	2	2	1	0	2	0	0	2	4	0
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1
	Gait	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	1	0	0	0	0	0	0	0	0	0	0

- : no comments, N : normal.

Appendix 2-9 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		10														1																					
		Administration weeks							Before																												
		Animal No.																																			
Parameters		1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312	1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312	1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312
Normal score																																					
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Behavior observations in the open field	Rearings	Counts	0	4	2	5	6	3	3	5	5	1	2	7	0	1	1	2	3	2	1	2	3	0	0	4	1	1	1	1	1	1	1	1	1	1	
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4		
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Urinations	Counts	0	0	0	0	3	4	1	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		: no comments, N : normal.																																			

- : no comments, N : normal.

Appendix 2-10 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		10															
Parameters		Administration weeks															
		2															
		3															
Animal No.		1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312				
Normal score																	
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2			
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1			
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2			
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1			
Behavior observations in the open field	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1			
	Rearings	Counts	0	0	0	1	0	0	0	0	2	1	2	2	0	1	3
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
Abnormal behavior	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Defecations	Counts	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: no comments, N : normal.																

- : no comments, N : normal.

Appendix 2-11 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		10														5										
Parameters		Administration weeks														5										
		Animal No.																								
		Normal score																								
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Behavior observations in the open field	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rearings	Counts	2	1	2	0	2	1	2	1	1	1	1	0	0	2	2	1	3	3	1	2	2	2	4	4
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
Urinations	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	

no comments, N : normal.

-, no comments, N : normal.

Appendix 2-12 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		10													
		6													
		Administration weeks													
Parameters		Animal No.													
		Normal score													
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rearings	Counts	1	0	4	1	2	0	0	1	1	3	1	5	
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	1	0	0	0	0	0
: no comments, N : normal.															

- : no comments, N : normal.

Appendix 2-13 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylamine by oral administration

Dose (mg/kg/day)		100														1													
Parameters	Administration weeks	Before																											
		Animal No.																											
		Normal score																											
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rearings	Counts	2	0	5	2	2	5	5	2	3	4	4	4	1	0	4	0	0	0	3	0	4	4	4	3			
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	2	0	0	0	0	0	0	2	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0

- : no comments, N : normal.

Appendix 2-14 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylamine by oral administration

Dose (mg/kg/day)		100																	
		2										3							
Administration weeks																			
Parameters		Animal No.																	
		Normal score																	
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Dark red discoloration of the skin	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rearings	Counts	0	0	1	0	0	0	2	0	1	1	1	1	0	0	2	0	0
Behavior observations in the open field	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0	0

- : no comments, N : normal.

Appendix 2-15 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		100															5												
		4																											
		Administration weeks																											
Parameters		Animal No.																											
		Normal score																											
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Dark red discoloration of the skin	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rearings	Counts	1	2	1	2	2	0	0	1	1	0	2	1	0	1	0	0	3	3	2	2	1	2	3	1	1	3	2
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Detailed clinical observations by the handling	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	- : no comments, N : normal.																												

Appendix 2-16 Detailed clinical observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		100																		
		6																		
Parameters		Administration weeks																		
		Animal No.																		
		Normal score																		
Handling at the grab	Reactivity	2																		
	Vocalization	1																		
	Myotony	2																		
	Hypothermia	1																		
	Piloerection	1																		
	Fur soiled	1																		
	Rough cast	1																		
	Pallor	1																		
	Rubor	1																		
	Cyanosis	1																		
Detailed clinical observations by the handler	Dark red discoloration of the skin	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rearings	Counts	0	3	3	0	2	0	3	1	1	1	2	2	2	2	2	2	2	2
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Behavior observations in the open field	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Appendix 3 Functional observations of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration
- 6 weeks of administration period -

Parameters	Dose (mg/kg/day)															
	0 ^{a)}								1							
	Animal No.		1101		1102		1103		1104		1105		1201		1202	
Normal score																
Approach and/or Touch response	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2
Sound response	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2
Tail pinch response	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2
Pupillary reflex	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2
Aerial righting reflex	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Forelimb grip strength (N)	1st	9.09	9.41	5.55	7.28	7.87	9.01	6.91	6.63	5.41	5.84	8.38	8.59	6.72	8.29	9.86
	2nd	7.88	7.87	7.78	6.19	5.53	8.09	8.20	7.99	6.86	5.72	8.00	9.59	5.88	6.79	8.98
	Mean	8.49	8.64	6.67	6.74	6.70	8.55	7.56	7.31	6.14	5.78	8.19	9.09	6.30	7.54	9.42
	±S.D.	0.86	1.09	1.58	0.77	1.65	0.65	0.91	0.96	1.03	0.08	0.27	0.71	0.59	1.06	0.62
Hind limb grip strength (N)	1st	1.69	1.33	1.41	1.30	1.90	1.07	2.64	2.12	1.44	1.29	1.35	2.08	1.77	1.33	2.02
	2nd	1.09	1.45	1.20	1.61	1.43	1.41	2.43	1.65	1.54	2.01	1.69	2.38	1.44	1.76	1.66
	Mean	1.39	1.39	1.31	1.46	1.67	1.24	2.54	1.89	1.49	1.65	1.52	2.23	1.61	1.55	1.84
	±S.D.	0.42	0.08	0.15	0.22	0.33	0.24	0.15	0.33	0.07	0.51	0.24	0.21	0.23	0.30	0.25
Responses	3 min	213	410	739	819	455	903	816	1019	836	897	63	612	917	866	650
	6 min	701	857	812	898	748	903	945	933	844	897	397	785	971	838	891
	9 min	826	879	868	949	656	914	925	895	723	885	761	783	833	843	785
	12 min	691	887	788	822	673	837	855	828	846	732	667	652	836	815	707
	15 min	755	973	717	805	634	860	842	851	601	806	895	829	822	850	396
	Total	3186	4006	3924	4293	3166	4417	4383	4526	3850	4217	2783	3661	4379	4212	3429

a) : Control animals were administered olive oil orally.

Appendix 4-1 Body weight changes of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Body weights on administration days (g)							Body weights on recovery days (g)				
		1	3	8	15	22	29	36	1	3	7	14	15
0 ^{a)}	1101	340.9	354.3	381.6	409.9	423.2	447.3	465.3					
	1102	359.3	366.2	391.7	406.9	436.3	457.5	474.1					
	1103	355.7	373.9	399.0	428.4	468.1	497.8	521.2					
	1104	356.0	371.0	397.6	429.4	453.9	478.9	500.5					
	1105	367.3	381.7	407.6	425.6	468.0	499.1	528.7					
	1106	371.0	392.8	426.3	451.6	480.1	518.1	542.5					
	1107	378.4	391.9	418.8	448.4	478.6	495.9	517.3					
1	1121	348.1	350.1	374.5	400.2	404.0	423.2	435.4	458.8	466.7	484.0	503.7	481.1
	1122	359.7	370.6	397.0	418.4	438.0	457.7	467.5	482.7	482.0	493.6	510.3	483.5
	1123	365.6	385.1	418.9	439.6	469.5	499.1	515.7	529.3	537.8	550.0	584.9	547.8
	1124	367.0	377.1	407.9	432.0	462.7	481.4	508.6	528.5	532.0	537.0	546.9	523.7
	1125	372.8	384.7	413.8	442.3	469.1	508.9	541.1	570.6	575.5	590.3	622.3	588.3
	1201	344.0	356.7	385.7	399.6	432.0	452.5	453.3					
	1202	343.5	361.1	384.1	395.3	425.5	452.7	469.7					
	1203	358.9	367.5	393.5	429.4	450.2	480.5	491.9					
	1204	357.9	375.6	402.6	426.2	458.0	480.5	509.4					
	1205	359.3	371.9	405.0	424.7	460.5	485.5	507.6					
	1206	359.0	365.7	387.7	421.0	443.2	462.4	473.1					
	1207	361.7	369.3	406.5	440.3	469.3	489.4	509.0					
	1208	366.8	379.5	413.4	441.8	460.2	490.7	507.2					
	1209	373.0	387.5	419.2	457.6	481.4	505.9	527.2					
	1210	369.3	385.1	413.5	440.9	473.5	501.7	514.3					
	1211	380.0	398.7	434.2	467.4	498.8	540.5	564.1					
	1212	377.2	388.7	429.8	473.0	503.2	546.5	563.9					

a) : Control animals were administered olive oil orally.

Appendix 4-2 Body weight changes of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Body weights on administration days (g)							Body weights on recovery days (g)				
		1	3	8	15	22	29	36	1	3	7	14	15
10	1301	336.7	350.2	369.4	388.2	412.9	447.5	471.8					
	1302	349.1	364.7	388.4	404.7	430.8	458.6	475.7					
	1303	358.6	373.5	399.1	429.1	453.7	490.5	511.2					
	1304	356.7	368.1	395.6	420.5	456.3	484.9	503.5					
	1305	356.5	374.9	405.6	429.4	455.2	483.0	500.0					
	1306	363.7	381.3	413.3	445.4	477.6	511.0	543.6					
	1307	368.1	383.5	414.7	447.7	469.3	493.5	522.1					
	1308	373.7	389.5	429.2	460.3	507.4	533.5	570.1					
	1309	371.3	379.9	420.4	453.9	490.9	532.3	549.9					
	1310	369.8	380.2	413.5	440.9	476.3	506.2	529.1					
	1311	381.4	390.2	428.1	442.3	475.1	516.2	539.6					
	1312	370.6	389.3	418.8	441.6	470.1	499.9	514.2					
100	1401	349.4	352.4	366.4	396.8	418.2	439.8	460.8					
	1402	349.5	357.0	373.4	401.3	426.6	445.1	452.9					
	1403	361.0	374.6	391.6	417.1	426.9	452.5	461.8					
	1404	361.9	375.2	362.7	421.1	455.4	480.0	494.1					
	1405	371.8	381.6	402.0	428.5	451.2	480.8	498.1					
	1406	373.8	381.8	405.9	442.4	479.2	522.0	542.1					
	1407	374.8	388.0	412.0	444.8	469.0	497.5	521.2					
	1421	359.8	364.1	378.9	405.2	434.2	458.1	466.7	473.9	478.6	489.2	513.8	495.0
	1422	361.7	364.7	381.7	414.8	436.8	468.3	481.5	491.9	507.2	522.1	539.4	507.9
	1423	368.0	377.5	397.9	427.2	456.2	489.8	508.7	523.0	526.6	542.4	566.5	532.6
	1424	360.0	373.2	391.2	420.4	450.8	466.6	488.2	505.6	514.3	521.4	547.4	515.6
	1425	376.7	393.1	431.7	487.3	527.9	561.6	598.9	620.9	629.3	643.7	675.2	644.9

Appendix 5-1 Food consumption of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Food consumption (g/day)													
		Administration days							Recovery days						
		1	3	8	20	22	29	36	1	3	7	14			
0 ^{a)}	1101	20.6	22.8	23.1	19.2	20.3	23.8	23.8							
	1102	28.1	24.8	24.9	23.6	23.5	25.9	22.5							
	1103	22.4	27.0	24.8	27.5	28.2	28.1	27.3							
	1104	23.6	23.3	23.9	24.0	21.0	25.6	26.5							
	1105	25.2	26.5	23.7	26.2	25.9	21.5	24.4							
	1106	28.6	31.1	27.4	25.8	22.4	25.4	28.3							
	1107	26.4	28.3	25.4	21.8	20.2	25.4	30.0							
	1121	21.7	22.1	22.5	23.0	19.6	26.5	23.7	21.6	27.0	29.1	26.5			
	1122	25.8	23.7	23.7	21.7	21.3	24.5	23.2	25.2	23.4	23.8	25.6			
	1123	27.9	29.2	26.1	23.6	24.6	25.6	27.0	21.1	24.9	23.3	29.1			
	1124	24.9	28.5	25.6	22.4	24.4	21.6	22.6	25.2	26.7	23.7	21.5			
	1125	26.1	26.4	25.9	26.2	26.1	29.7	30.5	26.1	29.5	29.9	34.3			
1	1201	23.0	22.0	24.8	24.4	23.5	26.0	20.0							
	1202	20.8	24.4	21.9	21.6	20.8	24.7	24.0							
	1203	22.0	23.0	21.6	19.9	22.5	21.4	20.7							
	1204	25.0	28.7	26.8	25.0	25.0	19.7	26.4							
	1205	24.4	26.5	22.5	24.3	21.5	24.3	22.4							
	1206	23.0	22.1	21.5	23.8	20.9	21.1	19.8							
	1207	24.6	25.6	23.6	23.1	23.0	23.5	25.1							
	1208	25.5	27.1	29.2	22.8	22.9	26.3	23.8							
	1209	26.2	29.3	25.5	23.4	26.2	23.1	26.2							
	1210	24.6	25.3	23.3	21.5	23.8	29.0	24.4							
	1211	27.5	29.4	26.6	26.2	25.9	26.8	24.7							
	1212	27.5	30.6	29.9	27.1	28.7	32.2	23.9							

a) : Control animals were administered olive oil orally.

Appendix 5-2 Food consumption of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Food consumption (g/day)													
		Administration days							Recovery days						
		1	3	8	20	22	29	36	1	3	7	14			
10	1301	17.0	21.7	18.8	23.2	22.6	21.3	18.9							
	1302	24.8	26.5	24.3	22.5	27.9	25.0	27.0							
	1303	25.3	24.8	22.4	21.8	22.4	33.6	23.2							
	1304	22.3	26.2	22.0	24.2	26.6	25.1	23.2							
	1305	24.4	27.5	25.2	24.9	24.4	27.5	23.5							
	1306	28.4	30.1	27.8	28.6	31.3	29.8	31.4							
	1307	26.3	26.5	23.7	22.1	23.5	24.3	25.1							
	1308	31.1	30.0	28.3	30.7	32.8	33.4	29.3							
	1309	30.7	32.3	25.2	29.4	26.5	33.6	27.9							
	1310	24.9	25.5	25.5	25.9	25.4	25.3	26.6							
	1311	27.8	29.5	28.1	28.4	27.5	30.0	29.8							
	1312	26.8	29.8	29.4	26.2	25.8	37.1	25.5							
100	1401	25.2	20.2	18.0	20.6	22.5	22.0	23.1							
	1402	24.2	26.9	22.0	21.7	24.4	23.3	21.0							
	1403	24.5	24.6	24.1	19.8	22.8	24.9	19.8							
	1404	22.3	25.5	15.0	21.6	29.9	25.7	19.7							
	1405	24.0	26.8	25.0	25.3	28.2	24.4	24.2							
	1406	23.6	25.2	26.6	24.7	27.9	32.4	25.3							
	1407	27.4	27.1	24.0	22.5	26.2	24.9	26.4							
	1421	25.4	22.2	20.8	20.9	23.6	21.6	20.0	19.8	24.4	21.7	23.9			
	1422	26.0	22.4	20.4	20.3	24.0	24.6	21.7	19.5	25.9	28.7	25.2			
	1423	27.0	27.3	20.9	23.7	24.1	25.0	20.2	24.6	25.8	26.2	29.6			
	1424	22.8	26.7	23.5	24.6	25.0	26.4	22.7	19.3	28.3	25.5	27.2			
	1425	25.7	28.5	29.0	28.9	32.4	32.0	28.6	31.0	34.6	32.6	34.0			

Appendix 6-1 Urinary findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen
0 ^{a)}	1101	8.0	+	-	+	-	-	0.1
	1102	7.5	++	-	+	-	-	0.1
	1103	7.5	++	-	+	-	-	0.1
	1104	8.0	+	-	+	-	-	0.1
	1105	8.0	+	-	+	-	-	0.1
1	1201	8.5	++	-	+	-	-	0.1
	1202	8.0	+	-	+	-	-	0.1
	1203	8.5	+	-	+	-	-	0.1
	1204	7.5	+	-	+	-	-	0.1
	1205	6.5	+	-	+	-	-	0.1
10	1301	8.5	+	-	+	-	-	0.1
	1302	8.0	+	-	+	-	-	0.1
	1303	8.5	+++	-	+	-	-	0.1
	1304	8.0	+	-	+	-	-	0.1
	1305	6.5	+	-	+	-	-	0.1
100	1401	6.5	+	-	+	-	-	0.1
	1402	7.5	++	-	+	-	-	0.1
	1403	7.5	+++	-	+	-	-	0.1
	1404	7.5	++	-	+	-	-	0.1
	1405	7.5	+	-	+	-	-	0.1

a) : Control animals were administered olive oil orally.

Protein : + ; 30 mg/dL, ++ ; 100 mg/dL, +++ ; 300 mg/dL.

Glucose : - ; Negative.

Ketone body : + ; 15 mg/dL.

Bilirubin : - ; Negative.

Occult blood : - ; Negative.

Urobilinogen : Ehrlich unit/dL.

Appendix 6-2 Urinary findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen
0 ^{a)}	1121	7.5	+	-	+	-	-	0.1
	1122	7.5	++	-	+	-	-	0.1
	1123	8.0	+	-	+	-	-	0.1
	1124	8.0	++	-	+	-	-	0.1
	1125	7.5	++	-	+	-	-	0.1
100	1421	8.0	+	-	+	-	-	0.1
	1422	8.5	++	-	+	-	-	0.1
	1423	8.0	±	-	+	-	-	0.1
	1424	8.0	++	-	+	-	-	0.1
	1425	7.5	+	-	+	-	-	0.1

a) : Control animals were administered olive oil orally.

Protein : ± ; < 30 mg/dL, + ; 30 mg/dL, ++ ; 100 mg/dL. Bilirubin : - ; Negative.
Glucose : - ; Negative. Occult blood : - ; Negative.
Ketone body : + ; 15 mg/dL. Urobilinogen : Ehrlich unit/dL.

Appendix 7-1 Hematological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	RBC ($\times 10^6/\mu\text{L}$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	WBC ($\times 10^9/\mu\text{L}$)	Differential WBC count (%)							PLT ($\times 10^9/\mu\text{L}$)	PT (second)	APTT (second)
									Bas	Eos	St	Seg	Lym	Mon	Other			
0 ^{a)}	1101	958	17.9	51.2	53.4	18.7	35.0	67	0	0	0	15	85	0	0	102.2	15.1	16.8
	1102	851	16.2	46.2	54.3	19.0	35.1	90	0	1	0	15	84	0	0	100.8	15.1	16.0
	1103	911	16.7	47.5	52.1	18.3	35.2	106	0	2	0	22	76	0	0	97.7	14.6	14.2
	1104	951	16.6	46.1	48.5	17.5	36.0	124	0	1	0	21	78	0	0	72.9	15.0	11.7
	1105	882	17.0	49.3	55.9	19.3	34.5	115	0	2	0	8	90	0	0	103.3	14.8	15.9
1	1201 ^{b)}	922	16.8	48.2	52.3	18.2	34.9	88	0	2	0	12	86	0	0	68.2	15.3	15.4
	1202	861	16.5	47.0	54.6	19.2	35.1	91	0	1	0	17	82	0	0	91.5	15.6	17.7
	1203	862	16.2	47.0	54.5	18.8	34.5	138	0	2	0	8	90	0	0	106.8	16.1	18.6
	1204	870	16.1	46.4	53.3	18.5	34.7	98	0	0	0	10	90	0	0	122.2	14.9	15.9
	1205	909	16.3	47.3	52.0	17.9	34.5	116	0	1	0	18	81	0	0	85.6	15.1	16.8
10	1301	899	16.8	49.1	54.6	18.7	34.2	79	0	2	0	11	87	0	0	95.1	14.9	16.5
	1302	906	16.9	48.5	53.5	18.7	34.8	91	0	0	0	21	79	0	0	123.4	14.4	14.1
	1303	850	15.9	44.7	52.6	18.7	35.6	94	0	0	0	9	91	0	0	131.4	15.2	17.0
	1304	784	15.2	43.5	55.5	19.4	34.9	107	0	0	0	11	89	0	0	87.3	15.2	15.6
	1305	936	16.3	48.9	52.2	17.4	33.3	126	0	3	0	10	87	0	0	117.8	15.2	16.4
100	1401	596	12.9	39.8	66.8	21.6	32.4	167	0	0	0	22	78	0	0	130.2	15.2	13.1
	1402	689	14.3	43.6	63.3	20.8	32.8	154	0	4	0	12	84	0	0	109.0	15.4	16.9
	1403	594	13.4	39.3	66.2	22.6	34.1	134	0	2	0	19	79	0	0	123.8	14.9	14.6
	1404	570	12.7	38.3	67.2	22.3	33.2	134	0	2	0	7	91	0	0	112.9	15.7	16.0
	1405	665	14.1	42.7	64.2	21.2	33.0	147	0	1	0	14	85	0	0	92.4	16.1	15.6

a) : Control animals were administered olive oil orally.

b) : Death of anesthetizing, excluded from calculation of mean value.

RBC : Red blood cell.

Hb : Hemoglobin.

Ht : Hematocrit.

MCV : Mean corpuscular volume.

MCH : Mean corpuscular hemoglobin level.

MCHC : Mean corpuscular hemoglobin concentration.

WBC : White blood cell.

Bas : Basophil.

Eos : Eosinophil.

St : Stab neutrophil.

Seg : Segmented neutrophil.

Lym : Lymphocyte.

Mon : Monocyte.

PLT : Platelet.

PT : Prothrombin time.

APTT : Activated partial thromboplastin time.

Appendix 7-2 Hematological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	RBC ($\times 10^6/\mu\text{L}$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	WBC ($\times 10^3/\mu\text{L}$)	Differential WBC count (%)							PLT ($\times 10^3/\mu\text{L}$)	PT (second)	APTT (second)
									Bas	Eos	St	Seg	Lym	Mon	Other			
0 ^{b)}	1121	909	16.6	49.0	53.9	18.3	33.9	106	0	0	0	6	94	0	0	108.1	14.6	15.8
	1122	924	17.1	47.9	51.8	18.5	35.7	86	0	1	0	12	87	0	0	125.7	14.1	15.3
	1123	868	16.6	46.4	53.5	19.1	35.8	118	0	0	0	14	86	0	0	112.8	14.5	14.7
	1124	766	14.5	40.2	52.5	18.9	36.1	129	0	0	0	34	66	0	0	80.9	16.1	18.8
	1125	899	16.4	45.9	51.1	18.2	35.7	105	0	1	0	12	87	0	0	131.5	14.8	16.3
100	1421	791	16.9	49.2	62.2	21.4	34.3	148	0	1	0	14	85	0	0	100.2	14.7	15.0
	1422	815	16.9	49.6	60.9	20.7	34.1	112	0	0	0	3	97	0	0	108.7	14.7	15.4
	1423	835	17.0	48.9	58.6	20.4	34.8	100	0	2	0	21	77	0	0	112.0	15.3	14.7
	1424	804	16.6	48.4	60.2	20.6	34.3	114	0	3	0	10	87	0	0	109.0	15.5	16.6
	1425	836	16.9	52.3	62.6	20.2	32.3	91	0	1	0	19	80	0	0	115.1	14.4	16.9

a) : Control animals were administered olive oil orally.

RBC : Red blood cell.
 Hb : Hemoglobin.
 Ht : Hematocrit.
 MCV : Mean corpuscular volume.
 MCH : Mean corpuscular hemoglobin level.
 MCHC : Mean corpuscular hemoglobin concentration.
 WBC : White blood cell.
 Bas : Basophil.
 Eos : Eosinophil.
 St : Stab neutrophil.
 Seg : Segmented neutrophil.
 Lym : Lymphocyte.
 Mon : Monocyte.
 PLT : Platelet.
 PT : Prothrombin time.
 APTT : Activated partial thromboplastin time.

Appendix 8-1 Blood biochemical findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TP (g/dL)	Alb (g/dL)	Plasma protein pattern (%)				Glu (mg/dL)	TC (mg/dL)	TG (mg/dL)	TB (mg/dL)	BUN (mg/dL)	Cre (mg/dL)	IP (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)		
							A/G		1	2													
							Alb	A/G															
0 ^{a)}	1101	80	28	342	6.3	3.7	57.1	22.2	6.2	12.8	1.7	1.33	161	110	75	0.01	21.5	0.34	6.3	10.0	149.2	4.50	103.4
	1102	122	64	320	6.4	3.7	58.3	22.2	4.6	13.1	1.8	1.39	159	77	39	0.02	18.2	0.32	6.3	10.2	147.5	4.57	105.7
	1103	71	27	245	6.4	3.7	57.2	22.0	3.6	13.9	3.3	1.33	167	49	56	0.01	18.9	0.30	5.6	10.2	148.5	4.59	105.5
	1104	105	48	215	6.5	3.7	54.9	23.0	6.3	13.2	2.6	1.21	122	64	47	0.05	16.6	0.30	7.5	10.4	148.3	4.95	104.4
	1105	80	28	220	6.6	3.7	54.1	23.1	4.6	16.4	1.8	1.17	157	68	83	0.04	13.8	0.30	6.9	10.4	148.9	4.03	104.0
1	1201 ^{b)}	91	37	254	6.4	3.7	55.9	19.9	5.2	15.3	3.7	1.26	150	61	53	0.04	21.4	0.35	9.0	10.4	145.9	9.09	103.5
	1202	69	26	207	6.4	3.3	53.9	25.9	4.5	13.4	2.3	1.16	150	65	49	0.00	17.0	0.33	5.9	10.5	148.7	4.70	105.7
	1203	74	46	268	6.5	3.5	53.9	23.4	5.8	14.7	2.2	1.16	142	61	84	0.05	14.3	0.28	6.9	10.5	148.6	4.26	105.9
	1204	59	23	277	6.5	3.7	54.8	22.3	5.2	15.3	2.4	1.21	139	87	91	0.04	17.4	0.26	6.7	10.8	147.2	4.34	103.3
	1205	67	24	300	6.1	3.5	56.6	22.1	4.3	14.3	2.7	1.30	151	63	44	0.05	14.8	0.31	6.2	10.2	147.3	4.14	104.1
10	1301	65	32	219	6.5	3.7	57.0	22.9	3.9	14.0	2.2	1.32	202	57	44	0.00	21.1	0.42	7.7	10.7	149.8	5.91	102.8
	1302	76	33	299	6.6	3.6	55.3	23.2	3.7	15.0	2.8	1.23	141	81	101	0.00	21.5	0.31	5.4	10.4	148.2	4.89	103.4
	1303	70	32	204	7.0	3.7	52.9	23.7	3.9	16.2	3.3	1.12	164	91	68	0.03	19.7	0.30	6.7	10.4	146.4	4.41	101.7
	1304	71	24	221	6.2	3.3	53.6	23.4	5.0	15.2	2.8	1.15	134	48	27	0.03	14.3	0.27	7.0	10.3	148.7	4.46	105.8
	1305	63	26	198	6.5	3.6	56.0	19.7	5.1	16.8	2.4	1.27	146	68	94	0.04	14.7	0.28	6.0	10.2	148.1	4.31	105.3
100	1401	80	33	231	6.2	3.4	55.0	19.9	5.1	17.9	2.1	1.22	163	45	43	0.10	22.4	0.36	6.1	10.2	146.9	4.81	105.1
	1402	71	26	178	6.2	3.4	56.6	20.8	4.9	14.4	3.3	1.30	139	48	23	0.13	21.4	0.29	7.3	10.5	147.3	4.35	104.8
	1403	84	41	210	6.2	3.7	59.7	18.9	5.5	13.7	2.2	1.48	150	52	46	0.17	16.0	0.24	6.5	10.5	147.7	4.81	105.0
	1404	73	25	148	6.1	3.3	54.6	20.4	5.1	17.2	2.7	1.20	149	50	43	0.23	19.6	0.32	7.9	10.3	146.8	4.61	102.6
	1405	112	56	210	6.2	3.6	56.2	21.1	4.3	14.7	3.7	1.28	176	37	32	0.16	18.3	0.29	6.6	10.2	147.7	4.55	104.3

a) : Control animals were administered olive oil orally.

b) : Death of anesthetizing, excluded from calculation of mean value.

AST : Glutamic oxaloacetic transaminase.

ALT : Glutamic pyruvic transaminase.

ALP : Alkaline phosphatase.

TP : Total protein.

Alb : Albumin.

A/G : Albumin/Globulin ratio.

1 : 1-globulin.

2 : 2-globulin.

-globulin.

-globulin.

A/G : Albumin/Globulin ratio.

Glu : Glucose.

TC : Total cholesterol.

TG : Triglyceride.

TB : Total bilirubin.

BUN : Blood urea nitrogen.

Cre : Creatinine.

IP : Inorganic phosphate.

Ca : Calcium.

Na : Sodium.

K : Potassium.

Cl : Chlorine.

Appendix 8-2 Blood biochemical findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TP (g/dL)	Alb (g/dL)	Plasma protein pattern (%)				Glu (mg/dL)	TC (mg/dL)	TG (mg/dL)	TB (mg/dL)	BUN (mg/dL)	Cre (mg/dL)	IP (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)		
							A/G																
							Alb	1	2														
0 ⁰	1121	66	30	241	6.2	3.4	55.3	21.1	4.5	14.4	4.7	1.23	171	57	35	0.03	17.5	0.30	5.9	9.9	146.5	4.19	104.6
	1122	66	25	201	6.2	3.7	55.6	22.1	4.9	15.2	2.2	1.25	125	89	35	0.03	20.2	0.36	6.1	10.2	146.5	4.28	104.1
	1123	120	58	227	6.3	3.5	56.3	21.0	4.2	15.8	2.7	1.28	147	63	29	0.07	18.4	0.34	5.7	10.2	148.1	4.18	105.0
	1124	154	82	238	6.5	2.4	31.3	30.5	6.7	29.4	2.1	0.45	115	41	102	0.01	19.6	0.45	6.0	10.6	145.7	4.60	103.6
	1125	94	37	268	6.5	3.6	53.2	21.3	5.3	17.7	2.5	1.13	157	68	126	0.00	19.5	0.32	5.8	9.7	145.8	4.45	102.4
100	1421	68	27	303	6.4	3.7	53.2	22.6	4.5	14.8	4.9	1.13	147	77	54	0.02	18.6	0.32	5.7	9.9	146.2	4.13	102.8
	1422	66	22	184	6.3	3.6	52.1	23.7	5.1	15.7	3.4	1.08	158	71	38	0.02	23.6	0.36	5.9	10.1	146.4	3.99	103.2
	1423	62	28	290	6.6	3.7	55.9	16.9	5.8	17.5	3.9	1.26	146	78	99	0.00	22.2	0.31	6.8	10.3	147.4	4.47	104.0
	1424	63	26	220	6.6	3.7	55.2	20.6	4.9	16.2	3.1	1.23	135	59	64	0.02	20.4	0.33	6.8	10.1	145.9	4.77	101.2
	1425	76	41	212	6.5	3.6	53.8	21.8	4.4	16.9	3.1	1.16	142	66	103	0.01	18.5	0.30	6.7	10.2	145.6	4.68	101.9

a) : Control animals were administered olive oil orally.

AST : Glutamic oxaloacetic transaminase. 1 : γ -globulin. Glu : Glucose. Cre : Creatinine. Cl : Chlorine.
 ALT : Glutamic pyruvic transaminase. 2 : α -globulin. TC : Total cholesterol. IP : Inorganic phosphate.
 ALP : Alkaline phosphatase. : β -globulin. TG : Triglyceride. Ca : Calcium.
 TP : Total protein. : γ -globulin. TB : Total bilirubin. Na : Sodium.
 Alb : Albumin. A/G : Albumin/Globulin ratio. BUN : Blood urea nitrogen. K : Potassium.

Appendix 9-1 Absolute organ weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Final body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Spleen (g)	Kidneys (g)	Adrenals (mg)	Testes (g)	Epididymides (g)
0 ^{a)}	1101	450.3	2.163	0.317	1.613	11.217	0.689	2.296	46.3	3.494	1.335
	1102	455.8	2.221	0.371	1.364	11.706	0.778	2.714	47.1	3.325	1.218
	1103	510.0	2.223	0.338	1.461	13.307	0.862	2.626	65.6	3.255	1.268
	1104	494.0	2.327	0.316	1.696	11.802	0.838	2.636	52.6	3.233	1.423
	1105	518.5	2.248	0.402	1.577	13.280	0.626	2.688	63.1	3.379	1.269
	1106	530.7	2.093	0.339	1.643	14.911	0.586	2.958	48.3	3.313	1.231
	1107	512.9	2.216	0.355	1.578	11.994	0.787	2.893	69.1	3.677	1.530
1	1121	481.1	2.069	0.428	1.634	13.373	0.559	3.038	58.9	3.155	1.220
	1122	483.5	2.282	0.354	1.568	12.376	0.835	2.998	55.1	3.029	1.332
	1123	547.8	2.441	0.596	1.508	13.601	0.903	3.202	66.6	3.324	1.301
	1124	523.7	2.167	0.494	1.499	18.208	1.806	2.902	65.6	3.215	1.358
	1125	588.3	2.216	0.332	1.608	16.373	1.013	3.404	78.1	3.562	1.582
	1201	436.1	2.264	0.374	1.395	11.554	0.682	2.545	74.8	3.430	1.416
	1202	451.4	2.086	0.372	1.345	13.479	0.911	2.918	64.2	3.442	1.373
1	1203	487.4	2.412	0.280	1.632	13.953	0.831	3.168	63.4	3.655	1.278
	1204	487.5	2.278	0.293	1.539	14.359	0.789	3.000	43.5	3.739	1.189
	1205	494.4	2.369	0.442	1.474	12.169	0.689	2.752	61.4	3.714	1.416
	1206	464.4	2.096	0.351	1.476	12.727	0.663	2.843	71.9	3.720	1.250
	1207	500.2	2.257	0.379	1.468	12.804	0.752	3.201	61.5	3.111	1.166
	1208	499.6	2.039	0.260	1.610	13.029	0.573	2.734	59.2	2.860	1.158
	1209	526.9	2.273	0.609	1.608	12.629	0.858	2.763	76.8	3.780	1.551
	1210	516.2	1.993	0.270	1.392	14.364	0.718	3.062	59.6	3.382	1.421
	1211	551.6	2.186	0.511	1.683	15.574	0.969	3.415	60.5	3.667	1.329
	1212	544.6	2.266	0.361	1.600	13.430	0.785	3.085	54.6	3.539	1.239

a) : Control animals were administered olive oil orally.

Appendix 9-2 Absolute organ weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Final body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Spleen (g)	Kidneys (g)	Adrenals (mg)	Testes (g)	Epididymides (g)
10	1301	463.2	2.234	0.327	1.387	11.755	0.698	2.316	44.5	3.137	1.133
	1302	457.2	2.102	0.421	1.364	12.699	0.724	2.644	55.4	3.262	1.496
	1303	497.1	2.322	0.509	1.409	14.522	0.888	2.787	52.5	2.739	1.057
	1304	488.6	2.095	0.515	1.444	12.678	0.902	2.958	58.2	3.275	1.321
	1305	478.4	2.114	0.446	1.549	11.672	0.872	2.906	77.9	3.400	1.492
	1306	532.5	2.171	0.567	1.655	17.079	0.859	3.323	69.5	3.417	1.644
	1307	506.2	1.997	0.463	1.417	14.342	0.786	2.502	56.7	3.488	1.338
	1308	562.9	2.135	0.497	1.569	16.852	0.986	3.119	59.8	3.341	1.082
	1309	539.5	2.113	0.762	1.534	16.014	0.923	2.641	52.2	3.625	1.545
	1310	503.4	2.171	0.277	1.295	15.110	0.805	2.778	58.1	3.558	1.189
	1311	536.9	2.234	0.638	1.497	13.686	0.705	2.874	64.5	3.488	1.331
	1312	501.4	2.283	0.431	1.586	13.916	0.924	3.100	60.0	3.198	1.252
100	1401	435.8	2.255	0.526	1.363	12.241	2.569	2.462	63.1	3.607	1.332
	1402	429.7	2.264	0.322	1.396	11.173	2.495	2.919	59.2	3.884	1.560
	1403	448.6	2.269	0.442	1.932	13.777	2.257	3.240	61.7	3.381	1.393
	1404	462.1	2.146	0.332	1.441	12.462	2.367	2.498	66.9	3.029	1.234
	1405	483.9	2.419	0.440	2.075	14.904	2.404	3.165	75.3	3.584	1.524
	1406	532.1	2.020	0.300	1.870	17.215	1.657	3.427	65.9	3.505	1.418
	1407	502.2	2.098	0.470	1.494	15.633	2.062	3.557	58.5	3.169	1.225
	1421	495.0	2.301	0.520	1.437	13.300	1.170	2.767	70.1	3.246	1.454
	1422	507.9	2.176	0.430	1.512	12.484	0.981	2.624	53.2	3.522	1.230
	1423	532.6	2.283	0.312	1.688	13.680	0.955	3.071	67.0	3.847	1.464
	1424	515.6	2.089	0.444	1.567	12.626	0.885	2.840	60.6	3.392	1.408
	1425	644.9	2.196	0.495	1.869	18.124	1.260	3.691	56.8	4.040	1.511

Appendix 10-1 Relative organ weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Brain (g%)	Thymus (g%)	Heart (g%)	Liver (g%)	Spleen (g%)	Kidneys (g%)	Adrenals (mg%)	Testes (g%)	Epididymides (g%)
0 ^{a)}	1101	0.480	0.070	0.358	2.491	0.153	0.510	10.3	0.776	0.296
	1102	0.487	0.081	0.299	2.568	0.171	0.595	10.3	0.729	0.267
	1103	0.436	0.066	0.286	2.609	0.169	0.515	12.9	0.638	0.249
	1104	0.471	0.064	0.343	2.389	0.170	0.534	10.6	0.654	0.288
	1105	0.434	0.078	0.304	2.561	0.121	0.518	12.2	0.652	0.245
	1106	0.394	0.064	0.310	2.810	0.110	0.557	9.1	0.624	0.232
	1107	0.432	0.069	0.308	2.338	0.153	0.564	13.5	0.717	0.298
I	1121	0.430	0.089	0.340	2.780	0.116	0.631	12.2	0.656	0.254
	1122	0.472	0.073	0.324	2.560	0.173	0.620	11.4	0.626	0.275
	1123	0.446	0.109	0.275	2.483	0.165	0.585	12.2	0.607	0.237
	1124	0.414	0.094	0.286	3.477	0.345	0.554	12.5	0.614	0.259
	1125	0.377	0.056	0.273	2.783	0.172	0.579	13.3	0.605	0.269
	1201	0.519	0.086	0.320	2.649	0.156	0.584	17.2	0.787	0.325
	1202	0.462	0.082	0.298	2.986	0.202	0.646	14.2	0.763	0.304
I	1203	0.495	0.057	0.335	2.863	0.170	0.650	13.0	0.750	0.262
	1204	0.467	0.060	0.316	2.945	0.162	0.615	8.9	0.767	0.244
	1205	0.479	0.089	0.298	2.461	0.139	0.557	12.4	0.751	0.286
	1206	0.451	0.076	0.318	2.741	0.143	0.612	15.5	0.801	0.269
	1207	0.451	0.076	0.293	2.560	0.150	0.640	12.3	0.622	0.233
	1208	0.408	0.052	0.322	2.608	0.115	0.547	11.8	0.572	0.232
	1209	0.431	0.116	0.305	2.397	0.163	0.524	14.6	0.717	0.294
	1210	0.386	0.052	0.270	2.783	0.139	0.593	11.5	0.655	0.275
	1211	0.396	0.093	0.305	2.823	0.176	0.619	11.0	0.665	0.241
	1212	0.416	0.066	0.294	2.466	0.144	0.566	10.0	0.650	0.228

a) : Control animals were administered olive oil orally.

Appendix 10-2 Relative organ weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Brain (g%)	Thymus (g%)	Heart (g%)	Liver (g%)	Spleen (g%)	Kidneys (g%)	Adrenals (mg%)	Testes (g%)	Epididymides (g%)
10	1301	0.482	0.071	0.299	2.538	0.151	0.500	9.6	0.677	0.245
	1302	0.460	0.092	0.298	2.778	0.158	0.578	12.1	0.713	0.327
	1303	0.467	0.102	0.283	2.921	0.179	0.561	10.6	0.551	0.213
	1304	0.429	0.105	0.296	2.595	0.185	0.605	11.9	0.670	0.270
	1305	0.442	0.093	0.324	2.440	0.182	0.607	16.3	0.711	0.312
	1306	0.408	0.106	0.311	3.207	0.161	0.624	13.1	0.642	0.309
	1307	0.395	0.091	0.280	2.833	0.155	0.494	11.2	0.689	0.264
	1308	0.379	0.088	0.279	2.994	0.175	0.554	10.6	0.594	0.192
	1309	0.392	0.141	0.284	2.968	0.171	0.490	9.7	0.672	0.286
	1310	0.431	0.055	0.257	3.002	0.160	0.552	11.5	0.707	0.236
	1311	0.416	0.119	0.279	2.549	0.131	0.535	12.0	0.650	0.248
	1312	0.455	0.086	0.316	2.775	0.184	0.618	12.0	0.638	0.250
100	1401	0.517	0.121	0.313	2.809	0.589	0.565	14.5	0.828	0.306
	1402	0.527	0.075	0.325	2.600	0.581	0.679	13.8	0.904	0.363
	1403	0.506	0.099	0.431	3.071	0.503	0.722	13.8	0.754	0.311
	1404	0.464	0.072	0.312	2.697	0.512	0.541	14.5	0.655	0.267
	1405	0.500	0.091	0.429	3.080	0.497	0.654	15.6	0.741	0.315
	1406	0.380	0.056	0.351	3.235	0.311	0.644	12.4	0.659	0.266
	1407	0.418	0.094	0.297	3.113	0.411	0.708	11.6	0.631	0.244
	1421	0.465	0.105	0.290	2.687	0.236	0.559	14.2	0.656	0.294
	1422	0.428	0.085	0.298	2.458	0.193	0.517	10.5	0.693	0.242
	1423	0.429	0.059	0.317	2.569	0.179	0.577	12.6	0.722	0.275
	1424	0.405	0.086	0.304	2.449	0.172	0.551	11.8	0.658	0.273
	1425	0.341	0.077	0.290	2.810	0.195	0.572	8.8	0.626	0.234

Appendix 11-1 Gross pathology of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Findings
0 ^{a)}	1101	No abnormality detected
	1102	No abnormality detected
	1103	No abnormality detected
	1104	No abnormality detected
	1105	No abnormality detected
	1106	No abnormality detected
	1107	No abnormality detected
	1121	No abnormality detected
	1122	No abnormality detected
	1123	No abnormality detected
	1124	Spleen : swelling (+) and nodule (+)
	1125	No abnormality detected
1	1201	No abnormality detected
	1202	No abnormality detected
	1203	No abnormality detected
	1204	No abnormality detected
	1205	No abnormality detected
	1206	No abnormality detected
	1207	No abnormality detected
	1208	No abnormality detected
	1209	No abnormality detected
	1210	No abnormality detected
	1211	No abnormality detected
	1212	No abnormality detected

a) : Control animals were administered olive oil orally.

Grade: + : Slight.

Appendix 11-2 Gross pathology of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Findings
10	1301	No abnormality detected
	1302	No abnormality detected
	1303	No abnormality detected
	1304	No abnormality detected
	1305	No abnormality detected
	1306	No abnormality detected
	1307	No abnormality detected
	1308	No abnormality detected
	1309	No abnormality detected
	1310	No abnormality detected
	1311	No abnormality detected
	1312	No abnormality detected
100	1401	Spleen : Swelling (++) and dark red discoloration
	1402	Spleen : Swelling (+++) and dark red discoloration
	1403	Spleen : Swelling (+++) and dark red discoloration
	1404	Spleen : Swelling (+++) and dark red discoloration
	1405	Spleen : Swelling (+++) and dark red discoloration
	1406	Spleen : Swelling (+++) and dark red discoloration
	1407	Spleen : Swelling (+++) and dark red discoloration
	1421	Spleen : Swelling (+)
	1422	Spleen : Swelling (+)
	1423	Spleen : Swelling (+)
	1424	No abnormality detected
	1425	Spleen : Swelling (+)

Grade: + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 12-1 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1101	Trachea	No abnormality detected
		Lung	Calcification of pulmonary aorta (+)
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	No abnormality detected
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Testis	No abnormality detected
		Epididymis	No abnormality detected
		Prostate	No abnormality detected
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Grade: + ; Slight.

Appendix 12-2 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1102	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	No abnormality detected
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Testis	No abnormality detected
		Epididymis	No abnormality detected
		Prostate	Inflammatory cell infiltration in stroma (+)
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Grade: + ; Slight.

Appendix 12-3 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1103	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Microgranuloma (+)
		Heart	Inflammatory cell infiltration (+)
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Testis	Focal atrophy of seminiferous tubules (+)
		Epididymis	No abnormality detected
		Prostate	No abnormality detected
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Grade: + ; Slight.

Appendix 12-4 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1104	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	No abnormality detected
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Testis	No abnormality detected
		Epididymis	No abnormality detected
		Prostate	Inflammatory cell infiltration in stroma (+)
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Grade: + ; Slight.

Appendix 12-5 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1105	Trachea	No abnormality detected
		Lung	Ectopic ossification (+)
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	No abnormality detected
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Testis	No abnormality detected
		Epididymis	No abnormality detected
		Prostate	No abnormality detected
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Grade: + ; Slight.

Appendix 12-6 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	1201	Liver	Microgranuloma (+)
			Hemorrhagic necrosis (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected
Grade: + ; Slight.			

Appendix 12-7 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	1202	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 12-8 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	1203	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 12-9 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	1204	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 12-10 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	1205	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 12-10 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	1205	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 12-12 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
10	1302	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 12-13 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
10	1303	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	Congestion (+)
Grade: + ; Slight.			

Appendix 12-14 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
10	1304	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 12-15 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
10	1305	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 12-16 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1401	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+) Extramedullary hematopoiesis (+)
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Testis	No abnormality detected
		Epididymis	No abnormality detected
		Prostate	No abnormality detected
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (+)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
			Congestion (+++)
		Spleen	Atrophy of white pulp (++) Extramedullary hematopoiesis (+) Yellowish-brown pigmentation (++)
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade : + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 12-17 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1402	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+) Extramedullary hematopoiesis (+)
		Heart	No abnormality detected
		Kidney	Inflammatory cell infiltration in stroma (+) Scar formation (+)
		Urinary bladder	No abnormality detected
		Testis	No abnormality detected
		Epididymis	No abnormality detected
		Prostate	Inflammatory cell infiltration in stroma (+)
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (++)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	Congestion (+++)
			Atrophy of white pulp (++)
			Extramedullary hematopoiesis (++)
		Thymus	Yellowish-brown pigmentation (++)
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade : + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 12-18 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1403	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+)
			Extramedullary hematopoiesis (+)
		Heart	Microgranuloma (+)
			No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Testis	No abnormality detected
		Epididymis	No abnormality detected
		Prostate	No abnormality detected
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (+)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	Congestion (+++)
			Atrophy of white pulp (++)
			Extramedullary hematopoiesis (+)
		Thymus	Yellowish-brown pigmentation (++)
			No abnormality detected
			No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade : + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 12-19 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1404	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+) Extramedullary hematopoiesis (+)
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Testis	No abnormality detected
		Epididymis	No abnormality detected
		Prostate	No abnormality detected
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (++)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
			Congestion (+++)
		Spleen	Atrophy of white pulp (++) Extramedullary hematopoiesis (++) Yellowish-brown pigmentation (++)
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade : + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 12-20 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1405	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+)
			Extramedullary hematopoiesis (+)
			Focal hemorrhage (+)
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Testis	Focal atrophy of seminiferous tubules (+)
		Epididymis	No abnormality detected
		Prostate	No abnormality detected
		Seminal vesicle	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (++)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
			Congestion (+++)
		Spleen	Atrophy of white pulp (++)
			Extramedullary hematopoiesis (++)
			Yellowish-brown pigmentation (++)
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade : + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 12-21 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1121	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected
a) : Control animals were administered olive oil orally.			

Appendix 12-22 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1122	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 12-23 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1123	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 12-24 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1124	Liver	Extramedullary hematopoiesis (++)
			Focal necrosis in hepatocytes (+)
			Histiocytic sarcoma (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	Histiocytic sarcoma (+)
			Hemorrhagic necrosis (++)

a) : Control animals were administered olive oil orally.

Grade: + ; Slight, ++ ; Moderate.

Appendix 12-25 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	1125	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected
a) : Control animals were administered olive oil orally.			

Appendix 12-26 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1421	Liver	Yellowish-brown pigmentation (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	Yellowish-brown pigmentation (++)
Grade : + ; Slight, ++ ; Moderate.			

Appendix 12-27 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1422	Liver	Microgranuloma (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	Yellowish-brown pigmentation (++)
Grade : + ; Slight, ++ ; Moderate.			

Appendix 12-28 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1423	Liver	Yellowish-brown pigmentation (+)
			Microgranuloma (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	Congestion (+)
			Yellowish-brown pigmentation (++)
Grade : + : Slight, ++ : Moderate.			

Appendix 12-29 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1424	Liver	Yellowish-brown pigmentation (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	Yellowish-brown pigmentation (++)
Grade : + ; Slight, ++ ; Moderate.			

Appendix 12-30 Histopathological findings of male rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	1425	Liver	Yellowish-brown pigmentation (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	Yellowish-brown pigmentation (++)
Grade : + ; Slight, ++ ; Moderate.			

Appendix 13-1 General signs of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Findings
0 ^{a)}	2101	No abnormality detected during administration period
	2102	No abnormality detected during administration period
	2103	No abnormality detected during administration period
	2104	No abnormality detected during administration period
	2105	No abnormality detected during administration period
	2106	No abnormality detected during administration period
	2107	No abnormality detected during administration period
	2108	No abnormality detected during administration period
	2109	No abnormality detected during administration period
	2110	No abnormality detected during administration period
	2111	No abnormality detected during administration period
	2112	No abnormality detected during administration period
1	2121	No abnormality detected during administration and recovery period
	2122	No abnormality detected during administration and recovery period
	2123	No abnormality detected during administration and recovery period
	2124	No abnormality detected during administration and recovery period
	2125	No abnormality detected during administration and recovery period
	2201	No abnormality detected during administration period
	2202	No abnormality detected during administration period
	2203	No abnormality detected during administration period
	2204	No abnormality detected during administration period
	2205	No abnormality detected during administration period
	2206	No abnormality detected during administration period
	2207	No abnormality detected during administration period
	2208	No abnormality detected during administration period
	2209	No abnormality detected during administration period
	2210	No abnormality detected during administration period
	2211	No abnormality detected during administration period
	2212	No abnormality detected during administration period

a) : Control animals were administered olive oil orally.

Appendix 13-2 General signs of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Findings
10	2301	No abnormality detected during administration period
	2302	No abnormality detected during administration period
	2303	No abnormality detected during administration period
	2304	No abnormality detected during administration period
	2305	No abnormality detected during administration period
	2306	No abnormality detected during administration period
	2307	No abnormality detected during administration period
	2308	No abnormality detected during administration period
	2309	No abnormality detected during administration period
	2310	No abnormality detected during administration period
	2311	No abnormality detected during administration period
	2312	No abnormality detected during administration period
100	2401	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2402	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2403	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2404	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2405	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2406	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2407	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2408	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2409	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2410	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2411	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2412	Dark red discoloration of the skin (+, Administration Day 2 - Day 4 post partum)
	2421	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)
	2422	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)
	2423	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)
	2424	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)
	2425	Dark red discoloration of the skin (+, Administration Day 2-42 and Recovery Day 1-14)

Grade: + ; Slight.

Appendix 14-1 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of N,N'-dimethylamine by oral administration

Dose (mg/kg/day)		0 ^{a)}																																		
Parameters	Administration weeks		Before												1																					
	Animal No.	Normal score	2101 2102 2103 2104 2105 2106 2107 2108 2109 2110 2111 2112 2121 2122 2123 2124 2125												2101 2102 2103 2104 2105 2106 2107 2108 2109 2110 2111 2112 2121 2122 2123 2124 2125																					
			2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2121	2122	2123	2124	2125	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2121	2122	2123	2124	2125
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
Detailed clinical observations by the handling	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Prorecton	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rearings	Counts	2	4	5	1	4	0	3	2	4	0	3	3	2	6	1	1	3	3	3	5	3	4	4	5	3	2	2	5	2	3	4	5	3	3
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Behavior observations in the open field	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Urinations	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

a): Control animals were administered olive oil orally, no comments, N: normal.

a): Control animals were administered olive oil orally.

- : no comments, N : normal.

Appendix 14-2 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylalanine by oral administration

[illegible]

a) : Control animals were administered olive oil orally.
- : no comments, N : normal

Appendix 14-4 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		0 ^{a)}																	
Parameters	Animal No.	Postpartum 4 day												Administration 6 weeks					
	Normal score	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2121	2122	2123	2124	2125	
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Behavior observations in the open field	Rearings	Counts	6	9	5	7	6	6	4	4	5	7	6	6	6	4	4	6	
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Urinations	Counts	1	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	

a) : Control animals were administered olive oil orally.

- : no comments, N : normal.

Appendix 14-5 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)			I																									
Parameters	Administration weeks	Before												I														
		Animal No.		2201		2202		2203		2204		2205		2206		2207		2208		2209		2210		2211		2212		
		Normal score																										
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Behavior observations in the open field	Rearings	Counts	2	1	2	5	3	2	4	2	4	3	7	0	2	4	2	3	4	2	4	4	8	5	1	3	
		Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Tonic involuntary movement		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Gait		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
Movements		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
Arousal		4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4		
Occurrence of stereotype		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Abnormal behavior		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Defecations		Counts	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0		
Urinations		Counts	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		

: no comments, N : normal.

-: no comments, N: normal.

Appendix 14-6 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

[illegible]

- : no comments, N : normal.

Appendix 14-7 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)			1																								
			4																								
Administration weeks			5																								
Parameters			Animal No.																								
Normal score			2201 2202 2203 2204 2205 2206 2207 2208 2209 2210 2211 2212																								
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Behavior observations in the open field	Rearings	Counts	2	4	4	3	4	0	1	3	6	2	3	1	6	3	4	5	7	2	3	2	2	2	3	3	
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4		
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
			: no comments, N : normal.																								

- : no comments, N : normal.

Appendix 14-8 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylamine by oral administration

Dose (mg/kg/day)				1															
Parameters	Animal No.	Postpartum 4 day																	
		2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212						
Normal score																			
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Behavior observations in the open field	Rearings	Counts	4	5	4	9	4	4	5	6	10	6	7	9					
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4		
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
no comments, N : normal.																			

Appendix 14-9 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		10																				
Parameters	Administration weeks		Before																			
	Animal No.		2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	1							
	Normal score																					
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2					
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2					
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
Behavior observations in the open field	Rearings	Counts	3	3	5	3	0	1	4	3	4	2	2	5	3	3	5	3	4	1	2	
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

: no comments, N : normal.

- : no comments, N : normal.

Appendix 14-10 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		10													
		2													
Administration weeks															
Parameters	Animal No.	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312		
	Normal score														
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2		
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1		
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2		
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1		
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1		
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1		
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1		
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1		
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1		
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1		
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1		
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1		
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1		
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1		
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1		
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1		
Behavior observations in the open field	Rearings	Counts	3	3	4	2	1	2	2	4	3	5	3	4	
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0

no comments, N : normal.

- : no comments, N : normal.

Appendix 14-11 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		10											
Administration weeks		4											
Parameters	Animal No.	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312
	Normal score												
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1
Behavior observations in the open field	Counts	7	2	4	1	0	4	2	6	3	5	4	4
	Rearings	1	1	1	1	1	1	1	1	1	1	1	1
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1
	Gait	N	N	N	N	N	N	N	N	N	N	N	N
	Movements	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0
Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	

: no comments, N : normal.

- : no comments, N : normal.

Appendix 14-12 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		10															
Parameters	Animal No.	Postpartum 4 day															
		2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312				
		Normal score															
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Detailed clinical observations by the handler	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Behavior observations in the open field	Rearings	Counts	6	7	4	4	8	4	8	7	6	7	10	4			
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Defecations	Counts	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	no comments, N : normal.																

- : no comments, N : normal.

Appendix 14-13 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of N,N-dimethylamine by oral administration

Dose (mg/kg/day)		100																							
Parameters	Administration weeks	Before												1											
		Animal No.																							
		Normal score																							
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Fur soaked	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Dark red discoloration of the skin	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Rearings	4	2	2	6	5	4	3	4	2	4	4	2	3	2	2	2	2	2	3	6	2	3	2	1
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Behavior observations in Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0
	Urinations	Counts	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- : no comments, N : normal.

Appendix 14-14 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of N,N-dimethylamine by oral administration

Dose (mg/kg/day)		2										3										100															
Administration weeks																																					
Parameters		Animal No.	Normal score																																		
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Prostration	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Detailed clinical observations by the handler	Dark red discoloration of the skin	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Counts		4	4	5	3	3	4	6	3	1	5	4	3	4	2	4	4	1	3	3	1	2	6	2	9	3	2	3	1	2	2	2	3	3	3	
	Rearings		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Clonic involuntary movement		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
	Tonic involuntary movement		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Behavior observations in the open field	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4		
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Abnormal behavior	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Urinations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
			no comments. N : normal.																																		

- : no comments, N : normal.

Appendix 14-15 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of N,N-dimethylamine by oral administration

Dose (mg/kg/day)		100																5																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
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Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Appendix 14-16 Detailed clinical observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of N,N -dimethylaniline by oral administration

Dose (mg/kg/day)		100																				
Parameters	Administration weeks		Postpartum 4 day																Administration 6 weeks			
	Animal No.		2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412								
	Normal score																					
Handling at the grab	Reactivity	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
	Vocalization	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
Detailed clinical observations by the handling	Myotony	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
	Hypothermia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Fur soiled	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Rough cast	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Pallor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Rubor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Cyanosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Dark red discoloration of the skin	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
	Lacrimation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
Behavior observations in the open field	Exophthalmos	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Mydriasis/Miosis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Salivation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Discharge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Rearings	Counts	4	5	5	8	4	8	8	7	7	5	6	3	2	0	4	3				
	Clonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
	Tonic involuntary movement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1					
Behavior observations in the open field	Gait	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N				
	Movements	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3				
	Arousal	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4				
	Occurrence of stereotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
	Abnormal behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
	Defecations	Counts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
	Urinations	Counts	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0				
: no comments, N : normal.																						

- : no comments, N : normal.

Appendix 15 Functional observations of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylamine by oral administration
- Day 4 of postpartum -

Parameters	Dose (mg/kg/day)	0 ^{a)}																				
		1						10						100								
		2101	2102	2105	2106	2108	2202	2204	2205	2207	2211	2301	2302	2304	2306	2307	2403	2406	2409	2410	2412	
		Normal score																				
Responses	Approach and/or Touch response	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Sound response	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Tail pinch response	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Pupillary reflex	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Aerial righting reflex	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Forelimb grip strength (N)	1st	6.37	5.05	6.87	7.45	6.61	6.27	5.46	5.19	6.88	5.29	5.97	5.13	6.95	7.04	7.01	7.45	6.44	8.01	7.18	6.13
	2nd	7.64	6.72	6.14	6.60	6.21	5.66	6.36	6.03	5.14	6.67	4.99	6.12	5.06	5.87	6.35	8.17	6.06	5.63	6.72	6.08	
	Mean		7.01	5.89	6.51	7.03	6.41	5.97	5.91	5.61	6.01	5.98	5.48	5.63	6.01	6.46	6.68	7.81	6.25	6.82	6.95	6.11
	±S.D.		0.90	1.18	0.52	0.60	0.28	0.43	0.64	0.59	1.23	0.98	0.69	0.70	1.34	0.83	0.47	0.51	0.27	1.68	0.33	0.04
	Hind limb grip strength (N)	1st	1.36	2.25	2.13	1.45	1.34	1.73	1.62	1.47	1.47	1.60	1.59	2.30	1.29	1.49	1.33	1.47	1.77	1.57	2.20	1.57
	2nd	1.70	1.87	1.65	2.26	1.64	2.10	2.29	1.74	2.01	1.51	1.23	1.41	2.04	1.72	1.23	1.79	2.11	2.14	1.83	1.15	
	Mean		1.53	2.06	1.89	1.86	1.49	1.92	1.96	1.61	1.74	1.56	1.41	1.86	1.67	1.61	1.28	1.63	1.94	1.86	2.02	1.36
	±S.D.		0.24	0.27	0.34	0.57	0.21	0.26	0.47	0.19	0.38	0.06	0.25	0.63	0.53	0.16	0.07	0.23	0.24	0.40	0.26	0.30
	Spontaneous locomotor activity	3 min		897	939	974	908	880	932	847	155	911	972	867	759	810	808	918	744	932	840	801
6 min			616	829	939	876	938	864	772	675	928	873	978	700	828	724	918	786	862	795	855	883
9 min			374	791	827	819	891	860	700	747	940	924	895	668	650	751	843	787	795	516	757	878
12 min			165	645	739	872	853	838	797	579	824	897	801	692	747	766	817	757	795	633	702	922
15 min			205	790	879	714	817	699	446	831	807	955	836	417	663	857	925	590	480	770	618	938
Total			2257	3994	4358	4189	4379	4193	3562	2987	4410	4621	4377	3236	3698	3906	4421	3664	3864	3554	3733	4533

a) : Control animals were administered olive oil orally.

Appendix 16-1 Body weight changes of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Body weights on administration days (g)							Body weights on recovery days (g)				
		1	3	8	15	22	29	36	1	3	7	14	15
0 ^{a)}	2121	227.9	231.4	239.3	257.8	264.7	275.9	280.4	290.1	295.8	297.6	301.1	285.9
	2122	226.5	228.6	246.5	258.1	266.4	277.7	283.6	296.5	299.0	309.1	312.0	293.7
	2123	233.9	230.2	241.7	249.2	272.9	288.4	300.8	299.1	310.6	312.2	314.9	300.1
	2124	237.3	232.6	243.1	269.0	281.9	298.5	303.0	314.4	317.4	321.6	330.4	313.8
	2125	234.7	243.4	253.8	268.2	272.6	275.7	285.5	290.3	288.8	291.8	298.8	284.0
100	2421	224.5	220.5	223.7	246.0	251.2	254.3	256.3	261.5	263.1	270.0	275.3	261.1
	2422	221.8	216.1	227.1	236.5	246.3	250.1	254.7	252.6	261.1	273.9	278.5	260.8
	2423	233.9	227.7	237.7	246.8	259.3	268.4	272.2	278.5	280.5	282.9	290.6	274.2
	2424	233.3	227.4	225.4	246.2	257.3	271.6	273.3	273.5	277.0	287.2	302.3	282.0
	2425	241.5	238.0	245.0	265.7	265.6	278.9	280.1	277.0	276.5	286.5	288.6	271.6

a) : Control animals were administered olive oil orally.

Appendix 16-2 Body weight changes of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Body weights on administration days (g)					Body weights on gestation days (g)					Body weights on lactation days (g)				
		1	3	7	14		0	7	14	17	20	0	4	5		
0 ^{a)}	2101	216.3	224.6	229.6	241.3		247.5	286.8	321.3	351.7	387.9	277.8	282.9	255.3		
	2102	221.7	220.4	235.2	245.5		243.4	277.6	307.6	330.8	367.1	262.0	283.9	265.2		
	2103	227.1	233.1	243.2	260.3		262.8	293.6	327.8	359.1	403.7	305.7	326.7	296.9		
	2104	222.7	226.5	233.1	242.0		244.6	285.5	323.5	355.8	406.4	288.7	315.5	298.8		
	2105	228.9	236.5	243.6	259.9		259.8	298.8	340.0	370.6	402.8	307.1	335.6	303.5		
	2106	238.0	241.1	252.2	261.9		248.5	282.9	321.0	346.3	381.7	274.3	306.2	291.2		
	2107	235.0	234.6	247.6	270.5		274.3	308.9	357.8	391.4	438.7	302.0	310.5	290.2		
	2108	235.2	238.8	245.2	255.4		261.2	286.9	323.4	355.1	402.7	277.6	312.1	290.6		
	2109	232.7	233.1	242.9	265.2		281.1	318.7	358.2	386.5	428.5	331.6	336.6	313.6		
	2110	233.7	247.6	251.1	260.8		257.8	308.4	344.7	378.9	429.9	332.0	353.7	323.2		
	2111	242.8	243.3	245.1	252.9		262.3	308.4	359.7	399.1	442.0	373.8	367.4	344.1		
	2112	250.5	254.6	253.0	265.3		269.1	305.4	334.9	373.9	424.0	321.2	365.8	320.5		
1	2201	226.8	226.9	233.1	244.9		248.5	268.8	301.7	333.9	369.9	303.1	303.5	290.2		
	2202	222.8	222.0	234.8	248.6		249.7	286.6	319.9	352.3	386.3	292.1	310.3	288.8		
	2203	233.2	239.3	253.6	263.0		269.4	310.1	353.2	389.2	425.9	325.4	335.7	321.8		
	2204	218.6	230.6	238.5	248.7		248.8	288.0	331.0	360.7	410.3	293.2	330.3	294.9		
	2205	222.3	229.6	237.1	242.9		247.3	284.7	313.9	334.6	379.5	266.9	311.1	285.1		
	2206	236.7	231.7	245.9	264.0		266.2	291.7	323.8	344.7	391.8	309.4	318.9	298.6		
	2207	227.9	235.8	245.0	255.2		259.3	278.5	302.3	316.3	342.6	290.4	302.9	282.1		
	2208	237.0	234.5	246.9	258.6		258.4	303.3	336.8	360.1	396.3	308.9	333.9	298.1		
	2209	239.8	246.8	253.6	261.9		265.6	312.6	344.7	376.1	413.9	327.4	359.1	328.6		
	2210	240.6	243.9	253.9	276.8		272.0	310.3	352.5	386.6	431.5	322.0	335.5	322.4		
	2211	232.1	243.1	249.1	260.9		261.0	297.0	336.4	369.9	423.8	302.2	326.4	299.7		
	2212	244.1	243.4	261.0	279.2		294.7	353.7	404.9	442.6	483.3	360.2	383.7	356.2		

a) : Control animals were administered olive oil for injection orally.

Appendix 16-3 Body weight changes of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Body weights on administration days (g)					Body weights on gestation days (g)					Body weights on lactation days (g)				
		1	3	7	14		0	7	14	17	20	0	4	5		
10	2301	215.2	216.0	217.8	222.1		230.8	262.1	296.9	322.5	357.4	269.5	283.6	260.3		
	2302	223.3	228.3	234.8	248.3		247.6	279.5	305.4	321.0	343.1	292.3	293.6	279.3		
	2303	222.0	224.8	236.3	249.2		263.2	296.5	334.4	369.9	414.6	290.0	322.7	298.4		
	2304	226.9	233.0	244.1	255.2		255.3	293.8	332.2	366.4	406.5	315.3	319.1	293.5		
	2305	225.9	225.7	229.1	242.3		252.6	291.8	336.4	351.8	387.6	322.5	330.2	302.1		
	2306	231.2	236.7	250.2	257.6		258.2	293.6	331.6	355.4	399.9	282.5	313.1	277.8		
	2307	236.4	240.1	248.8	262.9		273.9	306.9	345.6	372.8	406.2	284.9	327.9	294.4		
	2308	229.2	234.3	241.1	259.4		258.8	294.6	335.8	358.6	400.8	310.5	325.0	291.7		
	2309	234.1	237.6	244.4	253.3		258.8	293.3	326.0	350.6	389.0	288.1	304.0	272.8		
	2310	241.1	242.9	250.1	251.6		276.6	268.1	334.4	351.2	375.8	322.1	340.4	311.2		
	2311	234.8	235.6	247.0	259.1		272.3	307.3	344.9	373.9	417.0	308.9	343.5	323.7		
	2312	235.2	240.2	248.4	250.3		267.6	290.4	324.2	348.1	380.4	274.8	305.2	282.5		
100	2401	221.0	212.0	213.6	224.7		227.3	258.8	293.9	317.2	346.9	272.7	280.8	268.5		
	2402	216.2	215.6	216.1	225.9		234.2	257.2	300.6	326.2	364.4	292.2	279.4	261.6		
	2403	214.9	220.3	221.7	235.5		239.1	270.5	299.6	323.4	359.7	266.3	289.9	260.2		
	2404	226.1	224.9	227.9	241.1		230.8	265.6	295.5	319.5	341.9	266.8	288.1	260.2		
	2405	229.6	230.3	229.4	249.5		261.5	294.7	327.8	345.3	384.3	289.8	311.2	285.0		
	2406	225.6	228.9	239.1	259.9		250.7	295.0	330.3	354.7	392.1	300.8	307.7	288.8		
	2407	233.2	229.0	232.0	242.1		246.7	281.1	308.6	325.4	360.8	273.0	313.6	288.5		
	2408	235.4	223.8	228.1	253.8		257.6	290.9	326.9	348.2	374.1	310.4	330.3	300.1		
	2409	237.7	236.8	243.7	256.1		263.5	297.4	337.2	367.5	404.5	312.9	327.7	304.1		
	2410	235.6	239.3	244.0	257.4		266.5	295.0	333.2	348.9	385.0	293.7	313.9	294.0		
	2411	240.6	237.5	238.9	255.0		266.3	298.3	326.3	348.5	393.1	278.1	321.1	288.6		
	2412	234.8	234.8	239.9	257.2		272.3	297.0	325.7	342.7	375.7	294.0	310.8	286.9		

Appendix 17-1 Food consumption of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Food consumption (g/day)											
		Administration days			Gestation days						Lactation days		
		1	7	14	7	14	17	20	20	20	4	4	4
0 ^{a)}	2101	13.7	13.3	16.1	23.8	21.7	28.5	20.9	20.9	20.9	34.6	34.6	34.6
	2102	13.4	15.8	15.9	19.1	16.9	19.0	17.4	17.4	17.4	37.0	37.0	37.0
	2103	16.1	14.8	18.3	19.8	22.6	22.1	20.6	20.6	20.6	40.9	40.9	40.9
	2104	13.8	50.1	14.9	20.7	20.9	21.2	24.6	24.6	24.6	51.6	51.6	51.6
	2105	14.4	35.8	18.2	21.6	22.4	29.5	20.0	20.0	20.0	43.5	43.5	43.5
	2106	15.7	52.0	17.8	18.0	24.9	26.6	18.2	18.2	18.2	46.5	46.5	46.5
	2107	21.8	17.2	21.3	24.3	24.2	29.3	20.3	20.3	20.3	34.0	34.0	34.0
	2108	16.4	15.2	17.5	19.6	19.1	20.4	18.8	18.8	18.8	40.7	40.7	40.7
	2109	18.6	17.7	19.1	23.5	24.2	25.1	23.3	23.3	23.3	31.4	31.4	31.4
	2110	12.8	19.1	17.8	23.6	24.4	29.6	24.8	24.8	24.8	32.9	32.9	32.9
	2111	13.5	14.5	16.2	26.5	27.6	35.0	27.8	27.8	27.8	38.5	38.5	38.5
	2112	16.8	14.7	16.4	22.3	22.2	27.4	22.9	22.9	22.9	40.9	40.9	40.9
1	2201	16.3	14.0	15.0	16.8	20.1	13.1	20.1	20.1	20.1	33.7	33.7	33.7
	2202	14.2	12.5	16.8	21.7	19.7	24.0	19.3	19.3	19.3	38.0	38.0	38.0
	2203	19.0	20.9	19.4	25.3	25.2	30.7	22.7	22.7	22.7	37.7	37.7	37.7
	2204	10.9	15.9	16.0	19.9	21.4	22.8	21.8	21.8	21.8	44.6	44.6	44.6
	2205	14.3	15.2	12.9	21.1	18.9	18.0	20.2	20.2	20.2	48.7	48.7	48.7
	2206	16.0	14.5	18.3	19.6	20.2	22.9	17.0	17.0	17.0	35.4	35.4	35.4
	2207	13.4	15.9	14.8	17.2	18.9	19.1	18.5	18.5	18.5	27.6	27.6	27.6
	2208	15.3	15.2	16.5	26.0	23.1	28.6	23.0	23.0	23.0	43.3	43.3	43.3
	2209	16.6	14.7	10.7	26.5	25.3	25.4	23.9	23.9	23.9	48.6	48.6	48.6
	2210	16.3	16.5	21.2	23.3	23.1	26.9	19.1	19.1	19.1	35.1	35.1	35.1
	2211	10.9	16.8	13.5	22.2	22.0	19.2	24.5	24.5	24.5	43.0	43.0	43.0
	2212	17.2	18.2	17.7	29.6	23.3	27.4	25.2	25.2	25.2	46.3	46.3	46.3

a) : Control animals were administered olive oil orally.

Appendix 17-2 Food consumption of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Food consumption (g/day)									
		Administration days			Gestation days				Lactation days		
		1	7	14	7	14	17	20	4	4	4
10	2301	11.9	12.0	13.0	20.0	18.2	17.9	17.9	31.2		
	2302	15.8	14.7	19.8	22.2	21.6	22.5	18.9	25.4		
	2303	12.6	17.3	17.3	25.3	8.0	22.7	23.5	44.7		
	2304	13.8	15.9	17.2	21.4	22.6	28.1	25.2	36.6		
	2305	14.2	15.6	13.8	22.5	27.6	19.0	21.7	34.9		
	2306	15.5	18.0	16.1	23.3	23.2	25.5	19.0	41.5		
	2307	15.0	16.5	16.9	23.1	23.3	26.1	20.1	47.3		
	2308	14.0	12.2	18.7	18.9	15.1	19.7	21.0	37.3		
	2309	14.7	16.6	15.0	21.8	22.2	20.4	21.3	34.0		
	2310	16.8	17.7	11.7	11.5	21.7	22.8	20.9	36.0		
	2311	14.6	16.1	16.4	23.9	23.2	22.4	20.9	51.7		
	2312	15.0	15.8	11.8	20.6	21.5	19.6	19.3	39.2		
100	2401	13.3	8.7	13.8	17.7	18.0	21.7	9.0	26.4		
	2402	12.0	13.9	14.8	21.1	21.3	18.1	20.8	30.4		
	2403	10.3	14.7	16.5	22.1	15.2	22.0	18.1	37.4		
	2404	13.4	14.0	18.0	20.1	18.3	22.0	11.4	34.3		
	2405	15.2	12.0	18.1	22.1	21.1	18.5	22.0	36.9		
	2406	12.5	17.0	28.2	27.8	23.4	24.7	19.4	33.1		
	2407	16.7	13.6	15.1	23.1	22.6	22.1	22.3	46.2		
	2408	15.8	10.2	17.1	18.9	20.5	23.8	15.7	36.9		
	2409	16.3	14.9	18.3	22.4	26.4	27.8	24.3	38.5		
	2410	15.3	13.5	16.9	23.2	25.7	24.4	20.0	41.5		
	2411	18.3	13.7	19.5	23.7	22.0	16.3	20.6	45.3		
	2412	15.2	15.9	17.9	23.9	22.5	21.1	19.4	42.3		

Appendix 17-3 Food consumption of female rats in combined repeat dose and reproductive/developmental toxicity screening test of N,N-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Food consumption (g/day)											
		Administration days						Recovery days					
		1	3	8	15	22	29	36	1	3	7	14	
0 ^{a)}	2121	14.4	16.7	12.4	17.6	14.1	14.9	12.7	14.7	17.9	18.0	13.6	
	2122	14.7	15.1	17.1	15.1	17.0	18.1	17.9	17.9	20.2	20.4	17.4	
	2123	18.7	13.9	14.1	13.5	19.1	17.8	16.0	15.0	20.2	16.3	14.2	
	2124	17.5	17.2	16.4	20.8	17.0	18.9	18.8	16.6	17.4	16.7	17.7	
	2125	13.9	20.5	18.1	19.6	15.8	14.5	17.9	14.3	16.9	15.1	16.2	
100	2421	14.1	13.7	12.5	17.6	15.2	11.8	10.5	12.9	22.6	15.0	13.2	
	2422	14.1	11.1	15.8	12.4	14.2	18.4	14.7	11.7	11.3	20.7	16.2	
	2423	15.5	13.9	14.6	17.3	18.8	18.5	16.5	17.4	18.4	17.8	16.4	
	2424	13.5	11.7	12.7	19.1	15.2	18.1	12.5	12.5	16.4	15.9	17.5	
	2425	15.8	17.3	14.8	20.2	14.3	18.3	15.1	13.4	15.2	20.0	18.4	

a) : Control animals were administered olive oil orally.

Appendix 18-1 Urinary findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen
0 ^{a)}	2101	7.5	++	-	-	-	-	0.1
	2102	7.0	±	-	-	-	-	0.1
	2105	8.0	+	-	-	-	-	0.1
	2106	7.5	++	-	-	-	-	0.1
	2108	8.0	++	-	-	-	-	0.1
1	2202	8.0	+	-	-	-	-	0.1
	2204	7.5	++	-	-	-	-	0.1
	2205	7.0	+	-	-	-	-	0.1
	2207	8.0	++	-	-	-	-	0.1
	2211	7.5	+	-	-	-	-	0.1
10	2301	7.5	+	-	-	-	-	0.1
	2302	7.0	+	-	-	-	-	0.1
	2304	8.5	+	-	-	-	-	0.1
	2306	7.5	+	-	-	-	-	0.1
	2307	8.0	++	-	-	-	-	0.1
100	2403	8.0	±	-	-	-	-	0.1
	2406	7.5	++	-	-	-	-	0.1
	2409	8.0	+	-	-	-	-	0.1
	2410	7.5	+	-	-	-	-	0.1
	2412	7.0	++	-	-	-	-	0.1

a) : Control animals were administered olive oil orally.

Protein : ± ; < 30 mg/dL, + ; 30 mg/dL, ++ ; 100 mg/dL.

Glucose : - ; Negative.

Ketone body : - ; Negative.

Bilirubin : - ; Negative.

Occult blood : - ; Negative.

Urobilinogen : Ehrlich unit/dL.

Appendix 18-2 Urinary findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen
0 ^{a)}	2121	8.0	+	-	-	-	-	0.1
	2122	7.5	+	-	-	-	-	0.1
	2123	7.5	++	-	-	-	-	0.1
	2124	7.5	+	-	-	-	-	0.1
	2125	7.0	++	-	-	-	-	0.1
100	2421	7.0	+	-	-	-	-	0.1
	2422	8.5	±	-	-	-	-	0.1
	2423	7.0	+	-	-	-	-	0.1
	2424	8.0	++	-	-	-	-	0.1
	2425	7.5	++	-	-	-	-	0.1

a) : Control animals were administered olive oil orally.

Protein : ± ; < 30 mg/dL, + ; 30 mg/dL, ++ ; 100 mg/dL.

Glucose : - ; Negative.

Ketone body : - ; Negative.

Bilirubin : - ; Negative.

Occult blood : - ; Negative.

Urobilinogen : Ehrlich unit/dL.

Appendix 19-1 Hematological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	RBC ($\times 10^6/\mu\text{L}$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	WBC ($\times 10^3/\mu\text{L}$)	Differential WBC count (%)							PLT ($\times 10^3/\mu\text{L}$)	PT (second)	APTT (second)
									Bas	Eos	St	Seg	Lym	Mon	Other			
0 ^{a)}	2101	703	14.3	40.1	57.0	20.3	35.7	145	0	3	0	33	64	0	0	113.7	16.3	13.3
	2102	710	14.3	40.3	56.8	20.1	35.5	166	0	1	0	28	71	0	0	110.5	16.2	10.5
	2105	744	14.6	44.6	59.9	19.6	32.7	105	0	0	0	24	76	0	0	111.5	17.0	14.4
	2106	733	14.5	40.0	54.6	19.8	36.3	118	0	0	0	36	64	0	0	113.3	16.4	11.5
	2108	697	14.8	41.5	59.5	21.2	35.7	215	0	0	0	22	78	0	0	116.9	16.6	13.9
1	2202	703	13.6	37.9	53.9	19.3	35.9	101	0	0	0	26	74	0	0	124.3	16.3	10.7
	2204	740	15.1	43.4	58.6	20.4	34.8	166	0	0	0	30	70	0	0	122.2	16.5	11.3
	2205	686	14.7	42.5	62.0	21.4	34.6	98	0	1	0	21	78	0	0	102.3	16.9	13.6
	2207	712	15.2	43.3	60.8	21.3	35.1	148	0	0	0	12	88	0	0	116.2	16.8	12.3
	2211	689	14.2	40.5	58.8	20.6	35.1	73	0	0	0	30	70	0	0	110.8	16.1	11.1
10	2301	726	14.9	41.7	57.4	20.5	35.7	115	0	0	0	29	71	0	0	107.3	17.7	11.7
	2302	730	15.2	42.2	57.8	20.8	36.0	100	0	0	0	22	78	0	0	106.9	17.1	11.7
	2304	613	13.6	38.6	63.0	22.2	35.2	162	0	1	0	28	71	0	0	103.7	16.4	12.6
	2306	623	13.4	38.1	61.2	21.5	35.2	96	0	0	0	31	69	0	0	115.5	17.1	12.5
	2307	699	13.4	39.8	56.9	19.2	33.7	88	0	0	0	20	80	0	0	122.0	17.0	12.0
100	2402	440	12.2	37.0	84.1	27.7	33.0	94	0	1	0	30	69	0	0	90.9	17.4	12.7
	2403	501	12.2	36.8	73.5	24.4	33.2	134	0	0	0	31	69	0	0	115.0	16.1	10.4
	2406	527	13.0	39.9	75.7	24.7	32.6	108	0	0	0	22	78	0	0	131.1	17.1	11.4
	2409	486	12.6	38.1	78.4	25.9	33.1	104	0	0	0	7	93	0	0	104.2	16.1	11.1
	2410	496	12.2	36.4	73.4	24.6	33.5	166	0	0	0	26	74	0	0	105.4	16.5	11.0

a) : Control animals were administered olive oil orally.

RBC : Red blood cell.

Hb : Hemoglobin.

Ht : Hematocrit.

MCV : Mean corpuscular volume.

MCH : Mean corpuscular hemoglobin level.

MCHC : Mean corpuscular hemoglobin concentration.

WBC : White blood cell.

Bas : Basophil.

Eos : Eosinophil.

St : Stab neutrophil.

Seg : Segmented neutrophil.

Lym : Lymphocyte.

Mon : Monocyte.

PLT : Platelet.

PT : Prothrombin time.

APTT : Activated partial thromboplastin time.

Appendix 19-2 Hematological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	RBC ($\times 10^9/\mu\text{L}$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	WBC ($\times 10^9/\mu\text{L}$)	Differential WBC count (%)							PLT ($\times 10^9/\mu\text{L}$)	PT (second)	APTT (second)
									Bas	Eos	St	Seg	Lym	Mon	Other			
0 ^{a)}	2121	802	16.0	44.4	55.4	20.0	36.0	46	0	3	0	17	80	0	0	116.0	15.4	11.5
	2122	849	15.9	43.7	51.5	18.7	36.4	50	0	0	0	6	94	0	0	86.0	17.0	13.0
	2123 ^{b)}	925	18.0	50.5	54.6	19.5	35.6	103	0	2	0	13	85	0	0	128.8	16.4	13.7
	2124	800	15.8	45.1	56.4	19.8	35.0	67	0	1	0	12	87	0	0	110.5	15.3	13.7
	2125	827	16.1	45.3	54.8	19.5	35.5	69	0	3	0	11	86	0	0	109.4	16.1	13.5
100	2421	761	16.3	45.7	60.1	21.4	35.7	66	0	1	0	10	89	0	0	96.7	15.7	11.1
	2422	754	16.9	47.6	63.1	22.4	35.5	55	0	0	0	9	91	0	0	101.3	16.5	11.3
	2423	738	16.7	47.0	63.7	22.6	35.5	65	0	0	0	21	79	0	0	95.6	15.3	14.0
	2424	787	17.2	50.1	63.7	21.9	34.3	46	0	0	0	13	87	0	0	117.9	17.4	12.6
	2425	801	17.1	49.0	61.2	21.3	34.9	79	0	0	0	2	98	0	0	118.4	16.4	11.6

a) : Control animals were administered olive oil orally.

b) : Death of anesthetizing, excluded from calculation of mean value.

RBC : Red blood cell.

Hb : Hemoglobin.

Ht : Hematocrit.

MCV : Mean corpuscular volume.

MCH : Mean corpuscular hemoglobin level.

MCHC : Mean corpuscular hemoglobin concentration.

WBC : White blood cell.

Bas : Basophil.

Eos : Eosinophil.

St : Stab neutrophil.

Seg : Segmented neutrophil.

Lym : Lymphocyte.

Mon : Monocyte.

PLT : Platelet.

PT : Prothrombin time.

APTT : Activated partial thromboplastin time.

Appendix 20-1 Blood biochemical findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TP (g/dL)	Alb (g/dL)	Plasma protein pattern (%)				Glu (mg/dL)	TC (mg/dL)	TG (mg/dL)	TB (mg/dL)	BUN (mg/dL)	Cre (mg/dL)	IP (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)		
							A/G																
							Alb	1	2	A/G													
0 ^{a)}	2101	71	44	129	5.6	3.4	57.8	20.6	4.3	14.1	3.2	1.36	125	51	23	0.06	11.3	0.29	8.6	10.7	146.9	4.40	101.4
	2102	73	42	117	5.9	3.7	59.5	20.3	3.3	12.8	4.1	1.46	125	60	47	0.07	11.8	0.32	7.5	10.2	144.6	4.52	102.9
	2105	68	52	112	5.7	3.3	54.5	21.0	4.6	14.7	5.2	1.19	119	51	53	0.06	9.7	0.31	6.4	10.1	145.5	4.42	105.6
	2106	69	42	116	6.0	3.5	53.9	20.4	4.2	15.7	5.8	1.16	106	87	44	0.07	14.0	0.34	8.1	10.3	145.6	4.57	102.8
	2108	89	53	262	6.6	3.8	55.5	20.2	4.3	17.4	2.6	1.24	176	62	71	0.04	16.6	0.31	8.9	12.0	144.8	5.02	99.9
1	2202	78	43	178	5.7	3.2	53.6	22.0	4.2	16.9	3.3	1.15	99	67	32	0.05	15.5	0.32	9.9	10.7	145.0	4.84	103.5
	2204	83	50	135	5.9	3.5	55.2	21.0	4.4	15.6	3.8	1.23	131	86	35	0.06	13.7	0.29	8.6	11.1	146.9	5.69	106.4
	2205	72	48	257	6.4	3.7	55.2	19.6	4.2	18.5	2.5	1.23	144	77	104	0.03	17.2	0.28	8.0	10.9	144.6	4.43	100.5
	2207	68	31	144	5.8	3.3	54.8	18.6	4.6	17.1	4.9	1.21	114	60	27	0.04	18.8	0.35	6.5	9.7	143.1	4.26	104.0
	2211	68	34	114	5.8	3.5	55.2	22.3	4.1	14.7	3.7	1.23	121	57	22	0.05	19.2	0.32	8.4	10.6	145.1	4.71	105.4
10	2301	73	35	145	6.3	3.6	55.3	17.9	4.0	16.5	6.3	1.23	113	60	35	0.05	14.2	0.32	6.6	10.4	144.3	4.12	104.3
	2302	76	36	264	6.0	3.5	58.7	16.1	4.1	15.9	5.2	1.42	138	64	26	0.08	12.4	0.31	6.6	10.0	144.8	4.52	104.2
	2304	91	43	80	5.8	3.5	57.9	18.3	4.1	15.7	4.0	1.37	129	56	39	0.08	16.6	0.26	10.8	11.3	145.2	6.61	102.9
	2306	74	44	149	5.8	3.6	59.7	15.2	4.1	17.5	3.5	1.48	127	69	47	0.06	15.3	0.27	6.8	10.0	143.4	4.03	106.5
	2307	77	45	134	6.1	3.4	53.5	19.6	4.3	18.1	4.5	1.15	110	59	32	0.05	19.7	0.34	7.6	10.5	145.4	4.39	103.8
100	2402	79	43	142	6.2	3.8	61.9	16.8	3.8	13.5	4.0	1.62	124	53	24	0.25	21.5	0.23	8.8	10.7	144.0	4.38	103.7
	2403	81	48	112	6.6	3.9	60.0	18.3	3.6	14.3	3.8	1.50	115	85	46	0.23	17.7	0.30	8.5	10.5	144.1	5.13	102.1
	2406	79	41	111	5.8	3.2	56.0	18.6	4.7	17.0	3.7	1.27	118	61	20	0.12	15.4	0.28	7.3	9.9	144.2	5.07	104.3
	2409	85	60	174	5.9	3.6	57.1	15.0	4.9	18.9	4.1	1.33	118	77	36	0.28	18.6	0.32	8.8	10.4	144.7	5.24	103.5
	2410	85	58	235	6.0	3.5	58.8	18.0	3.5	14.1	5.6	1.42	106	70	43	0.22	24.4	0.36	9.5	10.4	145.4	4.94	104.1

a) : Control animals were administered olive oil orally.

AST : Glutamic oxaloacetic transaminase. 1 : 1-globulin. Glu : Glucose. Cre : Creatinine. Cl : Chlorine.
 ALT : Glutamic pyruvic transaminase. 2 : 2-globulin. TC : Total cholesterol. IP : Inorganic phosphate.
 ALP : Alkaline phosphatase. : -globulin. TG : Triglyceride. Ca : Calcium.
 TP : Total protein. : -globulin. TB : Total bilirubin. Na : Sodium.
 Alb : Albumin. A/G : Albumin/Globulin ratio. BUN : Blood urea nitrogen. K : Potassium.

Appendix 20-2 Blood biochemical findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TP (g/dL)	Alb (g/dL)	Plasma protein pattern (%)			Glu (mg/dL)	TC (mg/dL)	TG (mg/dL)	TB (mg/dL)	BUN (mg/dL)	Cre (mg/dL)	IP (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)			
							A/G																
							Alb	1	2														
0 ^{a)}	2121	52	21	105	7.6	4.9	67.1	13.1	3.6	12.4	3.8	2.03	138	106	38	0.06	16.7	0.36	4.7	10.3	144.5	3.87	105.1
	2122	62	26	72	6.7	4.3	61.9	16.8	4.8	12.7	3.8	1.62	155	67	37	0.07	16.8	0.33	4.4	9.8	145.4	3.37	106.7
	2123 ^{b)}	72	23	113	7.3	4.1	58.8	17.2	4.6	14.3	5.1	1.42	235	81	72	0.02	26.5	0.35	8.5	11.8	145.8	5.20	102.3
	2124	101	41	103	7.1	4.8	68.0	16.4	4.0	10.0	1.6	2.12	130	71	91	0.08	18.4	0.36	5.9	10.8	145.6	3.78	103.5
	2125	88	52	80	7.0	4.4	62.3	16.1	4.2	14.0	3.4	1.65	124	78	25	0.09	18.1	0.37	6.4	10.3	146.5	3.59	103.7
100	2421	48	20	108	6.7	4.3	66.0	14.5	3.8	12.3	3.4	1.94	134	85	38	0.02	15.7	0.30	4.8	9.9	144.5	3.98	106.6
	2422	68	31	141	6.4	3.9	60.2	17.5	4.8	13.7	3.8	1.51	140	49	16	0.02	15.4	0.28	5.2	10.0	145.0	3.62	106.5
	2423	125	36	78	7.8	5.1	68.5	15.0	3.6	10.7	2.2	2.17	136	80	66	0.03	17.1	0.30	5.5	11.2	146.5	3.16	102.0
	2424	59	19	138	7.0	4.6	66.6	13.2	4.7	12.5	3.0	1.99	144	60	18	0.02	18.1	0.35	5.0	10.3	146.6	3.46	106.0
	2425	53	20	116	7.1	4.6	65.2	14.8	4.0	11.7	4.3	1.87	121	58	17	0.04	14.4	0.28	5.8	10.4	146.6	3.60	105.8

a) : Control animals were administered olive oil orally.

b) : Death of anesthetizing, excluded from calculation of mean value.

AST : Glutamic oxaloacetic transaminase. 1 : 1-globulin.
 ALT : Glutamic pyruvic transaminase. 2 : 2-globulin.
 ALP : Alkaline phosphatase. : -globulin.
 TP : Total protein. : -globulin.
 Alb : Albumin. A/G : Albumin/Globulin ratio.

Glu : Glucose.
 TC : Total cholesterol.
 TG : Triglyceride.
 TB : Total bilirubin.
 BUN : Blood urea nitrogen.
 Cre : Creatinine.
 IP : Inorganic phosphate.
 Ca : Calcium.
 Na : Sodium.
 K : Potassium.
 Cl : Chlorine.

Appendix 21-1 Absolute organ weights of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Final body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Spleen (g)	Kidneys (g)	Adrenals (mg)
0 ^{a)}	2101	255.3	2.119	0.151	0.855	8.088	0.502	1.730	67.2
	2102	265.2	1.880	0.150	0.898	8.198	0.481	1.672	80.7
	2103	296.9	1.990	0.288	0.935	8.014	0.464	1.953	74.6
	2104	298.8	1.904	0.173	1.104	10.021	0.860	1.625	81.5
	2105	303.5	2.038	0.186	1.039	9.239	0.659	1.948	84.5
	2106	291.2	2.073	0.304	1.023	9.046	0.574	1.759	87.1
	2107	290.2	2.083	0.146	1.032	9.239	0.602	2.000	71.1
	2108	290.6	2.056	0.159	0.966	10.564	0.830	1.982	60.7
	2109	313.6	1.948	0.251	1.102	8.831	0.466	1.945	72.8
	2110	323.2	2.089	0.425	1.191	9.481	0.574	1.914	66.6
	2111	344.1	2.137	0.308	1.176	10.050	0.692	1.911	88.1
	2112	320.5	2.030	0.381	1.070	10.591	0.751	1.822	89.3
1	2121	285.9	2.078	0.391	1.048	7.434	0.454	1.771	73.3
	2122	293.7	2.005	0.556	0.930	6.659	0.541	1.511	56.6
	2123	300.1	2.016	0.333	0.813	6.780	0.488	1.582	67.3
	2124	313.8	1.975	0.393	0.880	7.568	0.487	1.556	78.4
	2125	284.0	2.066	0.366	0.897	7.044	0.527	1.548	71.6
	2201	290.2	2.044	0.189	0.897	8.354	0.414	1.452	50.9
	2202	288.8	2.034	0.327	1.068	8.803	0.689	1.724	87.1
	2203	321.8	2.149	0.304	1.131	10.508	0.723	2.003	83.5
	2204	294.9	2.196	0.220	0.982	10.395	0.722	2.041	81.2
	2205	285.1	2.105	0.201	0.934	10.681	0.815	1.852	84.3
	2206	298.6	2.095	0.182	1.035	9.594	0.763	1.980	72.9
	2207	282.1	2.066	0.344	1.063	7.766	0.745	1.615	62.1
	2208	298.1	2.082	0.366	1.146	9.831	0.590	1.967	84.3
	2209	328.6	2.176	0.475	1.195	11.369	0.602	1.906	80.0
	2210	322.4	2.101	0.268	1.030	9.627	0.644	1.956	68.7
	2211	299.7	1.917	0.274	1.089	9.971	0.603	1.802	81.0
	2212	356.2	1.934	0.328	1.171	10.831	0.661	2.015	88.2

a) : Control animals were administered olive oil orally.

Appendix 21-2 Absolute organ weights of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Final body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Spleen (g)	Kidneys (g)	Adrenals (mg)
10	2301	260.3	2.005	0.264	0.900	8.161	0.700	1.788	80.5
	2302	279.3	2.127	0.311	0.997	7.814	0.582	1.709	60.6
	2303	298.4	2.093	0.234	1.152	10.206	0.613	2.027	78.7
	2304	293.5	2.112	0.263	1.055	9.805	0.901	2.086	75.5
	2305	302.1	2.095	0.291	1.407	14.398	0.823	2.401	88.1
	2306	277.8	2.158	0.233	1.099	8.816	0.612	1.998	65.3
	2307	294.4	2.141	0.151	1.174	9.842	0.765	1.830	96.1
	2308	291.7	2.099	0.249	0.996	10.516	0.673	2.001	86.8
	2309	272.8	1.982	0.188	0.905	8.068	0.647	1.914	90.8
	2310	311.2	2.162	0.276	1.003	9.671	0.820	1.916	72.9
	2311	323.7	2.113	0.210	1.103	10.419	0.965	2.105	73.4
	2312	282.5	2.212	0.261	1.153	9.420	1.190	1.912	62.2
100	2401	268.5	2.043	0.172	0.920	8.268	1.734	1.617	62.3
	2402	261.6	2.185	0.290	1.005	9.265	2.243	2.018	79.2
	2403	260.2	2.001	0.163	1.060	9.231	1.659	1.656	76.9
	2404	260.2	1.942	0.242	0.858	7.983	1.736	1.847	79.0
	2405	285.0	2.138	0.181	1.042	8.830	1.879	1.916	61.7
	2406	288.8	2.075	0.386	1.102	9.127	2.106	2.005	90.6
	2407	288.5	1.993	0.282	1.139	10.256	2.285	1.828	75.5
	2408	300.1	2.017	0.247	1.038	9.592	1.421	2.004	79.2
	2409	304.1	2.135	0.284	1.246	11.059	1.960	1.824	94.5
	2410	294.0	2.051	0.320	1.105	10.213	1.972	2.015	71.2
	2411	288.6	2.085	0.288	1.069	9.894	2.230	2.145	71.5
	2412	286.9	1.973	0.262	1.160	10.296	1.585	1.879	96.5
	2421	261.1	2.049	0.313	0.934	6.174	0.492	1.629	58.4
	2422	260.8	1.994	0.438	0.838	6.722	0.614	1.685	84.0
	2423	274.2	2.071	0.186	0.948	7.507	0.647	1.818	59.0
	2424	282.0	2.007	0.222	0.894	6.604	0.525	1.585	62.8
	2425	271.6	2.100	0.333	1.019	7.096	0.661	1.722	95.2

Appendix 22-1 Relative organ weights of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Brain (g%)	Thymus (g%)	Heart (g%)	Liver (g%)	Spleen (g%)	Kidneys (g%)	Adrenals (mg%)
0 ^{a)}	2101	0.830	0.059	0.335	3.168	0.197	0.678	26.3
	2102	0.709	0.057	0.339	3.091	0.181	0.630	30.4
	2103	0.670	0.097	0.315	2.699	0.156	0.658	25.1
	2104	0.637	0.058	0.369	3.354	0.288	0.544	27.3
	2105	0.671	0.061	0.342	3.044	0.217	0.642	27.8
	2106	0.712	0.104	0.351	3.106	0.197	0.604	29.9
	2107	0.718	0.050	0.356	3.184	0.207	0.689	24.5
	2108	0.708	0.055	0.332	3.635	0.286	0.682	20.9
	2109	0.621	0.080	0.351	2.816	0.149	0.620	23.2
	2110	0.646	0.131	0.369	2.933	0.178	0.592	20.6
	2111	0.621	0.090	0.342	2.921	0.201	0.555	25.6
	2112	0.633	0.119	0.334	3.305	0.234	0.568	27.9
1	2121	0.727	0.137	0.367	2.600	0.159	0.619	25.6
	2122	0.683	0.189	0.317	2.267	0.184	0.514	19.3
	2123	0.672	0.111	0.271	2.259	0.163	0.527	22.4
	2124	0.629	0.125	0.280	2.412	0.155	0.496	25.0
	2125	0.727	0.129	0.316	2.480	0.186	0.545	25.2
	2201	0.704	0.065	0.309	2.879	0.143	0.500	17.5
	2202	0.704	0.113	0.370	3.048	0.239	0.597	30.2
	2203	0.668	0.094	0.351	3.265	0.225	0.622	25.9
	2204	0.745	0.075	0.333	3.525	0.245	0.692	27.5
	2205	0.738	0.071	0.328	3.746	0.286	0.650	29.6
	2206	0.702	0.061	0.347	3.213	0.256	0.663	24.4
	2207	0.732	0.122	0.377	2.753	0.264	0.572	22.0
	2208	0.698	0.123	0.384	3.298	0.198	0.660	28.3
	2209	0.662	0.145	0.364	3.460	0.183	0.580	24.3
	2210	0.652	0.083	0.319	2.986	0.200	0.607	21.3
	2211	0.640	0.091	0.363	3.327	0.201	0.601	27.0
	2212	0.543	0.092	0.329	3.041	0.186	0.566	24.8

a) : Control animals were administered olive oil orally.

Appendix 22-2 Relative organ weights of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Brain (g%)	Thymus (g%)	Heart (g%)	Liver (g%)	Spleen (g%)	Kidneys (g%)	Adrenals (mg%)
10	2301	0.770	0.101	0.346	3.135	0.269	0.687	30.9
	2302	0.762	0.111	0.357	2.798	0.208	0.612	21.7
	2303	0.701	0.078	0.386	3.420	0.205	0.679	26.4
	2304	0.720	0.090	0.359	3.341	0.307	0.711	25.7
	2305	0.693	0.096	0.466	4.766	0.272	0.795	29.2
	2306	0.777	0.084	0.396	3.174	0.220	0.719	23.5
	2307	0.727	0.051	0.399	3.343	0.260	0.622	32.6
	2308	0.720	0.085	0.341	3.605	0.231	0.686	29.8
	2309	0.727	0.069	0.332	2.957	0.237	0.702	33.3
	2310	0.695	0.089	0.322	3.108	0.263	0.616	23.4
	2311	0.653	0.065	0.341	3.219	0.298	0.650	22.7
	2312	0.783	0.092	0.408	3.335	0.421	0.677	22.0
100	2401	0.761	0.064	0.343	3.079	0.646	0.602	23.2
	2402	0.835	0.111	0.384	3.542	0.857	0.771	30.3
	2403	0.769	0.063	0.407	3.548	0.638	0.636	29.6
	2404	0.746	0.093	0.330	3.068	0.667	0.710	30.4
	2405	0.750	0.064	0.366	3.098	0.659	0.672	21.6
	2406	0.718	0.134	0.382	3.160	0.729	0.694	31.4
	2407	0.691	0.098	0.395	3.555	0.792	0.634	26.2
	2408	0.672	0.082	0.346	3.196	0.474	0.668	26.4
	2409	0.702	0.093	0.410	3.637	0.645	0.600	31.1
	2410	0.698	0.109	0.376	3.474	0.671	0.685	24.2
	2411	0.722	0.100	0.370	3.428	0.773	0.743	24.8
	2412	0.688	0.091	0.404	3.589	0.552	0.655	33.6
	2421	0.785	0.120	0.358	2.365	0.188	0.624	22.4
	2422	0.765	0.168	0.321	2.577	0.235	0.646	32.2
	2423	0.755	0.068	0.346	2.738	0.236	0.663	21.5
	2424	0.712	0.079	0.317	2.342	0.186	0.562	22.3
	2425	0.773	0.123	0.375	2.613	0.243	0.634	35.1

Appendix 23-1 Gross pathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Findings
0 ^{a)}	2101	No abnormality detected
	2102	No abnormality detected
	2103	No abnormality detected
	2104	No abnormality detected
	2105	No abnormality detected
	2106	No abnormality detected
	2107	No abnormality detected
	2108	No abnormality detected
	2109	No abnormality detected
	2110	No abnormality detected
	2111	No abnormality detected
	2112	No abnormality detected
	2121	No abnormality detected
	2122	No abnormality detected
	2123	No abnormality detected
	2124	No abnormality detected
	2125	No abnormality detected
1	2201	No abnormality detected
	2202	No abnormality detected
	2203	No abnormality detected
	2204	No abnormality detected
	2205	No abnormality detected
	2206	No abnormality detected
	2207	No abnormality detected
	2208	No abnormality detected
	2209	No abnormality detected
	2210	No abnormality detected
	2211	No abnormality detected
	2212	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 23-2 Gross pathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Findings
10	2301	No abnormality detected
	2302	No abnormality detected
	2303	No abnormality detected
	2304	No abnormality detected
	2305	No abnormality detected
	2306	No abnormality detected
	2307	No abnormality detected
	2308	No abnormality detected
	2309	No abnormality detected
	2310	No abnormality detected
	2311	No abnormality detected
	2312	No abnormality detected
100	2401	Spleen : Swelling (+++) and dark red discoloration
	2402	Spleen : Swelling (+++) and dark red discoloration
	2403	Spleen : Swelling (+++) and dark red discoloration
	2404	Spleen : Swelling (+++) and dark red discoloration
	2405	Spleen : Swelling (+++) and dark red discoloration
	2406	Spleen : Swelling (+++) and dark red discoloration
	2407	Spleen : Swelling (+++) and dark red discoloration
	2408	Spleen : Swelling (+++) and dark red discoloration
	2409	Spleen : Swelling (+++) and dark red discoloration
	2410	Spleen : Swelling (+++) and dark red discoloration
	2411	Spleen : Swelling (+++) and dark red discoloration
	2412	Spleen : Swelling (+++) and dark red discoloration
Grade: +++ ; Marked	2421	No abnormality detected
	2422	No abnormality detected
	2423	No abnormality detected
	2424	No abnormality detected
	2425	No abnormality detected

Appendix 24-1 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	2101	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	No abnormality detected
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 24-2 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	2102	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	No abnormality detected
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 24-3 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	2105	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	No abnormality detected
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 24-4 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	2106	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	No abnormality detected
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 24-5 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	2108	Trachea	No abnormality detected
		Lung	Calcification of pulmonary aorta (+) Ectopic ossification (+)
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	No abnormality detected
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
		Spleen	No abnormality detected
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

a) : Control animals were administered olive oil orally.

Grade: + ; Slight.

Appendix 24-6 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	2202	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	Congestion (+)
Grade: + ; Slight.			

Appendix 24-7 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	2204	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 24-8 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	2205	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	Congestion (+)
Grade: + ; Slight.			

Appendix 24-9 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	2207	Liver	Microgranuloma (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected
Grade: + ; Slight.			

Appendix 24-10 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
1	2211	Liver	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (+)
		Spleen	No abnormality detected
Grade: + ; Slight.			

Appendix 24-11 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
10	2301	Liver	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (+)
		Spleen	Congestion (+)
Grade: + ; Slight.			

Appendix 24-12 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
10	2302	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 24-13 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
10	2304	Liver	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (+)
		Spleen	Congestion (+)
Grade: + ; Slight.			

Appendix 24-14 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
10	2306	Liver	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (+)
		Spleen	Extramedullary hematopoiesis (+)
Grade: + ; Slight.			

Appendix 24-15 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
10	2307	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

Appendix 24-16 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2402	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+) Extramedullary hematopoiesis (+)
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (++)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
			Congestion (+++)
		Spleen	Atrophy of white pulp (++) Extramedullary hematopoiesis (++) Yellowish-brown pigmentation (++)
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade: + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 24-17 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2403	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+) Extramedullary hematopoiesis (+)
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (++)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
			Congestion (+++)
		Spleen	Atrophy of white pulp (++) Extramedullary hematopoiesis (++) Yellowish-brown pigmentation (++)
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade: + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 24-18 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2406	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+) Extramedullary hematopoiesis (+)
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (++)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
			Congestion (+++)
		Spleen	Atrophy of white pulp (++) Extramedullary hematopoiesis (++) Yellowish-brown pigmentation (++)
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade: + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 24-19 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2409	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+) Extramedullary hematopoiesis (+)
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (++)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
			Congestion (+++)
		Spleen	Atrophy of white pulp (++) Extramedullary hematopoiesis (++) Yellowish-brown pigmentation (++)
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade: + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 24-20 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2410	Trachea	No abnormality detected
		Lung	No abnormality detected
		Stomach	No abnormality detected
		Duodenum	No abnormality detected
		Ileum (including Peyer's patches)	No abnormality detected
		Colon	No abnormality detected
		Liver	Yellowish-brown pigmentation (+) Extramedullary hematopoiesis (+)
		Heart	No abnormality detected
		Kidney	No abnormality detected
		Urinary bladder	No abnormality detected
		Ovary	No abnormality detected
		Uterus	No abnormality detected
		Vagina	No abnormality detected
		Brain (cerebrum, cerebellum and pons)	No abnormality detected
		Spinal cord	No abnormality detected
		Sciatic nerve	No abnormality detected
		Bone marrow (femur)	Erythroid hyperplasia (++)
		Mesenteric lymph node	No abnormality detected
		Axillary lymph node	No abnormality detected
			Congestion (+++)
		Spleen	Atrophy of white pulp (++) Extramedullary hematopoiesis (++) Yellowish-brown pigmentation (++)
		Thymus	No abnormality detected
		Pituitary	No abnormality detected
		Thyroid gland	No abnormality detected
		Parathyroid	No abnormality detected
		Adrenal	No abnormality detected

Grade: + ; Slight, ++ ; Moderate, +++ ; Marked.

Appendix 24-21 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	2121	Liver	Microgranuloma (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

a) : Control animals were administered olive oil orally.
grade: + ; Slight.

Appendix 24-22 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	2122	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 24-23 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ		Findings
		Liver	Bone marrow (femur)	
0 ^{a)}	2123			Hemorrhagic necrosis (+)
				No abnormality detected
		Spleen		No abnormality detected

a) : Control animals were administered olive oil orally.
grade: + ; Slight.

Appendix 24-24 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	2124	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 24-25 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
0 ^{a)}	2125	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	No abnormality detected

a) : Control animals were administered olive oil orally.

Appendix 24-26 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2421	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	Yellowish-brown pigmentation (+++)
Grade: +++ ; Marked.			

Appendix 24-27 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2422	Liver	Yellowish-brown pigmentation (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	Yellowish-brown pigmentation (++)
Grade: + ; Slight, ++ ; Moderate.			

Appendix 24-28 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2423	Liver	Yellowish-brown pigmentation (+)
			Microgranuloma (+)
		Bone marrow (femur)	No abnormality detected
		Spleen	Yellowish-brown pigmentation (+++)
Grade: + ; Slight, +++ ; Marked.			

Appendix 24-29 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2424	Liver	Yellowish-brown pigmentation (+)
		Bone marrow (femur)	Erythroid hyperplasia (+)
		Spleen	Yellowish-brown pigmentation (+++)
Grade: + ; Slight, +++ ; Marked.			

Appendix 24-30 Histopathological findings of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Organ	Findings
100	2425	Liver	No abnormality detected
		Bone marrow (femur)	No abnormality detected
		Spleen	Yellowish-brown pigmentation (++)
Grade: +++ ; Marked.			

Appendix 25-1 Estrous cycles of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Before mating period														Mean days of estrous cycle before mating	1st mating period														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
0 ^{a)}	2101	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	D	4.0	D	P	+												
	2102	D	D	D	M1	M2	D	P	M1	M2	D	P	M1	M2	D	4.0	P	+													
	2103	D	D	D	M1	M2	D	P	M1	M2	D	P	M1	D	D	4.0	P	+													
	2104	M1	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.3	M2	D	P	+											
	2105	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	M2	D	4.0	P	+													
	2106	D	D	P	M1	D	D	M1	M2	D	P	M1	M2	D	D	4.0	P	+													
	2107	D	P	M1	M2	D	P	M1	M2	D	P	M1	D	D	P	4.0	+														
	2108	P	M1	M2	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.0	M2	D	P	+											
	2109	M1	M2	D	D	P	M1	M2	D	P	M1	D	D	P	M1	4.3	M2	D	P	+											
	2110	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	M2	4.0	D	P	+												
	2111	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	M2	D	4.0	P	+													
	2112	D	M2	D	M1	M2	D	P	M1	M2	D	P	M1	M2	D	4.0	P	+													
1	2201	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	M2	D	4.0	P	+													
	2202	D	P	M1	D	D	D	P	M1	M2	D	P	M1	M2	D	4.5	P	+													
	2203	D	D	P	M1	M2	D	P	M1	D	D	P	M1	D	D	4.0	P	+													
	2204	M1	M2	D	P	M1	M2	D	P	M1	M2	D	P	M1	D	4.0	D	D	+												
	2205	M1	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.3	D	D	P	+											
	2206	D	P	M1	M2	D	P	M1	M2	D	P	M1	D	D	P	4.0	+														
	2207	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	M2	4.0	D	P	+												
	2208	D	D	P	M1	M2	D	D	M1	M2	D	P	M1	M2	D	4.0	P	+													
	2209	M2	D	D	P	M2	D	D	M1	M2	D	D	D	P	M1	5.0	M2	D	D	P	+										
	2210	D	D	M1	M2	D	D	P	M1	D	D	P	M1	M2	D	4.5	P	+													
	2211	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	M2	4.0	D	D	P	+											
	2212	M1	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.3	M2	D	P	+											

Estrous cycles : P; Proestrus, M1; Metestrus-1, M2; Metestrus-2, D; Diestrus.

+ : Occurrence of copulation.

a) : Control animals were administered olive oil orally.

Appendix 25-2 Estrous cycles of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	Before mating period														Mean days of estrous cycle before mating	1st mating period													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14		1	2	3	4	5	6	7	8	9	10	11	12	13	14
10	2301	M1	M2	D	D	P	M1	D	D	P	M1	M2	D	P	M1	4.3	D	D	P	+										
	2302	D	D	P	M1	M2	D	D	M1	D	D	P	M1	M2	D	4.0	P	+												
	2303	M1	M2	D	D	P	M1	M2	D	P	M1	D	D	P	M1	4.3	M2	D	P	+										
	2304	D	D	P	M1	M2	D	P	M1	D	D	P	M1	M2	D	4.0	P	+												
	2305	M1	M2	D	D	P	M1	M2	D	P	M1	D	D	P	M1	4.3	M2	D	P	+										
	2306	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	M2	4.0	D	P	+											
	2307	D	D	P	M1	D	D	P	M1	M2	D	P	M1	M2	D	4.0	D	P	+											
	2308	D	P	M1	D	D	P	M1	M2	D	P	M1	M2	D	P	4.0	+													
	2309	M1	D	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.3	M2	D	P	+										
	2310	P	M1	M2	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.0	M2	D	P	+										
	2311	P	M1	M2	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.0	M2	D	P	+										
	2312	P	M1	M2	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.0	M2	D	P	+										
100	2401	D	P	M1	M2	D	P	M1	M2	D	P	M1	M2	D	P	4.0	+													
	2402	M1	M2	D	D	P	M1	M2	D	P	M1	D	D	P	M1	4.3	D	D	P	+										
	2403	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	M2	4.0	D	P	+											
	2404	D	D	P	M1	M2	D	P	M1	D	D	P	M1	M2	D	4.0	P	+												
	2405	M1	M2	D	D	P	M1	M2	D	P	M1	D	D	P	M1	4.3	M2	D	P	+										
	2406	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	D	4.0	D	P	+											
	2407	M1	D	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.3	M2	D	P	+										
	2408	D	P	M1	D	D	P	M1	D	D	P	M1	M2	D	P	4.0	+													
	2409	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	D	4.0	D	P	+											
	2410	M2	D	D	P	M1	M2	D	P	M1	D	D	P	M1	M2	4.0	D	P	+											
	2411	M1	M2	D	D	P	M1	M2	D	P	M1	M2	D	P	M1	4.3	M2	D	P	+										
	2412	M2	D	D	P	M1	M2	D	P	M1	D	D	P	M1	M2	4.0	D	P	+											

Estrous cycles : P; Proestrus, M1; Metestrus-1, M2; Metestrus-2, D; Diestrus.
+ : Occurrence of copulation.

Estrous cycles : P; Proestrus, M1; Metestrus-1, M2; Metestrus-2, D; Diestrus.
+ : Occurrence of copulation.

Appendix 26-1 Fertility data of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Mated pair		No. of days prior to mating	Results
	Female No.	Male No.		
0 ^{a)}	2101	1101	3	Pregnant
	2102	1102	2	Pregnant
	2103	1103	2	Pregnant
	2104	1104	4	Pregnant
	2105	1105	2	Pregnant
	2106	1106	2	Pregnant
	2107	1107	1	Pregnant
	2108	1121	4	Pregnant
	2109	1122	4	Pregnant
	2110	1123	3	Pregnant
	2111	1124	2	Pregnant
	2112	1125	2	Pregnant
	2201	1201	2	Pregnant
	2202	1202	2	Pregnant
	2203	1203	2	Pregnant
1	2204	1204	3	Pregnant
	2205	1205	4	Pregnant
	2206	1206	1	Pregnant
	2207	1207	3	Pregnant
	2208	1208	2	Pregnant
	2209	1209	5	Pregnant
	2210	1210	2	Pregnant
	2211	1211	4	Pregnant
	2212	1212	4	Pregnant

a) : Control animals were administered olive oil orally.

Appendix 26-2 Fertility data of female rats in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Mated pair		No. of days prior to mating	Results
	Female No.	Male No.		
10	2301	1301	4	Pregnant
	2302	1302	2	Pregnant
	2303	1303	4	Pregnant
	2304	1304	2	Pregnant
	2305	1305	4	Pregnant
	2306	1306	3	Pregnant
	2307	1307	3	Pregnant
	2308	1308	1	Pregnant
	2309	1309	4	Pregnant
	2310	1310	4	Pregnant
	2311	1311	4	Pregnant
	2312	1312	4	Pregnant
100	2401	1401	1	Pregnant
	2402	1402	4	Pregnant
	2403	1403	3	Pregnant
	2404	1404	2	Pregnant
	2405	1405	4	Pregnant
	2406	1406	3	Pregnant
	2407	1407	4	Pregnant
	2408	1421	1	Pregnant
	2409	1422	3	Pregnant
	2410	1423	3	Pregnant
	2411	1424	4	Pregnant
	2412	1425	3	Pregnant

Appendix 27-1 Observation of pups in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)	Animal No.	0 ^{a)}													
		2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114
Length of gestation (days)		22	23	22	23	23	23	22	22	23	23	22	22		
Corpora lutea		15	21	21	22	16	16	18	18	24	25	16	17		
Implantation scars		15	14	15	14	14	14	17	17	16	17	14	15		
Implantation index (%)		100	66.7	71.4	63.6	87.5	87.5	94.4	94.4	66.7	68.0	87.5	88.2		
Pups born		15	13	12	14	14	14	17	17	12	13	13	15		
Stillbirths	Male	0	0	1	0	0	0	0	0	0	0	0	0		
	Female	0	0	0	0	0	0	0	0	0	0	0	0		
	Unknown	0	0	0	0	0	0	0	0	0	0	0	0		
Live pups born	Male	4	7	7	8	10	6	9	10	5	7	5	8		
	Female	11	6	4	6	4	8	8	7	7	6	8	7		
	Total	15	13	11	14	14	14	17	17	12	13	13	15		
Delivery index (%)		100	92.9	80.0	100	100	100	100	100	75.0	76.5	92.9	100		
Birth index (%)		100	92.9	73.3	100	100	100	100	100	75.0	76.5	92.9	100		
Embryonic loss before implantation (%)		0	33.3	28.6	36.4	12.5	12.5	5.6	5.6	33.3	32.0	12.5	11.8		
Embryonic loss after implantation (%)		0	7.1	26.7	0	0	0	0	0	25.0	23.5	7.1	0		
Live birth index (%)		100	100	91.7	100	100	100	100	100	100	100	100	100		
Live pups on day 4 of lactation	Male	4	7	7	8	10	6	9	9	5	6	5	8		
	Female	11	6	4	6	4	8	8	7	7	5	8	7		
	Total	15	13	11	14	14	14	17	16	12	11	13	15		
Viability index (%)		100	100	100	100	100	100	100	94.1	100	84.6	100	100		
External anomalies		0	0	0	0	0	0	0	0	0	0	0	0		
Sex ratio at birth	Stillbirths included	0.27	0.54	0.64	0.57	0.71	0.43	0.53	0.53	0.42	0.46	0.38	0.53		
Sex ratio at birth	Stillbirths excluded	0.27	0.54	0.64	0.57	0.71	0.43	0.53	0.59	0.42	0.54	0.38	0.53		
Sex ratio on day 4 of lactation		0.27	0.54	0.64	0.57	0.71	0.43	0.53	0.56	0.42	0.55	0.38	0.53		
Body weight of pups (g)															
	Male Day 0	5.7	7.2	7.0	7.7	7.1	7.2	5.7	5.7	6.9	7.5	6.7	6.6		
	Female Day 0	7.6	11.4	10.0	12.9	11.6	11.1	7.5	7.9	11.2	10.3	9.9	7.6		
	Male Day 4	5.6	6.8	6.5	7.0	6.6	6.5	5.4	5.4	6.7	6.8	6.6	6.4		
	Female Day 4	7.5	10.9	9.8	12.2	10.5	10.2	7.5	7.5	10.6	8.8	9.6	7.3		

a) : Control animals were administered olive oil orally.

Implantation index (%) = (No. of implantation scars / No. of corpora lutea) × 100.

Delivery index (%) = (No. of pups born / No. of implantation scars) × 100.

Birth index (%) = (No. of live pups born / No. of implantation scars) × 100.

Embryonic loss before implantation (%) = ((No. of corpora lutea - No. of implantation scars) / No. of corpora lutea) × 100.

Embryonic loss after implantation (%) = ((No. of implantation scars - No. of live pups born) / No. of implantation scars) × 100.

Live birth index (%) = (No. of live pups born / No. of pups born) × 100.

Viability index (%) = (No. of live pups on day 4 / No. of live pups born) × 100.

External anomalies (%) = (No. of pups with external anomalies / No. of live pups) × 100.

Sex ratio = No. of males / No. of males and females.

Appendix 27-2 Observation of pups in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		1											
Animal No.		2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212
Length of gestation (days)		22	23	22	22	22	22	23	22	23	22	22	23
Corpora lutea		15	16	17	16	23	19	21	16	24	29	16	26
Implantation scars		12	16	15	16	15	13	11	12	13	15	16	15
Implantation index (%)		80.0	100	88.2	100	65.2	68.4	52.4	75.0	54.2	51.7	100	57.7
Pups born		11	14	14	16	15	11	6	10	10	15	16	15
Stillbirths	Male	0	0	0	0	0	0	0	0	0	0	0	0
	Female	0	0	0	0	0	0	0	0	0	0	0	0
	Total	0	0	0	0	0	0	0	0	0	0	0	0
Live pups born	Male	3	6	9	9	9	6	1	5	5	9	9	10
	Female	8	8	5	7	6	5	5	5	5	6	7	5
	Total	11	14	14	16	15	11	6	10	10	15	16	15
Delivery index (%)		91.7	87.5	93.3	100	100	84.6	54.5	83.3	76.9	100	100	100
Birth index (%)		91.7	87.5	93.3	100	100	84.6	54.5	83.3	76.9	100	100	100
Embryonic loss before implantation (%)		20.0	0	11.8	0	34.8	31.6	47.6	25.0	45.8	48.3	0	42.3
Embryonic loss after implantation (%)		8.3	12.5	6.7	0	0	15.4	45.5	16.7	23.1	0	0	0
Live birth index (%)		100	100	100	100	100	100	100	100	100	100	100	100
Live pups on day 4 of lactation	Male	3	6	9	9	9	6	1	5	5	9	9	9
	Female	8	8	5	7	6	5	5	5	5	4	7	5
	Total	11	14	14	16	15	11	6	10	10	13	16	14
Viability index (%)		100	100	100	100	100	100	100	100	100	86.7	100	93.3
External anomalies		0	0	0	0	0	0	0	0	0	0	0	0
Sex ratio at birth	Stillbirths included	0.27	0.43	0.64	0.56	0.60	0.55	0.17	0.50	0.50	0.60	0.56	0.60
Sex ratio at birth	Stillbirths declined	0.27	0.43	0.64	0.56	0.60	0.55	0.17	0.50	0.60	0.60	0.56	0.67
Sex ratio on day 4 of lactation		0.27	0.43	0.64	0.56	0.60	0.55	0.17	0.50	0.50	0.69	0.56	0.64
Body weight of pups (g)													
	Male Day 0	6.7	6.8	6.2	6.6	6.0	6.9	8.3	7.1	8.2	6.4	6.0	7.2
	4	10.4	9.5	9.2	9.1	9.3	10.8	13.1	12.1	14.0	9.4	9.1	10.9
	Female Day 0	6.5	6.4	5.7	6.1	5.7	6.7	7.3	6.5	7.4	6.1	5.7	7.1
	4	10.2	8.9	8.7	8.3	9.0	10.5	11.3	10.8	13.4	8.7	9.3	10.8

Implantation index (%) = (No. of implantation scars / No. of corpora lutea) × 100.

Delivery index (%) = (No. of pups born / No. of implantation scars) × 100.

Birth index (%) = (No. of live pups born / No. of implantation scars) × 100.

Embryonic loss before implantation (%) = ((No. of corpora lutea - No. of implantation scars) / No. of corpora lutea) × 100.

Embryonic loss after implantation (%) = ((No. of implantation scars - No. of live pups born) / No. of implantation scars) × 100.

Live birth index (%) = (No. of live pups born / No. of pups born) × 100.

Viability index (%) = (No. of live pups on day 4 / No. of live pups born) × 100.

External anomalies (%) = (No. of pups with external anomalies / No. of live pups) × 100.

Sex ratio = No. of males / No. of females.

Appendix 27-3 Observation of pups in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		10											
Animal No.		2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312
Length of gestation (days)		22	23	23	23	23	23	23	22	22	23	23	23
Corpora lutea		22	22	16	11	18	20	28	15	25	19	18	17
Implantation scars		12	7	14	11	13	16	17	14	15	7	16	14
Implantation index (%)		54.5	31.8	87.5	100	72.2	80.0	60.7	93.3	60.0	36.8	88.9	82.4
Pups born		12	5	13	11	10	14	13	14	15	6	14	11
Stillbirths		0	0	0	0	0	0	0	0	0	0	0	0
Male		0	0	0	0	0	0	0	0	0	0	0	0
Female		0	0	0	0	0	0	0	0	0	0	0	0
Unknown		0	0	0	0	0	0	0	0	0	0	0	0
Male		8	2	6	3	4	8	8	11	9	4	10	8
Female		4	3	7	8	6	6	5	3	6	2	4	3
Total		12	5	13	11	10	14	13	14	15	6	14	11
Delivery index (%)		100	71.4	92.9	100	76.9	87.5	76.5	100	100	85.7	87.5	78.6
Birth index (%)		100	71.4	92.9	100	76.9	87.5	76.5	100	100	85.7	87.5	78.6
Embryonic loss before implantation (%)		45.5	68.2	12.5	0	27.8	20.0	39.3	6.7	40.0	63.2	11.1	17.6
Embryonic loss after implantation (%)		0	28.6	7.1	0	23.1	12.5	23.5	0	0	14.3	12.5	21.4
Live birth index (%)		100	100	100	100	100	100	100	100	100	100	100	100
Live pups on day 4 of lactation		8	2	6	3	4	8	8	11	9	4	10	8
Male		4	3	7	8	6	6	5	3	6	2	4	3
Female		12	5	13	11	10	14	13	14	15	6	14	11
Total		100	100	100	100	100	100	100	100	100	100	100	100
Viability index (%)		0	0	0	0	0	0	0	0	0	0	0	0
External anomalies		0.67	0.40	0.46	0.27	0.40	0.57	0.62	0.79	0.60	0.67	0.71	0.73
Sex ratio at birth		0.67	0.40	0.46	0.27	0.40	0.57	0.62	0.79	0.60	0.67	0.71	0.73
Sex ratio on day 4 of lactation		0.67	0.40	0.46	0.27	0.40	0.57	0.62	0.79	0.60	0.67	0.71	0.73
Body weight of pups (g)													
Male Day 0		6.8	7.5	7.8	7.8	7.5	7.0	6.8	6.3	5.8	9.2	7.5	7.6
4		10.8	13.5	12.3	12.1	10.4	9.5	11.3	10.1	8.9	15.8	11.6	12.2
Female Day 0		6.3	6.9	7.2	7.4	6.9	6.1	6.5	5.6	5.5	8.8	7.4	6.9
4		9.9	12.1	11.9	12.0	9.7	8.3	11.0	9.3	8.4	15.0	10.7	12.1

Implantation index (%) = (No. of implantation scars / No. of corpora lutea) × 100.

Delivery index (%) = (No. of pups born / No. of implantation scars) × 100.

Birth index (%) = (No. of live pups born / No. of implantation scars) × 100.

Embryonic loss before implantation (%) = ((No. of corpora lutea - No. of implantation scars) / No. of corpora lutea) × 100.

Embryonic loss after implantation (%) = ((No. of implantation scars - No. of live pups born) / No. of implantation scars) × 100.

Live birth index (%) = (No. of live pups born / No. of pups born) × 100.

Viability index (%) = (No. of live pups on day 4 / No. of live pups born) × 100.

External anomalies (%) = (No. of pups with external anomalies / No. of live pups) × 100.

Sex ratio = No. of males / No. of males and females.

Appendix 27-4 Observation of pups in combined repeat dose and reproductive/developmental toxicity screening test of *N,N*-dimethylaniline by oral administration

Dose (mg/kg/day)		100											
Animal No.		2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412
Length of gestation (days)		23	22	22	22	22	22	23	23	22	22	23	22
Corpora lutea		27	16	19	19	18	17	15	27	15	20	16	19
Implantation scars		13	13	13	15	12	15	12	16	14	15	14	14
Implantation index (%)		48.1	81.3	68.4	78.9	66.7	88.2	80.0	59.3	93.3	75.0	87.5	73.7
Pups born		11	13	13	13	12	14	10	11	14	12	13	12
Stillbirths	Male	0	0	0	0	0	0	0	0	0	0	0	0
	Female	0	0	0	0	0	0	0	0	0	0	0	0
	Total	0	0	0	0	0	0	0	0	0	0	0	0
Live pups born	Male	4	7	6	6	5	4	2	4	4	4	5	4
	Female	7	6	7	7	7	10	8	7	10	8	8	8
	Total	11	13	13	13	12	14	10	11	14	12	13	12
Delivery index (%)		84.6	100	100	86.7	100	93.3	83.3	68.8	100	80.0	92.9	85.7
Birth index (%)		84.6	100	100	86.7	100	93.3	83.3	68.8	100	80.0	92.9	85.7
Embryonic loss before implantation (%)		51.9	18.8	31.6	21.1	33.3	11.8	20.0	40.7	6.7	25.0	12.5	26.3
Embryonic loss after implantation (%)		15.4	0	0	13.3	0	6.7	16.7	31.3	0	20.0	7.1	14.3
Live birth index (%)		100	100	100	100	100	100	100	100	100	100	100	100
Live pups on day 4 of lactation	Male	4	7	6	5	5	4	2	4	4	4	4	4
	Female	4	6	7	7	7	7	8	6	10	8	6	8
	Total	8	13	13	12	12	11	10	10	14	12	10	12
Viability index (%)		72.7	100	100	92.3	100	78.6	100	90.9	100	100	76.9	100
External anomalies		0	0	0	0	0	0	0	0	0	0	0	0
Sex ratio at birth	Stillbirths included	0.36	0.54	0.46	0.38	0.42	0.29	0.20	0.36	0.29	0.33	0.31	0.33
Sex ratio at birth	Stillbirths declined	0.36	0.54	0.46	0.46	0.42	0.29	0.20	0.36	0.29	0.33	0.38	0.33
Sex ratio on day 4 of lactation		0.50	0.54	0.46	0.42	0.42	0.36	0.20	0.40	0.29	0.33	0.40	0.33
Body weight of pups (g)													
	Male Day 0	5.8	6.5	6.5	6.1	6.8	6.4	7.8	6.3	6.3	6.6	7.2	6.4
	4	9.3	8.8	10.2	9.2	10.4	9.7	12.2	9.5	9.9	10.7	12.6	10.6
	Female Day 0	5.7	6.2	6.1	5.5	6.2	6.3	7.3	6.3	5.9	6.0	6.5	6.4
	4	9.9	8.5	9.5	7.8	9.5	9.5	11.7	10.5	9.1	10.2	11.3	10.3

Implantation index (%) = (No. of implantation scars / No. of corpora lutea) × 100.

Delivery index (%) = (No. of pups born / No. of implantation scars) × 100.

Birth index (%) = (No. of live pups born / No. of implantation scars) × 100.

Embryonic loss before implantation (%) = ((No. of corpora lutea - No. of implantation scars) / No. of corpora lutea) × 100.

Embryonic loss after implantation (%) = ((No. of implantation scars - No. of live pups born) / No. of implantation scars) × 100.

Live birth index (%) = (No. of live pups born / No. of pups born) × 100.

Viability index (%) = (No. of live pups on day 4 / No. of live pups born) × 100.

External anomalies (%) = (No. of pups with external anomalies / No. of live pups) × 100.

Sex ratio = No. of males / No. of males and females.