
1,4-ジクロロブタンのラットを用いる 28 日間反復経口投与毒性試験及び
14 日間回復試験

最 終 報 告 書

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株式会社日本バイオリサーチセンター
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2. 試験責任者陳述書

試験番号 : 502427

表 題：1,4-ジクロロブタンのラットを用いる 28 日間反復経口投与毒性試験及び 14 日間回復試験

本試験は、新規化学物質等に係る試験を実施する試験施設に関する基準について（平成 15 年 11 月 21 日、薬食発第 1121003 号、平成 15・11・17 製局第 3 号、環保企発第 031121004 号、平成 20 年 7 月 4 日最終改正）及び OECD PRINCIPLES OF GOOD LABORATORY PRACTICE (OECD 化学物質の安全性試験の実施に関する基準、1997 年 11 月 26 日) に従って実施したものである。

2011 年 9 月 13 日

株式会社日本バイオリサーチセンター 羽島研究所

試験責任者
[REDACTED]

3. 最終報告書作成者署名

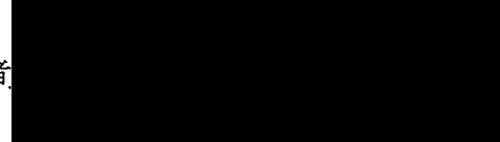
試験番号 : 502427

表　題：1,4-ジクロロブタンのラットを用いる 28 日間反復経口投与毒性試験及び 14 日間回復
試験

2011 年 9 月 13 日

株式会社日本バイオリサーチセンター 羽島研究所

試験責任者



4. 試験概要

試験番号 : 502427

表題 : 1,4-ジクロロブタンのラットを用いる 28 日間反復経口投与毒性試験及び 14 日間回復試験

試験委託者 : 厚生労働省 医薬食品局審査管理課 化学物質安全対策室
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試験施設 : 株式会社日本バイオリサーチセンター 羽島研究所
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試験目的 : 1,4-ジクロロブタンが継続的に人に摂取された場合の健康への影響を推定するため、1,4-ジクロロブタンを雌雄ラットに 28 日間反復経口投与し、さらに一部の動物には 14 日間の回復期間を設けた反復投与による毒性学的影響を検討した。

準拠したガイドライン :

新規化学物質等に係る試験の方法について(平成 15 年 11 月 21 日、薬食発第 1121002 号、平成 15・11・13 製局第 2 号、環保企発第 031121002 号、平成 18 年 11 月 20 日最終改正)及び OECD Guideline for Testing of Chemicals for Repeated Dose 28-day Oral Toxicity Study in Rodents (407)

遵守した GLP :

新規化学物質等に係る試験を実施する試験施設に関する基準について(平成 15 年 11 月 21 日、薬食発第 1121003 号、平成 15・11・17 製局第 3 号、環保企発第 031121004 号、平成 20 年 7 月 4 日最終改正)及び OECD PRINCIPLES OF GOOD LABORATORY PRACTICE (OECD 化学物質の安全性試験の実施に関する基準、1997 年 11 月 26 日)

遵守した動物の福祉に関する法令など :

法律第 105 号(昭和 48 年 10 月 1 日、平成 11 年 12 月 22 日一部改正、平成 17 年 6 月 22 日一部改正)「動物の愛護及び管理に関する法律」、環境省告示第 88 号(平成 18 年 4 月 28 日)「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」、厚生労働省通知 科発第 0601005 号(平成 18 年 6 月 1 日)「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針について」及び株式会社日本バイオリサーチセンター 羽島研究所「動物実験倫理委員会規則」

本試験は、試験施設の動物実験倫理委員会で審査され、試験施設の運営管理者により承認されたものである。

試験開始日：2008年9月19日

試験終了日：2011年9月13日

試験実施日：

動物入手日	2008年9月24日
雄の群分け日	2008年10月6日
実験開始日(雄の投与開始日)	2008年10月7日
雌の群分け日	2008年10月8日
雌の投与開始日	2008年10月9日
雄の投与期間終了日	2008年11月3日
雄投与期間終了時の剖検日	2008年11月4日
雌の投与期間終了日	2008年11月5日
雌投与期間終了時の剖検日	2008年11月6日
雄回復期間終了時の剖検日	2008年11月18日
雌回復期間終了時の剖検日	2008年11月20日
実験終了日(病理組織所見最終化日)	2009年2月18日

資料、標本及び保管すべき被験物質の保管場所：

資料(試験計画書の原本、生データ、最終報告書の原本)、標本及び保管すべき被験物質は試験施設の資料保存施設に最終報告書提出後10年間保管する。その後の処置は、試験委託者と協議の上、決定する。

SOP及び試験計画書に従わなかったこと：

SOP又は試験計画書に従わなかったことはなかった。

予見することができなかつた試験の信頼性に影響を及ぼす疑いのある事態：

当試験の実施期間中に予見することができなかつた試験の信頼性に影響を及ぼす疑いのある事態は認められなかつた。

5. 試験従事者及び業務分担

試験責任者 : [REDACTED]

(試験計画書の承認, 試験実施の指示, 尿検査, 血液学検査, 血液生化学検査, データの確認, 最終報告書の作成)

試験従事者 : [REDACTED]

(検体の投与, 一般状態観察, 行動機能観察, 感覚反応検査, 握力測定, 自発運動量測定, 尿量測定, 動物の一般飼育管理)

[REDACTED]
[REDACTED]
(剖検, 病理組織標本作製, 病理組織学検査)

[REDACTED]
[REDACTED]
(尿検査, 血液学検査, 血液生化学検査)

[REDACTED]
[REDACTED]
(被験物質の管理, 投与検体の調製)

[REDACTED]
[REDACTED]
(投与検体中の被験物質濃度の測定)

[REDACTED]
[REDACTED]
(統計処理)

6. 要約

1,4-ジクロロブタンが継続的に人に摂取された場合の健康への影響を推定するために、1,4-ジクロロブタンを雌雄ラットに28日間反復経口投与し、さらに一部の動物には14日間の回復期間を設けた反復投与による毒性学的影響を検討した。投与量は、300 mg/kg を高用量とし、以下、60及び12 mg/kg を設定した。媒体にはトウモロコシ油を用い、対照群には被験物質投与群と同容量のトウモロコシ油を投与した。各群の使用動物数は対照群及び300 mg/kg 群を雌雄各12例とし、各群ともそのうち半数を回復群とした。60及び12 mg/kg 群は雌雄各6例とした。

1) 一般状態及び死亡状況

死亡例は、雌雄とも認められなかった。一般状態では、雌雄とも300 mg/kg 群で投与後に一過性の流涎がみられたが毒性症状とはみなされなかった。

2) 体重、摂餌量及び摂水量

体重及び摂餌量では、雌雄のいずれの投与群とも投与に起因する変化は認められなかった。

摂水量では、雌雄とも300 mg/kg 群でほぼ投与期間を通して高値がみられた。回復期間中には、雌雄とも投与に起因する変化は認められなかった。

3) 行動機能 (FOB), 感覚反応, 握力及び自発運動量

行動機能 (FOB) 観察、感覚反応検査、握力測定及び自発運動量測定では、雌雄のいずれの投与群とも投与に起因する変化はみられなかった。

4) 尿検査、血液学検査及び血液生化学検査

尿検査において、投与期間終了時に雄では300 mg/kg 群で摂水量の増加に起因した尿量の高値がみられたが、雌ではいずれの投与群とも投与に起因する変化は認められなかった。回復期間終了時の尿検査では、雌雄とも投与に起因する変化は認められなかった。

血液学検査において、投与期間終了時に雄では300 mg/kg 群で単球比率の高値がみられたが、雌ではいずれの投与群とも投与に起因する変化は認められなかった。回復期間終了時には、雌雄とも投与に起因する変化は認められなかった。

血液生化学検査において、投与期間終了時に雄の300 mg/kg 群で γ -GTP、尿素窒素及び無機リンの高値、雌の300 mg/kg 群で γ -GTP 及び無機リンの高値、雌の300 及び60 mg/kg 群で尿素窒素の高値傾向又は高値がみられた。回復期間終了時には、雌雄とも投与に起因する変化は認められなかった。

5) 剖検所見及び器官重量

剖検において、投与期間終了時に雌雄とも300 及び60 mg/kg 群で肝臓の褪色がみられた。回復期間終了時には、雌雄とも投与に起因する変化は認められなかった。

器官重量において、投与期間終了時に雄の300 mg/kg 群で下垂体、肝臓及び腎臓の絶対重量及

び相対重量の高値、雌では 300 及び 60 mg/kg 群で肝臓の絶対重量及び相対重量の高値、300 mg/kg 群で腎臓の絶対重量及び相対重量の高値がみられた。回復期間終了時には、雌雄とも投与に起因する変化は認められなかった。

6) 病理組織学検査

投与期間終了時には、雄では、肝臓に門脈周囲性の肝細胞腫大及び脾臓にチモーゲン顆粒の減少が 300, 60 及び 12 mg/kg 群、胸腺に星空像及び腎臓に近位尿細管腫大が 300 mg/kg 群、肝臓に微小肉芽腫が 300 及び 60 mg/kg 群でみられた。雌では、肝臓に門脈周囲性の肝細胞腫大及び脾臓にチモーゲン顆粒の減少が 300, 60 及び 12 mg/kg 群、胸腺に星空像が 300 mg/kg 群、腎臓に近位尿細管の腫大が 300 及び 60 mg/kg 群、肝臓に微小肉芽腫が 300 mg/kg 群でみられた。

回復期間終了時には、雄では投与に起因する変化は認められなかった。雌では、肝臓に門脈周囲性の肝細胞腫大が 300 mg/kg 群でみられた。

以上のように、1,4-ジクロロブタンの無影響量は、雌雄とも 12 mg/kg 投与により肝臓に門脈周囲性の肝細胞腫大及び脾臓にチモーゲン顆粒の減少が認められたことから、12 mg/kg/day 未満と考えられる。

7. 緒言

1,4-ジクロロブタンが継続的に人に摂取された場合の健康への影響を推定するために、新規化物質等に係る試験の方法について（平成 15 年 11 月 21 日、薬食発第 1121002 号、平成 15・11・13 製局第 2 号、環保企発第 031121002 号、平成 18 年 11 月 20 日最終改正）及び OECD Guideline for Testing of Chemicals for Repeated Dose 28-day Oral Toxicity Study in Rodents (407)に基づいて 1,4-ジクロロブタンを雌雄ラットに 28 日間反復経口投与し、さらに一部の動物には 14 日間の回復期間を設けた反復投与による毒性学的影響を検討した。

8. 方法

8.1. 被験物質及び媒体

被験物質 1,4-ジクロロブタン（英語名称: 1,4-dichlorobutane, CAS No. 110-56-5, Fig. 1）は、化学式: $\text{Cl}(\text{CH}_2)_4\text{Cl}$, 分子量: 127.01, 物性・性状: 無色透明液体, 引火点: 53°C, 発火点: 220°C, 沸点: 155°C, 比重: 1.14 である¹⁾. 当試験には [製造元: [REDACTED] Lot No. [REDACTED] 純度 (GC): 99.8%]. 入手後は、被験物質保管室の保管庫に冷蔵・遮光・密閉の条件下で保管した。被験物質を保管した保管庫（冷蔵庫: BMS-500F3, 日本フリーザー株式会社）の温度 [設定温度: 4°C (許容範囲: 2.0~8.0°C; 実測値: 2.1~6.4°C)] に問題はなかった。

投与期間終了後、試験施設で保管する被験物質 (1.0001 g) を除いた残余被験物質は製造元に返却した。

当試験の投与期間終了後に実施した試験施設で保管した被験物質 (Lot No. FGH02) の品質試験成績から、使用期間中の安定性が確認された。

媒体には、トウモロコシ油（以下、Corn oil, Lot No.: V8K7807, 使用期限: 2013 年 9 月 8 日, 製造元: ナカライトスク株式会社, 保管条件: 室温, 保管場所: 被験物質保管室の保管庫）を用いた。Corn oil を保管した被験物質保管室の保管庫の温度 [設定温度: 23°C (許容範囲: 18.0~28.0°C; 実測値: 22.0~24.5°C)] 及び湿度 [設定湿度: 55% (許容範囲: 40.0~70.0%; 実測値: 49.9~61.1%)] に問題はなかった。

8.2. 投与検体及び濃度測定

最高濃度の投与検体を調製するために、1,4-ジクロロブタンの必要量（純度による補正は実施しなかった）を秤取（電子天秤: PM2500, メトラー・トレド株式会社）後、Corn oil で 60 mg/mL 濃度となるように溶解し、調製した。12 及び 2.4 mg/mL 濃度の各投与検体は、60 mg/mL 濃度液を Corn oil で段階希釈して調製した。

調製検体の安定性については、2, 20 及び 200 mg/mL の濃度で調製後、冷蔵（設定温度 4°C, 冷蔵庫: BMS-500F3, 日本フリーザー株式会社）遮光 8 日間とその後、室温（設定温度: 23°C）・遮光で 6 時間まで問題がないことが確認されている²⁾（Attachment 1）。従って、各投与検体は、ディスポーザブルポリプロピレン製容器に 1 日分ごとに小分け後、冷蔵（冷蔵庫: BMS-500F3, 日本フリ

一ザー株式会社)・遮光の条件下で保管し、調製後 7 日以内に使用した。各投与検体を保管した冷蔵庫の温度 [設定温度: 4°C (許容範囲: 2.0~8.0°C; 実測値: 3.5~5.8°C)] に問題はなかった。保管した各投与検体は、冷蔵庫から持ち出し後 4 時間 52 分以内に使用した。

雄投与開始日 (投与 1 日) 及び雌投与終了日に使用した各投与検体中の被験物質濃度をガスクロマトグラフ (GC-2010, 株式会社島津製作所) で測定した。その結果、被験物質濃度は表示濃度の 94.5~102.7% であり、規定値 ($100 \pm 10\%$) の範囲内であった (Attachments 2 及び 3)。

8.3. 試験動物及び飼育条件

8.3.1. 動物種及び系統

試験には、毒性試験に一般的に用いられている動物種で、その系統維持が明らかである Crl:CD (SD) 雌雄ラット (SPF) を用いた。動物は、2008 年 9 月 24 日に日本チャールス・リバー株式会社 日野飼育センターから 4 週齢で雌雄各 44 匹を入手した。入手後 1 日の体重範囲は、雄が 86~95 g、雌が 64~75 g であった。

8.3.2. 検疫及び馴化、群分け並びに個体識別

入手した動物には、検疫期間 (2008 年 9 月 24 日~29 日) と馴化期間 (雄: 2008 年 9 月 30 日~2008 年 10 月 6 日、雌: 2008 年 9 月 30 日~2008 年 10 月 8 日) を設け、この間に一般状態の観察を 1 日 1 回、体重測定 (電子天秤: PG2002-S 又は PB3002、メトラー・トレド株式会社) を雄は 3 回と雌は 4 回、行動機能 (FOB) 観察を 1 回行った。検疫・馴化期間中の一般状態及び体重推移に異常が認められなかった動物を群分けした (Attachments 4-1, 4-2, 5-1, 5-2, 6-1, 6-2, 7-1 及び 7-2)。

投与開始前日に、コンピュータを用いて体重を層別に分けた後に無作為抽出法により各群の平均体重及び分散がほぼ等しくなるように群分けした。但し、個々の動物の体重が平均値の $\pm 20\%$ 以内にあるものを選んで群分けした。群分け日の体重範囲は、雄が 173~207 g、雌が 132~179 g であった。群分け残余雄のうち、検疫・馴化動物番号の若い順に 2 匹を雌の回復期間終了日に実施した微生物モニタリング検査用動物とした。微生物モニタリング検査において、感染を示唆するような異常はみられなかった。群分け残余雄のうち微生物モニタリング検査に用いなかった雄及び群分け残余雌は、群分け日にジエチルエーテルによる麻酔下で腹大動脈から放血して安楽死させた。

動物の個体識別は、動物入手日に黒色油性インクを用いて尾へ検疫・馴化動物番号 (下 3 行) を記入して行った。

動物の検疫・馴化期間中の各ケージには試験番号、入手年月日及び検疫・馴化動物番号を記入したラベルを、群分け後の各ケージには試験番号、投与量、検疫・馴化動物番号及び動物番号を記入し、群ごとに色分けしたラベルをそれぞれ取り付けた。なお、FOB 観察は Blind で検査したため、検疫・馴化期間中のラベルを取り付けた。

8.3.3. 環境条件及び飼育管理

動物は、設定温度: 23°C、設定湿度: 55%、明暗各 12 時間 (照明: 午前 6 時~午後 6 時)、換気回数 12 回/時 (中性能フィルターを通した新鮮空気) に維持された動物飼育室 (E 棟 5 号室、但し、

検疫期間中は E 棟 7 号室) で飼育した。動物飼育室の温度 (許容範囲: 20.0~26.0°C; 実測値: 21.6~22.9°C) 及び湿度 (許容範囲: 40.0~70.0%; 実測値: 42.5~59.4%) に問題はなかった。

動物は、検疫・馴化期間中はステンレス製懸垂式ケージ (W: 240 × D: 380 × H: 200 mm) を用いて 1 ケージ当たり 2 匹の雌雄別群飼育とし、群分け後はステンレス製懸垂式ケージを用いて個別飼育した。ステンレス製懸垂式ケージ及び給餌器の交換は 2 週間に 1 回以上行い、給水瓶及びステンレス製懸垂式ケージの受皿の交換は 1 週間に 2 回以上行った。動物飼育室の清掃 (床の掃き掃除) 及び 0.02% 次亜塩素酸ナトリウム水溶液での床のモップ拭きによる消毒は毎日 1 回実施した。

8.3.4. 飼料及び飲料水

飼料は製造後 5 箇月以内の固型飼料 (CRF-1, オリエンタル酵母工業株式会社) を自由に摂取させた。但し、剖検前日には午後 4 時頃から給水・絶食させた。使用した飼料と同一ロットの分析結果は、Eurofins Scientific Analytics 及びオリエンタル酵母工業株式会社で実施したもの入手した。飼料の分析結果は、当試験施設で設定した基準値の範囲内であった。

飲料水は水道水を自由に摂取させた。飲料水の水質検査結果は、株式会社環境公害センターで約 6 箇月ごとに実施したもの入手した。飲料水の分析結果は、当試験施設で設定した基準値の範囲内であった。

8.4. 投与経路、投与方法、群構成、投与量及び投与期間

8.4.1. 投与経路及び投与方法

1,4-ジクロロブタンは、継続して経口的に人に摂取される可能性が考えられるため、投与経路として経口を選択した。

投与は、ディスポーザブルラット用金属製経口胃ゾンデ (有限会社フチガミ器械) を取り付けたディスポーザブルポリプロピレン製注射筒 (テルモ株式会社) を用いて強制的に行った。

投与液量は、投与日に最も近い測定日の体重を基準とし、5 mL/kg/day で算出した。

投与時刻は午前 8 時 30 分~11 時 51 分までの間で、投与回数は 1 日 1 回とした。

投与開始日の週齢は雌雄とも 6 週齢であり、体重範囲は雄が 188~211 g、雌が 140~167 g であった。

8.4.2. 群構成及び投与量

群構成は、以下に示したように被験物質投与群として3群を設定し、その他に対照群を設けた。各群の動物数は、対照群及び300 mg/kg群を雌雄各12例、60及び12 mg/kg群を雌雄各6例とした。

群	投与量 (mg/kg/day)	濃度 (mg/mL)	ラベル の色	動物数(動物番号)	
				雄	雌
1群 対照 (Corn oil)	0	0	白色	6 ^{1]} +6 ^{2]} (M01101～M01112)	6 ^{1]} +6 ^{2]} (F01151～F01162)
2群 1,4-ジクロロブタン	12	2.4	茶色	6 ^{1]} (M02201～M02206)	6 ^{1]} (F02251～F02256)
3群 1,4-ジクロロブタン	60	12	青色	6 ^{1]} (M03301～M03306)	6 ^{1]} (F03351～F03356)
4群 1,4-ジクロロブタン	300	60	紫色	6 ^{1]} +6 ^{2]} (M04401～M04412)	6 ^{1]} +6 ^{2]} (F04451～F04462)

^{1]}投与期間終了時に剖検

^{2]}回復期間終了時に剖検

1,4-ジクロロブタンの投与量は、当試験の予備試験³⁾（投与段階: 0, 100, 200, 500 及び 1000 mg/kg, 使用動物数: 各群雌雄各5例）の結果から決定した。すなわち、予備試験において 1000 mg/kg群の雌で瀕死例及び死亡例が各1例認められた。雄では瀕死及び死亡例はいずれの群にも認められなかった。一般状態において、流涎が 1000 及び 500 mg/kg群の雌雄でみられた。体重の有意な低値が 1000 及び 500 mg/kg群の雌雄、摂餌量の有意な低値が 1000 mg/kg群の雌雄及び 500 mg/kg群の雌でみられた。ヘモグロビン量の有意な低値が 1000 mg/kg群の雄、血小板数の有意な低値が 1000 mg/kg群の雌雄でみられた。ALTの有意な高値が 500 mg/kg群の雌雄、γ-GTPの有意な高値が 1000 mg/kg群の雄及び 500 及び 200 mg/kg群の雌、総コレステロールの有意な高値が 1000 mg/kg群の雄、トリグリセライドの有意な高値が 500 mg/kg群の雌でみられた。肝臓の褪色が 1000, 500 及び 200 mg/kg群の雌雄と 100 mg/kg群の雌、胸腺の小型が 1000 mg/kg群の雌雄でみられた。胸腺の絶対重量及び相対重量の有意な低値が 1000 mg/kg群の雌雄、肝臓の絶対重量の有意な高値が 500 mg/kg群の雌雄と 200 及び 100 mg/kg群の雌、肝臓の相対重量の有意な高値が 1000, 500, 200 及び 100 mg/kg群の雌雄、腎臓の相対重量の有意な高値が 1000, 500 及び 200 mg/kg群の雌雄でみられた。そこで、本試験では、300 mg/kgを高用量とし、以下公比5で60及び12 mg/kgの3投与群を設定した。

対照として媒体 (Corn oil) のみを被験物質投与群と同容量投与する群を設けた。

8.4.3. 投与期間

投与期間は、新規化学物質等に係る試験の方法について(平成 15 年 11 月 21 日、薬食発第 1121002 号、平成 15・11・13 製局第 2 号、環保企発第 031121002 号、平成 18 年 11 月 20 日最終改正)及びOECD Guideline for Testing of Chemicals for Repeated Dose 28-day Oral Toxicity Study in Rodents (407)に従って、雌雄とも 28 日間とした。28 日間の投与後に、対照群及び 300 mg/kg 群

の雌雄各半数の動物について 14 日間の回復期間を設けた。

投与開始日を投与 1 日と規定し、最終投与の翌日を回復 1 日とした。

8.5. 観察及び検査項目

8.5.1. 一般状態

死亡の有無の確認及び一般状態の観察は、投与期間中に投与前及び投与後の 1 日 2 回、回復期間中に毎日 1 回及び剖検日に 1 回行った。

8.5.2. 体重

体重は、1 週間に 2 回測定した [測定日：投与 1, 4, 8, 11, 15, 18, 22, 25, 28 日及び 29 日 (回復 1 日), 回復 4, 8, 11, 14 及び 15 日 (電子天秤：PB3002, PG2002-S 又は PB3002-S/FACT, メトラー・トレド株式会社)]。

8.5.3. 摂餌量

摂餌量は、1 週間に 2 回 1 日量を測定した [残量測定日：投与 2, 5, 9, 12, 16, 19, 23 及び 26 日, 回復 2, 5, 9 及び 12 日 (電子天秤：PB3002, PG2002-S 又は PB3002-S/FACT, メトラー・トレド株式会社)]。摂餌量の Tables, Figs 及び Appendices の表示は残量の測定日とした。

8.5.4. 摂水量

摂水量は、1 週間に 2 回 1 日量を測定した [残量測定日：投与 2, 5, 9, 12, 16, 19, 23 及び 26 日, 回復 2, 5, 9 及び 12 日 (電子天秤：PB3002, PG2002-S 又は PB3002-S/FACT, メトラー・トレド株式会社)]。摂水量の Tables, Figs 及び Appendices の表示は残量の測定日とした。

8.5.5. FOB

全例について投与開始前 (雄は投与開始 4 日前, 雌は投与開始 3 日前), 投与期間終了時剖検例について投与 7, 14, 21 及び 27 日に下記の 1)～3) の項目を観察した。観察時刻は、投与後 1 時間とした。なお、観察者はほぼ固定し、Blind で実施した。

- 1) 姿勢, 眼瞼閉鎖状態, かみつき行動及び痙攣はケージ内で観察した。
- 2) ケージからの出し易さ, 扱い易さ, 筋の緊張, 毛の状態, 流涙, 流涎及び呼吸は手を持って観察した。
- 3) 立ち上がり回数及び毛づくろい回数はオープンフィールド内で 2 分間観察した。また、同時に歩行状態, 眼瞼閉鎖状態, 觉醒度, 行動異常及び正向反射をオープンフィールド内で観察した。

8.5.6. 感覚反応

投与期間終了時剖検例について、投与 27 日の FOB 観察後に瞳孔反射, 接近反射, 触覚反射, 聴覚反射及び痛覚反射を作業台の上で検査した。

8.5.7. 握力

投与期間終了時剖検例について、投与 27 日の感覚反応検査終了後に Animal Grip Strength System (San Diego Instruments Inc.) を用いて、前肢及び後肢の握力を 5 回測定し、最高値と最低値を除いた中央の 3 測定値の平均値を採用した。

8.5.8. 自発運動量

投与期間終了時剖検例について、投与 26 日に Activity Monitor (MED Associates Inc.) を使用し、歩行量及び立ち上がり回数について投与後 1 時間から 2 時間まで 10 分間隔で測定した。

8.5.9. 尿検査

投与期間終了前（投与 23 日）の投与検体投与前に投与期間終了時の剖検用動物、回復期間終了前（回復 9 日）に回復期間終了時の剖検用動物について、採尿ケージを用いて絶食・給水下で新鮮尿を採取した。その後、引き続いて給餌・給水下で 24 時間尿を採取した。採取した尿について、以下の検査を実施した。検査後の尿は廃棄した。

新鮮尿：色調は、外観判定とした。pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血及びウロビリノーゲンは、尿検査試験紙（シーメンスメディカルソリューションズ・ダイアグノスティクス株式会社）に尿を滴下後、反射分光光度法により尿化学分析装置（クリニテック アドバンタス、シーメンスメディカルソリューションズ・ダイアグノスティクス株式会社）を用いて検査した。尿沈渣は、沈渣を尿沈渣染色液（新 Sternheimer 法、シスマックス株式会社）で染色後に顕微鏡下で観察した。

24 時間尿：尿量 (UV) は、尿比重 (S.G) と重量 (電子天秤: PB3002 又は PB3002-S/FACT、メトラー・トレド株式会社) から算出した。尿比重は、屈折率により屈折型尿比重計 (ユリペット-II D、株式会社ニコン) を用いて測定した。

8.5.10. 血液学検査

最終投与の翌日（投与 29 日）及び回復期間終了後（回復 15 日）にペントバルビタールナトリウムの腹腔内投与 (40 mg/kg) による麻酔下で腹大動脈から EDTA-2K コーティングチューブ（ベノジェクト[®]II 真空採血管、VP-DK052K05、テルモ株式会社）に血液を採取し、以下の血液学検査を実施した。測定後の残余血液は廃棄した。

赤血球数 (RBC) はシースフローDC 検出法、ヘモグロビン量は SLS ヘモグロビン法、ヘマトクリット値は赤血球パルス波高値検出法、血小板数はシースフローDC 検出法、白血球数 (WBC)、白血球分類及び網状赤血球比率はフローサイトメトリー法によりいずれも多項目自動血球分析装置 (XT-2000iV、シスマックス株式会社) を用いて測定した。平均赤血球容積 (MCV) は赤血球数とヘマトクリット値から、平均赤血球血色素量 (MCH) は赤血球数とヘモグロビン量から、平均赤血球血色素濃度 (MCHC) はヘマトクリット値とヘモグロビン量から多項目自動血球分析装置 (XT-2000iV、シスマックス株式会社) を用いて算出した。

プロトロンビン時間 (PT)、活性化部分トロンボプラスチン時間 (APTT) 及びフィブリノーゲン濃度は、血液を 3.2 w/v% クエン酸ナトリウムで処理後、遠心分離 [約 4°C, 3000 rpm (約 1972×g),

15 分間, 遠心機: CF 8DL, 日立工機株式会社] して得た血漿について, 光散乱検出方式により全自动血液凝固測定装置 (CA-530, シスメックス株式会社) を用いて測定した.

8.5.11. 血液生化学検査

血液学検査用の血液と同時期に腹大動脈から採取した血液から遠心分離 [約 4°C, 3000 rpm(約 1972×g), 15 分間, 遠心機: CF8DL, 日立工機株式会社] して得た血清は, 測定用血清と保管用血清に分けて分取して, 測定用血清について以下の血液生化学検査を実施した. 測定後の残余血清は廃棄し, 保管用血清は冷凍庫 (-80°C 設定, 超低温フリーザー: ULT1786-9JD, Kendro Laboratory Products) 内に保管した. その後, 保管用血清は再測定の必要がないことを確認後, 廃棄した.

AST は MDH-UV 法, ALT は LDH-UV 法, ALP は p-ニトロフェニルリン酸基質法, γ -GTP は L- γ -グルタミル-3-カルボキシ-4-ニトロアニリド基質法, 総蛋白は Biuret 法, 総ビリルビンはジアゾ法, 尿素窒素はウレアーゼ・GODH 法, クレアチニンはクレアチニナーゼ・F-DAOS 法, ブドウ糖はヘキソキナーゼ・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, Ca は o-CPC 法, 無機リンは PNP・XDH 法, Na, K 及び Cl はイオン選択電極法によりいずれも生化学自動分析装置 (AU 400, オリンパス株式会社) を用いて測定した.

アルブミンは総蛋白及び蛋白分画値 [電気泳動法, 自動電気泳動装置 (AES 310, オリンパス株式会社)] から, A/G (アルブミン/グロブリン) は蛋白分画値から算出した.

8.5.12. 剖検及び器官重量

上記の 8.5.10.及び 8.5.11.の項で採血した動物をさらに放血して安樂死させた後, 剖検した. 脳(大脳, 小脳, 延髄), 下垂体, 唾液腺(舌下腺・頸下腺), 甲状腺, 胸腺, 心臓, 肝臓, 脾臓, 腎臓, 副腎, 精巣, 精巣上体及び卵巣は重量を測定した(電子天秤: AB204, メトラー・トレド株式会社). 各器官重量を最終体重で除して相対重量も算出した. 下垂体及び甲状腺重量は, 20 vol% 中性緩衝ホルマリンで 1 晚固定後, 測定した. これらの器官は, 肺, 気管, 膀胱, 食道, 胃, 十二指腸, 空腸, 回腸, 盲腸, 結腸, 直腸, リンパ節(下頸・腸間膜), 膀胱, 精囊, 前立腺, 子宮, 膀胱, 上皮小体, 脊髄, 坐骨神経, 眼球, ハーダー腺, 胸骨, 大腿骨, 大腿筋, 乳腺(雌のみ)とともに 20 vol% 中性緩衝ホルマリンで固定した. ただし, 精巣及び精巣上体はブアン液で 2~3 時間固定後, 20 vol% 中性緩衝ホルマリンに再固定し, 眼球はグルタルアルデヒド・ホルマリンで 1 晚固定後, 20 vol% 中性緩衝ホルマリンに再固定した.

8.5.13. 病理組織学検査

対照群及び 300 mg/kg 群の投与期間終了時に剖検した例について, 心臓, 肺, 気管, 肝臓, 脾臓, 唾液腺(舌下腺・頸下腺), 食道, 胃, 十二指腸, 空腸, 回腸, 盲腸, 結腸, 直腸, 胸腺, 脾臓, リンパ節(下頸・腸間膜), 腎臓, 膀胱, 精巣, 精巣上体, 精囊, 前立腺, 卵巣, 子宮, 膀胱, 下垂体, 副腎, 甲状腺, 上皮小体, 脳(大脳・小脳・延髄), 脊髄, 坐骨神経, 眼球, ハーダー腺, 骨髄(胸骨・大腿骨), 骨(胸骨・大腿骨), 大腿筋, 乳腺(雌のみ)の HE 染色組織標本を作製し, 病理組織学検査を実施した. なお, 精巣については, PAS-ヘマトキシリソ染色組織標本も作製した. 300 mg/kg 群の検査において対照群と比べて異常を示す動物数に差があった肝臓, 脾臓, 胸

腺及び腎臓については、60 及び 12 mg/kg 群の雌雄並びに回復群の雌雄についても HE 染色組織標本を作製し、病理組織学検査を実施した。切り出し後の器官・組織は、10 vol%中性緩衝ホルマリンで保存した。

8.6. 統計学的方法

測定値の統計学的解析は、下記のように行った。有意水準は、両側 5%及び 1%とした。一般状態及び剖検所見は統計学的解析を行わなかった。

体重、摂餌量、摂水量、毛づくろい及び立ち上がり回数 (FOB)、握力、自発運動量、尿量、尿比重、血液学検査、血液生化学検査及び器官重量 (相対重量を含む) については、各群で平均値及び標準偏差を算出した。次に、Bartlett検定⁴⁾により分散の一様性を検定した。その結果、等分散の場合には対照群と各被験物質投与群との間でDunnett検定⁵⁾を実施した。不等分散の場合には、対照群と各被験物質投与群との間でSteel検定⁶⁾を実施した。

行動機能 (FOB)(但し、毛づくろい及び立ち上がり回数を除く) 及び感覚反応は、各群で平均値及び範囲を算出した。その後、Steel 検定を実施した。

但し、回復期間の対照群と 300 mg/kg群については、F検定⁴⁾による等分散性の検定を行い、等分散の場合にはStudentのt検定⁴⁾を行い、等分散と認められなかつた場合はAspin-Welch検定⁴⁾を用いて行った。

病理組織学検査において、300 mg/kg群で毒性学的影響が示唆され、60 及び 12 mg/kg群についても検査を実施した器官・組織の所見については、対照群との群間比較を上記のSteel検定を用いて行った。300 mg/kg群において対照群との間に有意差が認められた場合は、Cochran・Armitage の傾向検定^{7),8)}を用いて用量反応性の検定を行った。

Dunnett検定及びSteel検定には、統計パッケージSASのPROBMC関数⁹⁾を使用した。

9. 試験結果

9.1. 一般状態

9.1.1. 雄 (Table 1; Appendices 1-1 - 1-4)

死亡例及び瀕死例はいずれの群にも認められなかった.

投与期間中には、300 mg/kg 群で投与後に一過性の流涎が 12 例にみられた。60, 12 mg/kg 群及び対照群では、一般状態の異常はみられなかった。

回復期間中には、いずれの群とも一般状態の異常はみられなかった。

9.1.2. 雌 (Table 2; Appendices 2-1 - 2-4)

死亡例及び瀕死例はいずれの群にも認められなかった.

投与期間中には、300 mg/kg 群で投与後に一過性の流涎が 12 例にみられた。60, 12 mg/kg 群及び対照群では、一般状態の異常はみられなかった。

回復期間中には、いずれの群とも一般状態の異常はみられなかった。

9.2. 体重

9.2.1. 雄 (Table 3; Fig. 2; Appendices 3-1 - 3-4)

投与期間中には、各投与群とも対照群と比べて各測定日の体重に有意差はみられなかった。

回復期間中には、300 mg/kg 群で対照群と比べて各測定日の体重に有意差はみられなかった。

9.2.2. 雌 (Table 4; Fig. 3; Appendices 4-1 - 4-4)

投与期間中には、各投与群とも対照群と比べて各測定日の体重に有意差はみられなかった。

回復期間中には、300 mg/kg 群で対照群と比べて各測定日の体重に有意差はみられなかった。

9.3. 摂餌量

9.3.1. 雄 (Table 5; Fig. 4; Appendices 5-1 - 5-4)

投与期間中には、各投与群とも対照群と比べて各測定日の摂餌量に有意差はみられなかった。

回復期間中には、300 mg/kg 群で対照群と比べて各測定日の摂餌量に有意差はみられなかった。

9.3.2. 雌 (Table 6; Fig. 5; Appendices 6-1 - 6-4)

投与期間中には、各投与群とも対照群と比べて各測定日の摂餌量に有意差はみられなかった。

回復期間中には、300 mg/kg 群で対照群と比べて回復 5 日に有意な高値がみられたが、一過性の変化であることから、被験物質による影響とは判断しなかった。

9.4. 摂水量

9.4.1. 雄 (Table 7; Fig. 6; Appendices 7-1 - 7-4)

投与期間中には、300 mg/kg 群で対照群と比べて投与 9, 12, 16, 19, 23 及び 26 日に摂水量の有意な高値がみられた。60 及び 12 mg/kg 群では、対照群と比べて各測定日の摂水量に有意差は

みられなかった。

回復期間中には、300 mg/kg 群で対照群と比べて各測定日の摂水量に有意差はみられなかった。

9.4.2. 雌 (Table 8; Fig. 7; Appendices 8-1 - 8-4)

投与期間中には、300 mg/kg 群で対照群と比べて投与 9, 16, 19 及び 26 日に摂水量の有意な高値がみられた。60 及び 12 mg/kg 群では、対照群と比べて各測定日の摂水量に有意差はみられなかつた。

回復期間中には、300 mg/kg 群で対照群と比べて各測定日の摂水量に有意差はみられなかつた。

9.5. FOB

9.5.1. 雄 (Table 9; Appendices 9-1 - 9-4)

300 mg/kg 群では、流涎がみられたが、投与後の流涎が継続したものと考えられる。60 及び 12 mg/kg 群では、各測定日のいずれの項目にも異常はみられなかつた。

9.5.2. 雌 (Table 10; Appendices 10-1 - 10-4)

300 mg/kg 群では、流涎がみられたが、投与後の流涎が継続したものと考えられる。60 及び 12 mg/kg 群では、各測定日のいずれの項目にも異常はみられなかつた。

9.6. 感覚反応

9.6.1. 雄 (Table 11; Appendices 11-1 - 11-4)

各投与群とも、いずれの項目にも異常はみられなかつた。

9.6.2. 雌 (Table 12; Appendices 12-1 - 12-4)

各投与群とも、いずれの項目にも異常はみられなかつた。

9.7. 握力

9.7.1. 雄 (Table 13; Appendices 13-1 - 13-4)

各投与群とも、対照群と比べて前肢及び後肢の握力に有意差はみられなかつた。

9.7.2. 雌 (Table 14; Appendices 14-1 - 14-4)

各投与群とも、対照群と比べて前肢及び後肢の握力に有意差はみられなかつた。

9.8. 自発運動量

9.8.1. 雄 (Table 15; Appendices 15-1 - 15-4)

300 及び 60 mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかつた。12 mg/kg 群では、立ち上がり回数(総数)の有意な高値がみられたが、投与量に関連しない変化であることから、被験物質による影響とは判断しなかつた。

9.8.2. 雌 (Table 16; Appendices 16-1 - 16-4)

各投与群とも、対照群と比べて各測定項目に有意差はみられなかった。

9.9. 尿検査

9.9.1. 投与期間終了時雄 (Table 17; Appendices 17-1 - 17-4)

300 mg/kg 群では、対照群と比べて尿量の有意な高値がみられた。60 及び 12 mg/kg 群では、対照群と比べて尿量及び尿比重に有意差はみられなかった。

各投与群とも、色調、pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血、ウロビリノーゲン及び沈渣は対照群とほぼ同程度であった。

9.9.2. 投与期間終了時雌 (Table 18; Appendices 18-1 - 18-4)

各投与群とも、対照群と比べて尿量及び尿比重に有意差はみられなかった。

各投与群とも、色調、pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血、ウロビリノーゲン及び沈渣は対照群とほぼ同程度であった。

9.9.3. 回復期間終了時雄 (Table 19; Appendices 19-1, 19-2)

300 mg/kg 群では、対照群と比べて尿量及び尿比重に有意差はみられなかった。

300 mg/kg 群では、色調、pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血、ウロビリノーゲン及び沈渣は対照群とほぼ同程度であった。

9.9.4. 回復期間終了時雌 (Table 20; Appendices 20-1, 20-2)

300 mg/kg 群では、対照群と比べて尿量及び尿比重に有意差はみられなかった。

300 mg/kg 群では、色調、pH、蛋白質、ブドウ糖、ケトン体、ビリルビン、潜血、ウロビリノーゲン及び沈渣は対照群とほぼ同程度であった。

9.10. 血液学検査

9.10.1. 投与期間終了時雄 (Table 21; Appendices 21-1 - 21-4)

300 mg/kg 群では、対照群と比べて単球比率の有意な高値がみられた。60 mg/kg 群では、対照群と比べて MCV の有意な高値がみられたが、投与量に関連した変化ではないことから、被験物質による影響とは判断しなかった。12 mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかった。

9.10.2. 投与期間終了時雌 (Table 22; Appendices 22-1 - 22-4)

60 mg/kg 群では、対照群と比べてフィブリノーゲン濃度の有意な低値がみられたが、投与量に関連した変化ではないことから、被験物質による影響とは判断しなかった。300 及び 12 mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかった。

9.10.3. 回復期間終了時雄 (Table 23; Appendices 23-1, 23-2)

300 mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかった。

9.10.4. 回復期間終了時雌 (Table 24; Appendices 24-1, 24-2)

300 mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかった。

9.11. 血液生化学検査

9.11.1. 投与期間終了時雄 (Table 25; Appendices 25-1 - 25-4)

300 mg/kg 群では、対照群と比べて γ -GTP、尿素窒素及び無機リンの有意な高値がみられた。

300 mg/kg 群では、対照群と比べて A/G 有意な高値がみられたが、対照群との差はわずかであること及び当所の背景データ付近 [A/G: 1.09 ± 0.09; Attachment 8] の変化であることから、被験物質による影響とは判断しなかった。60 及び 12 mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかった。

9.11.2. 投与期間終了時雌 (Table 26; Appendices 26-1 - 26-4)

300 mg/kg 群では、対照群と比べて γ -GTP 及び無機リンの有意な高値、並びに尿素窒素の高値傾向がみられた。60 mg/kg 群では、対照群と比べて尿素窒素の有意な高値がみられた。その他、12 mg/kg 群では K の有意な高値みられたが、投与量に関連した変化ではないことから、被験物質による影響とは判断しなかった。

9.11.3. 回復期間終了時雄 (Table 27; Appendices 27-1, 27-2)

300 mg/kg 群では、対照群と比べて総コレステロールの有意な高値及び K の有意な低値がみられたが、投与期間終了時には認められなかった変化であることから、被験物質による影響とは判断しなかった。

9.11.4. 回復期間終了時雌 (Table 28; Appendices 28-1, 28-2)

300mg/kg 群では、対照群と比べて各測定項目に有意差はみられなかった。

9.12. 剖検所見

9.12.1. 投与期間終了時雄 (Table 29; Appendices 29-1 - 29-4)

肝臓の褪色が 300 及び 60 mg/kg 群で 6 及び 1 例にみられた。12 mg/kg 群では、腎孟拡張 (右側) が 1 例にみられたが、投与量に関連した変化ではないことから、被験物質による影響とは判断しなかった。対照群では、異常はみられなかった。

9.12.2. 投与期間終了時雌 (Table 30; Appendices 30-1 - 30-4)

肝臓の褪色が 300 及び 60 mg/kg 群で 6 及び 4 例にみられた。12 mg/kg 群及び対照群では、異常はみられなかった。

9.12.3. 回復期間終了時雄 (Table 31; Appendices 31-1, 31-2)

300mg/kg 群及び対照群とも、異常はみられなかった。

9.12.4. 回復期間終了時雌 (Table 32; Appendices 32-1, 32-2)

300mg/kg 群及び対照群とも、異常はみられなかった。

9.13. 器官重量

9.13.1. 投与期間終了時雄 (Table 33; Appendices 33-1 - 33-4)

剖検日の体重は、各投与群とも対照群と比べて有意差はみられなかった。

300 mg/kg 群では対照群と比べて下垂体、肝臓及び腎臓の絶対及び相対重量の有意な高値がみられた。60 及び 12mg/kg 群では、対照群と比べて各器官の絶対及び相対重量に有意差はみられなかった。

9.13.2. 投与期間終了時雌 (Table 34; Appendices 34-1 - 34-4)

剖検日の体重は、各投与群とも対照群と比べて有意差はみられなかった。

300 及び 60 mg/kg 群では対照群と比べて肝臓の絶対及び相対重量の有意な高値、300 mg/kg 群では対照群と比べて腎臓の絶対及び相対重量の有意な高値がみられた。

300 mg/kg 群では、対照群と比べて脾臓の絶対重量の有意な低値がみられたが、相対重量に差が認められないことから、被験物質による影響とは判断しなかった。12 mg/kg 群では、対照群と比べて各器官の絶対及び相対重量に有意差はみられなかった。

9.13.3. 回復期間終了時雄 (Table 35; Appendices 35-1, 35-2)

剖検日の体重において、300 mg/kg 群では対照群と比べて有意差はみられなかった。

300 mg/kg 群では対照群と比べて各器官の絶対及び相対重量に有意差はみられなかった。

9.13.4. 回復期間終了時雌 (Table 36; Appendices 36-1, 36-2)

剖検日の体重において、300 mg/kg 群では対照群と比べて有意差はみられなかった。

300 mg/kg 群では対照群と比べて各器官の絶対及び相対重量に有意差はみられなかった。

9.14. 病理組織学所見

9.14.1. 投与期間終了時雄 (Table 37; Appendices 37-1 - 37-4)

肝臓: 門脈周囲性の肝細胞腫大が 300 mg/kg 群で 6 例全例、60 mg/kg 群で 5 例及び 12 mg/kg 群で 2 例にみられ、その程度は 300 mg/kg 群で軽度又は中等度、60 及び 12 mg/kg 群でごく軽度であった。門脈周囲性の肝細胞腫大は、対照群と比べて 300 及び 60 mg/kg 群で有意差が認められ、かつ、用量反応性も確認された。微小肉芽腫が 300 mg/kg 群で 4 例及び 60 mg/kg 群で 2 例にみられ、その程度はごく軽度であった。

脾臓: チモーベン顆粒の減少が 300 及び 60 mg/kg 群で 6 例全例及び 12 mg/kg 群で 1 例にみられ、その程度は 300 mg/kg 群で軽度、60 及び 12 mg/kg 群でごく軽度であった。チモーベン顆粒の減少

は、300 及び 60 mg/kg 群で対照群と比べて有意差が認められ、かつ、用量反応性も確認された。

胸腺: 星空像が 300 mg/kg 群で 4 例にみられ、その程度はごく軽度であった。

腎臓: 近位尿細管の腫大が 300 mg/kg 群で 6 例全例にみられ、その程度はごく軽度であった。

近位尿細管の腫大は、300 mg/kg 群で対照群と比べて有意差が認められ、かつ、用量反応性も確認された。

その他の変化として以下に示した所見が得られた。

空腸: パイエル板の鉱質沈着が対照群で 1 例にみられた。

腎臓: 水腎症が 12 mg/kg 群で 1 例、硝子円柱が対照群、300 mg/kg 群で各 1 例及び 60 mg/kg 群で 2 例、囊胞が対照群で 1 例にみられた。

眼球: 網膜異形成が対照群で 1 例にみられた。

なお、これらの変化は対照群でも通常観察される変化であること、それらの程度はいずれもごく軽度であることから、偶発的変化と判断される。

300 mg/kg 群及び対照群では、心臓、肺、気管、舌下腺、顎下腺、食道、胃、十二指腸、回腸、盲腸、結腸、直腸、脾臓、下頸リンパ節、腸間膜リンパ節、膀胱、精巢、精巢上体、精嚢、前立腺、下垂体、副腎、甲状腺、上皮小体、大脳、小脳、延髄、脊髄、坐骨神経、ハーダー腺、骨髓(胸骨・大腿骨)、骨(胸骨・大腿骨) 及び大腿筋に異常はみられなかった。

9.14.2. 投与期間終了時雌 (Table 38; Appendices 38-1 - 38-4)

肝臓: 門脈周囲性の肝細胞腫大が 300 及び 60 mg/kg 群で 6 例全例及び 12 mg/kg 群で 5 例にみられ、その程度は 300 mg/kg 群で軽度、60 及び 12 mg/kg 群でごく軽度であった。門脈周囲性の肝細胞腫大は、対照群と比べて 300, 60 及び 12 mg/kg 群で有意差が認められ、かつ、用量反応性も確認された。微小肉芽腫が 300 mg/kg 群で 3 例にみられ、その程度はごく軽度であった。なお、12 mg/kg 群の 1 例にもごく軽度の微小肉芽腫がみられたが、投与量に関連した変化ではないことから、偶発的変化と判断される。

脾臓: チモーゲン顆粒の減少が 300 及び 60 mg/kg 群で 6 例全例及び 12 mg/kg 群で 5 例にみられ、その程度は 300 及び 60 mg/kg 群で軽度、12 mg/kg 群でごく軽度であった。チモーゲン顆粒の減少は、300, 60 及び 12 mg/kg 群で対照群と比べて有意差が認められ、かつ、用量反応性も確認された。

胸腺: 星空像が 300 mg/kg 群で 3 例にみられ、その程度はごく軽度であった。

腎臓: 近位尿細管の腫大が 300 mg/kg 群で 6 例全例及び 60 mg/kg 群で 1 例にみられ、その程度はごく軽度であった。近位尿細管の腫大は、300 mg/kg 群で対照群と比べて有意差が認められ、かつ、用量反応性も確認された。

その他の変化として以下に示した所見が得られた。

肺: 血管壁への鉱質沈着が 300 mg/kg 群で 1 例にみられた。

腎臓: 水腎症が対照群で 1 例にみられた。

甲状腺: 異所性胸腺が対照群で 2 例にみられた。

なお、これらの変化は対照群でも通常観察される変化であること、それらの程度はいずれもごく軽度であることから、偶発的変化と判断される。

300 mg/kg 群及び対照群では、心臓、気管、舌下腺、頸下腺、食道、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、脾臓、下顎リンパ節、腸間膜リンパ節、膀胱、卵巢、子宮、腎、下垂体、副腎、上皮小体、大脳、小脳、延髄、脊髄、坐骨神経、眼球、ハーダー腺、骨髓(胸骨・大腿骨)、骨(胸骨・大腿骨)、大腿筋及び乳腺に異常はみられなかった。

9.14.3. 回復期間終了時雄 (Table 39; Appendices 39-1, 39-2)

腎臓: 囊胞が 300 mg/kg 群で 1 例にみられたが、対照群でも通常観察される変化であること、その程度はごく軽度であることから、偶発的変化と判断される。

300 mg/kg 群並びに対照群では、肝臓、脾臓及び胸腺に異常はみられなかった。

9.14.4. 回復期間終了時雌 (Table 40; Appendices 40-1, 40-2)

肝臓: 門脈周囲性の肝細胞腫大が 300 mg/kg 群で 2 例にみられ、その程度はごく軽度であった。

腎臓: ごく軽度の囊胞が対照群で 1 例にみられた。

300 mg/kg 群並びに対照群では、脾臓及び胸腺に異常はみられなかった。

10. 考察

1,4-ジクロロブタンを雌雄ラットに 28 日間反復経口投与し、さらに一部の動物には 14 日間の回復期間を設けた反復投与による毒性学的影響を検討した。

死亡例は雌雄ともいずれの群にも認められなかつた。

一般状態では、雌雄の 300 mg/kg 群で流涎がみられたが、投与後に一過性に認められたのみであり、痙攣などの神経症状あるいは唾液腺の重量及び形態学的变化は認められないことから、被験物質の刺激性に基づく变化と判断され、毒性症状とはみなさなかつた。

体重、摂餌量、行動機能 (FOB) 観察、感覚反応検査、握力測定、自発運動量測定では、雌雄のいずれの投与群にも投与に起因する变化は認められなかつた。

被験物質に起因すると考えられる影響は、以下の器官・組織でみられた。

腎臓では、投与期間終了時に雌雄の 300 mg/kg 群及び雌の 60 mg/kg 群で用量に依存した近位尿細管の腫大が認められ、雌雄の 300 mg/kg 群で絶対重量及び相対重量の有意な高値みられた。また、尿検査では、雄の 300 mg/kg 群で尿量の高値がみられ、さらに、雌雄の 300 mg/kg 群及び雌の 60 mg/kg 群で尿素窒素の有意な高値あるいは高値傾向、雌雄の 300 mg/kg 群で無機リンの有意な高値がみられた。雌雄の 300 mg/kg 群では、ほぼ投与期間を通して摂水量の有意な高値がみられており、腎機能低下に伴い尿排泄量が亢進し、摂水量が増加したものと推察され、腎臓が 1,4-ジクロロブタン投与による標的臓器の一つであると考えられる。なお、回復期間中には、雌雄とも投与に起因する摂水量の変化は認められず、回復期間終了時の尿検査、血液生化学検査、剖検所見、器官重量及び病理組織学検査においても、雌雄とも投与に起因する腎臓への影響は認められなかつた。

肝臓では、投与期間終了時の剖検時に雌雄の 300 及び 60 mg/kg 群で褪色がみられ、雌雄の 300 mg/kg 群及び雌の 60 mg/kg 群で絶対重量及び相対重量の有意な高値がみられた。また、病理組織学検査では、雌雄の 300, 60 及び 12 mg/kg 群で用量に依存した細胞内小器官の増大によると考えられる門脈周囲性の肝細胞腫大、雌雄の 300 mg/kg 群及び雄の 60 mg/kg 群で微小肉芽腫がみられ、1,4-ジクロロブタン投与による肝臓への毒性変化が認められた。さらに、これに関連した所見として、雌雄の 300 mg/kg 群で γ -GTP の有意な高値がみられた。回復期間終了時には、雌の 300 mg/kg 群で門脈周囲性の肝細胞腫大が 2 例にみられたが、投与期間終了時と比べてその出現例数及びその程度が軽減していること、雄では 300 mg/kg 群で異常が認められなかつたことから回復傾向にあったと考えられる。

膵臓では、投与期間終了時の病理組織学検査において、雌雄の 300, 60 及び 12 mg/kg 群で用量に依存したチモーゲン顆粒の減少がみられた。膵腺房細胞の酵素原顆粒 (チモーゲン顆粒) にはアミラーゼ、リパーゼ、キモトリプシン、トリプシンなどの消化酵素が含まれており¹⁰⁾、1,4-ジクロロブタン投与による消化酵素分泌抑制が示唆された。なお、回復期間終了時に膵臓のチモーゲン顆粒の減少は認められなかつた。

胸腺では、投与期間終了時に雌雄の 300 mg/kg 群で星空像が認められた。胸腺などのリンパ系組織においては、化学物質投与あるいはストレスによりリンパ系細胞の低形成あるいは退縮が急速に生じた場合にアポトーシスを介して、しばしば星空像が観察される^{11), 12)}。また、こうした毒

性を示す薬物あるいは化学物質等に暴露された場合、最初の影響は胸腺に現れやすいとされており¹³⁾、1,4-ジクロロブタン投与による免疫組織系への影響が示唆された。なお、回復期間終了時の各検査では、雌雄とも胸腺への影響を示唆する変化は認められなかった。

その他、投与期間終了時に雄の 300 mg/kg群で単球比率の高値が認められたが、骨髄の病理組織学検査及び関連するその他のパラメータには異常はみられず、その機序は不明であった。また、雄の 300 mg/kg群で下垂体の絶対重量及び相対重量の有意な高値が認められたが、病理組織学検査では、雌雄の 300 mg/kg群の下垂体に異常は認められず、本試験の予備試験³⁾でも下垂体重量に変化は認められていないことから、毒性学的影響は低いと考えられる。

以上のように、1,4-ジクロロブタンの無影響量は、雌雄とも 12 mg/kg 投与により肝臓に門脈周囲性の肝細胞腫大及び膵臓にチモーゲン顆粒の減少が認められたことから、12 mg/kg/day 未満と考えられる。

11. 文献

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Table 1. General signs in male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	mg/kg	Number of males and general signs	Days of administration																											
			1		2		3		4		5		6		7		8		9		10		11		12		13		14	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post				
Control	0	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			
1,4-dichlorobutane	12	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
	60	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
	300	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			
		Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	3	0	5	0	6

Pre: Before administration, Post: after administration.

(Continued)

Table 1. (Continued) General signs in male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	mg/kg	Number of males and general signs	Days of administration																								Total ^{a)}					
			15		16		17		18		19		20		21		22		23		24		25		26		27		28			
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post				
Control	0	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	12		
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	-		
1,4-dichlorobutane	12	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	-	
	60	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	-	
	300	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	12	
		Normal	12	4	12	5	12	4	12	4	12	5	12	5	12	5	12	3	12	1	12	4	12	2	12	4	12	3	12	3	6	-
		Salivation	0	8	0	7	0	8	0	8	0	7	0	7	0	7	0	9	0	11	0	8	0	10	0	8	0	9	0	9	0	12

Pre: Before administration, Post: after administration.

(Continued)

a): Number of males showing abnormal signs at least once between Days 1 and 29 of administration.

Table 1. (Continued) General signs in male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	mg/kg	Number of males and general signs	Days of recovery													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
Control	0	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6
1,4-dichlorobutane	300	Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Table 2. General signs in female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	mg/kg	Number of females and general signs	Days of administration																											
			1		2		3		4		5		6		7		8		9		10		11		12		13		14	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post				
Control	0	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			
1,4-dichlorobutane	12	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6				
	60	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6				
	300	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12				
		Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	2	0	3	0	4	0			

Pre: Before administration, Post: after administration.

(Continued)

Table 2. (Continued) General signs in female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	mg/kg	Number of females and general signs	Days of administration																								Total ^{a)}						
			15		16		17		18		19		20		21		22		23		24		25		26		27		28				
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post					
Control	0	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	12			
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	-				
1,4-dichlorobutane	12	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	-			
	60	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	-			
	300	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			
		Normal	12	7	12	4	12	9	12	7	12	3	12	4	12	5	12	6	12	5	12	2	12	3	12	2	12	6	6	-			
		Salivation	0	5	0	8	0	3	0	5	0	9	0	8	0	7	0	6	0	7	0	7	0	10	0	9	0	10	0	6	0	12	

Pre: Before administration, Post: after administration.

(Continued)

a): Number of females showing abnormal signs at least once between Days 1 and 29 of administration.

Table 2. (Continued) General signs in female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	mg/kg	Number of females and general signs	Days of recovery														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control	0	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
1,4-dichlorobutane	300	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
		Normal	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Table 3. Body weights of male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	12	6	6	12	
Days of administration					
1	202 ± 6	200 ± 5	201 ± 8	201 ± 5	
4	227 ± 6	226 ± 7	227 ± 10	220 ± 8	
8	259 ± 7	257 ± 11	261 ± 13	252 ± 12	
11	284 ± 11	282 ± 15	287 ± 16	279 ± 13	
15	313 ± 12	309 ± 19	313 ± 18	308 ± 14	
18	335 ± 16	331 ± 23	340 ± 21	326 ± 13	
22	359 ± 18	355 ± 24	366 ± 23	351 ± 18	
25	375 ± 19	373 ± 23	386 ± 25	367 ± 20	
28	390 ± 20	386 ± 27	397 ± 23	384 ± 20	
Number of males	6	0	0	6	
Days of recovery					
1	400 ± 17	-	-	384 ± 14	
4	416 ± 18	-	-	397 ± 12	
8	439 ± 21	-	-	424 ± 16	
11	448 ± 21	-	-	433 ± 17	
14	467 ± 21	-	-	455 ± 21	

Each value shows mean (g) ± S.D.

Table 4. Body weights of female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control		1,4-dichlorobutane		
mg/kg	0	12	60	300	
Number of females	12		6		12
Days of administration					
1	152 ± 6	153 ± 7	153 ± 5	155 ± 7	
4	162 ± 7	161 ± 4	166 ± 6	162 ± 7	
8	173 ± 10	173 ± 3	175 ± 6	175 ± 9	
11	187 ± 10	185 ± 3	188 ± 9	189 ± 11	
15	197 ± 11	194 ± 4	197 ± 8	197 ± 10	
18	206 ± 12	205 ± 7	211 ± 9	205 ± 13	
22	214 ± 13	213 ± 8	220 ± 9	211 ± 12	
25	221 ± 15	223 ± 10	228 ± 13	219 ± 12	
28	226 ± 15	229 ± 14	235 ± 14	225 ± 11	
Number of females	6	0	0	6	
Days of recovery					
1	238 ± 17	-	-	222 ± 14	
4	243 ± 16	-	-	227 ± 13	
8	248 ± 19	-	-	238 ± 12	
11	251 ± 17	-	-	245 ± 14	
14	257 ± 19	-	-	249 ± 14	

Each value shows mean (g) ± S.D.

Table 5. Food consumption in male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	12	6	6	12	
Days of administration					
2	22 ± 1	23 ± 1	22 ± 2	21 ± 2	
5	21 ± 3	22 ± 2	22 ± 3	19 ± 3	
9	22 ± 3	22 ± 3	23 ± 2	22 ± 1	
12	23 ± 2	22 ± 4	20 ± 4	23 ± 1	
16	24 ± 3	24 ± 2	26 ± 1	23 ± 4	
19	24 ± 2	24 ± 2	25 ± 1	23 ± 3	
23	24 ± 3	24 ± 1	27 ± 1	25 ± 2	
26	25 ± 3	26 ± 3	25 ± 2	25 ± 2	
Number of males	6	0	0	6	
Days of recovery	2	28 ± 1	-	-	29 ± 3
	5	27 ± 2	-	-	28 ± 2
	9	27 ± 2	-	-	27 ± 1
	12	30 ± 2	-	-	30 ± 3

Each value shows mean (g/day) ± S.D.

Table 6. Food consumption in female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	12	6	6	12	
Days of administration					
2	16 ± 2	15 ± 2	16 ± 1	15 ± 2	
5	16 ± 2	16 ± 1	16 ± 1	15 ± 2	
9	16 ± 2	16 ± 2	18 ± 1	16 ± 3	
12	15 ± 2	13 ± 2	17 ± 2	14 ± 4	
16	16 ± 2	16 ± 2	18 ± 3	17 ± 2	
19	16 ± 2	15 ± 2	15 ± 3	16 ± 4	
23	15 ± 2	15 ± 2	16 ± 2	15 ± 3	
26	17 ± 4	18 ± 3	20 ± 1	17 ± 3	
Number of females	6	0	0	6	
Days of recovery	2	18 ± 3	-	18 ± 2	
	5	19 ± 2	-	21 ± 1 †	
	9	19 ± 3	-	19 ± 3	
	12	19 ± 2	-	20 ± 3	

Each value shows mean (g/day) ± S.D.

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

Table 7. Water consumption in male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	12	6	6	12	
Days of administration					
2	29 ± 4	30 ± 4	29 ± 4	26 ± 3	
5	30 ± 3	33 ± 4	33 ± 5	33 ± 5	
9	30 ± 5	29 ± 3	30 ± 5	36 ± 5 **	
12	33 ± 4	31 ± 6	31 ± 3	39 ± 6 *	
16	33 ± 5	34 ± 5	36 ± 5	40 ± 7 *	
19	33 ± 5	34 ± 5	35 ± 5	39 ± 7 *	
23	35 ± 5	36 ± 5	40 ± 7	44 ± 6 **	
26	34 ± 5	35 ± 7	39 ± 9	43 ± 7 **	
Number of males	6	0	0	6	
Days of recovery	2	40 ± 5	-	46 ± 8	
	5	38 ± 6	-	40 ± 5	
	9	38 ± 7	-	40 ± 8	
	12	38 ± 5	-	42 ± 9	

Each value shows mean (g/day) ± S.D.

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

Table 8. Water consumption in female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	12	6	6	12	
Days of administration					
2	23 ± 2	23 ± 2	25 ± 3	22 ± 3	
5	24 ± 3	24 ± 1	25 ± 3	29 ± 5	
9	26 ± 5	26 ± 4	32 ± 2	33 ± 7 **	
12	24 ± 4	22 ± 3	30 ± 6	31 ± 11	
16	25 ± 7	26 ± 6	31 ± 3	36 ± 7 **	
19	25 ± 4	22 ± 3	25 ± 6	33 ± 8 *	
23	27 ± 10	24 ± 3	27 ± 6	35 ± 12	
26	25 ± 6	27 ± 5	32 ± 4	37 ± 13 #	
Number of females	6	0	0	6	
Days of recovery	2	29 ± 8	-	33 ± 5	
	5	31 ± 8	-	34 ± 9	
	9	32 ± 12	-	31 ± 7	
	12	31 ± 6	-	29 ± 6	

Each value shows mean (g/day) ± S.D.

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

Significantly different from the control group (#: p<0.05 by Steel's test).

Table 9. FOB of male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	6	6	6	6	
Observation of animals in cages					
Posture	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Palpebral closure	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Biting behavior	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Clonic convulsions	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows:

(Continued)

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Table 9. (Continued) FOB of male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane	
	0	12	60	300
Number of males	6	6	6	6
Observation of animals in cages				
Tonic convulsions	Pre	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows:

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions, 5: asphyxial convulsions.

(Continued)

Table 9. (Continued) FOB of male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	6	6	6	6	
Observation of animals on observer's palm					
Ease of removal from cage	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Ease of handling	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Muscle tone	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Fur conditions	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows:

(Continued)

Ease of removal from cage

1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling

1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing, 3: struggling and trying to bite observer's hand.

Muscle tone

1: Decreased, 2: normal, 3: increased.

Fur conditions

1: Normal, 2: slightly soiled, 3: markedly soiled.

Table 9. (Continued) FOB of male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	6	6	6	6	
Observation of animals on observer's palm					
Lacrimation	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Salivation	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.7 (1-2)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.7 (1-2)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.5 (1-2)
Respiration	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

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Findings were graded as follows:

(Continued)

- Lacrimation 1: None, 2: mild, 3: marked.
 Salivation 1: None, 2: mild, 3: marked.
 Respiration 1: Normal, 2: bradypnea, 3: dyspnea.

Table 9. (Continued) FOB of male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control		1,4-dichlorobutane			
mg/kg	0	12	60	300		
Number of males	6	6	6	6		
Open-field test						
Frequency of rearing	Pre	4.8 ± 3.3	5.0 ± 3.5	6.7 ± 4.6	5.7 ± 3.5	
Mean ± S.D.	Day 7	5.3 ± 4.4	6.2 ± 4.4	6.8 ± 3.9	6.8 ± 4.4	
	Day 14	2.5 ± 2.7	6.0 ± 5.6	2.2 ± 2.6	2.0 ± 2.3	
	Day 21	5.5 ± 3.7	4.2 ± 4.2	2.8 ± 3.5	3.8 ± 4.0	
	Day 27	2.7 ± 2.9	4.3 ± 1.5	3.2 ± 3.5	4.2 ± 2.6	
Frequency of grooming	Pre	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Mean ± S.D.	Day 7	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
	Day 14	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
	Day 21	0.2 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
	Day 27	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Gait	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
Palpebral closure	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	

Frequency of rearing (during a 2-minute period).

Frequency of grooming (during a 2-minute period).

Findings were graded as follows:

Gait 1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

(Continued)

Table 9. (Continued) FOB of male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg		Control	1,4-dichlorobutane		
		0	12	60	300
Number of males		6	6	6	6
Open-field test					
Consciousness	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Behavioral abnormalities	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Righting reflex	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

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Findings were graded as follows:

Consciousness

1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities

1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Table 10. FOB of female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	6	6	6	6	
Observation of animals in cages					
Posture	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Palpebral closure	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Biting behavior	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Clonic convulsions	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows:

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

(Continued)

Table 10. (Continued) FOB of female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane	
	0	12	60	300
Number of females	6	6	6	6
Observation of animals in cages				
Tonic convulsions	Pre	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows:

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions, 5: asphyxial convulsions.

(Continued)

Table 10. (Continued) FOB of female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	6	6	6	6	
Observation of animals on observer's palm					
Ease of removal from cage	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Ease of handling	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Muscle tone	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Fur conditions	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Findings were graded as follows:

(Continued)

Ease of removal from cage

1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling

1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing, 3: struggling and trying to bite observer's hand.

Muscle tone

1: Decreased, 2: normal, 3: increased.

Fur conditions

1: Normal, 2: slightly soiled, 3: markedly soiled.

Table 10. (Continued) FOB of female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	6	6	6	6	
Observation of animals on observer's palm					
Lacrimation	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Salivation	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.2 (1-2)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.3 (1-2)
Respiration	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

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Findings were graded as follows:

(Continued)

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

Respiration 1: Normal, 2: bradypnea, 3: dyspnea.

Table 10. (Continued) FOB of female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control		1,4-dichlorobutane			
mg/kg	0	12	60	300		
Number of females	6	6	6	6		
Open-field test						
Frequency of rearing	Pre	5.8 ± 3.7	6.8 ± 3.3	4.0 ± 4.4	8.0 ± 3.5	
Mean ± S.D.	Day 7	6.8 ± 3.5	7.5 ± 4.2	5.5 ± 2.7	6.3 ± 5.8	
	Day 14	1.5 ± 1.6	6.3 ± 4.7	6.7 ± 3.7	6.7 ± 4.7	
	Day 21	4.3 ± 2.5	8.0 ± 4.7	9.2 ± 2.6	8.2 ± 6.7	
	Day 27	4.7 ± 3.1	9.8 ± 7.1	7.7 ± 3.7	8.8 ± 3.4	
Frequency of grooming	Pre	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Mean ± S.D.	Day 7	0.0 ± 0.0	0.2 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	
	Day 14	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
	Day 21	0.0 ± 0.0	0.2 ± 0.4	0.2 ± 0.4	0.3 ± 0.5	
	Day 27	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Gait	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
Palpebral closure	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)	

Frequency of rearing (during a 2-minute period).

Frequency of grooming (during a 2-minute period).

Findings were graded as follows:

Gait 1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

(Continued)

Table 10. (Continued) FOB of female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg		Control	1,4-dichlorobutane		
		0	12	60	300
Number of females		6	6	6	6
Open-field test					
Consciousness	Pre	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Mean (range)	Day 7	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 14	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 21	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
	Day 27	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Behavioral abnormalities	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Righting reflex	Pre	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Mean (range)	Day 7	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 14	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 21	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
	Day 27	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

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Findings were graded as follows:

Consciousness

1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities

1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Table 11. Sensory response of male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control	1,4-dichlorobutane		
mg/kg	0	12	60	300
Number of males	6	6	6	6
Pupillary reflex				
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Approaching behavior				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Response to touch				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Auditory reflex				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Pain reflex				
Mean (range)	3.0 (3)	3.0 (3)	3.0 (3)	3.0 (3)

Findings were graded as follows:

1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.

Approaching behavior
1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing,
4: jumping at or biting at stimulus.

Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing, 4: jumping at or biting at stimulus.

1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.

1: Not observed; 2: Resisting all stimuli or moving slow; 3: Jumping at and trying to bite at the stimulus.

1: Not observed; 2: slowly looking back or slowly moving forward to escape from stimulus;
3: quickly moving forward to escape from stimulus or biting at it immediately after looking back

4: jumping forward to escape from stimulus or biting at it immediately after looking back; 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Table 12. Sensory response of female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control	1,4-dichlorobutane		
		12	60	300
Number of females	6	6	6	6
Pupillary reflex				
Mean (range)	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)
Approaching behavior				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Response to touch				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Auditory reflex				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
Pain reflex				
Mean (range)	3.0 (3)	3.0 (3)	3.0 (3)	3.0 (3)

Findings were graded as follows:

- §
- Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
 - Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing, 4: jumping at or biting at stimulus.
 - Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing, 4: jumping at or biting at stimulus.
 - Auditory reflex 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
 - Pain reflex 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus, 3: quickly moving forward to escape from stimulus or biting at it immediately after looking back, 4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Table 13. Grip strength of male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	6	6	6	6	
Forelimb	1090 ± 196	955 ± 108	1026 ± 332	1013 ± 221	
Hindlimb	446 ± 98	414 ± 74	471 ± 137	458 ± 85	

Each value shows mean (g) ± S.D.

Table 14. Grip strength of female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	6	6	6	6	
Forelimb	754 ± 53	684 ± 105	741 ± 66	711 ± 146	
Hindlimb	352 ± 55	377 ± 31	372 ± 35	341 ± 63	

Each value shows mean (g) ± S.D.

Table 15. Spontaneous motor activity of male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	6	6	6	6	
Ambulatory counts					
Minutes after administration					
70	334 ± 189	376 ± 114	428 ± 240	425 ± 76	
80	154 ± 212	159 ± 153	180 ± 114	131 ± 99	
90	40 ± 39	130 ± 137	76 ± 99	63 ± 85	
100	29 ± 38	55 ± 59	28 ± 44	21 ± 50	
110	9 ± 17	20 ± 28	3 ± 8	0 ± 0	
120	30 ± 74	21 ± 42	25 ± 62	0 ± 1	
Total	596 ± 450	761 ± 336	741 ± 386	639 ± 181	
Vertical counts					
Minutes after administration					
70	40 ± 15	59 ± 14	55 ± 24	54 ± 6	
80	9 ± 9	21 ± 13	21 ± 13	17 ± 12	
90	5 ± 5	17 ± 19	8 ± 10	4 ± 6	
100	6 ± 6	10 ± 16	3 ± 4	3 ± 8	
110	3 ± 4	5 ± 5	1 ± 2	0 ± 0	
120	0 ± 1	3 ± 4	7 ± 16	0 ± 0	
Total	63 ± 29	114 ± 41 *	96 ± 43	78 ± 15	

Each value shows mean ± S.D.

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

Table 16. Spontaneous motor activity of female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	6	6	6	6	
Ambulatory counts					
Minutes after administration					
70	552 ± 174	579 ± 245	475 ± 182	684 ± 296	
80	131 ± 140	183 ± 163	257 ± 274	107 ± 114	
90	21 ± 36	58 ± 81	112 ± 146	28 ± 39	
100	0 ± 0	0 ± 0	7 ± 11	51 ± 124	
110	3 ± 5	52 ± 84	94 ± 220	34 ± 84	
120	33 ± 66	110 ± 170	12 ± 19	0 ± 0	
Total	740 ± 252	980 ± 260	957 ± 756	903 ± 442	
Vertical counts					
Minutes after administration					
70	59 ± 26	66 ± 32	69 ± 28	73 ± 16	
80	22 ± 22	33 ± 29	32 ± 25	13 ± 13	
90	2 ± 2	9 ± 12	19 ± 19	5 ± 8	
100	0 ± 0	0 ± 0	1 ± 2	6 ± 15	
110	1 ± 2	8 ± 11	7 ± 16	5 ± 11	
120	6 ± 10	16 ± 27	1 ± 2	0 ± 0	
Total	89 ± 42	132 ± 62	128 ± 70	101 ± 34	

Each value shows mean ± S.D.

Table 17. Urinary findings in male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane			
	0	12	60	300		
Number of males	6	6	6	6		
Volume (mL): Mean±S.D.	9.8 ± 4.5	10.7 ± 2.6	13.3 ± 4.8	16.2 ± 1.7 *		
Specific gravity: Mean±S.D.	1.056 ± 0.015	1.053 ± 0.010	1.048 ± 0.014	1.045 ± 0.007		
Color						
Light yellow	6	6	6	6		
pH						
8.0	0	0	2	0		
8.5	6	6	4	6		
Protein						
Negative	0	0	0	2		
Trace	0	2	3	3		
30 mg/dL	2	3	3	1		
100 mg/dL	4	1	0	0		
Glucose						
Negative	6	6	6	6		
Ketone body						
Negative	1	1	1	1		
Trace	1	2	2	3		
Slight	3	3	3	2		
Moderate	1	0	0	0		
Bilirubin						
Negative	6	4	6	6		
Slight	0	2	0	0		
Occult blood						
Negative	5	6	4	5		
Trace	1	0	1	1		
Slight	0	0	1	0		
Urobilinogen						
0.1 E.U./dL	5	5	6	6		
1.0 E.U./dL	1	1	0	0		

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

(Continued)

Table 17. (Continued) Urinary findings in male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control	1,4-dichlorobutane		
		12	60	300
Number of males	6	6	6	6
Urinary sediments				
Epithelial cells				
0-20 cells/100 fields	6	6	6	6
Erythrocytes				
0-20 cells/100 fields	6	6	6	6
Leukocytes				
0-20 cells/100 fields	6	6	6	6
Casts				
Not observed	6	6	6	6
Crystals				
Not observed	3	2	1	2
Observed	3	4	5	4

Table 18. Urinary findings in female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane			
	0	12	60	300		
Number of females	6		6		6	
Volume (mL): Mean±S.D.	7.5 ± 2.3		7.6 ± 1.8		9.0 ± 4.3	
Specific gravity: Mean±S.D.	1.046 ± 0.014		1.041 ± 0.011		1.049 ± 0.017	
Color						
Light yellow	6	6	6	6	6	6
pH						
7.5	0	2	0	1		
8.0	1	1	1	1		
8.5	2	2	5	4		
≥9.0	3	1	0	0		
Protein						
Negative	5	3	4	5		
Trace	1	2	1	1		
30 mg/dL	0	1	1	0		
Glucose						
Negative	6	6	6	6		
Ketone body						
Negative	6	5	4	4		
Trace	0	1	1	1		
Slight	0	0	1	1		
Bilirubin						
Negative	6	6	6	6		
Occult blood						
Negative	5	4	4	6		
Trace	0	1	2	0		
Slight	0	1	0	0		
Moderate	1	0	0	0		
Urobilinogen						
0.1 E.U./dL	6	5	6	6		
1.0 E.U./dL	0	1	0	0		

(Continued)

Table 18. (Continued) Urinary findings in female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control				1,4-dichlorobutane			
	0	12	60	300				
Number of females	6	6	6	6				
Urinary sediments								
Epithelial cells								
0-20 cells/100 fields	6	6	6	6				
Erythrocytes								
0-20 cells/100 fields	5	6	6	6				
21-100 cells/100fields	1							
Leukocytes								
0-20 cells/100 fields	6	6	6	6				
Casts								
Not observed	6	6	6	6				
Crystals								
Not observed	3	2	2	3				
Observed	3	4	4	3				

Table 19. Urinary findings in male rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control	1,4-dichlorobutane
mg/kg	0	300
Number of males	6	6
Volume (mL): Mean±S.D.	14.2 ± 2.4	16.3 ± 6.2
Specific gravity: Mean±S.D.	1.049 ± 0.009	1.041 ± 0.014
Color		
Light yellow	6	6
pH		
8.5	6	6
Protein		
Negative	2	0
Trace	3	2
30 mg/dL	1	3
100 mg/dL	0	1
Glucose		
Negative	6	6
Ketone body		
Negative	2	0
Trace	2	2
Slight	2	4
Bilirubin		
Negative	6	6
Occult blood		
Negative	5	5
Trace	1	1
Urobilinogen		
0.1 E.U./dL	6	6

(Continued)

Table 19. (Continued) Urinary findings in male rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control	1,4-dichlorobutane
mg/kg	0	300
Number of males	6	6
Urinary sediments		
Epithelial cells		
0-20 cells/100 fields	6	6
Erythrocytes		
0-20 cells/100 fields	6	6
Leukocytes		
0-20 cells/100 fields	6	6
Casts		
Not observed	6	6
Crystals		
Not observed	0	3
Observed	6	3

Table 20. Urinary findings in female rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control	1,4-dichlorobutane
mg/kg	0	300
Number of females	6	6
Volume (mL): Mean±S.D.	13.3 ± 7.2	11.8 ± 3.6
Specific gravity: Mean±S.D.	1.043 ± 0.021	1.044 ± 0.012
Color		
Light yellow	6	6
pH		
8.0	0	2
8.5	5	3
≥9.0	1	1
Protein		
Negative	4	5
Trace	1	0
30 mg/dL	1	1
Glucose		
Negative	6	6
Ketone body		
Negative	4	5
Trace	2	1
Bilirubin		
Negative	6	6
Occult blood		
Negative	6	5
Trace	0	1
Urobilinogen		
0.1 E.U./dL	6	5
1.0 E.U./dL	0	1

(Continued)

Table 20. (Continued) Urinary findings in female rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control	1,4-dichlorobutane
mg/kg	0	300
Number of females	6	6
Urinary sediments		
Epithelial cells		
0-20 cells/100 fields	6	6
Erythrocytes		
0-20 cells/100 fields	6	6
Leukocytes		
0-20 cells/100 fields	6	6
Casts		
Not observed	6	6
Crystals		
Not observed	1	2
Observed	5	4

Table 21. Hematological findings in male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	6	6	6	6	
RBC ($10^4/\mu\text{L}$)	823 ± 28	789 ± 55	770 ± 44	777 ± 18	
Hemoglobin (g/dL)	15.5 ± 0.4	14.8 ± 0.7	15.0 ± 0.6	14.9 ± 0.4	
Hematocrit (%)	43.7 ± 1.2	41.8 ± 1.7	42.7 ± 1.2	42.0 ± 0.9	
MCV (fL)	53.0 ± 1.1	53.1 ± 2.2	55.6 ± 2.0 *	54.1 ± 0.9	
MCH (pg)	18.8 ± 0.5	18.8 ± 0.6	19.5 ± 0.6	19.1 ± 0.5	
MCHC (g/dL)	35.4 ± 0.4	35.3 ± 0.5	35.1 ± 0.4	35.3 ± 0.5	
Platelet ($10^4/\mu\text{L}$)	122.7 ± 15.4	117.6 ± 12.7	112.2 ± 9.2	118.9 ± 11.4	
Reticulocyte (%)	3.15 ± 0.33	3.62 ± 0.53	3.43 ± 0.68	3.96 ± 0.71	
PT (sec.)	21.5 ± 5.6	20.6 ± 2.6	21.8 ± 5.0	19.4 ± 1.1	
APTT (sec.)	25.4 ± 3.2	24.4 ± 2.5	25.0 ± 4.0	24.5 ± 0.8	
Fibrinogen (mg/dL)	199.3 ± 8.2	210.4 ± 9.7	214.8 ± 26.9	197.4 ± 13.2	
WBC ($10^2/\mu\text{L}$)	87.2 ± 29.5	77.3 ± 15.2	68.6 ± 18.0	75.8 ± 22.9	
Differential leukocyte (%)					
Lymphocyte	80.3 ± 7.2	80.4 ± 4.4	77.7 ± 9.6	77.7 ± 6.2	
Neutrophil	16.1 ± 7.4	16.0 ± 4.6	17.1 ± 7.9	17.1 ± 5.1	
Eosinophil	1.1 ± 0.2	1.2 ± 0.3	1.2 ± 0.6	0.9 ± 0.4	
Basophil	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Monocyte	2.4 ± 0.4	2.4 ± 0.9	4.0 ± 1.8	4.3 ± 1.3 #	

Each value shows mean ± S.D.

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

Significantly different from the control group (#: p<0.05 by Steel's test).

Table 22. Hematological findings in female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	6	6	6	6	
RBC ($10^4/\mu\text{L}$)	775 ± 49	770 ± 37	748 ± 32	772 ± 36	
Hemoglobin (g/dL)	14.6 ± 0.6	14.4 ± 0.6	14.4 ± 0.7	14.6 ± 0.5	
Hematocrit (%)	40.5 ± 1.8	39.9 ± 2.0	40.3 ± 2.0	40.7 ± 1.3	
MCV (fL)	52.4 ± 1.1	51.8 ± 1.3	53.9 ± 2.1	52.8 ± 1.4	
MCH (pg)	18.9 ± 0.5	18.7 ± 0.4	19.2 ± 0.6	18.9 ± 0.5	
MCHC (g/dL)	36.0 ± 0.3	36.1 ± 0.2	35.7 ± 0.4	35.8 ± 0.6	
Platelet ($10^4/\mu\text{L}$)	119.6 ± 13.6	127.5 ± 9.5	114.3 ± 7.3	122.2 ± 13.8	
Reticulocyte (%)	2.64 ± 0.51	2.79 ± 0.62	2.93 ± 0.38	3.13 ± 0.64	
PT (sec.)	15.0 ± 0.7	15.2 ± 0.7	15.9 ± 0.9	15.8 ± 0.6	
APTT (sec.)	17.5 ± 1.0	17.5 ± 1.3	18.1 ± 1.3	17.7 ± 2.0	
Fibrinogen (mg/dL)	177.7 ± 15.0	163.1 ± 5.9	157.6 ± 15.4 *	188.7 ± 14.9	
WBC ($10^2/\mu\text{L}$)	59.0 ± 22.7	58.2 ± 9.5	53.0 ± 16.8	44.3 ± 6.4	
Differential leukocyte (%)					
Lymphocyte	79.8 ± 8.4	82.3 ± 2.4	84.1 ± 6.5	72.3 ± 11.1	
Neutrophil	16.1 ± 7.7	13.0 ± 2.5	11.4 ± 5.6	22.0 ± 10.2	
Eosinophil	1.8 ± 1.0	1.7 ± 0.7	2.3 ± 1.2	1.6 ± 0.8	
Basophil	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Monocyte	2.3 ± 1.4	3.0 ± 1.3	2.3 ± 0.6	4.1 ± 2.0	

Each value shows mean ± S.D.

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

Table 23. Hematological findings in male rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane	
	0	300		
Number of males	6	6		
RBC (10 ⁶ /μL)	830 ± 50		817 ± 46	
Hemoglobin (g/dL)	15.1 ± 0.5		15.3 ± 0.6	
Hematocrit (%)	41.8 ± 1.3		42.2 ± 1.6	
MCV (fL)	50.5 ± 2.3		51.8 ± 2.6	
MCH (pg)	18.3 ± 0.8		18.7 ± 0.7	
MCHC (g/dL)	36.2 ± 0.3		36.1 ± 0.4	
Platelet (10 ³ /μL)	119.6 ± 9.9		119.0 ± 10.5	
Reticulocyte (%)	3.30 ± 0.36		3.72 ± 0.71	
PT (sec.)	16.3 ± 1.4		18.2 ± 3.7	
APTT (sec.)	22.7 ± 2.7		26.4 ± 4.5	
Fibrinogen (mg/dL)	208.7 ± 16.1		211.2 ± 16.4	
WBC (10 ³ /μL)	75.0 ± 16.7		66.7 ± 19.8	
Differential leukocyte (%)				
Lymphocyte	77.5 ± 3.8		80.6 ± 2.3	
Neutrophil	17.8 ± 4.0		14.4 ± 1.9	
Eosinophil	1.4 ± 0.4		1.3 ± 0.4	
Basophil	0.0 ± 0.0		0.0 ± 0.0	
Monocyte	3.3 ± 0.6		3.7 ± 0.8	

Each value shows mean ± S.D.

Table 24. Hematological findings in female rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control 0	1,4-dichlorobutane 300
Number of females	6	6
RBC ($10^4/\mu\text{L}$)	766 ± 44	785 ± 39
Hemoglobin (g/dL)	14.3 ± 0.5	14.3 ± 0.5
Hematocrit (%)	39.6 ± 1.3	39.7 ± 1.6
MCV (fL)	51.7 ± 2.3	50.6 ± 1.8
MCH (pg)	18.7 ± 0.7	18.3 ± 0.7
MCHC (g/dL)	36.1 ± 0.4	36.1 ± 0.2
Platelet ($10^4/\mu\text{L}$)	119.7 ± 7.0	115.4 ± 10.4
Reticulocyte (%)	2.81 ± 0.32	3.20 ± 0.61
PT (sec.)	14.8 ± 0.8	15.4 ± 0.5
APTT (sec.)	17.5 ± 0.8	17.8 ± 0.8
Fibrinogen (mg/dL)	172.6 ± 7.8	169.2 ± 15.1
WBC ($10^2/\mu\text{L}$)	39.0 ± 10.4	35.5 ± 10.7
Differential leukocyte (%)		
Lymphocyte	80.2 ± 6.4	77.0 ± 7.0
Neutrophil	16.6 ± 6.1	19.2 ± 7.3
Eosinophil	1.3 ± 0.5	1.6 ± 0.5
Basophil	0.0 ± 0.1	0.0 ± 0.0
Monocyte	1.8 ± 0.5	2.2 ± 0.8

Each value shows mean ± S.D.

Table 25. Blood chemical findings in male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	6	6	6	6	
AST (IU/L)	80.6 ± 11.2	77.3 ± 8.2	85.0 ± 10.9	89.2 ± 15.4	
ALT (IU/L)	29.6 ± 1.9	25.9 ± 2.3	29.7 ± 6.3	35.8 ± 13.1	
ALP (IU/L)	555.7 ± 110.9	609.3 ± 133.2	626.4 ± 132.4	682.0 ± 141.2	
γ-GTP (IU/L)	0.72 ± 0.12	0.79 ± 0.25	0.73 ± 0.11	1.03 ± 0.17 *	
Total protein (g/dL)	5.52 ± 0.18	5.41 ± 0.15	5.45 ± 0.17	5.45 ± 0.34	
Albumin (g/dL)	2.89 ± 0.06	2.84 ± 0.07	2.89 ± 0.12	3.06 ± 0.22	
A/G	1.11 ± 0.05	1.11 ± 0.05	1.13 ± 0.11	1.28 ± 0.06 **	
Total bilirubin (mg/dL)	0.11 ± 0.01	0.11 ± 0.02	0.11 ± 0.01	0.15 ± 0.04	
Urea nitrogen (mg/dL)	13.9 ± 1.3	13.0 ± 2.7	16.5 ± 2.1	26.2 ± 2.0 **	
Creatinine (mg/dL)	0.22 ± 0.03	0.22 ± 0.03	0.23 ± 0.03	0.22 ± 0.02	
Glucose (mg/dL)	119.5 ± 9.6	120.8 ± 10.2	121.6 ± 11.3	116.8 ± 15.8	
Total cholesterol (mg/dL)	53.9 ± 10.0	58.9 ± 13.9	56.9 ± 8.2	45.6 ± 11.1	
Triglyceride (mg/dL)	32.5 ± 7.3	41.2 ± 11.2	49.3 ± 21.4	119.0 ± 63.8	
Na (mEq/L)	143.3 ± 1.2	143.7 ± 1.1	143.4 ± 1.5	140.4 ± 4.0	
K (mEq/L)	4.10 ± 0.22	4.01 ± 0.28	4.36 ± 0.14	4.29 ± 0.17	
Cl (mEq/L)	104.9 ± 1.8	104.5 ± 1.2	104.8 ± 1.2	102.3 ± 3.5	
Ca (mg/dL)	9.5 ± 0.2	9.5 ± 0.3	9.3 ± 0.2	9.2 ± 0.4	
Inorganic phosphate (mg/dL)	7.9 ± 0.6	8.2 ± 0.5	8.3 ± 0.6	9.0 ± 0.4 **	

Each value shows mean ± S.D.

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

Table 26. Blood chemical findings in female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	6	6	6	6	
AST (IU/L)	78.5 ± 16.7	86.2 ± 13.6	82.2 ± 10.1	75.4 ± 8.7	
ALT (IU/L)	22.5 ± 3.2	25.3 ± 4.4	23.4 ± 3.8	25.2 ± 1.4	
ALP (IU/L)	373.5 ± 113.1	360.1 ± 54.8	321.2 ± 57.7	880.7 ± 410.6	
γ-GTP (IU/L)	0.97 ± 0.15	0.93 ± 0.16	0.86 ± 0.13	1.29 ± 0.12 **	
Total protein (g/dL)	5.51 ± 0.32	5.24 ± 0.30	5.75 ± 0.18	5.58 ± 0.27	
Albumin (g/dL)	3.20 ± 0.22	2.95 ± 0.20	3.36 ± 0.19	3.26 ± 0.24	
A/G	1.39 ± 0.07	1.28 ± 0.06	1.41 ± 0.12	1.41 ± 0.10	
Total bilirubin (mg/dL)	0.12 ± 0.02	0.12 ± 0.01	0.12 ± 0.02	0.13 ± 0.03	
Urea nitrogen (mg/dL)	13.4 ± 2.2	15.3 ± 2.5	17.0 ± 1.9 #	19.7 ± 6.0	
Creatinine (mg/dL)	0.24 ± 0.03	0.26 ± 0.03	0.24 ± 0.02	0.21 ± 0.03	
Glucose (mg/dL)	123.9 ± 7.7	115.9 ± 9.6	118.1 ± 13.9	111.6 ± 17.8	
Total cholesterol (mg/dL)	61.9 ± 5.1	66.1 ± 17.5	49.8 ± 15.8	55.5 ± 12.9	
Triglyceride (mg/dL)	28.4 ± 12.3	23.0 ± 8.5	22.8 ± 9.3	39.1 ± 13.6	
Na (mEq/L)	143.0 ± 2.0	142.6 ± 0.4	142.8 ± 0.8	142.6 ± 2.1	
K (mEq/L)	3.98 ± 0.21	4.34 ± 0.20 *	4.33 ± 0.24	4.30 ± 0.30	
Cl (mEq/L)	106.2 ± 1.7	106.6 ± 0.8	108.2 ± 0.9	105.4 ± 3.0	
Ca (mg/dL)	9.7 ± 0.4	9.4 ± 0.2	9.5 ± 0.1	9.3 ± 0.4	
Inorganic phosphate (mg/dL)	6.7 ± 0.3	7.4 ± 0.4	7.4 ± 0.4	8.7 ± 0.8 **	

Each value shows mean ± S.D.

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

Significantly different from the control group (#: p<0.05 by Steel's test).

Table 27. Blood chemical findings in male rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group		Control	1,4-dichlorobutane
mg/kg		0	12
Number of males		6	6
AST	(IU/L)	91.8 ± 12.4	85.7 ± 7.0
ALT	(IU/L)	25.9 ± 2.5	27.0 ± 2.8
ALP	(IU/L)	441.6 ± 70.6	431.1 ± 36.3
γ-GTP	(IU/L)	0.66 ± 0.27	0.86 ± 0.16
Total protein	(g/dL)	5.71 ± 0.20	5.82 ± 0.15
Albumin	(g/dL)	2.87 ± 0.09	3.00 ± 0.12
A/G		1.02 ± 0.05	1.07 ± 0.07
Total bilirubin	(mg/dL)	0.11 ± 0.02	0.13 ± 0.01
Urea nitrogen	(mg/dL)	15.9 ± 1.1	14.6 ± 2.2
Creatinine	(mg/dL)	0.24 ± 0.01	0.24 ± 0.02
Glucose	(mg/dL)	112.9 ± 15.1	118.5 ± 15.1
Total cholesterol	(mg/dL)	51.3 ± 13.1	71.5 ± 12.2 †
Triglyceride	(mg/dL)	42.8 ± 13.3	64.9 ± 23.2
Na	(mEq/L)	143.9 ± 0.7	145.1 ± 1.4
K	(mEq/L)	4.48 ± 0.12	4.30 ± 0.07 †
Cl	(mEq/L)	103.6 ± 0.6	104.1 ± 1.0
Ca	(mg/dL)	9.4 ± 0.2	9.7 ± 0.2
Inorganic phosphate	(mg/dL)	7.9 ± 0.4	8.0 ± 0.2

Each value shows mean ± S.D.

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

Table 28. Blood chemical findings in female rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group		Control	1,4-dichlorobutane
mg/kg		0	12
Number of females		6	6
AST	(IU/L)	81.3 ± 18.7	87.5 ± 34.9
ALT	(IU/L)	22.2 ± 1.7	31.7 ± 24.6
ALP	(IU/L)	298.5 ± 48.4	234.6 ± 53.2
γ-GTP	(IU/L)	1.05 ± 0.28	1.03 ± 0.17
Total protein	(g/dL)	5.99 ± 0.22	5.92 ± 0.57
Albumin	(g/dL)	3.29 ± 0.14	3.24 ± 0.43
A/G		1.22 ± 0.07	1.21 ± 0.11
Total bilirubin	(mg/dL)	0.15 ± 0.02	0.13 ± 0.01
Urea nitrogen	(mg/dL)	17.0 ± 2.4	19.0 ± 1.7
Creatinine	(mg/dL)	0.28 ± 0.03	0.26 ± 0.02
Glucose	(mg/dL)	114.6 ± 9.8	107.3 ± 8.2
Total cholesterol	(mg/dL)	71.4 ± 9.2	71.7 ± 10.7
Triglyceride	(mg/dL)	16.2 ± 5.5	16.7 ± 5.3
Na	(mEq/L)	143.0 ± 0.6	143.8 ± 0.7
K	(mEq/L)	4.24 ± 0.27	4.15 ± 0.20
Cl	(mEq/L)	105.8 ± 0.9	105.9 ± 0.8
Ca	(mg/dL)	9.5 ± 0.1	9.6 ± 0.3
Inorganic phosphate	(mg/dL)	7.8 ± 0.6	7.4 ± 0.6

Each value shows mean ± S.D.

Table 29. Necropsy findings in male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control	1,4-dichlorobutane		
		12	60	300
Number of males	6	6	6	6
Findings				
Normal	6	5	5	0
Kidney				
Dilatation, right pelvis	0	1	0	0
Liver				
Discoloration	0	0	1	6

Table 30. Necropsy findings in female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control	1,4-dichlorobutane		
		12	60	300
mg/kg	0			
Number of females	6	6	6	6
Findings				
Normal	6	6	2	0
Liver				
Discoloration	0	0	4	6

Table 31. Necropsy findings in male rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control	1,4-dichlorobutane
mg/kg	0	300
Number of males	6	6
Findings		
Normal	6	6

Table 32. Necropsy findings in female rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control	1,4-dichlorobutane
mg/kg	0	300
Number of females	6	6
Findings		
Normal	6	6

Table 33. Organ weights of male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of males	6	6	6	6	
Body weight (g)	357 ± 22	363 ± 25	369 ± 23	356 ± 25	
Brain (g)	2.04 ± 0.09	2.04 ± 0.08	2.01 ± 0.05	2.06 ± 0.11	
(g%)	0.57 ± 0.04	0.57 ± 0.06	0.55 ± 0.04	0.58 ± 0.04	
Pituitary (mg)	13.8 ± 2.0	14.4 ± 1.3	13.8 ± 2.0	16.5 ± 1.8 *	
(mg%)	3.9 ± 0.4	4.0 ± 0.3	3.8 ± 0.4	4.7 ± 0.8 *	
Salivary glands (mg)	611 ± 72	595 ± 45	614 ± 38	564 ± 69	
(mg%)	172 ± 20	164 ± 14	167 ± 10	159 ± 14	
Thyroids (mg)	25.2 ± 5.0	21.0 ± 5.3	23.6 ± 5.0	20.6 ± 5.0	
(mg%)	7.1 ± 1.3	5.8 ± 1.4	6.5 ± 1.6	5.8 ± 1.3	
Thymus (mg)	472 ± 143	526 ± 33	503 ± 150	578 ± 65	
(mg%)	131 ± 35	145 ± 11	136 ± 34	164 ± 24	
Heart (g)	1.34 ± 0.11	1.34 ± 0.07	1.31 ± 0.14	1.25 ± 0.09	
(g%)	0.38 ± 0.03	0.37 ± 0.03	0.36 ± 0.03	0.35 ± 0.03	
Liver (g)	11.21 ± 1.40	11.88 ± 0.95	12.08 ± 0.96	15.17 ± 1.31 **	
(g%)	3.14 ± 0.25	3.27 ± 0.13	3.27 ± 0.09	4.26 ± 0.15 **	
Spleen (mg)	711 ± 122	673 ± 107	647 ± 51	659 ± 82	
(mg%)	200 ± 38	185 ± 23	176 ± 10	186 ± 21	
Kidneys (g)	2.74 ± 0.13	2.78 ± 0.19	2.77 ± 0.22	3.23 ± 0.24 **	
(g%)	0.77 ± 0.03	0.77 ± 0.05	0.75 ± 0.04	0.91 ± 0.07 **	
Adrenals (mg)	57.6 ± 9.3	61.7 ± 12.9	57.9 ± 5.7	67.0 ± 11.0	
(mg%)	16.1 ± 2.0	17.0 ± 3.3	15.7 ± 1.3	18.8 ± 2.3	
Testes (g)	3.00 ± 0.30	3.15 ± 0.21	3.20 ± 0.15	3.14 ± 0.22	
(g%)	0.85 ± 0.12	0.87 ± 0.07	0.87 ± 0.05	0.89 ± 0.10	
Epididymides (mg)	831 ± 65	874 ± 48	827 ± 41	814 ± 70	
(mg%)	235 ± 32	242 ± 14	225 ± 17	230 ± 32	

Each value shows mean ± S.D.

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

Table 34. Organ weights of female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane		
	0	12	60	300	
Number of females	6	6	6	6	
Body weight (g)	204 ± 9	213 ± 13	217 ± 12	209 ± 9	
Brain (g)	1.83 ± 0.08	1.83 ± 0.08	1.92 ± 0.07	1.84 ± 0.06	
(g%)	0.90 ± 0.04	0.86 ± 0.02	0.89 ± 0.06	0.88 ± 0.05	
Pituitary (mg)	13.6 ± 2.2	15.1 ± 2.1	15.9 ± 1.0	15.8 ± 1.8	
(mg%)	6.7 ± 1.0	7.1 ± 1.0	7.4 ± 0.6	7.6 ± 1.1	
Salivary glands (mg)	386 ± 34	432 ± 17	416 ± 33	380 ± 49	
(mg%)	190 ± 18	203 ± 8	192 ± 14	181 ± 16	
Thyroids (mg)	16.3 ± 2.3	17.0 ± 2.2	17.1 ± 3.9	17.4 ± 1.6	
(mg%)	8.0 ± 0.9	8.0 ± 1.0	8.0 ± 2.4	8.3 ± 0.7	
Thymus (mg)	414 ± 133	478 ± 68	411 ± 69	437 ± 68	
(mg%)	204 ± 66	225 ± 34	190 ± 27	209 ± 30	
Heart (g)	0.77 ± 0.04	0.77 ± 0.07	0.81 ± 0.05	0.79 ± 0.04	
(g%)	0.38 ± 0.02	0.36 ± 0.01	0.38 ± 0.02	0.38 ± 0.02	
Liver (g)	6.26 ± 0.44	6.60 ± 0.72	7.59 ± 0.78 *	9.02 ± 0.90 **	
(g%)	3.08 ± 0.23	3.09 ± 0.17	3.50 ± 0.21 *	4.31 ± 0.32 **	
Spleen (mg)	430 ± 42	510 ± 114	489 ± 56	361 ± 35 #	
(mg%)	212 ± 23	238 ± 42	225 ± 20	173 ± 13	
Kidneys (g)	1.68 ± 0.09	1.69 ± 0.18	1.81 ± 0.14	2.03 ± 0.11 **	
(g%)	0.83 ± 0.05	0.79 ± 0.06	0.84 ± 0.05	0.97 ± 0.04 **	
Adrenals (mg)	67.3 ± 7.9	66.1 ± 7.7	70.3 ± 5.7	67.5 ± 11.6	
(mg%)	33.0 ± 3.5	31.0 ± 2.6	32.6 ± 3.4	32.2 ± 4.2	
Ovaries (mg)	80.2 ± 5.2	88.1 ± 12.7	88.2 ± 5.8	80.3 ± 10.8	
(mg%)	39.4 ± 2.6	41.3 ± 4.8	40.8 ± 1.5	38.3 ± 4.0	

Each value shows mean ± S.D.

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

Significantly different from the control group (#: p<0.05 by Steel's test).

Table 35. Organ weights of male rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control		1,4-dichlorobutane	
	0		300	
Number of males	6		6	
Body weight (g)	439 ± 20		430 ± 19	
Brain (g)	2.11 ± 0.09		2.03 ± 0.04	
(g%)	0.48 ± 0.01		0.47 ± 0.02	
Pituitary (mg)	15.3 ± 1.6		16.1 ± 1.6	
(mg%)	3.5 ± 0.3		3.8 ± 0.3	
Salivary glands (mg)	679 ± 61		665 ± 52	
(mg%)	155 ± 12		155 ± 14	
Thyroids (mg)	22.9 ± 4.1		23.5 ± 3.4	
(mg%)	5.2 ± 0.8		5.5 ± 0.9	
Thymus (mg)	463 ± 109		504 ± 81	
(mg%)	105 ± 22		118 ± 19	
Heart (g)	1.48 ± 0.11		1.44 ± 0.03	
(g%)	0.34 ± 0.02		0.34 ± 0.02	
Liver (g)	11.87 ± 0.98		11.93 ± 1.00	
(g%)	2.71 ± 0.26		2.78 ± 0.17	
Spleen (mg)	801 ± 102		743 ± 86	
(mg%)	182 ± 19		173 ± 15	
Kidneys (g)	2.96 ± 0.19		2.88 ± 0.18	
(g%)	0.67 ± 0.03		0.67 ± 0.04	
Adrenals (mg)	60.1 ± 5.1		64.0 ± 5.3	
(mg%)	13.7 ± 1.0		14.9 ± 1.2	
Testes (g)	3.17 ± 0.13		3.08 ± 0.27	
(g%)	0.72 ± 0.04		0.72 ± 0.06	
Epididymides (mg)	1073 ± 53		1042 ± 146	
(mg%)	245 ± 16		243 ± 36	

Each value shows mean ± S.D.

Table 36. Organ weights of female rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group	Control		1,4-dichlorobutane	
mg/kg	0		300	
Number of females	6		6	
Body weight (g)	239	± 17	231	± 15
Brain (g)	1.86	± 0.07	1.87	± 0.05
(g%)	0.78	± 0.06	0.81	± 0.04
Pituitary (mg)	15.7	± 3.0	15.3	± 1.0
(mg%)	6.6	± 1.4	6.6	± 0.4
Salivary glands (mg)	423	± 65	431	± 61
(mg%)	177	± 19	187	± 20
Thyroids (mg)	16.9	± 3.0	18.8	± 1.9
(mg%)	7.1	± 1.3	8.2	± 0.9
Thymus (mg)	428	± 95	427	± 73
(mg%)	180	± 44	185	± 24
Heart (g)	0.87	± 0.06	0.82	± 0.04
(g%)	0.36	± 0.03	0.36	± 0.02
Liver (g)	6.54	± 0.69	6.60	± 0.54
(g%)	2.73	± 0.20	2.86	± 0.17
Spleen (mg)	475	± 90	501	± 70
(mg%)	198	± 31	217	± 21
Kidneys (g)	1.73	± 0.13	1.70	± 0.15
(g%)	0.73	± 0.06	0.74	± 0.04
Adrenals (mg)	68.5	± 6.6	63.2	± 11.6
(mg%)	28.7	± 3.4	27.4	± 4.1
Ovaries (mg)	86.5	± 16.2	77.3	± 12.7
(mg%)	36.1	± 5.1	33.4	± 3.7

Each value shows mean ± S.D.

Table 37. Histopathological findings in male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control						1,4-dichlorobutane											
	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+
Grade																		
Findings																		
Heart	[6] ^{c)}						[0] ^{c)}						[0] ^{c)}					[6] ^{c)}
Lung	[6]						[0]						[0]					[6]
Trachea	[6]						[0]						[0]					[6]
Liver	[6]						[6]						[6]					[6]
Swelling, hepatocyte, periportal	6	0	0	0	0	0	4	2	2	0	0	0	1	5	5	0	0	#
Microgranuloma	6	0	0	0	0	0	6	0	0	0	0	0	4	2	2	0	0	0
Pancreas	[6]						[6]						[6]					[6]
Decreased, zymogen granules	6	0	0	0	0	0	5	1	1	0	0	0	0	6	6	0	0	##
Sublingual gland	[6]						[0]						[0]					[6]
Submandibular gland	[6]						[0]						[0]					[6]
Esophagus	[6]						[0]						[0]					[6]
Stomach	[6]						[0]						[0]					[6]
Duodenum	[6]						[0]						[0]					[6]
Jejunum	[6]						[0]						[0]					[6]
Mineralization, Peyer's patch	5	1	1	0	0	0												6
Ileum	[6]						[0]						[0]					[6]
Cecum	[6]						[0]						[0]					[6]
Colon	[6]						[0]						[0]					[6]
Rectum	[6]						[0]						[0]					[6]
Thymus	[6]						[6]						[6]					[6]
Starry sky appearance	6	0	0	0	0	0	6	0	0	0	0	0	6	0	0	0	0	2
Spleen	[6]						[0]						[0]					[6]
Mandibular lymph node	[6]						[0]						[0]					[6]
Mesenteric lymph node	[6]						[0]						[0]					[6]

Grade of histopathological findings; ±: slight, +: mild, 2+: moderate, 3+: marked.

(Continued)

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of males examined.

Significantly different from the control group (#: P<0.05, ##: P<0.01 by Steel's test).

Significantly different by dose response test (&&: p<0.01 by Cochran-Armitage exact test).

Table 37. (Continued) Histopathological findings in male rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control						1,4-dichlorobutane																	
	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+
Grade																								
Findings																								
Kidney	[6] ^{c)}						[6] ^{c)}						[6] ^{c)}						[6] ^{c)}					
Swelling, proximal tubule	6	0	0	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0	0	6	6	6	0	0
Hydronephrosis, right	6	0	0	0	0	0	5	1	1	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0
Cast, hyaline, lateral	5	1	1	0	0	0	6	0	0	0	0	0	4	2	2	0	0	0	5	1	1	0	0	0
Cyst, left	5	1	1	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0
Urinary bladder	[6]						[0]						[0]						[6]					
Testis	[6]						[0]						[0]						[6]					
Epididymis	[6]						[0]						[0]						[6]					
Seminal vesicle	[6]						[0]						[0]						[6]					
Prostate	[6]						[0]						[0]						[6]					
Pituitary	[6]						[0]						[0]						[6]					
Adrenal	[6]						[0]						[0]						[6]					
Thyroid	[6]						[0]						[0]						[6]					
Parathyroid	[6]						[0]						[0]						[6]					
Cerebrum	[6]						[0]						[0]						[6]					
Cerebellum	[6]						[0]						[0]						[6]					
Medulla oblongata	[6]						[0]						[0]						[6]					
Spinal cord	[6]						[0]						[0]						[6]					
Sciatic nerve	[6]						[0]						[0]						[6]					
Eyeball	[6]						[0]						[0]						[6]					
Dysplasia, retina, left	5	1	1	0	0	0												6	0	0	0	0	0	
Harderian gland	[6]						[0]						[0]						[6]					
Bone marrow (sternum, femur)	[6]						[0]						[0]						[6]					
Bone (sternum, femur)	[6]						[0]						[0]						[6]					
Femur muscle	[6]						[0]						[0]						[6]					

Grade of histopathological findings; ±: slight, +: mild, 2+: moderate, 3+: marked.

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of males examined.

Significantly different from the control group (##: p<0.01 by Steel's test).

Significantly different by dose response test (&&: p<0.01 by Cochran-Armitage exact test).

Table 38. Histopathological findings in female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control						1,4-dichlorobutane												
	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	
Grade																			
Findings																			
Heart	[6] ^{c)}						[0] ^{c)}						[0] ^{c)}					[6] ^{c)}	
Lung	[6]						[0]						[0]					[6]	
Mineralization, vascular wall, left	6	0	0	0	0	0								5	1	1	0	0	0
Trachea	[6]						[0]						[0]					[6]	
Liver	[6]						[6]						[6]					[6]	
Swelling, hepatocyte, periportal	6	0	0	0	0	0	1	5	5	0	0	0	#	0	6	6	0	6	&&
Microgranuloma	6	0	0	0	0	0	5	1	1	0	0	0		6	0	0	0	0	
Pancreas	[6]						[6]						[6]					[6]	
Decreased, zymogen granules	6	0	0	0	0	0	1	5	5	0	0	0	#	0	6	0	6	0	&&
Sublingual gland	[6]						[0]						[0]					[6]	
Submandibular gland	[6]						[0]						[0]					[6]	
Esophagus	[6]						[0]						[0]					[6]	
Stomach	[6]						[0]						[0]					[6]	
Duodenum	[6]						[0]						[0]					[6]	
Jejunum	[6]						[0]						[0]					[6]	
Ileum	[6]						[0]						[0]					[6]	
Cecum	[6]						[0]						[0]					[6]	
Colon	[6]						[0]						[0]					[6]	
Rectum	[6]						[0]						[0]					[6]	
Thymus	[6]						[6]						[6]					[6]	
Starry sky appearance	6	0	0	0	0	0	6	0	0	0	0	0		6	0	0	0	0	
Spleen	[6]						[0]						[0]					[6]	
Mandibular lymph node	[6]						[0]						[0]					[6]	
Mesenteric lymph node	[6]						[0]						[0]					[6]	

Grade of histopathological findings; ±: slight, +: mild, 2+: moderate, 3+: marked.

(Continued)

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of females examined.

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

Significantly different by dose response test (&&: p<0.01 by Cochran-Armitage exact test).

Table 38. (Continued) Histopathological findings in female rats on termination of administration period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control						1,4-dichlorobutane											
	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+
Grade																		
Findings																		
Kidney	[6] ^{c)}						[6] ^{c)}						[6] ^{c)}					[6] ^{c)}
Swelling, proximal tubule	6	0	0	0	0	0	6	0	0	0	0	0	5	1	1	0	0	0
Hydronephrosis, right	5	1	1	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0
Urinary bladder	[6]						[0]						[0]					[6]
Ovary	[6]						[0]						[0]					[6]
Uterus	[6]						[0]						[0]					[6]
Vagina	[6]						[0]						[0]					[6]
Pituitary	[6]						[0]						[0]					[6]
Adrenal	[6]						[0]						[0]					[6]
Thyroid	[6]						[0]						[0]					[6]
Ectopic, thymic tissue	4	2	2	0	0	0								6	0	0	0	0
Parathyroid	[6]						[0]						[0]					[6]
Cerebrum	[6]						[0]						[0]					[6]
Cerebellum	[6]						[0]						[0]					[6]
Medulla oblongata	[6]						[0]						[0]					[6]
Spinal cord	[6]						[0]						[0]					[6]
Sciatic nerve	[6]						[0]						[0]					[6]
Eyeball	[6]						[0]						[0]					[6]
Harderian gland	[6]						[0]						[0]					[6]
Bone marrow (sternum, femur)	[6]						[0]						[0]					[6]
Bone (sternum, femur)	[6]						[0]						[0]					[6]
Femur muscle	[6]						[0]						[0]					[6]
Mammary gland	[6]						[0]						[0]					[6]

Grade of histopathological findings; ±: slight, +: mild, 2+: moderate, 3+: marked.

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of females examined.

Significantly different from the control group (##: p<0.01 by Steel's test).

Significantly different by dose response test (&&: p<0.01 by Cochran-Armitage exact test).

Table 39. Histopathological findings in male rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control						1,4-dichlorobutane					
	0						300					
Grade	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+
Findings												
Liver	[6] ^{c)}						[6] ^{c)}					
Pancreas	[6]						[6]					
Thymus	[6]						[6]					
Kidney	[6]						[6]					
Cyst, left	6	0	0	0	0	0	5	1	1	0	0	0

Grade of histopathological findings; ±: slight, +: mild, 2+: moderate, 3+: marked.

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of males examined.

Table 40. Histopathological findings in female rats on termination of recovery period in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane

Group mg/kg	Control						1,4-dichlorobutane					
	0						300					
Grade	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+
Findings												
Liver	[6] ^{c)}						[6] ^{c)}					
Swelling, hepatocyte, periportal	6	0	0	0	0	0	4	2	2	0	0	0
Pancreas	[6]						[6]					
Thymus	[6]						[6]					
Kidney	[6]						[6]					
Cyst, left	5	1	1	0	0	0	6	0	0	0	0	0

Grade of histopathological findings; ±: slight, +: mild, 2+: moderate, 3+: marked.

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of females examined.

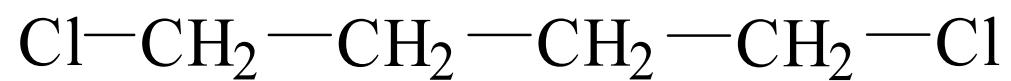


Fig. 1. Chemical structure of 1,4-dichlorobutane.

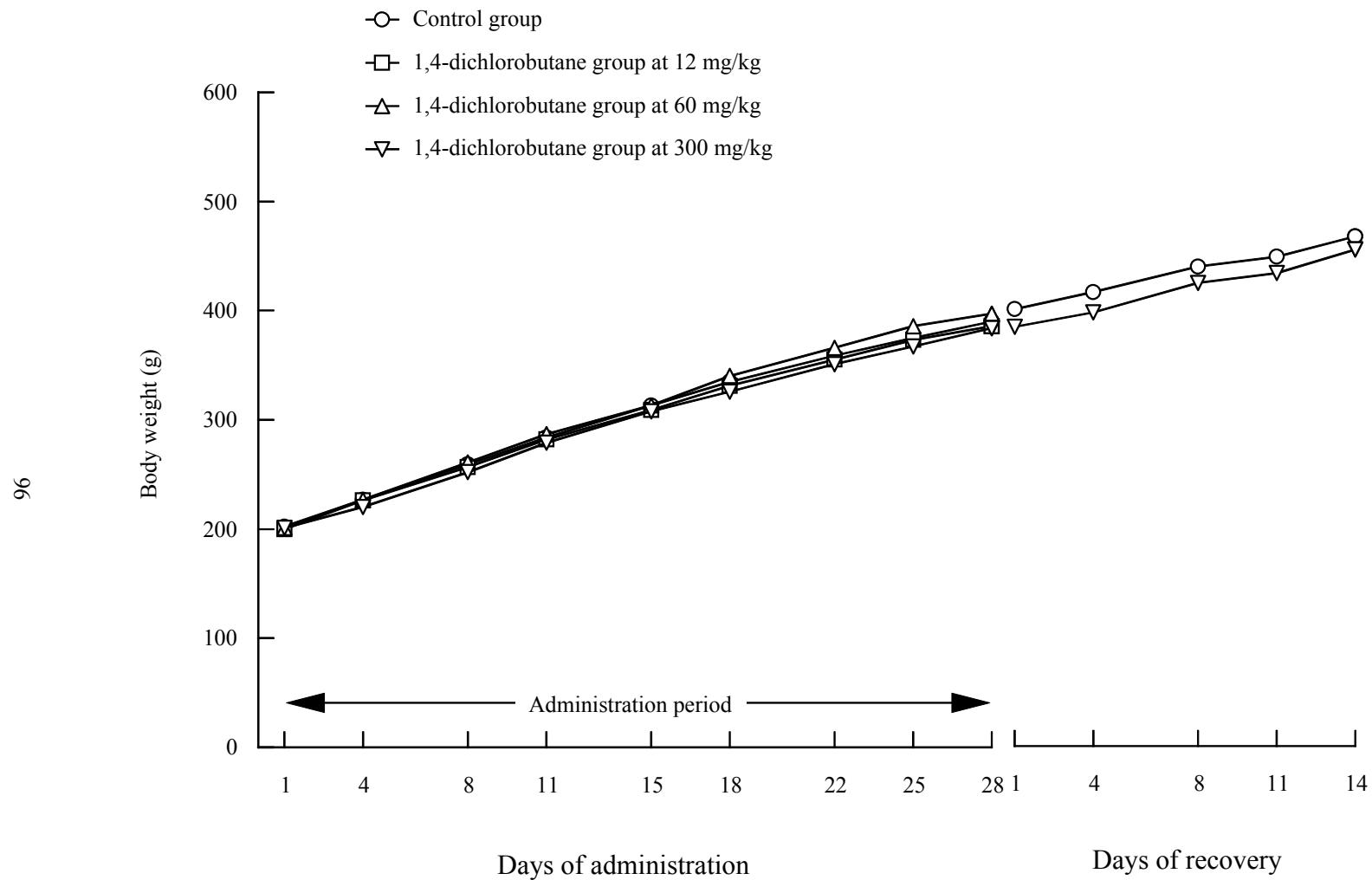


Fig. 2. Body weights of male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane.

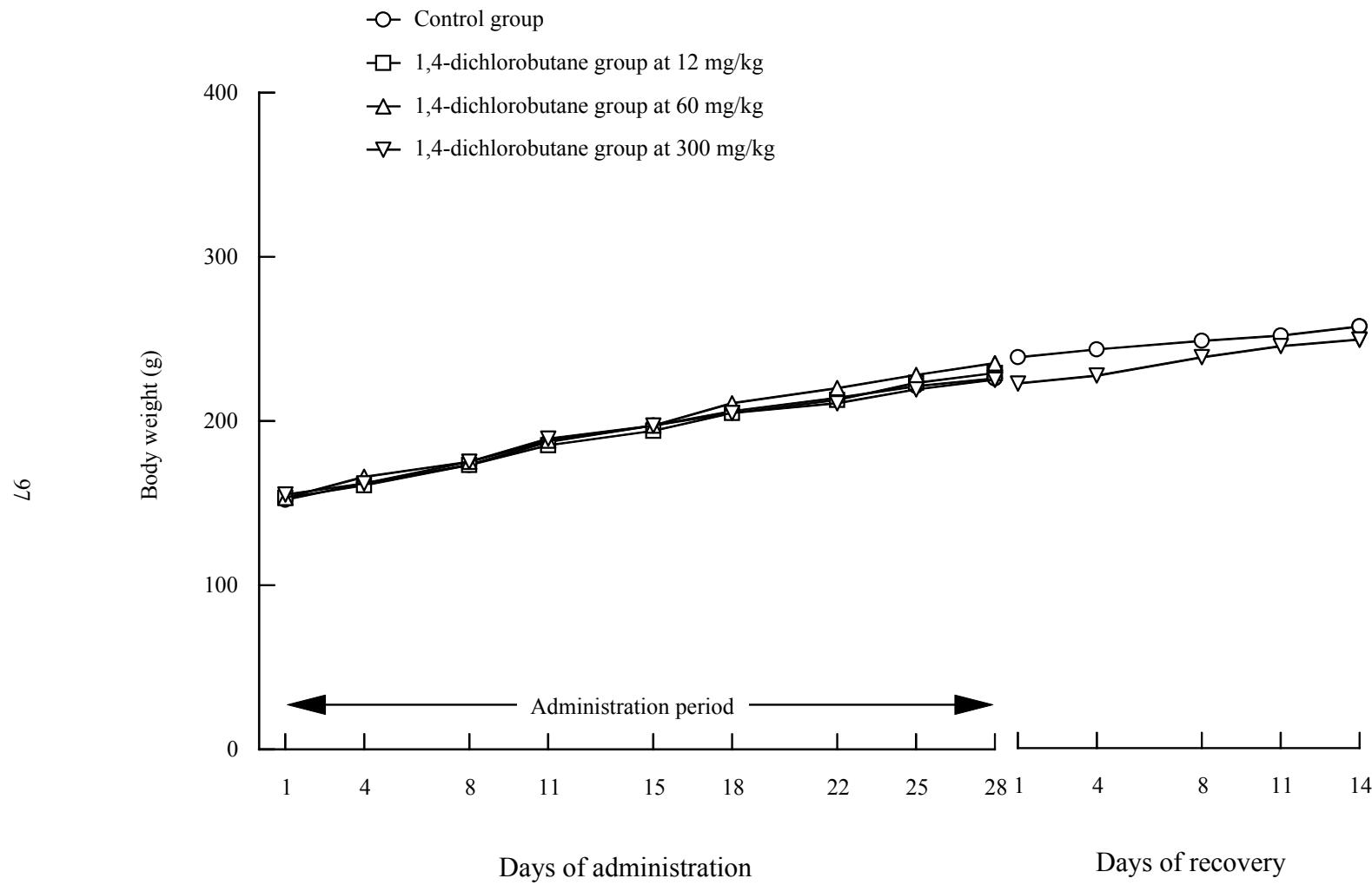
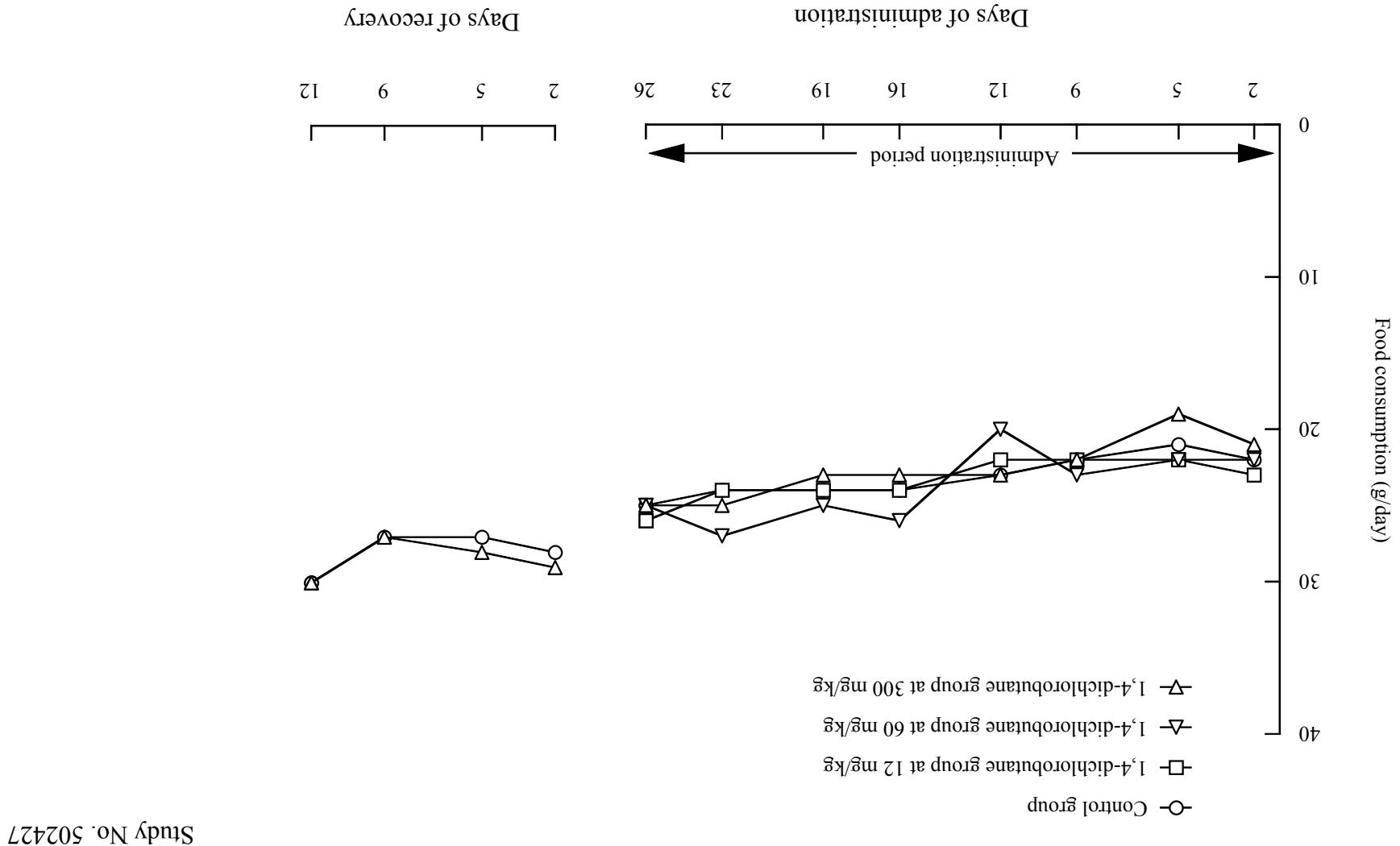


Fig. 3. Body weights of female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane.

Fig. 4. Food consumption in male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane.



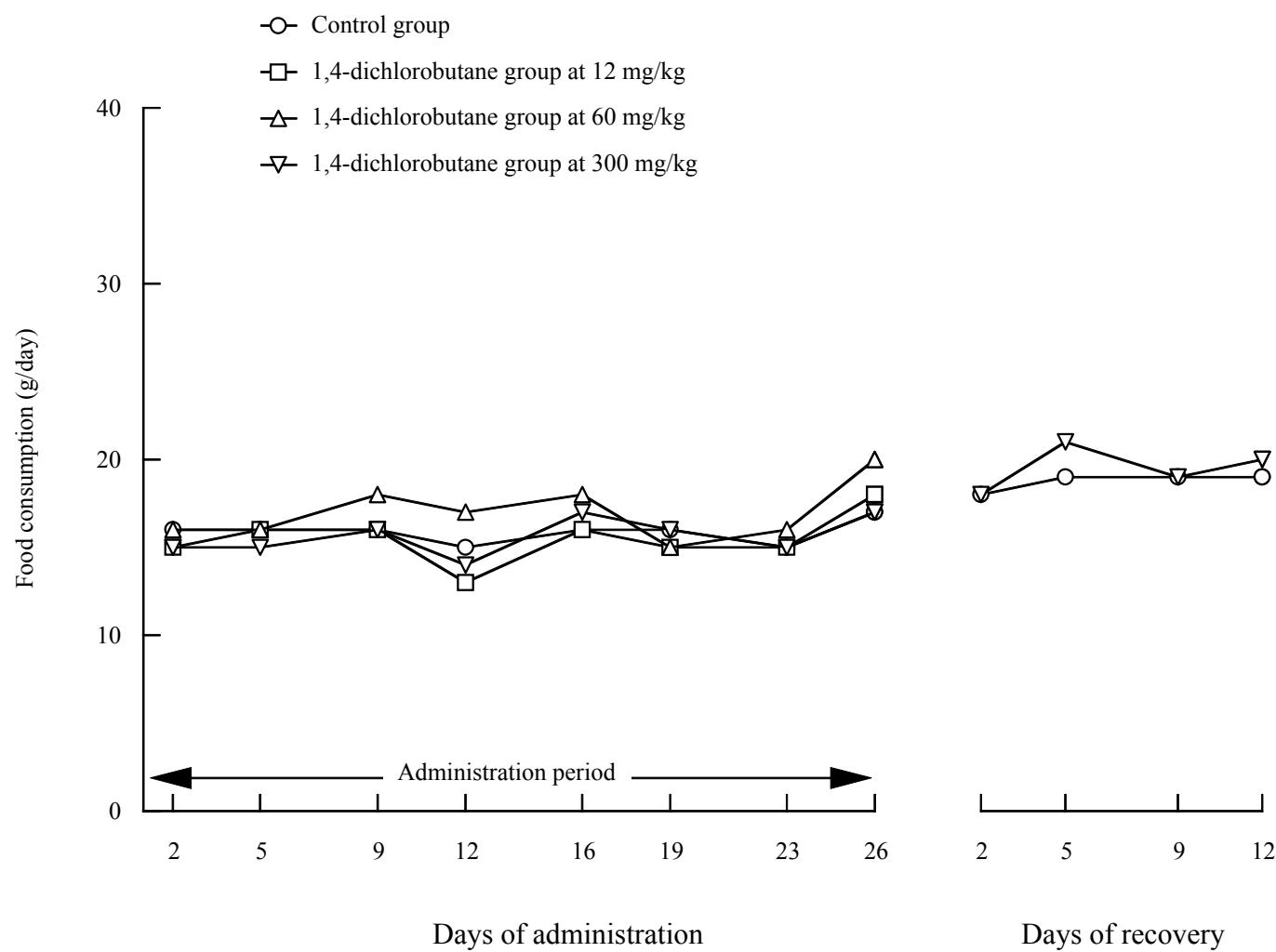


Fig. 5. Food consumption in female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane.

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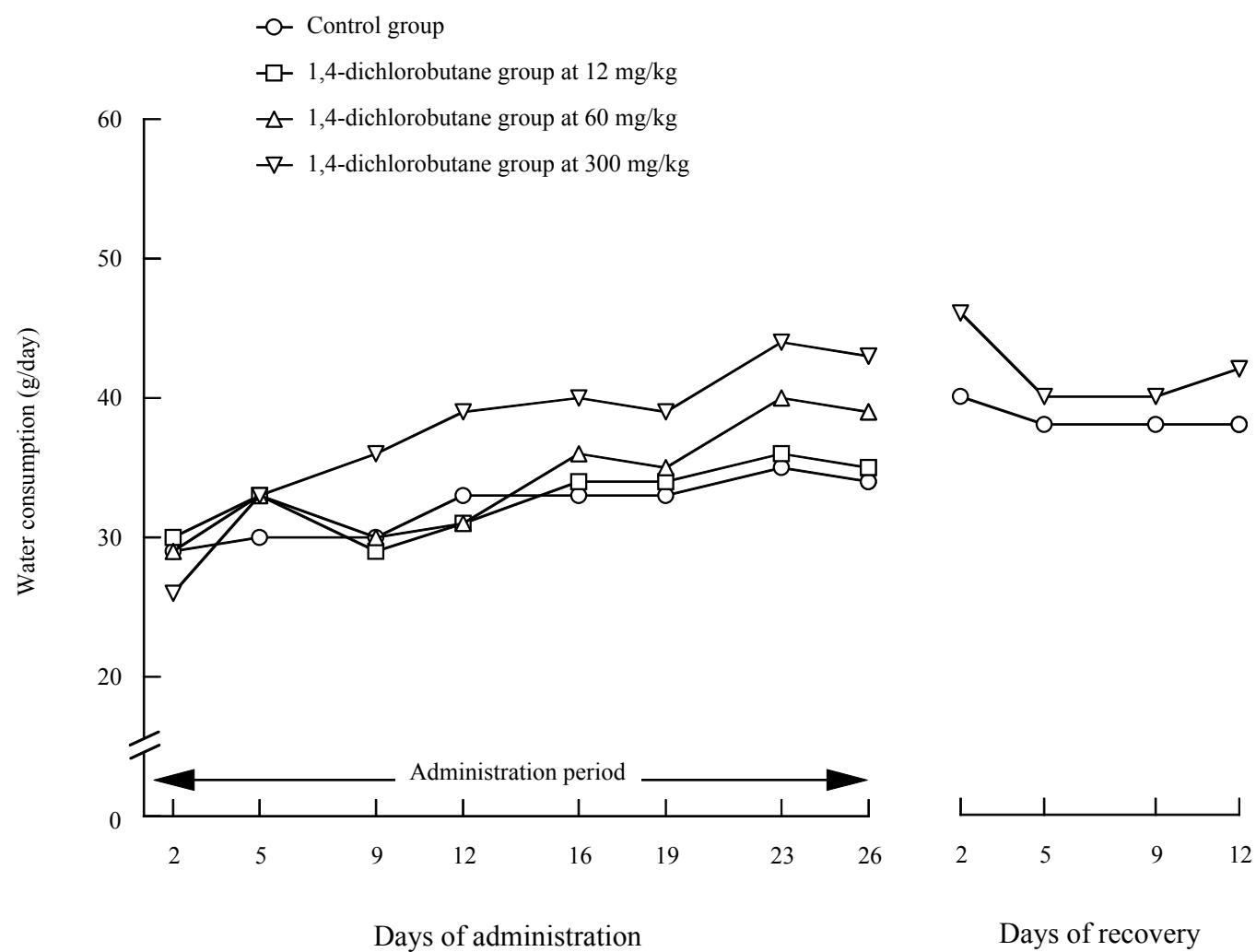


Fig. 6. Water consumption in male rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane.

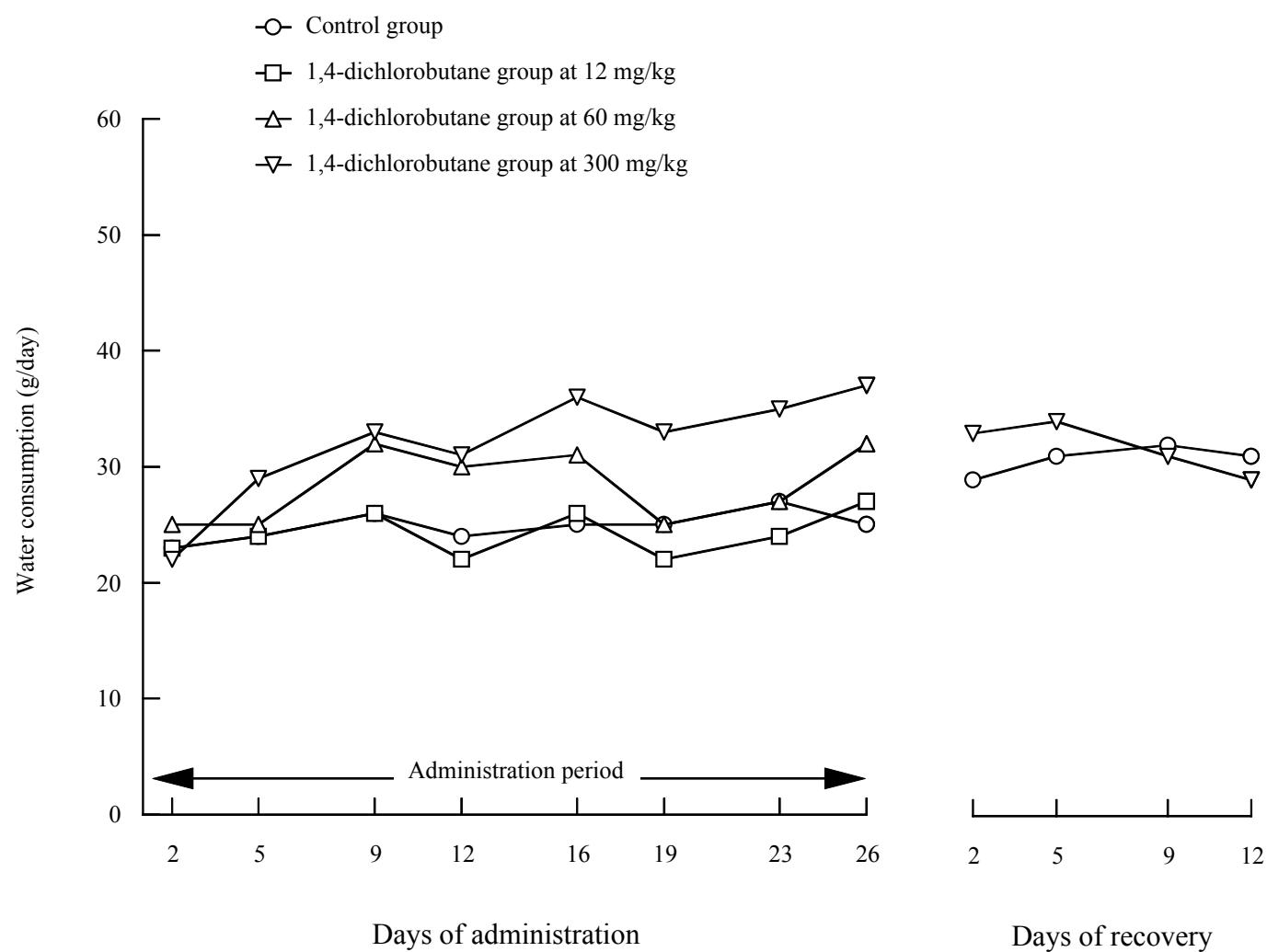


Fig. 7. Water consumption in female rats in repeated dose 28-day oral toxicity study of 1,4-dichlorobutane.

Appendix 1-1. Individual general signs in male rats

Control group

Male No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
M01101	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	
M01102	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		
M01103	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		
M01104	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		
M01105	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		
M01106	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		
M01107	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		
M01108	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		
M01109	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		
M01110	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		
M01111	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		
M01112	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		
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

Appendix 1-1. (Continued) Individual general signs in male rats

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Control group		Days of administration																										
Male No.	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
M01101	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	*	
M01102	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	*	
M01103	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	*	
M01104	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	*	
M01105	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	*	
M01106	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	*	
M01107	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		
M01108	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		
M01109	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		
M01110	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		
M01111	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		
M01112	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		
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	

Pre: Before administration, Post: after administration.

(Continued)

*: Euthanized.

N: Normal.

Appendix 1-1. (Continued) Individual general signs in male rats

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M01107	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M01108	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M01109	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M01110	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M01111	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M01112	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

*: Euthanized.

N: Normal.

Appendix 1-2. Individual general signs in male rats

Male No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
M02201	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	
M02202	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		
M02203	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		
M02204	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		
M02205	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		
M02206	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		
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

Appendix 1-2. (Continued) Individual general signs in male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
M02201	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	*		
M02202	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	*		
M02203	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	*		
M02204	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	*		
M02205	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	*		
M02206	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	*		
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			

Pre: Before administration, Post: after administration.

*: Euthanized.

N: Normal.

Appendix 1-3. Individual general signs in male rats

Male No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
M03301	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	
M03302	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		
M03303	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		
M03304	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		
M03305	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		
M03306	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		
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

Appendix 1-3. (Continued) Individual general signs in male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
M03301	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	*		
M03302	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	*		
M03303	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	*		
M03304	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	*		
M03305	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	*		
M03306	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	*		
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			

Pre: Before administration, Post: after administration.

*: Euthanized.

N: Normal.

Appendix 1-4. Individual general signs in male rats

Male No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
M04401	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	A	N	A		
M04402	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A		
M04403	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	A			
M04404	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	A		
M04405	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	A		
M04406	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		
M04407	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		
M04408	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		
M04409	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		
M04410	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N		
M04411	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		
M04412	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	A		
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	10	12	9	12	7	12	6	
	A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	3	0	5	0	6	

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

A: Salivation.

Appendix 1-4. (Continued) Individual general signs in male rats

1,4-dichlorobutane group at 300 mg/kg

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Male No.	Days of administration																								Total ^{a)}				
	15		16		17		18		19		20		21		22		23		24		25		26		27		28		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	A
M04401	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	*	+
M04402	N	A	N	N	N	N	N	N	N	A	N	N	A	N	N	A	N	N	A	N	N	A	N	N	N	N	*	+	
M04403	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	*	+
M04404	N	N	N	N	N	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	*	+	
M04405	N	A	N	A	N	A	N	A	N	N	N	N	N	N	A	N	A	N	A	N	A	N	N	N	N	N	*	+	
M04406	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	A	*	+
M04407	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	A	+	
M04408	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	N	A	N	A	N	A	N	A	+	
M04409	N	A	N	A	N	A	N	A	N	A	N	N	N	N	N	N	N	N	A	N	N	N	A	N	N	A	N	+	
M04410	N	N	N	A	N	A	N	A	N	N	N	A	N	N	A	N	N	A	N	A	N	A	N	A	N	A	+		
M04411	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	A	+		
M04412	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	A	N	A	N	A	+		
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	12		
N	12	4	12	5	12	4	12	4	12	5	12	5	12	5	12	3	12	1	12	4	12	2	12	4	12	3	12	-	
A	0	8	0	7	0	8	0	8	0	7	0	7	0	7	0	9	0	11	0	8	0	10	0	8	0	9	0	12	

Pre: Before administration, Post: after administration.

(Continued)

*: Euthanized.

a): Number of males showing abnormal signs at least once between Days 1 and 29 of administration.

-: Not observed, +: observed.

N: Normal.

A: Salivation.

Appendix 1-4. (Continued) Individual general signs in male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M04407	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M04408	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M04409	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M04410	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M04411	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
M04412	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

*: Euthanized.

N: Normal.

Appendix 2-1. Individual general signs in female rats

Control group		Days of administration																											
Female No.		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F01151		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	
F01152		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	
F01153		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	
F01154		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	
F01155		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	
F01156		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	
F01157		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	
F01158		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	
F01159		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	
F01160		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	
F01161		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	
F01162		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	
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

Appendix 2-1. (Continued) Individual general signs in female rats

Control group

Female No.	Days of administration																													
	15		16		17		18		19		20		21		22		23		24		25		26		27		28		29	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01151	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	*
F01152	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	*
F01153	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	*
F01154	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	*
F01155	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	*
F01156	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	*
F01157	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	
F01158	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	
F01159	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	
F01160	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	
F01161	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	
F01162	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	
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	

Pre: Before administration, Post: after administration.

(Continued)

*: Euthanized.

N: Normal.

Appendix 2-1. (Continued) Individual general signs in female rats

Female No.	Control group														
	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F01157	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F01158	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F01159	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F01160	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F01161	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F01162	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

*: Euthanized.

N: Normal.

Appendix 2-2. Individual general signs in female rats

Female No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F02251	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	
F02252	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		
F02253	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		
F02254	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		
F02255	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		
F02256	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		
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		

Pre: Before administration, Post: after administration.

N: Normal.

(Continued)

Appendix 2-2. (Continued) Individual general signs in female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F02251	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	*		
F02252	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	*		
F02253	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	*		
F02254	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	*		
F02255	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	*		
F02256	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	*		
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		

Pre: Before administration, Post: after administration.

*: Euthanized.

N: Normal.

Appendix 2-3. Individual general signs in female rats

		Days of administration																											
		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
Female No.		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F03351		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	
F03352		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	
F03353		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	
F03354		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	
F03355		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	
F03356		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	
Number of females		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

Appendix 2-3. (Continued) Individual general signs in female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F03351	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	*		
F03352	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	*		
F03353	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	*		
F03354	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	*		
F03355	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	*		
F03356	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	*		
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			

Pre: Before administration, Post: after administration.

*: Euthanized.

N: Normal.

Appendix 2-4. Individual general signs in female rats

		Days of administration																											
		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
Female No.		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F04451		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	
F04452		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	A	N	A	N	A	
F04453		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	
F04454		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	
F04455		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	
F04456		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	A	
F04457		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	
F04458		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	
F04459		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	
F04460		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	
F04461		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	A	N	A	N	A	
F04462		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A		
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	10	12	10	12	9	12	8	12	7	
	A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	2	0	3	0	4	0	5	

Pre: Before administration, Post: after administration.

(Continued)

N: Normal.

A: Salivation.

Appendix 2-4. (Continued) Individual general signs in female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Days of administration																												Total ^{a)}		
	15		16		17		18		19		20		21		22		23		24		25		26		27		28				
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	A		
F04451	N	N	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	*	+		
F04452	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	*	+		
F04453	N	N	N	A	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	N	N	A	N	*	+	
F04454	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	A	N	A	N	A	N	A	N	N	N	*	+			
F04455	N	N	N	A	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	*	+		
F04456	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	A	N	N	*	+	
F04457	N	A	N	A	N	N	N	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	N	N	A	N	A	+			
F04458	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	N	+		
F04459	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	A	N	A	N	N	+	
F04460	N	A	N	A	N	N	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	+		
F04461	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A	+		
F04462	N	A	N	A	N	N	N	A	N	A	N	A	N	A	N	N	N	N	N	A	N	N	N	A	N	N	N	+			
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	12		
N	12	7	12	4	12	9	12	7	12	3	12	4	12	5	12	6	12	5	12	5	12	2	12	3	12	2	12	6	6	-	
A	0	5	0	8	0	3	0	5	0	9	0	8	0	7	0	6	0	7	0	7	0	10	0	9	0	10	0	6	0	12	

Pre: Before administration, Post: after administration.

(Continued)

*: Euthanized.

a): Number of females showing abnormal signs at least once between Days 1 and 29 of administration.

-: Not observed, +: observed.

N: Normal.

A: Salivation.

Appendix 2-4. (Continued) Individual general signs in female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F04457	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F04458	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F04459	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F04460	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F04461	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
F04462	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N *
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

*: Euthanized.

N: Normal.

Appendix 3-1. Individual body weights (g) of male rats

Male No.	Days of administration								Days of recovery					
	1	4	8	11	15	18	22	25	28	1	4	8	11	14
M01101	200	223	253	272	299	317	345	359	364					
M01102	202	232	267	294	326	353	386	405	420					
M01103	203	226	256	283	305	314	333	344	359					
M01104	194	217	245	264	295	316	336	352	365					
M01105	210	235	269	292	321	347	374	386	405					
M01106	205	228	264	301	327	348	370	383	395					
M01107	210	232	267	294	328	350	373	394	404	413	426	447	459	474
M01108	188	215	251	269	312	334	366	383	406	404	429	455	466	484
M01109	199	227	257	277	297	318	342	361	378	377	394	407	414	429
M01110	203	227	261	286	317	339	361	377	394	400	412	443	449	476
M01111	200	229	259	283	311	334	350	366	380	384	396	419	432	455
M01112	205	227	260	288	322	354	377	395	411	422	438	462	469	481
Number of males	12	12	12	12	12	12	12	12	12	6	6	6	6	6
Mean	202	227	259	284	313	335	359	375	390	400	416	439	448	467
S.D.	6	6	7	11	12	16	18	19	20	17	18	21	21	21

Appendix 3-2. Individual body weights (g) of male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Days of administration								
	1	4	8	11	15	18	22	25	28
M02201	200	226	249	278	318	344	372	389	402
M02202	203	228	259	284	307	330	356	375	383
M02203	190	212	238	255	271	286	307	328	334
M02204	206	232	269	285	319	339	362	375	388
M02205	202	229	261	292	312	339	361	384	399
M02206	201	230	265	299	325	346	372	387	407
Number of males	6	6	6	6	6	6	6	6	6
Mean	200	226	257	282	309	331	355	373	386
S.D.	5	7	11	15	19	23	24	23	27
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 3-3. Individual body weights (g) of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Days of administration								
	1	4	8	11	15	18	22	25	28
M03301	206	234	271	301	330	360	394	413	424
M03302	199	228	258	278	310	335	356	372	387
M03303	211	240	278	306	330	357	383	405	412
M03304	204	224	266	294	323	357	382	408	414
M03305	194	215	245	269	288	315	343	359	372
M03306	189	218	248	272	295	317	338	359	371
Number of males	6	6	6	6	6	6	6	6	6
Mean	201	227	261	287	313	340	366	386	397
S.D.	8	10	13	16	18	21	23	25	23
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 3-4. Individual body weights (g) of male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Days of administration								Days of recovery					
	1	4	8	11	15	18	22	25	28	1	4	8	11	14
M04401	205	225	260	288	308	334	362	378	388					
M04402	200	209	240	269	292	310	323	331	343					
M04403	207	233	269	298	335	344	373	387	404					
M04404	198	218	245	272	299	327	366	389	407					
M04405	194	207	242	267	298	313	340	357	371					
M04406	200	223	253	278	311	332	366	385	407					
M04407	191	209	229	248	284	298	317	339	359	361	382	400	401	418
M04408	203	229	267	293	324	343	370	389	395	391	389	422	438	463
M04409	202	219	259	280	309	326	346	360	376	380	390	416	429	446
M04410	195	218	258	286	317	326	346	364	383	387	404	432	442	460
M04411	208	223	251	278	310	325	354	377	394	402	416	449	448	480
M04412	204	227	256	285	306	332	344	350	375	381	400	424	442	462
Number of males	12	12	12	12	12	12	12	12	12	6	6	6	6	6
Mean	201	220	252	279	308	326	351	367	384	384	397	424	433	455
S.D.	5	8	12	13	14	13	18	20	20	14	12	16	17	21
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

TT: Analysis by Student's t-test.

Appendix 4-1. Individual body weights (g) of female rats

Control group Female No.	Days of administration								Days of recovery					
	1	4	8	11	15	18	22	25	28	1	4	8	11	14
F01151	150	148	171	188	200	209	217	222	224					
F01152	148	162	176	189	201	212	220	222	225					
F01153	148	158	161	184	193	200	212	211	216					
F01154	147	155	160	168	174	178	188	194	199					
F01155	150	164	172	190	198	204	211	216	224					
F01156	148	158	166	182	194	203	208	215	220					
F01157	155	167	179	190	200	213	223	235	239	246	249	257	262	272
F01158	153	163	172	188	197	212	221	229	231	235	236	239	243	252
F01159	165	173	192	203	215	228	240	251	260	265	270	280	278	287
F01160	159	173	187	201	212	211	219	231	234	236	242	248	248	245
F01161	147	162	172	186	198	204	212	218	227	225	239	239	243	249
F01162	148	156	167	174	186	195	201	208	214	218	222	224	229	238
Number of females	12	12	12	12	12	12	12	12	12	6	6	6	6	6
Mean	152	162	173	187	197	206	214	221	226	238	243	248	251	257
S.D.	6	7	10	10	11	12	13	15	15	17	16	19	17	19

Appendix 4-2. Individual body weights (g) of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Days of administration								
	1	4	8	11	15	18	22	25	28
F02251	148	156	168	183	193	205	206	215	213
F02252	167	169	178	183	196	212	225	233	247
F02253	150	161	173	183	188	194	203	207	214
F02254	150	161	172	186	195	212	217	225	227
F02255	151	158	171	190	199	201	212	226	238
F02256	153	161	173	187	195	205	216	229	235
Number of females	6	6	6	6	6	6	6	6	6
Mean	153	161	173	185	194	205	213	223	229
S.D.	7	4	3	3	4	7	8	10	14
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 4-3. Individual body weights (g) of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Days of administration								
	1	4	8	11	15	18	22	25	28
F03351	158	169	177	193	202	213	225	239	241
F03352	149	168	176	182	196	206	216	218	231
F03353	148	157	173	187	196	208	215	225	229
F03354	160	170	179	196	204	221	226	238	243
F03355	148	158	164	173	182	198	205	209	212
F03356	156	171	181	195	204	220	230	239	251
Number of females	6	6	6	6	6	6	6	6	6
Mean	153	166	175	188	197	211	220	228	235
S.D.	5	6	6	9	8	9	9	13	14
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 4-4. Individual body weights (g) of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Days of administration								Days of recovery					
	1	4	8	11	15	18	22	25	28	1	4	8	11	14
F04451	158	170	185	191	204	215	215	223	231					
F04452	161	163	190	216	216	228	237	245	248					
F04453	153	165	175	190	203	209	214	220	227					
F04454	157	163	175	190	193	203	211	216	228					
F04455	149	153	165	176	181	192	200	208	212					
F04456	160	168	178	195	196	209	216	219	226					
F04457	147	157	169	175	185	182	196	204	213	212	221	227	235	238
F04458	140	147	158	173	188	185	194	202	207	204	206	219	221	229
F04459	159	167	182	194	206	210	222	231	234	236	243	252	261	267
F04460	162	166	177	186	203	212	212	224	230	236	235	243	252	256
F04461	157	166	176	189	197	209	214	228	226	229	231	246	251	256
F04462	155	159	170	188	192	204	204	211	218	215	228	238	247	250
Number of females	12	12	12	12	12	12	12	12	12	6	6	6	6	6
Mean	155	162	175	189	197	205	211	219	225	222	227	238	245	249
S.D.	7	7	9	11	10	13	12	12	11	14	13	12	14	14
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

TT: Analysis by Student's t-test.

Appendix 5-1. Individual food consumption (g/day) in male rats

Male No.	Days of administration							Days of recovery				
	2	5	9	12	16	19	23	26	2	5	9	12
M01101	21	21	23	21	19	24	17	18				
M01102	24	22	25	25	28	27	28	27				
M01103	20	21	25	24	24	24	22	21				
M01104	21	19	18	22	23	19	20	22				
M01105	22	26	22	26	26	27	27	27				
M01106	22	23	24	24	26	27	27	29				
M01107	20	23	24	23	23	23	24	23	27	25	28	31
M01108	23	19	15	19	23	23	26	24	27	28	28	29
M01109	24	21	23	19	25	23	25	24	28	25	23	27
M01110	22	22	22	26	19	25	23	27	27	29	29	31
M01111	24	25	24	24	25	25	26	26	29	27	27	29
M01112	22	15	24	24	25	22	26	28	30	28	27	31
Number of males	12	12	12	12	12	12	12	12	6	6	6	6
Mean	22	21	22	23	24	24	24	25	28	27	27	30
S.D.	1	3	3	2	3	2	3	3	1	2	2	2

Appendix 5-2. Individual food consumption (g/day) in male rats

1,4-dichlorobutane group at 12 mg/kg		Days of administration							
Male No.		2	5	9	12	16	19	23	26
M02201		22	23	23	25	27	26	26	25
M02202		24	22	17	22	22	23	25	26
M02203		23	22	20	14	22	21	23	21
M02204		23	18	22	25	26	24	25	29
M02205		23	22	25	21	22	24	23	27
M02206		23	22	25	24	25	26	24	27
Number of males		6	6	6	6	6	6	6	6
Mean		23	22	22	22	24	24	24	26
S.D.		1	2	3	4	2	2	1	3
Significance		NS	NS	NS	NS	NS	NS	NS	NS
Statistical method		DU	DU	DU	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 5-3. Individual food consumption (g/day) in male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Days of administration							
	2	5	9	12	16	19	23	26
M03301	23	24	24	25	25	26	26	26
M03302	21	19	23	22	27	24	29	23
M03303	24	25	27	22	26	25	28	24
M03304	24	23	21	22	26	25	28	29
M03305	18	20	21	16	25	27	27	24
M03306	21	19	21	15	24	25	25	23
Number of males	6	6	6	6	6	6	6	6
Mean	22	22	23	20	26	25	27	25
S.D.	2	3	2	4	1	1	1	2
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 5-4. Individual food consumption (g/day) in male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Days of administration							Days of recovery				
	2	5	9	12	16	19	23	26	2	5	9	12
M04401	21	21	24	24	22	25	26	22				
M04402	21	20	22	23	23	20	23	24				
M04403	22	21	24	24	15	26	24	24				
M04404	22	19	22	26	29	25	29	30				
M04405	22	17	23	24	21	25	24	25				
M04406	20	20	24	23	26	27	29	28				
M04407	17	11	20	23	21	20	24	23	26	25	26	28
M04408	24	22	22	23	26	25	21	28	33	29	29	33
M04409	20	20	21	22	22	16	22	24	26	25	27	27
M04410	20	21	21	23	25	22	24	26	29	29	27	30
M04411	23	18	23	22	25	27	26	26	30	31	27	34
M04412	21	18	20	22	23	23	24	23	27	28	28	30
Number of males	12	12	12	12	12	12	12	12	6	6	6	6
Mean	21	19	22	23	23	23	25	25	29	28	27	30
S.D.	2	3	1	1	4	3	2	2	3	2	1	3
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	STL	DU	DU	DU	DU	TT	TT	TT	TT

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

TT: Analysis by Student's t-test.

Appendix 6-1. Individual food consumption (g/day) in female rats

Female No.	Days of administration							Days of recovery				
	2	5	9	12	16	19	23	26	2	5	9	12
F01151	15	15	17	12	14	17	16	18				
F01152	15	15	14	17	17	15	15	11				
F01153	16	16	16	14	12	15	13	13				
F01154	13	14	15	16	17	15	15	12				
F01155	17	13	16	15	16	19	18	20				
F01156	14	14	18	12	15	16	13	16				
F01157	15	16	17	18	16	16	15	20	22	22	23	19
F01158	17	16	17	18	17	12	13	19	18	19	20	22
F01159	16	18	18	13	18	17	16	20	21	20	21	20
F01160	18	18	16	18	19	18	17	14	16	18	19	18
F01161	18	16	17	18	18	19	18	21	17	16	16	17
F01162	15	15	13	14	16	12	13	15	16	18	16	16
Number of females	12	12	12	12	12	12	12	12	6	6	6	6
Mean	16	16	16	15	16	16	15	17	18	19	19	19
S.D.	2	2	2	2	2	2	2	4	3	2	3	2

Appendix 6-2. Individual food consumption (g/day) in female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Days of administration							
	2	5	9	12	16	19	23	26
F02251	14	15	16	11	14	14	16	17
F02252	14	16	12	15	18	14	14	17
F02253	12	15	16	15	16	15	13	13
F02254	17	18	19	14	19	13	13	18
F02255	16	15	17	12	16	16	15	21
F02256	16	17	17	11	13	18	19	22
Number of females	6	6	6	6	6	6	6	6
Mean	15	16	16	13	16	15	15	18
S.D.	2	1	2	2	2	2	2	3
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 6-3. Individual food consumption (g/day) in female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Days of administration							
	2	5	9	12	16	19	23	26
F03351	16	17	18	19	16	11	15	20
F03352	17	15	17	12	15	16	16	19
F03353	17	17	19	17	17	18	19	21
F03354	15	16	18	17	19	16	18	20
F03355	15	17	16	17	19	11	13	19
F03356	17	16	20	18	22	17	17	22
Number of females	6	6	6	6	6	6	6	6
Mean	16	16	18	17	18	15	16	20
S.D.	1	1	1	2	3	3	2	1
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 6-4. Individual food consumption (g/day) in female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Days of administration							Days of recovery				
	2	5	9	12	16	19	23	26	2	5	9	12
F04451	16	17	19	18	17	10	12	18				
F04452	18	17	12	9	18	21	19	14				
F04453	14	16	18	11	17	14	15	19				
F04454	15	13	17	18	20	13	22	22				
F04455	15	13	12	11	18	11	13	21				
F04456	16	13	19	14	18	21	11	17				
F04457	14	17	14	11	18	17	16	18	20	22	20	19
F04458	13	16	17	14	13	16	15	14	17	19	14	17
F04459	14	16	17	19	18	19	19	13	20	22	19	21
F04460	14	11	18	20	18	18	17	13	15	21	18	17
F04461	12	15	17	14	12	14	13	19	19	22	18	19
F04462	14	10	10	13	16	21	12	18	19	22	23	24
Number of females	12	12	12	12	12	12	12	12	6	6	6	6
Mean	15	15	16	14	17	16	15	17	18	21	19	20
S.D.	2	2	3	4	2	4	3	3	2	1	3	3
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	†	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

TT: Analysis by Student's t-test.

Appendix 7-1. Individual water consumption (g/day) in male rats

Control group Male No.	Days of administration							Days of recovery				
	2	5	9	12	16	19	23	26	2	5	9	12
M01101	24	26	23	27	27	28	24	22				
M01102	34	32	36	35	38	38	42	38				
M01103	29	33	34	35	39	42	40	35				
M01104	26	25	26	31	26	25	30	29				
M01105	31	33	34	38	36	42	42	42				
M01106	27	28	29	30	31	33	33	35				
M01107	26	30	29	32	29	30	31	28	32	33	38	37
M01108	26	25	20	26	30	30	34	34	40	37	37	36
M01109	30	28	25	33	37	30	32	30	38	32	32	32
M01110	30	32	28	33	30	32	37	38	39	40	41	40
M01111	33	35	33	35	32	33	35	35	41	38	30	34
M01112	35	29	37	40	38	37	38	37	49	49	50	46
Number of males	12	12	12	12	12	12	12	12	6	6	6	6
Mean	29	30	30	33	33	33	35	34	40	38	38	38
S.D.	4	3	5	4	5	5	5	5	5	6	7	5

Appendix 7-2. Individual water consumption (g/day) in male rats

Male No.	Days of administration							
	2	5	9	12	16	19	23	26
M02201	23	29	33	34	43	36	38	45
M02202	34	37	27	32	31	40	39	36
M02203	29	30	24	24	33	31	32	29
M02204	32	36	27	40	38	36	36	38
M02205	31	28	28	25	30	25	27	27
M02206	30	35	32	31	31	35	41	37
Number of males	6	6	6	6	6	6	6	6
Mean	30	33	29	31	34	34	36	35
S.D.	4	4	3	6	5	5	5	7
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 7-3. Individual water consumption (g/day) in male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Days of administration							
	2	5	9	12	16	19	23	26
M03301	25	31	26	31	37	31	36	39
M03302	30	31	31	35	32	32	36	33
M03303	29	32	34	28	39	34	40	37
M03304	35	43	37	35	42	44	52	55
M03305	24	27	24	27	31	29	31	29
M03306	28	31	30	30	32	37	43	42
Number of males	6	6	6	6	6	6	6	6
Mean	29	33	30	31	36	35	40	39
S.D.	4	5	5	3	5	5	7	9
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 7-4. Individual water consumption (g/day) in male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Days of administration							Days of recovery				
	2	5	9	12	16	19	23	26	2	5	9	12
M04401	26	32	36	37	30	37	41	36				
M04402	25	30	32	31	36	32	36	35				
M04403	28	36	36	38	32	50	40	41				
M04404	27	29	34	43	49	44	56	54				
M04405	30	45	38	46	37	39	42	42				
M04406	24	30	34	34	41	38	38	39				
M04407	22	25	29	37	36	32	38	38	37	33	36	35
M04408	30	33	33	41	44	40	51	48	55	44	40	39
M04409	24	38	43	47	52	36	44	56	57	45	56	57
M04410	24	35	41	43	45	46	52	48	44	43	38	38
M04411	29	33	42	39	43	48	45	42	45	40	35	46
M04412	22	28	30	29	33	29	43	41	39	36	33	35
Number of males	12	12	12	12	12	12	12	12	6	6	6	6
Mean	26	33	36	39	40	39	44	43	46	40	40	42
S.D.	3	5	5	6	7	7	6	7	8	5	8	9
Significance	NS	NS	**	*	*	*	**	**	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

TT: Analysis by Student's t-test.

Appendix 8-1. Individual water consumption (g/day) in female rats

Female No.	Days of administration							Days of recovery				
	2	5	9	12	16	19	23	26	2	5	9	12
F01151	24	27	23	19	21	27	24	27				
F01152	22	19	22	23	22	21	22	21				
F01153	23	22	26	23	22	25	24	24				
F01154	20	22	25	25	27	26	24	19				
F01155	22	22	24	22	22	26	24	27				
F01156	21	26	27	22	21	27	20	22				
F01157	27	28	33	33	36	30	36	41	43	45	43	39
F01158	23	22	27	25	25	16	18	22	25	24	27	25
F01159	26	31	35	28	43	27	54	34	32	38	49	38
F01160	24	24	21	25	21	30	28	20	23	27	26	31
F01161	24	22	27	23	25	30	28	23	26	28	20	27
F01162	20	21	19	21	20	20	22	24	24	26	24	25
Number of females	12	12	12	12	12	12	12	12	6	6	6	6
Mean	23	24	26	24	25	25	27	25	29	31	32	31
S.D.	2	3	5	4	7	4	10	6	8	8	12	6

Appendix 8-2. Individual water consumption (g/day) in female rats

1,4-dichlorobutane group at 12 mg/kg		Days of administration							
Female No.		2	5	9	12	16	19	23	26
F02251		24	24	31	18	36	23	27	29
F02252		21	22	20	22	24	18	22	28
F02253		19	23	23	21	23	22	21	17
F02254		24	25	31	28	28	19	21	27
F02255		25	23	28	20	25	24	23	29
F02256		25	24	25	22	19	26	29	29
Number of females		6	6	6	6	6	6	6	6
Mean		23	24	26	22	26	22	24	27
S.D.		2	1	4	3	6	3	3	5
Significance		NS	NS	NS	NS	NS	NS	NS	NS
Statistical method		DU	STL	DU	STL	DU	DU	STL	STL

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 8-3. Individual water consumption (g/day) in female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Days of administration							
	2	5	9	12	16	19	23	26
F03351	22	23	33	28	26	18	22	29
F03352	25	21	30	24	31	27	29	31
F03353	28	29	34	38	34	32	35	39
F03354	28	29	34	34	33	29	32	30
F03355	22	25	30	23	28	17	19	27
F03356	23	24	29	30	33	25	23	34
Number of females	6	6	6	6	6	6	6	6
Mean	25	25	32	30	31	25	27	32
S.D.	3	3	2	6	3	6	6	4
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	STL	DU	STL	DU	DU	STL	STL

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 8-4. Individual water consumption (g/day) in female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Days of administration							Days of recovery				
	2	5	9	12	16	19	23	26	2	5	9	12
F04451	25	29	36	49	44	25	41	37				
F04452	25	40	42	32	36	36	43	34				
F04453	17	26	28	24	27	22	31	34				
F04454	22	28	36	34	44	33	38	41				
F04455	19	32	26	23	38	34	32	36				
F04456	21	20	28	25	29	28	20	24				
F04457	18	23	31	19	35	37	30	28	31	26	27	25
F04458	23	26	29	15	26	26	24	20	28	26	25	23
F04459	24	31	36	37	43	50	61	43	41	39	37	31
F04460	25	34	50	48	48	43	46	70	33	48	38	37
F04461	22	23	28	35	32	25	34	33	27	26	22	26
F04462	21	30	30	30	33	38	20	42	36	38	36	34
Number of females	12	12	12	12	12	12	12	12	6	6	6	6
Mean	22	29	33	31	36	33	35	37	33	34	31	29
S.D.	3	5	7	11	7	8	12	13	5	9	7	6
Significance	NS	NS	**	NS	**	*	NS	#	NS	NS	NS	NS
Statistical method	DU	STL	DU	STL	DU	DU	STL	STL	TT	TT	TT	TT

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

Significantly different from the control group (#: p<0.05 by Steel's test).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

TT: Analysis by Student's t-test.

Appendix 9-1. Individual FOB of male rats

Control group

Male No.	Blind No.	Observation of animals in cages									
		Posture					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	2	2	2	2	2	1	1	1	1	1
M01102	M00008	2	2	2	2	2	1	1	1	1	1
M01103	M00028	2	2	2	2	2	1	1	1	1	1
M01104	M00044	2	2	2	2	2	1	1	1	1	1
M01105	M00035	2	2	2	2	2	1	1	1	1	1
M01106	M00036	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1

Findings were graded as follows:

(Continued)

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 9-1. (Continued) Individual FOB of male rats

Control group

Male No.	Blind No.	Observation of animals in cages									
		Biting behavior					Clonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	1	1	1	1	1	1	1	1	1	1
M01102	M00008	1	1	1	1	1	1	1	1	1	1
M01103	M00028	1	1	1	1	1	1	1	1	1	1
M01104	M00044	1	1	1	1	1	1	1	1	1	1
M01105	M00035	1	1	1	1	1	1	1	1	1	1
M01106	M00036	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1

Findings were graded as follows:

(Continued)

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Appendix 9-1. (Continued) Individual FOB of male rats

Control group		Observation of animals in cages				
Male No.	Blind No.	Tonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	1	1	1	1	1
M01102	M00008	1	1	1	1	1
M01103	M00028	1	1	1	1	1
M01104	M00044	1	1	1	1	1
M01105	M00035	1	1	1	1	1
M01106	M00036	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1

Findings were graded as follows:

(Continued)

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions,
 5: asphyxial convulsions.

Appendix 9-1. (Continued) Individual FOB of male rats

Control group

Male No.	Blind No.	Observation of animals on observer's palm									
		Ease of removal from cage					Ease of handling				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	2	2	2	2	2	2	2	2	2	2
M01102	M00008	2	2	2	2	2	2	2	2	2	2
M01103	M00028	2	2	2	2	2	2	2	2	2	2
M01104	M00044	2	2	2	2	2	2	2	2	2	2
M01105	M00035	2	2	2	2	2	2	2	2	2	2
M01106	M00036	2	2	2	2	2	2	2	2	2	2
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2

Findings were graded as follows:

(Continued)

Ease of removal from cage 1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling 1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing,
3: struggling and trying to bite observer's hand.

Appendix 9-1. (Continued) Individual FOB of male rats

Control group

Male No.	Blind No.	Observation of animals on observer's palm									
		Muscle tone					Fur conditions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	2	2	2	2	2	1	1	1	1	1
M01102	M00008	2	2	2	2	2	1	1	1	1	1
M01103	M00028	2	2	2	2	2	1	1	1	1	1
M01104	M00044	2	2	2	2	2	1	1	1	1	1
M01105	M00035	2	2	2	2	2	1	1	1	1	1
M01106	M00036	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1

Findings were graded as follows:

(Continued)

Muscle tone 1: Decreased, 2: normal, 3: increased.

Fur conditions 1: Normal, 2: slightly soiled, 3: markedly soiled.

Appendix 9-1. (Continued) Individual FOB of male rats

Control group		Observation of animals on observer's palm									
Male No.	Blind No.	Lacrimation					Salivation				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	1	1	1	1	1	1	1	1	1	1
M01102	M00008	1	1	1	1	1	1	1	1	1	1
M01103	M00028	1	1	1	1	1	1	1	1	1	1
M01104	M00044	1	1	1	1	1	1	1	1	1	1
M01105	M00035	1	1	1	1	1	1	1	1	1	1
M01106	M00036	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1

Findings were graded as follows:

(Continued)

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

Appendix 9-1. (Continued) Individual FOB of male rats

Control group

Male No.	Blind No.	Observation of animals on observer's palm				
		Respiration				
		Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	1	1	1	1	1
M01102	M00008	1	1	1	1	1
M01103	M00028	1	1	1	1	1
M01104	M00044	1	1	1	1	1
M01105	M00035	1	1	1	1	1
M01106	M00036	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1

Findings were graded as follows:

(Continued)

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

Appendix 9-1. (Continued) Individual FOB of male rats

Control group		Open-field test									
Male No.	Blind No.	Frequency of rearing (during a 2-minute period)					Frequency of grooming (during a 2-minute period)				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	7	1	1	5	0	0	0	0	1	0
M01102	M00008	10	9	6	2	1	0	0	0	0	0
M01103	M00028	3	5	0	11	1	0	0	0	0	0
M01104	M00044	5	12	1	1	2	0	0	0	0	0
M01105	M00035	3	4	6	6	8	0	0	0	0	0
M01106	M00036	1	1	1	8	4	0	0	0	0	0
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		4.8	5.3	2.5	5.5	2.7	0.0	0.0	0.0	0.2	0.0
S.D.		3.3	4.4	2.7	3.7	2.9	0.0	0.0	0.0	0.4	0.0

(Continued)

Appendix 9-1. (Continued) Individual FOB of male rats

Control group

Male No.	Blind No.	Open-field test									
		Gait					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	1	1	1	1	1	1	1	1	1	1
M01102	M00008	1	1	1	1	1	1	1	1	1	1
M01103	M00028	1	1	1	1	1	1	1	1	1	1
M01104	M00044	1	1	1	1	1	1	1	1	1	1
M01105	M00035	1	1	1	1	1	1	1	1	1	1
M01106	M00036	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1

Findings were graded as follows:

(Continued)

Gait

1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended,
6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

Palpebral closure

1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 9-1. (Continued) Individual FOB of male rats

Control group		Open-field test									
Male No.	Blind No.	Consciousness					Behavioral abnormalities				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	2	2	2	2	2	1	1	1	1	1
M01102	M00008	2	2	2	2	2	1	1	1	1	1
M01103	M00028	2	2	2	2	2	1	1	1	1	1
M01104	M00044	2	2	2	2	2	1	1	1	1	1
M01105	M00035	2	2	2	2	2	1	1	1	1	1
M01106	M00036	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1

Findings were graded as follows:

(Continued)

Consciousness 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities 1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Appendix 9-1. (Continued) Individual FOB of male rats

Control group

Male No.	Blind No.	Open-field test				
		Righting reflex				
		Pre	Day 7	Day 14	Day 21	Day 27
M01101	M00026	1	1	1	1	1
M01102	M00008	1	1	1	1	1
M01103	M00028	1	1	1	1	1
M01104	M00044	1	1	1	1	1
M01105	M00035	1	1	1	1	1
M01106	M00036	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1

Findings were graded as follows:

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Appendix 9-2. Individual FOB of male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Blind No.	Observation of animals in cages									
		Posture					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	2	2	2	2	2	1	1	1	1	1
M02202	M00041	2	2	2	2	2	1	1	1	1	1
M02203	M00033	2	2	2	2	2	1	1	1	1	1
M02204	M00010	2	2	2	2	2	1	1	1	1	1
M02205	M00012	2	2	2	2	2	1	1	1	1	1
M02206	M00019	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 9-2. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Blind No.	Observation of animals in cages									
		Biting behavior					Clonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	1	1	1	1	1	1	1	1	1	1
M02202	M00041	1	1	1	1	1	1	1	1	1	1
M02203	M00033	1	1	1	1	1	1	1	1	1	1
M02204	M00010	1	1	1	1	1	1	1	1	1	1
M02205	M00012	1	1	1	1	1	1	1	1	1	1
M02206	M00019	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Appendix 9-2. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Blind No.	Observation of animals in cages				
		Tonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	1	1	1	1	1
M02202	M00041	1	1	1	1	1
M02203	M00033	1	1	1	1	1
M02204	M00010	1	1	1	1	1
M02205	M00012	1	1	1	1	1
M02206	M00019	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions,
 5: asphyxial convulsions.

Appendix 9-2. (Continued) Individual FOB of male rats

		1,4-dichlorobutane group at 12 mg/kg									
Male No.	Blind No.	Observation of animals on observer's palm									
		Ease of removal from cage					Ease of handling				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	2	2	2	2	2	2	2	2	2	2
M02202	M00041	2	2	2	2	2	2	2	2	2	2
M02203	M00033	2	2	2	2	2	2	2	2	2	2
M02204	M00010	2	2	2	2	2	2	2	2	2	2
M02205	M00012	2	2	2	2	2	2	2	2	2	2
M02206	M00019	2	2	2	2	2	2	2	2	2	2
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Ease of removal from cage 1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling 1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing,
3: struggling and trying to bite observer's hand.

Appendix 9-2. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm									
		Muscle tone					Fur conditions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	2	2	2	2	2	1	1	1	1	1
M02202	M00041	2	2	2	2	2	1	1	1	1	1
M02203	M00033	2	2	2	2	2	1	1	1	1	1
M02204	M00010	2	2	2	2	2	1	1	1	1	1
M02205	M00012	2	2	2	2	2	1	1	1	1	1
M02206	M00019	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Muscle tone 1: Decreased, 2: normal, 3: increased.

Fur conditions 1: Normal, 2: slightly soiled, 3: markedly soiled.

Appendix 9-2. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm									
		Lacrimation					Salivation				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	1	1	1	1	1	1	1	1	1	1
M02202	M00041	1	1	1	1	1	1	1	1	1	1
M02203	M00033	1	1	1	1	1	1	1	1	1	1
M02204	M00010	1	1	1	1	1	1	1	1	1	1
M02205	M00012	1	1	1	1	1	1	1	1	1	1
M02206	M00019	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

- Lacrimation 1: None, 2: mild, 3: marked.
 Salivation 1: None, 2: mild, 3: marked.

Appendix 9-2. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm				
		Respiration				
		Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	1	1	1	1	1
M02202	M00041	1	1	1	1	1
M02203	M00033	1	1	1	1	1
M02204	M00010	1	1	1	1	1
M02205	M00012	1	1	1	1	1
M02206	M00019	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

Appendix 9-2. (Continued) Individual FOB of male rats

		Open-field test									
Male No.	Blind No.	Frequency of rearing (during a 2-minute period)					Frequency of grooming (during a 2-minute period)				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	8	14	16	11	5	0	0	0	0	0
M02202	M00041	10	7	7	2	7	0	0	0	0	0
M02203	M00033	1	6	7	1	4	0	0	0	0	0
M02204	M00010	2	5	4	7	3	0	0	0	0	0
M02205	M00012	5	4	0	0	3	0	0	0	0	0
M02206	M00019	4	1	2	4	4	0	0	0	0	0
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		5.0	6.2	6.0	4.2	4.3	0.0	0.0	0.0	0.0	0.0
S.D.		3.5	4.4	5.6	4.2	1.5	0.0	0.0	0.0	0.0	0.0
Significance		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

Appendix 9-2. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 12 mg/kg

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Gait 1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 9-2. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Blind No.	Open-field test									
		Consciousness					Behavioral abnormalities				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	2	2	2	2	2	1	1	1	1	1
M02202	M00041	2	2	2	2	2	1	1	1	1	1
M02203	M00033	2	2	2	2	2	1	1	1	1	1
M02204	M00010	2	2	2	2	2	1	1	1	1	1
M02205	M00012	2	2	2	2	2	1	1	1	1	1
M02206	M00019	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Consciousness 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities 1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Appendix 9-2. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 12 mg/kg

Male No.	Blind No.	Open-field test				
		Righting reflex				
		Pre	Day 7	Day 14	Day 21	Day 27
M02201	M00040	1	1	1	1	1
M02202	M00041	1	1	1	1	1
M02203	M00033	1	1	1	1	1
M02204	M00010	1	1	1	1	1
M02205	M00012	1	1	1	1	1
M02206	M00019	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Appendix 9-3. Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Observation of animals in cages									
		Posture					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	2	2	2	2	2	1	1	1	1	1
M03302	M00003	2	2	2	2	2	1	1	1	1	1
M03303	M00037	2	2	2	2	2	1	1	1	1	1
M03304	M00002	2	2	2	2	2	1	1	1	1	1
M03305	M00006	2	2	2	2	2	1	1	1	1	1
M03306	M00023	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Observation of animals in cages									
		Biting behavior					Clonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	1	1	1	1	1	1	1	1	1	1
M03302	M00003	1	1	1	1	1	1	1	1	1	1
M03303	M00037	1	1	1	1	1	1	1	1	1	1
M03304	M00002	1	1	1	1	1	1	1	1	1	1
M03305	M00006	1	1	1	1	1	1	1	1	1	1
M03306	M00023	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Observation of animals in cages				
		Tonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	1	1	1	1	1
M03302	M00003	1	1	1	1	1
M03303	M00037	1	1	1	1	1
M03304	M00002	1	1	1	1	1
M03305	M00006	1	1	1	1	1
M03306	M00023	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions,
 5: asphyxial convulsions.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm									
		Ease of removal from cage					Ease of handling				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	2	2	2	2	2	2	2	2	2	2
M03302	M00003	2	2	2	2	2	2	2	2	2	2
M03303	M00037	2	2	2	2	2	2	2	2	2	2
M03304	M00002	2	2	2	2	2	2	2	2	2	2
M03305	M00006	2	2	2	2	2	2	2	2	2	2
M03306	M00023	2	2	2	2	2	2	2	2	2	2
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Ease of removal from cage 1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling 1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing,
3: struggling and trying to bite observer's hand.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm									
		Muscle tone					Fur conditions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	2	2	2	2	2	1	1	1	1	1
M03302	M00003	2	2	2	2	2	1	1	1	1	1
M03303	M00037	2	2	2	2	2	1	1	1	1	1
M03304	M00002	2	2	2	2	2	1	1	1	1	1
M03305	M00006	2	2	2	2	2	1	1	1	1	1
M03306	M00023	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Muscle tone 1: Decreased, 2: normal, 3: increased.

Fur conditions 1: Normal, 2: slightly soiled, 3: markedly soiled.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm									
		Lacrimation					Salivation				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	1	1	1	1	1	1	1	1	1	1
M03302	M00003	1	1	1	1	1	1	1	1	1	1
M03303	M00037	1	1	1	1	1	1	1	1	1	1
M03304	M00002	1	1	1	1	1	1	1	1	1	1
M03305	M00006	1	1	1	1	1	1	1	1	1	1
M03306	M00023	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Lacrimation	1: None, 2: mild, 3: marked.
Salivation	1: None, 2: mild, 3: marked.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm				
		Respiration				
		Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	1	1	1	1	1
M03302	M00003	1	1	1	1	1
M03303	M00037	1	1	1	1	1
M03304	M00002	1	1	1	1	1
M03305	M00006	1	1	1	1	1
M03306	M00023	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Open-field test									
		Frequency of rearing (during a 2-minute period)					Frequency of grooming (during a 2-minute period)				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	4	3	0	0	1	0	0	0	0	0
M03302	M00003	7	10	7	6	5	0	0	0	0	0
M03303	M00037	1	5	0	0	0	0	0	0	0	0
M03304	M00002	13	6	2	8	9	0	0	0	0	0
M03305	M00006	11	13	1	0	0	0	0	0	0	0
M03306	M00023	4	4	3	3	4	0	0	0	0	0
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		6.7	6.8	2.2	2.8	3.2	0.0	0.0	0.0	0.0	0.0
S.D.		4.6	3.9	2.6	3.5	3.5	0.0	0.0	0.0	0.0	0.0
Significance		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Open-field test									
		Gait					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	1	1	1	1	1	1	1	1	1	1
M03302	M00003	1	1	1	1	1	1	1	1	1	1
M03303	M00037	1	1	1	1	1	1	1	1	1	1
M03304	M00002	1	1	1	1	1	1	1	1	1	1
M03305	M00006	1	1	1	1	1	1	1	1	1	1
M03306	M00023	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Gait

1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended,
6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

Palpebral closure

1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Open-field test									
		Consciousness					Behavioral abnormalities				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	2	2	2	2	2	1	1	1	1	1
M03302	M00003	2	2	2	2	2	1	1	1	1	1
M03303	M00037	2	2	2	2	2	1	1	1	1	1
M03304	M00002	2	2	2	2	2	1	1	1	1	1
M03305	M00006	2	2	2	2	2	1	1	1	1	1
M03306	M00023	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Consciousness 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities 1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Appendix 9-3. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 60 mg/kg

Male No.	Blind No.	Open-field test				
		Righting reflex				
		Pre	Day 7	Day 14	Day 21	Day 27
M03301	M00007	1	1	1	1	1
M03302	M00003	1	1	1	1	1
M03303	M00037	1	1	1	1	1
M03304	M00002	1	1	1	1	1
M03305	M00006	1	1	1	1	1
M03306	M00023	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Appendix 9-4. Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Blind No.	Observation of animals in cages									
		Posture					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	2	2	2	2	2	1	1	1	1	1
M04402	M00017	2	2	2	2	2	1	1	1	1	1
M04403	M00015	2	2	2	2	2	1	1	1	1	1
M04404	M00022	2	2	2	2	2	1	1	1	1	1
M04405	M00034	2	2	2	2	2	1	1	1	1	1
M04406	M00039	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 9-4. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Blind No.	Observation of animals in cages									
		Biting behavior					Clonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	1	1	1	1	1	1	1	1	1	1
M04402	M00017	1	1	1	1	1	1	1	1	1	1
M04403	M00015	1	1	1	1	1	1	1	1	1	1
M04404	M00022	1	1	1	1	1	1	1	1	1	1
M04405	M00034	1	1	1	1	1	1	1	1	1	1
M04406	M00039	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Appendix 9-4. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Blind No.	Observation of animals in cages				
		Tonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	1	1	1	1	1
M04402	M00017	1	1	1	1	1
M04403	M00015	1	1	1	1	1
M04404	M00022	1	1	1	1	1
M04405	M00034	1	1	1	1	1
M04406	M00039	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions,
 5: asphyxial convulsions.

Appendix 9-4. (Continued) Individual FOB of male rats

		1,4-dichlorobutane group at 300 mg/kg									
Male No.	Blind No.	Observation of animals on observer's palm									
		Ease of removal from cage					Ease of handling				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	2	2	2	2	2	2	2	2	2	2
M04402	M00017	2	2	2	2	2	2	2	2	2	2
M04403	M00015	2	2	2	2	2	2	2	2	2	2
M04404	M00022	2	2	2	2	2	2	2	2	2	2
M04405	M00034	2	2	2	2	2	2	2	2	2	2
M04406	M00039	2	2	2	2	2	2	2	2	2	2
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Ease of removal from cage 1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling 1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing,
3: struggling and trying to bite observer's hand.

Appendix 9-4. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm									
		Muscle tone					Fur conditions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	2	2	2	2	2	1	1	1	1	1
M04402	M00017	2	2	2	2	2	1	1	1	1	1
M04403	M00015	2	2	2	2	2	1	1	1	1	1
M04404	M00022	2	2	2	2	2	1	1	1	1	1
M04405	M00034	2	2	2	2	2	1	1	1	1	1
M04406	M00039	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Muscle tone 1: Decreased, 2: normal, 3: increased.

Fur conditions 1: Normal, 2: slightly soiled, 3: markedly soiled.

Appendix 9-4. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm									
		Lacrimation					Salivation				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	1	1	1	1	1	1	1	2	2	2
M04402	M00017	1	1	1	1	1	1	1	2	2	1
M04403	M00015	1	1	1	1	1	1	1	2	2	2
M04404	M00022	1	1	1	1	1	1	1	2	2	2
M04405	M00034	1	1	1	1	1	1	1	1	1	1
M04406	M00039	1	1	1	1	1	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.7	1.7	1.5
Range		1	1	1	1	1	1	1	1-2	1-2	1-2
Significance		---	---	---	---	---	---	---	NS	NS	NS
Statistical method		UA	UA	UA	UA	UA	UA	UA	STL	STL	STL

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

NS: Not significantly different from the control group.

STL: Analysis by Steel's test.

Findings were graded as follows:

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

Appendix 9-4. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Blind No.	Observation of animals on observer's palm				
		Respiration				
		Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	1	1	1	1	1
M04402	M00017	1	1	1	1	1
M04403	M00015	1	1	1	1	1
M04404	M00022	1	1	1	1	1
M04405	M00034	1	1	1	1	1
M04406	M00039	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

Appendix 9-4. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg											
Male No.	Blind No.	Open-field test									
		Frequency of rearing (during a 2-minute period)					Frequency of grooming (during a 2-minute period)				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	6	11	6	5	5	0	0	0	0	0
M04402	M00017	11	11	3	2	2	0	0	0	0	0
M04403	M00015	4	10	0	0	9	0	0	0	0	0
M04404	M00022	4	4	2	1	2	0	0	0	0	0
M04405	M00034	1	4	0	4	4	0	0	0	0	0
M04406	M00039	8	1	1	11	3	0	0	0	0	0
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		5.7	6.8	2.0	3.8	4.2	0.0	0.0	0.0	0.0	0.0
S.D.		3.5	4.4	2.3	4.0	2.6	0.0	0.0	0.0	0.0	0.0
Significance		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

Appendix 9-4. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Gait 1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body. 7: standing on tiptoe.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 9-4. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg											
Male No.	Blind No.	Open-field test									
		Consciousness					Behavioral abnormalities				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	2	2	2	2	2	1	1	1	1	1
M04402	M00017	2	2	2	2	2	1	1	1	1	1
M04403	M00015	2	2	2	2	2	1	1	1	1	1
M04404	M00022	2	2	2	2	2	1	1	1	1	1
M04405	M00034	2	2	2	2	2	1	1	1	1	1
M04406	M00039	2	2	2	2	2	1	1	1	1	1
Number of males		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Consciousness 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities 1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Appendix 9-4. (Continued) Individual FOB of male rats

1,4-dichlorobutane group at 300 mg/kg

Male No.	Blind No.	Open-field test				
		Righting reflex				
		Pre	Day 7	Day 14	Day 21	Day 27
M04401	M00030	1	1	1	1	1
M04402	M00017	1	1	1	1	1
M04403	M00015	1	1	1	1	1
M04404	M00022	1	1	1	1	1
M04405	M00034	1	1	1	1	1
M04406	M00039	1	1	1	1	1
Number of males		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Appendix 10-1. Individual FOB of female rats

Control group

Female No.	Blind No.	Observation of animals in cages									
		Posture					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	2	2	2	2	2	1	1	1	1	1
F01152	F00001	2	2	2	2	2	1	1	1	1	1
F01153	F00022	2	2	2	2	2	1	1	1	1	1
F01154	F00020	2	2	2	2	2	1	1	1	1	1
F01155	F00019	2	2	2	2	2	1	1	1	1	1
F01156	F00011	2	2	2	2	2	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1

Findings were graded as follows:

(Continued)

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 10-1. (Continued) Individual FOB of female rats

Control group

Female No.	Blind No.	Observation of animals in cages									
		Biting behavior					Clonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	1	1	1	1	1	1	1	1	1	1
F01152	F00001	1	1	1	1	1	1	1	1	1	1
F01153	F00022	1	1	1	1	1	1	1	1	1	1
F01154	F00020	1	1	1	1	1	1	1	1	1	1
F01155	F00019	1	1	1	1	1	1	1	1	1	1
F01156	F00011	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1

Findings were graded as follows:

(Continued)

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Appendix 10-1. (Continued) Individual FOB of female rats

Control group		Observation of animals in cages				
Female No.	Blind No.	Tonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	1	1	1	1	1
F01152	F00001	1	1	1	1	1
F01153	F00022	1	1	1	1	1
F01154	F00020	1	1	1	1	1
F01155	F00019	1	1	1	1	1
F01156	F00011	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1

Findings were graded as follows:

(Continued)

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions,
 5: asphyxial convulsions.

Appendix 10-1. (Continued) Individual FOB of female rats

Control group

Female No.	Blind No.	Observation of animals on observer's palm									
		Ease of removal from cage					Ease of handling				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	2	2	2	2	2	2	2	2	2	2
F01152	F00001	2	2	2	2	2	2	2	2	2	2
F01153	F00022	2	2	2	2	2	2	2	2	2	2
F01154	F00020	2	2	2	2	2	2	2	2	2	2
F01155	F00019	2	2	2	2	2	2	2	2	2	2
F01156	F00011	2	2	2	2	2	2	2	2	2	2
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2

Findings were graded as follows:

(Continued)

Ease of removal from cage 1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling 1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing,
3: struggling and trying to bite observer's hand.

Appendix 10-1. (Continued) Individual FOB of female rats

Control group

Female No.	Blind No.	Observation of animals on observer's palm									
		Muscle tone					Fur conditions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	2	2	2	2	2	1	1	1	1	1
F01152	F00001	2	2	2	2	2	1	1	1	1	1
F01153	F00022	2	2	2	2	2	1	1	1	1	1
F01154	F00020	2	2	2	2	2	1	1	1	1	1
F01155	F00019	2	2	2	2	2	1	1	1	1	1
F01156	F00011	2	2	2	2	2	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1

Findings were graded as follows:

(Continued)

Muscle tone 1: Decreased, 2: normal, 3: increased.

Fur conditions 1: Normal, 2: slightly soiled, 3: markedly soiled.

Appendix 10-1. (Continued) Individual FOB of female rats

Control group

Female No.	Blind No.	Observation of animals on observer's palm									
		Lacrimation					Salivation				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	1	1	1	1	1	1	1	1	1	1
F01152	F00001	1	1	1	1	1	1	1	1	1	1
F01153	F00022	1	1	1	1	1	1	1	1	1	1
F01154	F00020	1	1	1	1	1	1	1	1	1	1
F01155	F00019	1	1	1	1	1	1	1	1	1	1
F01156	F00011	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1

Findings were graded as follows:

(Continued)

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

Appendix 10-1. (Continued) Individual FOB of female rats

Control group

Female No.	Blind No.	Observation of animals on observer's palm				
		Respiration				
		Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	1	1	1	1	1
F01152	F00001	1	1	1	1	1
F01153	F00022	1	1	1	1	1
F01154	F00020	1	1	1	1	1
F01155	F00019	1	1	1	1	1
F01156	F00011	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1

Findings were graded as follows:

(Continued)

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

Appendix 10-1. (Continued) Individual FOB of female rats

Control group		Open-field test									
Female No.	Blind No.	Frequency of rearing (during a 2-minute period)					Frequency of grooming (during a 2-minute period)				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	12	13	0	1	3	0	0	0	0	0
F01152	F00001	6	8	1	8	8	0	0	0	0	0
F01153	F00022	4	5	4	3	5	0	0	0	0	0
F01154	F00020	7	7	3	6	0	0	0	0	0	0
F01155	F00019	1	5	0	5	8	0	0	0	0	0
F01156	F00011	5	3	1	3	4	0	0	0	0	0
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		5.8	6.8	1.5	4.3	4.7	0.0	0.0	0.0	0.0	0.0
S.D.		3.7	3.5	1.6	2.5	3.1	0.0	0.0	0.0	0.0	0.0

(Continued)

Appendix 10-1. (Continued) Individual FOB of female rats

Findings were graded as follows:

(Continued)

Gait 1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.
 Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 10-1. (Continued) Individual FOB of female rats

Control group

Female No.	Blind No.	Open-field test									
		Consciousness					Behavioral abnormalities				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	2	2	2	2	2	1	1	1	1	1
F01152	F00001	2	2	2	2	2	1	1	1	1	1
F01153	F00022	2	2	2	2	2	1	1	1	1	1
F01154	F00020	2	2	2	2	2	1	1	1	1	1
F01155	F00019	2	2	2	2	2	1	1	1	1	1
F01156	F00011	2	2	2	2	2	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1

Findings were graded as follows:

(Continued)

Consciousness 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities 1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Appendix 10-1. (Continued) Individual FOB of female rats

Control group

Female No.	Blind No.	Open-field test				
		Righting reflex				
		Pre	Day 7	Day 14	Day 21	Day 27
F01151	F00002	1	1	1	1	1
F01152	F00001	1	1	1	1	1
F01153	F00022	1	1	1	1	1
F01154	F00020	1	1	1	1	1
F01155	F00019	1	1	1	1	1
F01156	F00011	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1

Findings were graded as follows:

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Appendix 10-2. Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Observation of animals in cages									
		Posture					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	2	2	2	2	2	1	1	1	1	1
F02252	F00041	2	2	2	2	2	1	1	1	1	1
F02253	F00015	2	2	2	2	2	1	1	1	1	1
F02254	F00033	2	2	2	2	2	1	1	1	1	1
F02255	F00005	2	2	2	2	2	1	1	1	1	1
F02256	F00037	2	2	2	2	2	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 10-2. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Observation of animals in cages									
		Biting behavior					Clonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	1	1	1	1	1	1	1	1	1	1
F02252	F00041	1	1	1	1	1	1	1	1	1	1
F02253	F00015	1	1	1	1	1	1	1	1	1	1
F02254	F00033	1	1	1	1	1	1	1	1	1	1
F02255	F00005	1	1	1	1	1	1	1	1	1	1
F02256	F00037	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Appendix 10-2. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Observation of animals in cages				
		Tonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	1	1	1	1	1
F02252	F00041	1	1	1	1	1
F02253	F00015	1	1	1	1	1
F02254	F00033	1	1	1	1	1
F02255	F00005	1	1	1	1	1
F02256	F00037	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions,
 5: asphyxial convulsions.

Appendix 10-2. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm									
		Ease of removal from cage					Ease of handling				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	2	2	2	2	2	2	2	2	2	2
F02252	F00041	2	2	2	2	2	2	2	2	2	2
F02253	F00015	2	2	2	2	2	2	2	2	2	2
F02254	F00033	2	2	2	2	2	2	2	2	2	2
F02255	F00005	2	2	2	2	2	2	2	2	2	2
F02256	F00037	2	2	2	2	2	2	2	2	2	2
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Ease of removal from cage 1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling 1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing,
3: struggling and trying to bite observer's hand.

Appendix 10-2. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm									
		Muscle tone					Fur conditions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	2	2	2	2	2	1	1	1	1	1
F02252	F00041	2	2	2	2	2	1	1	1	1	1
F02253	F00015	2	2	2	2	2	1	1	1	1	1
F02254	F00033	2	2	2	2	2	1	1	1	1	1
F02255	F00005	2	2	2	2	2	1	1	1	1	1
F02256	F00037	2	2	2	2	2	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Muscle tone 1: Decreased, 2: normal, 3: increased.

Fur conditions 1: Normal, 2: slightly soiled, 3: markedly soiled.

Appendix 10-2. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm									
		Lacrimation					Salivation				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	1	1	1	1	1	1	1	1	1	1
F02252	F00041	1	1	1	1	1	1	1	1	1	1
F02253	F00015	1	1	1	1	1	1	1	1	1	1
F02254	F00033	1	1	1	1	1	1	1	1	1	1
F02255	F00005	1	1	1	1	1	1	1	1	1	1
F02256	F00037	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

- Lacrimation 1: None, 2: mild, 3: marked.
 Salivation 1: None, 2: mild, 3: marked.

Appendix 10-2. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm				
		Respiration				
		Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	1	1	1	1	1
F02252	F00041	1	1	1	1	1
F02253	F00015	1	1	1	1	1
F02254	F00033	1	1	1	1	1
F02255	F00005	1	1	1	1	1
F02256	F00037	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

Appendix 10-2. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Open-field test									
		Frequency of rearing (during a 2-minute period)					Frequency of grooming (during a 2-minute period)				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	8	4	5	6	19	0	0	0	0	0
F02252	F00041	11	10	13	7	8	0	0	0	1	0
F02253	F00015	8	4	1	4	0	0	0	0	0	0
F02254	F00033	7	4	3	5	6	0	1	0	0	0
F02255	F00005	6	14	11	17	17	0	0	0	0	0
F02256	F00037	1	9	5	9	9	0	0	0	0	0
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		6.8	7.5	6.3	8.0	9.8	0.0	0.2	0.0	0.2	0.0
S.D.		3.3	4.2	4.7	4.7	7.1	0.0	0.4	0.0	0.4	0.0
Significance		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

Appendix 10-2. (Continued) Individual FOB of female rats

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Gait 1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 10-2. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Open-field test										
		Consciousness					Behavioral abnormalities					
		Pre	Day 7	Day 14	Day 21	Day 27		Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	2	2	2	2	2	1	1	1	1	1	1
F02252	F00041	2	2	2	2	2	1	1	1	1	1	1
F02253	F00015	2	2	2	2	2	1	1	1	1	1	1
F02254	F00033	2	2	2	2	2	1	1	1	1	1	1
F02255	F00005	2	2	2	2	2	1	1	1	1	1	1
F02256	F00037	2	2	2	2	2	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Consciousness 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities 1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Appendix 10-2. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Open-field test				
		Righting reflex				
		Pre	Day 7	Day 14	Day 21	Day 27
F02251	F00003	1	1	1	1	1
F02252	F00041	1	1	1	1	1
F02253	F00015	1	1	1	1	1
F02254	F00033	1	1	1	1	1
F02255	F00005	1	1	1	1	1
F02256	F00037	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Appendix 10-3. Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Observation of animals in cages									
		Posture					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	2	2	2	2	2	1	1	1	1	1
F03352	F00031	2	2	2	2	2	1	1	1	1	1
F03353	F00024	2	2	2	2	2	1	1	1	1	1
F03354	F00017	2	2	2	2	2	1	1	1	1	1
F03355	F00039	2	2	2	2	2	1	1	1	1	1
F03356	F00038	2	2	2	2	2	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Observation of animals in cages									
		Biting behavior					Clonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	1	1	1	1	1	1	1	1	1	1
F03352	F00031	1	1	1	1	1	1	1	1	1	1
F03353	F00024	1	1	1	1	1	1	1	1	1	1
F03354	F00017	1	1	1	1	1	1	1	1	1	1
F03355	F00039	1	1	1	1	1	1	1	1	1	1
F03356	F00038	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Observation of animals in cages				
		Tonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	1	1	1	1	1
F03352	F00031	1	1	1	1	1
F03353	F00024	1	1	1	1	1
F03354	F00017	1	1	1	1	1
F03355	F00039	1	1	1	1	1
F03356	F00038	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions,
 5: asphyxial convulsions.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm									
		Ease of removal from cage					Ease of handling				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	2	2	2	2	2	2	2	2	2	2
F03352	F00031	2	2	2	2	2	2	2	2	2	2
F03353	F00024	2	2	2	2	2	2	2	2	2	2
F03354	F00017	2	2	2	2	2	2	2	2	2	2
F03355	F00039	2	2	2	2	2	2	2	2	2	2
F03356	F00038	2	2	2	2	2	2	2	2	2	2
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Ease of removal from cage 1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling 1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing,
3: struggling and trying to bite observer's hand.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm									
		Muscle tone					Fur conditions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	2	2	2	2	2	1	1	1	1	1
F03352	F00031	2	2	2	2	2	1	1	1	1	1
F03353	F00024	2	2	2	2	2	1	1	1	1	1
F03354	F00017	2	2	2	2	2	1	1	1	1	1
F03355	F00039	2	2	2	2	2	1	1	1	1	1
F03356	F00038	2	2	2	2	2	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Muscle tone 1: Decreased, 2: normal, 3: increased.

Fur conditions 1: Normal, 2: slightly soiled, 3: markedly soiled.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm									
		Lacrimation					Salivation				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	1	1	1	1	1	1	1	1	1	1
F03352	F00031	1	1	1	1	1	1	1	1	1	1
F03353	F00024	1	1	1	1	1	1	1	1	1	1
F03354	F00017	1	1	1	1	1	1	1	1	1	1
F03355	F00039	1	1	1	1	1	1	1	1	1	1
F03356	F00038	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

- Lacrimation 1: None, 2: mild, 3: marked.
 Salivation 1: None, 2: mild, 3: marked.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm				
		Respiration				
		Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	1	1	1	1	1
F03352	F00031	1	1	1	1	1
F03353	F00024	1	1	1	1	1
F03354	F00017	1	1	1	1	1
F03355	F00039	1	1	1	1	1
F03356	F00038	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Open-field test									
		Frequency of rearing (during a 2-minute period)					Frequency of grooming (during a 2-minute period)				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	0	1	9	11	11	0	0	0	0	0
F03352	F00031	4	8	11	8	12	0	0	0	0	0
F03353	F00024	12	5	4	13	8	0	0	0	1	0
F03354	F00017	4	7	1	6	5	0	0	0	0	0
F03355	F00039	4	4	9	7	2	0	0	0	0	0
F03356	F00038	0	8	6	10	8	0	0	0	0	0
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		4.0	5.5	6.7	9.2	7.7	0.0	0.0	0.0	0.2	0.0
S.D.		4.4	2.7	3.7	2.6	3.7	0.0	0.0	0.0	0.4	0.0
Significance		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Gait 1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Open-field test										
		Consciousness					Behavioral abnormalities					
		Pre	Day 7	Day 14	Day 21	Day 27		Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	2	2	2	2	2	1	1	1	1	1	1
F03352	F00031	2	2	2	2	2	1	1	1	1	1	1
F03353	F00024	2	2	2	2	2	1	1	1	1	1	1
F03354	F00017	2	2	2	2	2	1	1	1	1	1	1
F03355	F00039	2	2	2	2	2	1	1	1	1	1	1
F03356	F00038	2	2	2	2	2	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Consciousness 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities 1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Appendix 10-3. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 60 mg/kg

Female No.	Blind No.	Open-field test				
		Righting reflex				
		Pre	Day 7	Day 14	Day 21	Day 27
F03351	F00036	1	1	1	1	1
F03352	F00031	1	1	1	1	1
F03353	F00024	1	1	1	1	1
F03354	F00017	1	1	1	1	1
F03355	F00039	1	1	1	1	1
F03356	F00038	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Appendix 10-4. Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Observation of animals in cages									
		Posture					Palpebral closure				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	2	2	2	2	2	1	1	1	1	1
F04452	F00025	2	2	2	2	2	1	1	1	1	1
F04453	F00034	2	2	2	2	2	1	1	1	1	1
F04454	F00029	2	2	2	2	2	1	1	1	1	1
F04455	F00021	2	2	2	2	2	1	1	1	1	1
F04456	F00028	2	2	2	2	2	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Posture 1: Prone or recumbent position, 2: resting normally, 3: moving or running about, 4: jumping.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Observation of animals in cages									
		Biting behavior					Clonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	1	1	1	1	1	1	1	1	1	1
F04452	F00025	1	1	1	1	1	1	1	1	1	1
F04453	F00034	1	1	1	1	1	1	1	1	1	1
F04454	F00029	1	1	1	1	1	1	1	1	1	1
F04455	F00021	1	1	1	1	1	1	1	1	1	1
F04456	F00028	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Biting behavior 1: Not observed, 2: observed.

Clonic convulsions 1: Not observed, 2: jaw convulsions, 3: tremor.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Observation of animals in cages				
		Tonic convulsions				
		Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	1	1	1	1	1
F04452	F00025	1	1	1	1	1
F04453	F00034	1	1	1	1	1
F04454	F00029	1	1	1	1	1
F04455	F00021	1	1	1	1	1
F04456	F00028	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Tonic convulsions 1: Not observed, 2: tonic extension, 3: opisthotonus convulsions, 4: saltatory convulsions,
 5: asphyxial convulsions.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm									
		Ease of removal from cage					Ease of handling				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	2	2	2	2	2	2	2	2	2	2
F04452	F00025	2	2	2	2	2	2	2	2	2	2
F04453	F00034	2	2	2	2	2	2	2	2	2	2
F04454	F00029	2	2	2	2	2	2	2	2	2	2
F04455	F00021	2	2	2	2	2	2	2	2	2	2
F04456	F00028	2	2	2	2	2	2	2	2	2	2
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Range		2	2	2	2	2	2	2	2	2	2
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Ease of removal from cage 1: Docile and allowing itself to be handled, 2: rearing or cowering, 3: running about; hard to catch.

Ease of handling 1: Docile and allowing itself to be handled, 2: struggling slightly or vocalizing,
3: struggling and trying to bite observer's hand.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm									
		Muscle tone					Fur conditions				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	2	2	2	2	2	1	1	1	1	1
F04452	F00025	2	2	2	2	2	1	1	1	1	1
F04453	F00034	2	2	2	2	2	1	1	1	1	1
F04454	F00029	2	2	2	2	2	1	1	1	1	1
F04455	F00021	2	2	2	2	2	1	1	1	1	1
F04456	F00028	2	2	2	2	2	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Muscle tone 1: Decreased, 2: normal, 3: increased.

Fur conditions 1: Normal, 2: slightly soiled, 3: markedly soiled.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm									
		Lacrimation					Salivation				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	1	1	1	1	1	1	1	1	1	2
F04452	F00025	1	1	1	1	1	1	1	2	1	2
F04453	F00034	1	1	1	1	1	1	1	1	1	1
F04454	F00029	1	1	1	1	1	1	1	1	1	1
F04455	F00021	1	1	1	1	1	1	1	1	1	1
F04456	F00028	1	1	1	1	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.2	1.0	1.3
Range		1	1	1	1	1	1	1	1-2	1	1-2
Significance		---	---	---	---	---	---	---	NS	---	NS
Statistical method		UA	UA	UA	UA	UA	UA	UA	STL	UA	STL

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

NS: Not significantly different from the control group.

STL: Analysis by Steel's test.

Findings were graded as follows:

Lacrimation 1: None, 2: mild, 3: marked.

Salivation 1: None, 2: mild, 3: marked.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Observation of animals on observer's palm				
		Respiration				
		Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	1	1	1	1	1
F04452	F00025	1	1	1	1	1
F04453	F00034	1	1	1	1	1
F04454	F00029	1	1	1	1	1
F04455	F00021	1	1	1	1	1
F04456	F00028	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Respiration

1: Normal, 2: bradypnea, 3: dyspnea.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Open-field test									
		Frequency of rearing (during a 2-minute period)					Frequency of grooming (during a 2-minute period)				
		Pre	Day 7	Day 14	Day 21	Day 27	Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	8	10	15	8	8	0	0	0	0	0
F04452	F00025	13	4	4	3	12	0	0	0	1	0
F04453	F00034	7	16	9	20	14	0	0	0	0	0
F04454	F00029	5	3	4	1	7	0	0	0	0	0
F04455	F00021	11	5	6	10	6	0	0	0	1	0
F04456	F00028	4	0	2	7	6	0	0	0	0	0
Number of females		6	6	6	6	6	6	6	6	6	6
Mean		8.0	6.3	6.7	8.2	8.8	0.0	0.0	0.0	0.3	0.0
S.D.		3.5	5.8	4.7	6.7	3.4	0.0	0.0	0.0	0.5	0.0
Significance		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Gait 1: Normal, 2: unmoving, 3: staggering, 4: hind-limbs extended and dragged, 5: all fours extended, 6: forelimbs extended and dragged; unable to support body, 7: standing on tiptoe.

Palpebral closure 1: Eyelids open normally, 2: eyelids half-closed, 3: eyelids closed.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Open-field test										
		Consciousness					Behavioral abnormalities					
		Pre	Day 7	Day 14	Day 21	Day 27		Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	2	2	2	2	2	1	1	1	1	1	1
F04452	F00025	2	2	2	2	2	1	1	1	1	1	1
F04453	F00034	2	2	2	2	2	1	1	1	1	1	1
F04454	F00029	2	2	2	2	2	1	1	1	1	1	1
F04455	F00021	2	2	2	2	2	1	1	1	1	1	1
F04456	F00028	2	2	2	2	2	1	1	1	1	1	1
Number of females		6	6	6	6	6	6	6	6	6	6	6
Mean		2.0	2.0	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0
Range		2	2	2	2	2	1	1	1	1	1	1
Significance		---	---	---	---	---	---	---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

(Continued)

Findings were graded as follows:

Consciousness 1: Comatose; no response, 2: exploring behavior, 3: excited and moving spasmodically.

Behavioral abnormalities 1: Not observed, 2: straub's reaction, 3: moving backward, 4: writhing.

Appendix 10-4. (Continued) Individual FOB of female rats

1,4-dichlorobutane group at 300 mg/kg

Female No.	Blind No.	Open-field test				
		Righting reflex				
		Pre	Day 7	Day 14	Day 21	Day 27
F04451	F00035	1	1	1	1	1
F04452	F00025	1	1	1	1	1
F04453	F00034	1	1	1	1	1
F04454	F00029	1	1	1	1	1
F04455	F00021	1	1	1	1	1
F04456	F00028	1	1	1	1	1
Number of females		6	6	6	6	6
Mean		1.0	1.0	1.0	1.0	1.0
Range		1	1	1	1	1
Significance		--	--	--	--	--
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

Righting reflex

1: Righting itself immediately, 2: requiring 3 seconds or longer to right itself, 3: unable to right itself.

Appendix 11-1. Individual sensory response of male rats on termination of administration period

<u>Control group</u>						
Male No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
M01101	M00026	1	2	2	2	3
M01102	M00008	1	2	2	2	3
M01103	M00028	1	2	2	2	3
M01104	M00044	1	2	2	2	3
M01105	M00035	1	2	2	2	3
M01106	M00036	1	2	2	2	3
Number of males		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3

Findings were graded as follows:

- Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
 Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing,
 4: jumping at or biting at stimulus.
 Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing,
 4: jumping at or biting at stimulus.
 Auditory reflex 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
 Pain reflex 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus,
 3: quickly moving forward to escape from stimulus or biting at it immediately after looking back,
 4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Appendix 11-2. Individual sensory response of male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg						
Male No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
M02201	M00040	1	2	2	2	3
M02202	M00041	1	2	2	2	3
M02203	M00033	1	2	2	2	3
M02204	M00010	1	2	2	2	3
M02205	M00012	1	2	2	2	3
M02206	M00019	1	2	2	2	3
Number of males		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

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- Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
- Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing, 4: jumping at or biting at stimulus.
- Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing, 4: jumping at or biting at stimulus.
- Auditory reflex 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
- Pain reflex 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus, 3: quickly moving forward to escape from stimulus or biting at it immediately after looking back, 4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Appendix 11-3. Individual sensory response of male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg						
Male No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
M03301	M00007	1	2	2	2	3
M03302	M00003	1	2	2	2	3
M03303	M00037	1	2	2	2	3
M03304	M00002	1	2	2	2	3
M03305	M00006	1	2	2	2	3
M03306	M00023	1	2	2	2	3
Number of males		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

- Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
- Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing, 4: jumping at or biting at stimulus.
- Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing, 4: jumping at or biting at stimulus.
- Auditory reflex 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
- Pain reflex 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus, 3: quickly moving forward to escape from stimulus or biting at it immediately after looking back, 4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Appendix 11-4. Individual sensory response of male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg						
Male No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
M04401	M00030	1	2	2	2	3
M04402	M00017	1	2	2	2	3
M04403	M00015	1	2	2	2	3
M04404	M00022	1	2	2	2	3
M04405	M00034	1	2	2	2	3
M04406	M00039	1	2	2	2	3
Number of males		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

- Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
 Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing,
 4: jumping at or biting at stimulus.
 Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing,
 4: jumping at or biting at stimulus.
 Auditory reflex 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
 Pain reflex 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus,
 3: quickly moving forward to escape from stimulus or biting at it immediately after looking back,
 4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Appendix 12-1. Individual sensory response of female rats on termination of administration period

Control group						
Female No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
F01151	F00002	1	2	2	2	3
F01152	F00001	1	2	2	2	3
F01153	F00022	1	2	2	2	3
F01154	F00020	1	2	2	2	3
F01155	F00019	1	2	2	2	3
F01156	F00011	1	2	2	2	3
Number of females		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3

Findings were graded as follows:

- Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
 Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing,
 4: jumping at or biting at stimulus.
 Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing,
 4: jumping at or biting at stimulus.
 Auditory reflex 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
 Pain reflex 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus,
 3: quickly moving forward to escape from stimulus or biting at it immediately after looking back,
 4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Appendix 12-2. Individual sensory response of female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Female No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
F02251	F00003	1	2	2	2	3
F02252	F00041	1	2	2	2	3
F02253	F00015	1	2	2	2	3
F02254	F00033	1	2	2	2	3
F02255	F00005	1	2	2	2	3
F02256	F00037	1	2	2	2	3
Number of females		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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Findings were graded as follows:

- Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
- Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing,
4: jumping at or biting at stimulus.
- Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing,
4: jumping at or biting at stimulus.
- Auditory reflex 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
- Pain reflex 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus,
3: quickly moving forward to escape from stimulus or biting at it immediately after looking back,
4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Appendix 12-3. Individual sensory response of female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg						
Female No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
F03351	F00036	1	2	2	2	3
F03352	F00031	1	2	2	2	3
F03353	F00024	1	2	2	2	3
F03354	F00017	1	2	2	2	3
F03355	F00039	1	2	2	2	3
F03356	F00038	1	2	2	2	3
Number of females		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Findings were graded as follows:

- Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
 Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing,
 4: jumping at or biting at stimulus.
 Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing,
 4: jumping at or biting at stimulus.
 Auditory reflex 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
 Pain reflex 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus,
 3: quickly moving forward to escape from stimulus or biting at it immediately after looking back,
 4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Appendix 12-4. Individual sensory response of female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg						
Female No.	Blind No.	Pupillary reflex	Approaching behavior	Response to touch	Auditory reflex	Pain reflex
F04451	F00035	1	2	2	2	3
F04452	F00025	1	2	2	2	3
F04453	F00034	1	2	2	2	3
F04454	F00029	1	2	2	2	3
F04455	F00021	1	2	2	2	3
F04456	F00028	1	2	2	2	3
Number of females		6	6	6	6	6
Mean		1.0	2.0	2.0	2.0	3.0
Range		1	2	2	2	3
Significance		---	---	---	---	---
Statistical method		UA	UA	UA	UA	UA

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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Findings were graded as follows:

- Pupillary reflex 1: Normal pupillary contraction observed, 2: pupils completely dilated, 3: pupils completely contracted.
- Approaching behavior 1: Not observed, 2: approaching and sniffing stimulus, 3: reacting to stimulus, including vocalizing,
4: jumping at or biting at stimulus.
- Response to touch 1: No response, 2: looking back and leaving stimulus, 3: reacting to stimulus, including vocalizing,
4: jumping at or biting at stimulus.
- Auditory reflex 1: Not observed, 2: hesitating at stimulus or moving ears, 3: jumping at and trying to bite at the source of sound.
- Pain reflex 1: Not observed, 2: slowly looking back or slowly moving forward to escape from stimulus,
3: quickly moving forward to escape from stimulus or biting at it immediately after looking back,
4: jumping forward to escape from stimulus, 5: loudly vocalizing and biting at stimulus after suddenly looking back.

Appendix 13-1. Individual grip strength (g) of male rats on termination of administration period

Control group		
Male No.	Forelimb	Hindlimb
M01101	1403	627
M01102	959	391
M01103	852	487
M01104	998	417
M01105	1182	369
M01106	1144	387
Number of males	6	6
Mean	1090	446
S.D.	196	98

Appendix 13-2. Individual grip strength (g) of male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg		
Male No.	Forelimb	Hindlimb
M02201	1072	555
M02202	787	426
M02203	1050	373
M02204	901	362
M02205	1005	359
M02206	915	410
Number of males	6	6
Mean	955	414
S.D.	108	74
Significance	NS	NS
Statistical method	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 13-3. Individual grip strength (g) of male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg		
Male No.	Forelimb	Hindlimb
M03301	1700	724
M03302	907	516
M03303	886	388
M03304	830	450
M03305	921	398
M03306	913	347
Number of males	6	6
Mean	1026	471
S.D.	332	137
Significance	NS	NS
Statistical method	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 13-4. Individual grip strength (g) of male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg		
Male No.	Forelimb	Hindlimb
M04401	1414	579
M04402	938	479
M04403	921	509
M04404	778	333
M04405	927	408
M04406	1101	442
Number of males	6	6
Mean	1013	458
S.D.	221	85
Significance	NS	NS
Statistical method	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 14-1 Individual grip strength (g) of female rats on termination of administration period

Control group		
Female No.	Forelimb	Hindlimb
F01151	794	407
F01152	753	281
F01153	811	357
F01154	778	424
F01155	721	326
F01156	667	316
Number of females	6	6
Mean	754	352
S.D.	53	55

Appendix 14-2 Individual grip strength (g) of female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Female No.	Forelimb	Hindlimb
F02251	835	426
F02252	718	389
F02253	726	373
F02254	696	378
F02255	574	363
F02256	553	332
Number of females	6	6
Mean	684	377
S.D.	105	31
Significance	NS	NS
Statistical method	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 14-3 Individual grip strength (g) of female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Female No.	Forelimb	Hindlimb
F03351	752	379
F03352	709	400
F03353	762	309
F03354	857	360
F03355	679	382
F03356	689	403
Number of females	6	6
Mean	741	372
S.D.	66	35
Significance	NS	NS
Statistical method	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 14-4 Individual grip strength (g) of female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg		
Female No.	Forelimb	Hindlimb
F04451	767	358
F04452	859	331
F04453	536	314
F04454	881	237
F04455	582	391
F04456	642	414
Number of females	6	6
Mean	711	341
S.D.	146	63
Significance	NS	NS
Statistical method	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 15-1. Individual spontaneous motor activity of male rats on termination of administration period

Control group Male No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	70	80	90	100	110	120		70	80	90	100	110	120	
M01101	174	19	0	0	0	0	193	27	6	0	0	0	0	33
M01102	421	2	57	20	44	0	544	36	0	7	12	11	0	66
M01103	184	19	0	0	0	0	203	31	1	0	0	0	0	32
M01104	187	135	72	85	4	0	483	29	7	11	8	1	0	56
M01105	649	559	17	0	0	182	1407	58	23	3	0	0	2	86
M01106	387	188	92	69	8	0	744	61	18	11	13	3	0	106
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	334	154	40	29	9	30	596	40	9	5	6	3	0	63
S.D.	189	212	39	38	17	74	450	15	9	5	6	4	1	29

Appendix 15-2. Individual spontaneous motor activity of male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Male No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	70	80	90	100	110	120	70	80	90	100	110	120		
M02201	186	44	0	0	26	0	256	43	13	1	0	9	1	67
M02202	340	19	210	61	72	19	721	55	3	27	17	9	5	116
M02203	516	134	14	91	0	2	757	77	31	1	3	0	0	112
M02204	422	158	15	0	0	0	595	70	25	3	0	0	0	98
M02205	349	149	231	151	22	106	1008	64	18	48	40	10	10	190
M02206	444	448	312	27	0	0	1231	43	38	20	1	0	0	102
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	376	159	130	55	20	21	761	59	21	17	10	5	3	114
S.D.	114	153	137	59	28	42	336	14	13	19	16	5	4	41
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*
Statistical method	DU	DU	DU	DU	STL	STL	DU	DU	STL	STL	STL	STL	STL	DU

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 15-3. Individual spontaneous motor activity of male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Male No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	70	80	90	100	110	120	70	80	90	100	110	120		
M03301	46	20	23	0	0	0	89	7	16	3	2	4	0	32
M03302	495	124	1	0	0	0	620	67	9	1	0	0	0	77
M03303	309	125	23	0	20	152	629	66	29	3	0	4	40	142
M03304	559	336	212	76	0	0	1183	69	43	22	9	0	0	143
M03305	405	271	194	93	0	0	963	55	18	21	9	0	0	103
M03306	753	205	5	0	0	0	963	66	11	0	0	0	0	77
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	428	180	76	28	3	25	741	55	21	8	3	1	7	96
S.D.	240	114	99	44	8	62	386	24	13	10	4	2	16	43
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	STL	STL	DU	DU	STL	STL	STL	STL	STL	DU

252

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 15-4. Individual spontaneous motor activity of male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Male No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	70	80	90	100	110	120	70	80	90	100	110	120		
M04401	330	74	0	123	0	0	527	59	13	0	20	0	0	92
M04402	487	16	0	0	0	0	503	49	2	0	0	0	0	51
M04403	368	170	23	0	0	0	561	51	25	6	0	0	0	82
M04404	491	303	199	0	0	1	994	46	35	6	0	0	0	87
M04405	500	125	16	0	0	0	641	62	11	0	0	0	0	73
M04406	372	96	137	0	0	1	606	56	15	14	0	0	0	85
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	425	131	63	21	0	0	639	54	17	4	3	0	0	78
S.D.	76	99	85	50	0	1	181	6	12	6	8	0	0	15
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	STL	STL	DU	DU	STL	STL	STL	STL	STL	DU

253

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 16-1. Individual spontaneous motor activity of female rats on termination of administration period

Control group Female No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	70	80	90	100	110	120		70	80	90	100	110	120	
F01151	411	105	1	0	11	164	692	50	14	0	0	6	24	94
F01152	480	1	89	0	8	32	610	44	0	5	0	1	13	63
F01153	332	36	0	0	0	0	368	22	6	2	0	0	0	30
F01154	654	74	0	0	0	0	728	64	13	0	0	0	0	77
F01155	797	180	0	0	0	0	977	98	45	0	0	0	0	143
F01156	637	388	38	0	0	0	1063	73	53	3	0	0	0	129
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	552	131	21	0	3	33	740	59	22	2	0	1	6	89
S.D.	174	140	36	0	5	66	252	26	22	2	0	2	10	42

Appendix 16-2. Individual spontaneous motor activity of female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Female No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	70	80	90	100	110	120	70	80	90	100	110	120		
F02251	509	115	20	0	0	0	644	35	12	0	0	0	0	47
F02252	503	117	160	0	0	0	780	61	27	27	0	0	0	115
F02253	175	506	1	0	5	402	1089	32	88	3	0	2	65	190
F02254	635	184	1	0	103	234	1157	80	31	0	0	18	32	161
F02255	859	97	163	0	201	21	1341	120	31	21	0	25	1	198
F02256	791	76	0	0	0	0	867	70	8	0	0	0	0	78
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	579	183	58	0	52	110	980	66	33	9	0	8	16	132
S.D.	245	163	81	0	84	170	260	32	29	12	0	11	27	62
Significance	NS	NS	NS	---	NS	NS	NS	NS	NS	NS	---	NS	NS	NS
Statistical method	DU	DU	STL	UA	STL	STL	DU	DU	STL	UA	STL	STL	DU	

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NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 16-3. Individual spontaneous motor activity of female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Female No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	70	80	90	100	110	120	70	80	90	100	110	120		
F03351	466	63	99	16	19	33	696	83	4	15	5	1	3	111
F03352	217	152	2	0	0	0	371	23	19	12	0	0	0	54
F03353	728	261	218	0	0	0	1207	103	29	46	0	0	0	178
F03354	454	188	0	0	0	0	642	63	41	0	0	0	0	104
F03355	622	797	352	25	543	40	2379	86	77	38	0	40	3	244
F03356	364	81	0	0	0	0	445	54	24	0	0	0	0	78
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	475	257	112	7	94	12	957	69	32	19	1	7	1	128
S.D.	182	274	146	11	220	19	756	28	25	19	2	16	2	70
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	STL	STL	STL	STL	DU	DU	STL	STL	STL	STL	STL	DU

256

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 16-4. Individual spontaneous motor activity of female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Female No.	Ambulatory counts							Vertical counts						
	Minutes after administration						Total	Minutes after administration						Total
	70	80	90	100	110	120	70	80	90	100	110	120		
F04451	495	4	0	0	0	0	499	52	8	0	0	0	0	60
F04452	544	63	15	304	0	0	926	74	5	0	36	0	0	115
F04453	997	281	94	0	205	0	1577	80	33	11	0	27	0	151
F04454	292	0	57	0	0	0	349	58	0	20	0	0	0	78
F04455	730	207	0	0	0	0	937	98	25	0	0	0	0	123
F04456	1043	86	0	0	0	0	1129	76	4	0	0	0	0	80
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	684	107	28	51	34	0	903	73	13	5	6	5	0	101
S.D.	296	114	39	124	84	0	442	16	13	8	15	11	0	34
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	STL	STL	STL	STL	DU	DU	STL	STL	STL	STL	STL	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 17-1. Individual urinary findings in male rats on termination of administration period

Control group Male No.	Urinary sediments														
	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M01101	9.2	1.052	Light yellow	8.5	++	-	++	-	-	1.0	±	±	±	-	+
M01102	11.0	1.052	Light yellow	8.5	+	-	-	-	-	0.1	±	±	±	-	-
M01103	12.3	1.046	Light yellow	8.5	+	-	+	-	-	0.1	±	±	±	-	-
M01104	5.7	1.074	Light yellow	8.5	++	-	+	-	-	0.1	±	±	±	-	+
M01105	16.6	1.038	Light yellow	8.5	++	-	+	-	-	0.1	±	±	±	-	+
M01106	4.2	1.074	Light yellow	8.5	++	-	±	-	±	0.1	±	±	±	-	-
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	9.8	1.056	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	4.5	0.015	---	---	---	---	---	---	---	---	---	---	---	---	---

Protein: -; negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -; negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; slight, ++; moderate, +++; marked.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

Appendix 17-2. Individual urinary findings in male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Male No.	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Urinary sediments				
											Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M02201	14.4	1.046	Light yellow	8.5	+	-	±	-	-	0.1	±	±	±	-	+
M02202	12.1	1.041	Light yellow	8.5	+	-	+	-	-	0.1	±	±	±	-	-
M02203	8.8	1.060	Light yellow	8.5	±	-	±	-	-	0.1	±	±	±	-	+
M02204	9.6	1.054	Light yellow	8.5	++	-	+	+	-	1.0	±	±	±	-	-
M02205	7.2	1.068	Light yellow	8.5	+	-	+	+	-	0.1	±	±	±	-	+
M02206	11.9	1.050	Light yellow	8.5	±	-	-	-	-	0.1	±	±	±	-	+
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	10.7	1.053	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	2.6	0.010	---	---	---	---	---	---	---	---	---	---	---	---	---
Significance	NS	NS													
Statistical method	DU	DU													

Protein: -: negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -: negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -: negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -: negative, +; slight, ++; moderate, +++; marked.

Occult blood: -: negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -: not observed, +; observed.

Crystals: -: not observed, +; observed.

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 17-3. Individual urinary findings in male rats on termination of administration period

Male No.	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Urinary sediments				
											Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M03301	12.5	1.043	Light yellow	8.0	±	-	+	-	-	0.1	±	±	±	-	+
M03302	10.3	1.054	Light yellow	8.0	±	-	-	-	-	0.1	±	±	±	-	+
M03303	12.1	1.050	Light yellow	8.5	+	-	+	-	-	0.1	±	±	±	-	-
M03304	22.7	1.030	Light yellow	8.5	+	-	±	-	±	0.1	±	±	±	-	+
M03305	9.4	1.070	Light yellow	8.5	±	-	+	-	-	0.1	±	±	±	-	+
M03306	12.7	1.040	Light yellow	8.5	+	-	±	-	+	0.1	±	±	±	-	+
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	13.3	1.048	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	4.8	0.014	---	---	---	---	---	---	---	---	---	---	---	---	---
Significance	NS	NS													
Statistical method	DU	DU													

Protein: -: negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -: negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -: negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -: negative, +; slight, ++; moderate, +++; marked.

Occult blood: -: negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -: not observed, +; observed.

Crystals: -: not observed, +; observed.

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 17-4. Individual urinary findings in male rats on termination of administration period

Male No.	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Urinary sediments				
											Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M04401	16.2	1.041	Light yellow	8.5	±	-	+	-	±	0.1	±	±	±	-	-
M04402	18.4	1.036	Light yellow	8.5	+	-	+	-	-	0.1	±	±	±	-	+
M04403	15.6	1.044	Light yellow	8.5	±	-	±	-	-	0.1	±	±	±	-	+
M04404	16.0	1.048	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	-
M04405	17.3	1.042	Light yellow	8.5	-	-	±	-	-	0.1	±	±	±	-	+
M04406	13.5	1.056	Light yellow	8.5	±	-	±	-	-	0.1	±	±	±	-	+
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	16.2	1.045	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	1.7	0.007	---	---	---	---	---	---	---	---	---	---	---	---	---
Significance	*	NS													
Statistical method	DU	DU													

Protein: -: negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -: negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -: negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -: negative, +; slight, ++; moderate, +++; marked.

Occult blood: -: negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -: not observed, +; observed.

Crystals: -: not observed, +; observed.

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 18-1. Individual urinary findings in female rats on termination of administration period

Female No.	Control group										Urinary sediments				
	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F01151	7.3	1.050	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	-
F01152	7.4	1.043	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	-
F01153	3.9	1.056	Light yellow	≥ 9.0	-	-	-	-	-	0.1	±	±	±	-	+
F01154	9.9	1.042	Light yellow	≥ 9.0	-	-	-	-	-	0.1	±	±	±	-	+
F01155	9.9	1.022	Light yellow	≥ 9.0	-	-	-	-	-	0.1	±	±	±	-	+
F01156	6.5	1.060	Light yellow	8.0	±	-	-	-	++	0.1	±	+	±	-	-
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	7.5	1.046	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	2.3	0.014	---	---	---	---	---	---	---	---	---	---	---	---	---

Protein: -; negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -; negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; slight, ++; moderate, +++; marked.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 10-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

Appendix 18-2. Individual urinary findings in female rats on termination of administration period

Female No.	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Urinary sediments				
											Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F02251	10.7	1.028	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F02252	6.4	1.054	Light yellow	7.5	+	-	-	-	-	1.0	±	±	±	-	-
F02253	7.0	1.031	Light yellow	8.0	±	-	±	-	-	0.1	±	±	±	-	+
F02254	5.6	1.052	Light yellow	8.5	-	-	-	-	+	0.1	±	±	±	-	+
F02255	7.8	1.034	Light yellow	≥ 9.0	±	-	-	-	±	0.1	±	±	±	-	+
F02256	7.8	1.048	Light yellow	7.5	-	-	-	-	-	0.1	±	±	±	-	-
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	7.6	1.041	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	1.8	0.011	---	---	---	---	---	---	---	---	---	---	---	---	---
Significance	NS	NS													
Statistical method	DU	DU													

Protein: -; negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -; negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; slight, ++; moderate, +++; marked.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 10-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 18-3. Individual urinary findings in female rats on termination of administration period

Female No.	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Urinary sediments				
											Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F03351	7.2	1.056	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F03352	14.3	1.031	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F03353	13.8	1.028	Light yellow	8.0	-	-	-	-	-	0.1	±	±	±	-	-
F03354	7.9	1.056	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F03355	2.9	1.072	Light yellow	8.5	±	-	±	-	±	0.1	±	±	±	-	-
F03356	7.8	1.052	Light yellow	8.5	+	-	+	-	±	0.1	±	±	±	-	+
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	9.0	1.049	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	4.3	0.017	---	---	---	---	---	---	---	---	---	---	---	---	---
Significance	NS	NS													
Statistical method	DU	DU													

Protein: -; negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -; negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; slight, ++; moderate, +++; marked.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 10-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 18-4. Individual urinary findings in female rats on termination of administration period

Female No.	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Urinary sediments				
											Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F04451	23.5	1.022	Light yellow	8.0	-	-	-	-	-	0.1	±	±	±	-	+
F04452	14.1	1.037	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	-
F04453	7.2	1.054	Light yellow	8.5	-	-	±	-	-	0.1	±	±	±	-	-
F04454	9.4	1.056	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F04455	13.5	1.032	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F04456	10.7	1.052	Light yellow	7.5	±	-	+	-	-	0.1	±	±	±	-	-
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	13.1	1.042	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	5.7	0.014	---	---	---	---	---	---	---	---	---	---	---	---	---
Significance	NS	NS													
Statistical method	DU	DU													

Protein: -; negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -; negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; slight, ++; moderate, +++; marked.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 10-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 19-1. Individual urinary findings in male rats on termination of recovery period

Control group Male No.	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Urinary sediments				
											Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M01107	15.6	1.038	Light yellow	8.5	-	-	±	-	-	0.1	±	±	±	-	+
M01108	11.7	1.062	Light yellow	8.5	±	-	+	-	-	0.1	±	±	±	-	+
M01109	12.3	1.052	Light yellow	8.5	±	-	-	-	-	0.1	±	±	±	-	+
M01110	12.3	1.056	Light yellow	8.5	±	-	-	-	-	0.1	±	±	±	-	+
M01111	17.6	1.042	Light yellow	8.5	-	-	±	-	-	0.1	±	±	±	-	+
M01112	15.5	1.046	Light yellow	8.5	+	-	+	-	±	0.1	±	±	±	-	+
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	14.2	1.049	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	2.4	0.009	---	---	---	---	---	---	---	---	---	---	---	---	---

Protein: -; negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -; negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; slight, ++; moderate, +++; marked.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

Appendix 19-2. Individual urinary findings in male rats on termination of recovery period

Male No.	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Urinary sediments				
											Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
M04407	11.6	1.036	Light yellow	8.5	+	-	+	-	-	0.1	±	±	±	-	-
M04408	14.0	1.048	Light yellow	8.5	±	-	±	-	-	0.1	±	±	±	-	+
M04409	28.0	1.022	Light yellow	8.5	±	-	+	-	-	0.1	±	±	±	-	-
M04410	14.5	1.048	Light yellow	8.5	+	-	±	-	±	0.1	±	±	±	-	-
M04411	18.2	1.032	Light yellow	8.5	++	-	+	-	-	0.1	±	±	±	-	+
M04412	11.7	1.060	Light yellow	8.5	+	-	+	-	-	0.1	±	±	±	-	+
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	16.3	1.041	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	6.2	0.014	---	---	---	---	---	---	---	---	---	---	---	---	---
Significance	NS	NS													
Statistical method	TT	TT													

Protein: -: negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -: negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -: negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -: negative, +; slight, ++; moderate, +++; marked.

Occult blood: -: negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -: not observed, +; observed.

Crystals: -: not observed, +; observed.

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Appendix 20-1. Individual urinary findings in female rats on termination of recovery period

Female No.	Control group										Urinary sediments				
	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F01157	19.2	1.030	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F01158	11.3	1.038	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F01159	23.7	1.016	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F01160	3.4	1.078	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F01161	12.1	1.044	Light yellow	8.5	+	-	±	-	-	0.1	±	±	±	-	-
F01162	10.1	1.052	Light yellow	≥ 9.0	±	-	±	-	-	0.1	±	±	±	-	+
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	13.3	1.043	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	7.2	0.021	---	---	---	---	---	---	---	---	---	---	---	---	---

Protein: -; negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -; negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; slight, ++; moderate, +++; marked.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

Appendix 20-2. Individual urinary findings in female rats on termination of recovery period

Female No.	UV mL	S.G.	Color	pH	Protein	Glucose	Ketone body	Bilirubin	Occult blood	Urobili- nogen E.U./dL	Urinary sediments				
											Epithelial cells	Erythrocytes	Leukocytes	Casts	Crystals
F04457	10.3	1.044	Light yellow	8.0	-	-	-	-	-	0.1	±	±	±	-	+
F04458	8.3	1.044	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	-
F04459	12.5	1.044	Light yellow	8.5	-	-	-	-	-	0.1	±	±	±	-	+
F04460	14.0	1.034	Light yellow	8.0	-	-	-	-	-	0.1	±	±	±	-	+
F04461	8.1	1.066	Light yellow	8.5	+	-	±	-	-	1.0	±	±	±	-	-
F04462	17.4	1.030	Light yellow	≥ 9.0	-	-	-	-	±	0.1	±	±	±	-	+
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	11.8	1.044	---	---	---	---	---	---	---	---	---	---	---	---	---
S.D.	3.6	0.012	---	---	---	---	---	---	---	---	---	---	---	---	---
Significance	NS	NS													
Statistical method	TT	TT													

Protein: -; negative, ±; trace, +; 30 mg/dL, ++; 100 mg/dL, +++; ≥300 mg/dL.

Glucose: -; negative, +; 100 mg/dL, ++; 250 mg/dL, +++; 500 mg/dL, +++; ≥1000 mg/dL.

Ketone body: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Bilirubin: -; negative, +; slight, ++; moderate, +++; marked.

Occult blood: -; negative, ±; trace, +; slight, ++; moderate, +++; marked.

Epithelial cells: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; ≥201 cells/100 fields.

Erythrocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Leukocytes: ±; 0-20 cells/100 fields, +; 21-100 cells/100 fields, ++; 101-200 cells/100 fields, +++; 201-500 cells/100 fields, +++; ≥501 cells/100 fields.

Casts: -; not observed, +; observed.

Crystals: -; not observed, +; observed.

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Appendix 21-1. Individual hematological findings in male rats on termination of administration period

Control group											
Male No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
M01101	822	15.7	44.8	54.5	19.1	35.0	112.9	3.19	17.5	23.0	194.5
M01102	827	15.6	43.8	53.0	18.9	35.6	124.9	3.35	17.7	23.2	200.3
M01103	782	15.3	42.5	54.3	19.6	36.0	105.2	2.75	23.4	27.4	185.5
M01104	807	14.7	42.0	52.0	18.2	35.0	123.4	3.05	18.7	21.8	204.4
M01105	837	15.5	43.8	52.3	18.5	35.4	119.7	3.67	19.7	26.7	208.6
M01106	865	15.9	45.1	52.1	18.4	35.3	150.3	2.88	32.1	30.0	202.3
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	823	15.5	43.7	53.0	18.8	35.4	122.7	3.15	21.5	25.4	199.3
S.D.	28	0.4	1.2	1.1	0.5	0.4	15.4	0.33	5.6	3.2	8.2

(Continued)

Appendix 21-1. (Continued) Individual hematological findings in male rats on termination of administration period

<u>Control group</u>						
Male No.	WBC 10 ³ /μL	LYMPH %	NEUT %	EO %	BASO %	MONO %
M01101	139.2	76.9	19.2	1.1	0.1	2.7
M01102	97.1	87.8	8.6	1.0	0.0	2.6
M01103	63.7	83.5	13.0	1.1	0.0	2.4
M01104	73.3	72.2	25.3	0.8	0.1	1.6
M01105	59.3	73.2	22.8	1.5	0.0	2.5
M01106	90.8	88.4	7.9	0.9	0.0	2.8
Number of males	6	6	6	6	6	6
Mean	87.2	80.3	16.1	1.1	0.0	2.4
S.D.	29.5	7.2	7.4	0.2	0.1	0.4

Appendix 21-2. Individual hematological findings in male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg											
Male No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
M02201	752	14.7	42.5	56.5	19.5	34.6	104.1	3.86	17.6	20.3	198.3
M02202	800	15.3	42.6	53.3	19.1	35.9	108.6	4.44	21.9	26.4	206.5
M02203	786	14.5	41.1	52.3	18.4	35.3	107.4	2.99	24.8	27.2	227.5
M02204	791	14.6	41.3	52.2	18.5	35.4	134.8	3.48	18.4	23.4	208.6
M02205	721	13.8	39.3	54.5	19.1	35.1	121.5	3.79	19.5	23.6	213.0
M02206	885	15.8	44.2	49.9	17.9	35.7	129.0	3.13	21.2	25.7	208.6
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	789	14.8	41.8	53.1	18.8	35.3	117.6	3.62	20.6	24.4	210.4
S.D.	55	0.7	1.7	2.2	0.6	0.5	12.7	0.53	2.6	2.5	9.7
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	STL	STL	STL

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 21-2. (Continued) Individual hematological findings in male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg						
Male No.	WBC 10 ² /μL	LYMPH %	NEUT %	EO %	BASO %	MONO %
M02201	93.9	87.6	9.3	1.0	0.0	2.1
M02202	67.2	78.9	17.0	1.0	0.0	3.1
M02203	70.3	75.0	21.0	1.4	0.0	2.6
M02204	67.2	79.9	17.3	1.3	0.0	1.5
M02205	65.5	78.0	19.7	0.8	0.0	1.5
M02206	99.4	83.1	11.4	1.6	0.1	3.8
Number of males	6	6	6	6	6	6
Mean	77.3	80.4	16.0	1.2	0.0	2.4
S.D.	15.2	4.4	4.6	0.3	0.0	0.9
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	STL

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 21-3. Individual hematological findings in male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg											
Male No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
M03301	683	14.0	40.6	59.4	20.5	34.5	111.0	4.62	14.8	18.4	267.5
M03302	810	15.4	43.9	54.2	19.0	35.1	100.9	3.03	23.6	28.4	206.5
M03303	788	15.6	43.6	55.3	19.8	35.8	105.1	2.71	17.8	23.0	190.8
M03304	778	15.1	43.1	55.4	19.4	35.0	113.1	3.41	20.8	24.1	213.0
M03305	778	15.0	42.6	54.8	19.3	35.2	115.7	3.06	26.3	28.5	202.3
M03306	783	14.9	42.4	54.2	19.0	35.1	127.3	3.74	27.7	27.6	208.6
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	770	15.0	42.7	55.6	19.5	35.1	112.2	3.43	21.8	25.0	214.8
S.D.	44	0.6	1.2	2.0	0.6	0.4	9.2	0.68	5.0	4.0	26.9
Significance	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	STL	STL	STL

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

(Continued)

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 21-3. (Continued) Individual hematological findings in male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg						
Male No.	WBC 10 ³ /μL	LYMPH %	NEUT %	EO %	BASO %	MONO %
M03301	98.1	84.4	11.4	0.5	0.0	3.7
M03302	75.4	81.6	13.2	1.1	0.0	4.1
M03303	56.1	77.4	17.8	1.2	0.0	3.6
M03304	76.0	84.9	10.0	1.7	0.0	3.4
M03305	51.7	59.0	31.7	2.1	0.0	7.2
M03306	54.5	78.9	18.7	0.6	0.0	1.8
Number of males	6	6	6	6	6	6
Mean	68.6	77.7	17.1	1.2	0.0	4.0
S.D.	18.0	9.6	7.9	0.6	0.0	1.8
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	STL

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 21-4. Individual hematological findings in male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg											
Male No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
M04401	787	14.7	42.2	53.6	18.7	34.8	120.0	4.04	20.3	23.9	192.6
M04402	784	14.5	41.4	52.8	18.5	35.0	124.1	3.42	18.5	25.8	192.6
M04403	768	14.8	41.3	53.8	19.3	35.8	125.5	3.53	19.4	23.7	222.4
M04404	753	14.9	41.6	55.2	19.8	35.8	106.8	5.14	17.7	24.3	198.3
M04405	804	15.6	43.7	54.4	19.4	35.7	103.7	3.28	20.0	24.9	183.8
M04406	766	14.6	41.9	54.7	19.1	34.8	133.0	4.36	20.7	24.5	194.5
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	777	14.9	42.0	54.1	19.1	35.3	118.9	3.96	19.4	24.5	197.4
S.D.	18	0.4	0.9	0.9	0.5	0.5	11.4	0.71	1.1	0.8	13.2
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	STL	STL	STL

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 21-4. (Continued) Individual hematological findings in male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Male No.	WBC 10 ³ /μL	LYMPH %	NEUT %	EO %	BASO %	MONO %
M04401	80.1	76.4	18.8	0.4	0.0	4.4
M04402	56.9	82.6	12.8	1.6	0.0	3.0
M04403	117.2	67.0	25.8	0.9	0.1	6.2
M04404	64.6	78.3	16.8	0.9	0.0	4.0
M04405	56.0	84.8	11.5	0.7	0.0	3.0
M04406	80.1	77.0	17.0	0.6	0.0	5.4
Number of males	6	6	6	6	6	6
Mean	75.8	77.7	17.1	0.9	0.0	4.3
S.D.	22.9	6.2	5.1	0.4	0.0	1.3
Significance	NS	NS	NS	NS	NS	#
Statistical method	DU	DU	DU	DU	DU	STL

Significantly different from the control group (#: p<0.05 by Steel's test).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 22-1. Individual hematological findings in female rats on termination of administration period

Control group											
Female No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
F01151	800	14.8	41.6	52.0	18.5	35.6	122.5	1.94	15.9	16.8	179.4
F01152	785	14.5	40.6	51.7	18.5	35.7	127.5	3.10	15.7	16.0	201.8
F01153	724	13.9	38.6	53.3	19.2	36.0	105.8	2.17	14.4	17.5	176.4
F01154	714	14.0	38.4	53.8	19.6	36.5	108.8	3.07	15.2	17.8	165.3
F01155	778	14.7	40.8	52.4	18.9	36.0	111.4	3.08	14.1	19.0	159.0
F01156	846	15.6	43.1	50.9	18.4	36.2	141.4	2.50	14.7	17.9	184.1
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	775	14.6	40.5	52.4	18.9	36.0	119.6	2.64	15.0	17.5	177.7
S.D.	49	0.6	1.8	1.1	0.5	0.3	13.6	0.51	0.7	1.0	15.0

(Continued)

Appendix 22-1. (Continued) Individual hematological findings in female rats on termination of administration period

Control group						
Female No.	WBC 10 ³ /µL	LYMPH %	NEUT %	EO %	BASO %	MONO %
F01151	64.0	80.9	12.1	2.0	0.2	4.8
F01152	87.5	84.6	11.0	1.7	0.1	2.6
F01153	82.9	89.7	8.0	1.0	0.0	1.3
F01154	34.1	84.5	14.0	0.6	0.0	0.9
F01155	44.2	69.2	26.0	3.4	0.0	1.4
F01156	41.0	69.8	25.3	2.2	0.0	2.7
Number of females	6	6	6	6	6	6
Mean	59.0	79.8	16.1	1.8	0.1	2.3
S.D.	22.7	8.4	7.7	1.0	0.1	1.4

Appendix 22-2. Individual hematological findings in female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Female No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
F02251	841	15.4	42.8	50.9	18.3	36.0	145.0	1.86	14.1	17.2	173.5
F02252	739	13.9	38.5	52.1	18.8	36.1	122.2	2.96	15.8	15.8	162.7
F02253	751	14.5	40.0	53.3	19.3	36.3	128.4	3.03	14.6	18.9	165.3
F02254	766	14.4	40.0	52.2	18.8	36.0	125.4	2.40	15.6	18.8	156.6
F02255	747	13.5	37.1	49.7	18.1	36.4	116.8	3.71	15.9	17.8	160.2
F02256	774	14.6	40.8	52.7	18.9	35.8	127.0	2.75	15.0	16.2	160.2
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	770	14.4	39.9	51.8	18.7	36.1	127.5	2.79	15.2	17.5	163.1
S.D.	37	0.6	2.0	1.3	0.4	0.2	9.5	0.62	0.7	1.3	5.9
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

Appendix 22-2. (Continued) Individual hematological findings in female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg						
Female No.	WBC 10 ³ /μL	LYMPH %	NEUT %	EO %	BASO %	MONO %
F02251	49.3	82.6	9.9	2.6	0.0	4.9
F02252	72.1	84.6	11.3	1.0	0.0	3.1
F02253	57.2	82.7	14.7	0.9	0.0	1.7
F02254	48.0	79.2	16.2	2.5	0.0	2.1
F02255	66.4	79.7	14.5	1.7	0.0	4.1
F02256	56.3	85.1	11.4	1.4	0.0	2.1
Number of females	6	6	6	6	6	6
Mean	58.2	82.3	13.0	1.7	0.0	3.0
S.D.	9.5	2.4	2.5	0.7	0.0	1.3
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 22-3. Individual hematological findings in female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Female No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
F03351	723	14.0	39.4	54.5	19.4	35.5	106.7	2.96	17.5	17.7	137.2
F03352	769	13.9	38.4	49.9	18.1	36.2	121.6	2.98	15.9	17.3	162.7
F03353	756	14.7	41.0	54.2	19.4	35.9	124.7	3.32	16.4	16.1	177.9
F03354	781	15.4	43.6	55.8	19.7	35.3	108.3	2.44	14.9	18.5	159.0
F03355	696	13.5	38.2	54.9	19.4	35.3	113.7	2.53	15.5	19.4	141.9
F03356	760	14.7	41.1	54.1	19.3	35.8	110.8	3.33	15.3	19.3	166.6
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	748	14.4	40.3	53.9	19.2	35.7	114.3	2.93	15.9	18.1	157.6
S.D.	32	0.7	2.0	2.1	0.6	0.4	7.3	0.38	0.9	1.3	15.4
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

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

(Continued)

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 22-3. (Continued) Individual hematological findings in female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg						
Female No.	WBC 10 ³ /μL	LYMPH %	NEUT %	EO %	BASO %	MONO %
F03351	64.8	91.7	5.4	1.4	0.0	1.5
F03352	81.3	88.7	7.0	2.5	0.0	1.8
F03353	45.8	84.7	11.4	1.3	0.0	2.6
F03354	40.8	86.0	9.8	2.0	0.0	2.2
F03355	37.7	79.6	13.5	4.5	0.0	2.4
F03356	47.3	73.8	21.1	1.9	0.0	3.2
Number of females	6	6	6	6	6	6
Mean	53.0	84.1	11.4	2.3	0.0	2.3
S.D.	16.8	6.5	5.6	1.2	0.0	0.6
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 22-4. Individual hematological findings in female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Female No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
F04451	789	15.3	41.8	53.0	19.4	36.6	114.2	3.96	14.9	19.9	207.8
F04452	752	14.1	39.1	52.0	18.8	36.1	149.3	3.20	15.5	18.9	166.6
F04453	722	13.9	39.7	55.0	19.3	35.0	119.3	3.63	16.2	14.5	189.1
F04454	829	15.0	42.5	51.3	18.1	35.3	117.2	3.16	15.6	18.9	179.4
F04455	772	14.5	39.9	51.7	18.8	36.3	121.8	2.19	16.3	17.9	201.8
F04456	769	14.6	41.2	53.6	19.0	35.4	111.3	2.66	16.5	16.1	187.4
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	772	14.6	40.7	52.8	18.9	35.8	122.2	3.13	15.8	17.7	188.7
S.D.	36	0.5	1.3	1.4	0.5	0.6	13.8	0.64	0.6	2.0	14.9
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

Appendix 22-4. (Continued) Individual hematological findings in female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Female No.	WBC 10 ² /μL	LYMPH %	NEUT %	EO %	BASO %	MONO %
F04451	38.7	59.9	31.5	0.8	0.0	7.8
F04452	53.5	90.1	4.3	2.6	0.0	3.0
F04453	41.8	71.1	23.6	1.0	0.0	4.3
F04454	37.0	68.6	26.8	2.2	0.0	2.4
F04455	44.7	64.0	29.7	2.0	0.0	4.3
F04456	49.9	80.0	16.0	1.0	0.0	3.0
Number of females	6	6	6	6	6	6
Mean	44.3	72.3	22.0	1.6	0.0	4.1
S.D.	6.4	11.1	10.2	0.8	0.0	2.0
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 23-1. Individual hematological findings in male rats on termination of recovery period

Control group											
Male No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
M01107	841	15.4	42.6	50.7	18.3	36.2	128.9	3.78	16.1	23.1	221.2
M01108	885	14.9	41.4	46.8	16.8	36.0	135.2	3.03	16.7	24.5	205.4
M01109	768	14.4	39.5	51.4	18.8	36.5	111.5	3.36	15.7	21.1	205.4
M01110	771	14.8	41.3	53.6	19.2	35.8	112.6	3.53	15.7	22.8	217.1
M01111	872	15.6	42.8	49.1	17.9	36.4	114.4	3.31	18.8	26.2	223.4
M01112	842	15.6	43.1	51.2	18.5	36.2	115.1	2.78	14.7	18.3	179.8
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	830	15.1	41.8	50.5	18.3	36.2	119.6	3.30	16.3	22.7	208.7
S.D.	50	0.5	1.3	2.3	0.8	0.3	9.9	0.36	1.4	2.7	16.1

(Continued)

Appendix 23-1. (Continued) Individual hematological findings in male rats on termination of recovery period

<u>Control group</u>						
Male No.	WBC 10 ³ /µL	LYMPH %	NEUT %	EO %	BASO %	MONO %
M01107	100.3	74.7	21.4	1.3	0.0	2.6
M01108	71.1	78.5	17.8	0.7	0.0	3.0
M01109	65.2	73.9	21.2	2.0	0.0	2.9
M01110	64.8	83.3	11.6	1.4	0.0	3.7
M01111	57.9	74.6	20.2	1.6	0.0	3.6
M01112	90.8	80.2	14.5	1.1	0.0	4.2
Number of males	6	6	6	6	6	6
Mean	75.0	77.5	17.8	1.4	0.0	3.3
S.D.	16.7	3.8	4.0	0.4	0.0	0.6

Appendix 23-2. Individual hematological findings in male rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg											
Male No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
M04407	885	15.9	43.2	48.8	18.0	36.8	111.2	2.85	15.0	24.7	215.0
M04408	849	15.6	43.0	50.6	18.4	36.3	130.8	3.83	17.3	23.9	234.7
M04409	791	15.1	42.0	53.1	19.1	36.0	116.4	3.70	16.0	24.7	205.4
M04410	829	15.1	41.6	50.2	18.2	36.3	131.0	3.15	21.0	27.6	215.0
M04411	761	14.2	39.6	52.0	18.7	35.9	119.8	4.89	24.4	34.9	213.0
M04412	784	15.6	44.0	56.1	19.9	35.5	104.7	3.90	15.7	22.6	184.1
Number of males	6	6	6	6	6	6	6	6	6	6	6
Mean	817	15.3	42.2	51.8	18.7	36.1	119.0	3.72	18.2	26.4	211.2
S.D.	46	0.6	1.6	2.6	0.7	0.4	10.5	0.71	3.7	4.5	16.4
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

(Continued)

TT: Analysis by Student's t-test.

Appendix 23-2. (Continued) Individual hematological findings in male rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Male No.	WBC 10 ³ /μL	LYMPH %	NEUT %	EO %	BASO %	MONO %
M04407	56.0	84.5	11.0	1.3	0.0	3.2
M04408	67.3	81.4	14.6	1.3	0.0	2.7
M04409	95.4	78.1	15.3	1.6	0.1	4.9
M04410	49.1	79.6	15.3	1.8	0.0	3.3
M04411	85.0	81.2	13.8	1.1	0.0	3.9
M04412	47.2	78.6	16.4	0.6	0.0	4.4
Number of males	6	6	6	6	6	6
Mean	66.7	80.6	14.4	1.3	0.0	3.7
S.D.	19.8	2.3	1.9	0.4	0.0	0.8
Significance	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Appendix 24-1. Individual hematological findings in female rats on termination of recovery period

Control group											
Female No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
F01157	735	14.4	40.3	54.8	19.6	35.7	113.3	3.02	14.3	18.4	176.1
F01158	794	14.3	39.5	49.7	18.0	36.2	117.5	2.65	14.7	16.1	184.7
F01159	736	14.1	39.7	53.9	19.2	35.5	127.7	3.20	14.5	18.1	172.1
F01160	715	13.4	37.1	51.9	18.7	36.1	126.5	2.90	14.0	17.9	169.5
F01161	830	14.8	40.4	48.7	17.8	36.6	122.4	2.29	16.3	17.2	161.1
F01162	784	14.6	40.3	51.4	18.6	36.2	110.8	2.82	14.7	17.3	172.1
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	766	14.3	39.6	51.7	18.7	36.1	119.7	2.81	14.8	17.5	172.6
S.D.	44	0.5	1.3	2.3	0.7	0.4	7.0	0.32	0.8	0.8	7.8

(Continued)

Appendix 24-1. (Continued) Individual hematological findings in female rats on termination of recovery period

Control group						
Female No.	WBC $10^2/\mu\text{L}$	LYMPH %	NEUT %	EO %	BASO %	MONO %
F01157	46.7	80.1	17.1	1.5	0.0	1.3
F01158	45.1	77.2	19.2	1.6	0.2	1.8
F01159	39.6	69.4	26.6	1.5	0.0	2.5
F01160	27.6	87.3	9.5	1.4	0.0	1.8
F01161	25.1	84.5	11.5	1.6	0.0	2.4
F01162	49.8	82.9	15.5	0.4	0.0	1.2
Number of females	6	6	6	6	6	6
Mean	39.0	80.2	16.6	1.3	0.0	1.8
S.D.	10.4	6.4	6.1	0.5	0.1	0.5

Appendix 24-2. Individual hematological findings in female rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Female No.	RBC 10 ⁴ /µL	Hemoglobin g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10 ⁴ /µL	Reticulocyte %	PT sec.	APTT sec.	Fibrinogen mg/dL
F04457	776	14.5	39.9	51.4	18.7	36.3	111.0	4.11	15.4	18.8	152.5
F04458	769	14.4	39.7	51.6	18.7	36.3	102.4	2.98	15.5	18.7	151.5
F04459	830	14.8	41.3	49.8	17.8	35.8	119.3	2.47	15.7	17.8	178.9
F04460	754	13.3	36.8	48.8	17.6	36.1	129.1	2.69	16.0	16.5	165.8
F04461	746	14.3	39.6	53.1	19.2	36.1	106.8	3.57	15.4	17.6	178.9
F04462	836	14.7	40.7	48.7	17.6	36.1	123.9	3.40	14.6	17.6	187.7
Number of females	6	6	6	6	6	6	6	6	6	6	6
Mean	785	14.3	39.7	50.6	18.3	36.1	115.4	3.20	15.4	17.8	169.2
S.D.	39	0.5	1.6	1.8	0.7	0.2	10.4	0.61	0.5	0.8	15.1
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

(Continued)

TT: Analysis by Student's t-test.

Appendix 24-2. (Continued) Individual hematological findings in female rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg						
Female No.	WBC 10 ³ /μL	LYMPH %	NEUT %	EO %	BASO %	MONO %
F04457	32.2	79.8	16.7	1.9	0.0	1.6
F04458	22.8	76.8	20.1	1.3	0.0	1.8
F04459	43.5	64.1	32.5	1.1	0.0	2.3
F04460	24.3	84.4	11.5	2.5	0.0	1.6
F04461	41.2	76.0	20.3	1.5	0.0	2.2
F04462	48.9	80.6	14.3	1.4	0.0	3.7
Number of females	6	6	6	6	6	6
Mean	35.5	77.0	19.2	1.6	0.0	2.2
S.D.	10.7	7.0	7.3	0.5	0.0	0.8
Significance	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Appendix 25-1. Individual blood chemical findings in male rats on termination of administration period

Control group		AST IU/L	ALT IU/L	ALP IU/L	γ -GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
M01101	73.1	28.2	374.9	0.88	5.56	2.94	1.12	
M01102	92.8	30.0	714.9	0.51	5.46	2.93	1.16	
M01103	75.8	33.1	520.3	0.80	5.23	2.80	1.16	
M01104	95.5	28.3	565.6	0.69	5.46	2.83	1.08	
M01105	67.5	29.6	601.0	0.73	5.72	2.92	1.04	
M01106	78.6	28.2	557.7	0.71	5.68	2.94	1.07	
Number of males	6	6	6	6	6	6	6	
Mean	80.6	29.6	555.7	0.72	5.52	2.89	1.11	
S.D.	11.2	1.9	110.9	0.12	0.18	0.06	0.05	

(Continued)

Appendix 25-1. (Continued) Individual blood chemical findings in male rats on termination of administration period

Control group

Male No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
M01101	0.12	13.8	0.25	105.9	68.2	39.2
M01102	0.11	15.6	0.24	132.2	62.2	32.1
M01103	0.11	14.9	0.22	128.4	47.4	29.5
M01104	0.11	12.4	0.23	115.2	40.5	21.4
M01105	0.12	12.5	0.19	119.9	53.0	41.8
M01106	0.09	14.1	0.19	115.4	52.1	31.2
Number of males	6	6	6	6	6	6
Mean	0.11	13.9	0.22	119.5	53.9	32.5
S.D.	0.01	1.3	0.03	9.6	10.0	7.3

(Continued)

Appendix 25-1. (Continued) Individual blood chemical findings in male rats on termination of administration period

Control group		Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
Male No.						
M01101		143.5	4.03	105.3	9.7	7.3
M01102		141.0	4.07	101.4	9.3	8.7
M01103		143.1	3.92	106.0	9.2	8.4
M01104		144.0	4.53	105.7	9.2	7.9
M01105		144.2	4.05	104.7	9.6	7.3
M01106		143.8	3.98	106.3	9.7	7.7
Number of males		6	6	6	6	6
Mean		143.3	4.10	104.9	9.5	7.9
S.D.		1.2	0.22	1.8	0.2	0.6

Appendix 25-2. Individual blood chemical findings in male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg							
Male No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
M02201	83.9	24.4	483.2	0.60	5.59	2.85	1.04
M02202	68.4	26.9	435.7	0.69	5.55	2.90	1.10
M02203	77.2	26.0	604.6	1.30	5.35	2.75	1.06
M02204	89.8	29.9	622.6	0.75	5.29	2.82	1.14
M02205	73.9	23.6	748.3	0.69	5.21	2.78	1.14
M02206	70.3	24.3	761.6	0.71	5.46	2.93	1.16
Number of males	6	6	6	6	6	6	6
Mean	77.3	25.9	609.3	0.79	5.41	2.84	1.11
S.D.	8.2	2.3	133.2	0.25	0.15	0.07	0.05
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	STL	DU	DU	DU	STL	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 25-2. (Continued) Individual blood chemical findings in male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Male No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
M02201	0.09	9.4	0.20	110.8	52.8	44.6
M02202	0.11	13.9	0.23	119.8	54.0	58.4
M02203	0.12	12.3	0.20	134.2	86.8	47.1
M02204	0.11	13.4	0.18	119.8	49.3	26.7
M02205	0.10	11.4	0.23	109.0	52.8	35.7
M02206	0.15	17.5	0.26	131.0	57.5	34.6
Number of males	6	6	6	6	6	6
Mean	0.11	13.0	0.22	120.8	58.9	41.2
S.D.	0.02	2.7	0.03	10.2	13.9	11.2
Significance	NS	NS	NS	NS	NS	NS
Statistical method	STL	DU	DU	DU	DU	STL

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 25-2. (Continued) Individual blood chemical findings in male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
M02201	143.5	3.90	104.6	9.2	7.5
M02202	143.5	3.82	103.8	9.9	7.7
M02203	142.3	3.62	104.8	9.4	7.8
M02204	143.9	4.36	104.6	9.3	8.6
M02205	145.6	4.29	106.5	9.2	8.5
M02206	143.4	4.04	102.8	9.8	8.8
Number of males	6	6	6	6	6
Mean	143.7	4.01	104.5	9.5	8.2
S.D.	1.1	0.28	1.2	0.3	0.5
Significance	NS	NS	NS	NS	NS
Statistical method	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 25-3. Individual blood chemical findings in male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg							
Male No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
M03301	80.8	21.7	627.8	0.81	5.43	2.77	1.04
M03302	84.3	33.1	540.9	0.61	5.45	2.71	0.99
M03303	81.5	31.6	805.8	0.58	5.28	2.94	1.26
M03304	98.8	26.4	466.2	0.77	5.25	2.92	1.25
M03305	95.8	39.4	557.7	0.84	5.60	2.98	1.14
M03306	68.9	26.1	759.8	0.74	5.67	2.99	1.12
Number of males	6	6	6	6	6	6	6
Mean	85.0	29.7	626.4	0.73	5.45	2.89	1.13
S.D.	10.9	6.3	132.4	0.11	0.17	0.12	0.11
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	STL	DU	DU	DU	STL	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 25-3. (Continued) Individual blood chemical findings in male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Male No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
M03301	0.11	19.1	0.25	127.3	67.6	44.7
M03302	0.11	16.2	0.28	119.9	66.0	50.0
M03303	0.11	15.0	0.20	114.1	47.3	30.4
M03304	0.11	13.4	0.22	104.7	55.7	77.9
M03305	0.11	17.3	0.23	136.8	53.3	69.6
M03306	0.09	17.8	0.21	127.0	51.5	23.4
Number of males	6	6	6	6	6	6
Mean	0.11	16.5	0.23	121.6	56.9	49.3
S.D.	0.01	2.1	0.03	11.3	8.2	21.4
Significance	NS	NS	NS	NS	NS	NS
Statistical method	STL	DU	DU	DU	DU	STL

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 25-3. (Continued) Individual blood chemical findings in male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
M03301	141.6	4.50	103.6	9.4	8.1
M03302	142.9	4.31	105.2	9.4	7.6
M03303	142.4	4.37	104.0	9.3	8.0
M03304	144.3	4.53	104.2	8.9	8.6
M03305	145.8	4.15	106.9	9.5	9.2
M03306	143.1	4.27	104.8	9.0	8.3
Number of males	6	6	6	6	6
Mean	143.4	4.36	104.8	9.3	8.3
S.D.	1.5	0.14	1.2	0.2	0.6
Significance	NS	NS	NS	NS	NS
Statistical method	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 25-4. Individual blood chemical findings in male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg							
Male No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
M04401	91.5	29.2	613.4	0.82	5.49	3.06	1.26
M04402	66.0	29.1	489.7	1.10	5.18	2.84	1.22
M04403	110.0	62.4	820.0	0.96	5.18	2.83	1.20
M04404	100.1	32.3	867.8	1.28	5.15	2.97	1.36
M04405	80.0	31.2	685.9	1.10	5.76	3.25	1.29
M04406	87.6	30.6	615.3	0.90	5.93	3.38	1.33
Number of males	6	6	6	6	6	6	6
Mean	89.2	35.8	682.0	1.03	5.45	3.06	1.28
S.D.	15.4	13.1	141.2	0.17	0.34	0.22	0.06
Significance	NS	NS	NS	*	NS	NS	**
Statistical method	DU	STL	DU	DU	DU	STL	DU

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

(Continued)

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 25-4. (Continued) Individual blood chemical findings in male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Male No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
M04401	0.17	29.6 a)	0.20	139.2	36.6	74.8
M04402	0.10	24.9 a)	0.23	128.5	45.2	30.4
M04403	0.21	25.2 a)	0.22	116.2	51.5	208.6 a)
M04404	0.17	25.5 a)	0.24	100.8	64.3	163.6 a)
M04405	0.12	24.4 a)	0.20	117.9	33.9	101.6 a)
M04406	0.12	27.5 a)	0.21	98.2	42.0	135.0 a)
Number of males	6	6	6	6	6	6
Mean	0.15	26.2	0.22	116.8	45.6	119.0
S.D.	0.04	2.0	0.02	15.8	11.1	63.8
Significance	NS	**	NS	NS	NS	NS
Statistical method	STL	DU	DU	DU	DU	STL

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

(Continued)

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

a): Obtained in the scheduled measurement (1st measurement); the value, which is abnormally higher than that in other animals, was confirmed to be correct in the 2nd measurement.

Appendix 25-4. (Continued) Individual blood chemical findings in male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
M04401	140.4	4.06	101.0	9.3	8.7
M04402	141.3	4.40	106.0	8.8	8.9
M04403	134.0	4.26	97.7	8.9	8.6
M04404	138.1	4.29	99.2	8.8	9.6
M04405	145.1	4.18	104.6	9.5	9.1
M04406	143.7	4.55	105.3	9.9	9.2
Number of males	6	6	6	6	6
Mean	140.4	4.29	102.3	9.2	9.0
S.D.	4.0	0.17	3.5	0.4	0.4
Significance	NS	NS	NS	NS	**
Statistical method	STL	DU	DU	DU	DU

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 26-1. Individual blood chemical findings in female rats on termination of administration period

<u>Control group</u>		AST IU/L	ALT IU/L	ALP IU/L	γ -GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
F01151		72.5	22.0	344.3	1.05	5.46	3.23	1.45
F01152		64.7	25.7	387.8	1.10	5.17	2.95	1.33
F01153		72.7	23.5	277.8	1.02	5.16	2.92	1.30
F01154		76.0	16.5	530.8	0.69	5.70	3.33	1.41
F01155		111.7	24.7	232.0	1.00	5.61	3.35	1.48
F01156		73.3	22.6	468.5	0.95	5.97	3.44	1.36
Number of females		6	6	6	6	6	6	6
Mean		78.5	22.5	373.5	0.97	5.51	3.20	1.39
S.D.		16.7	3.2	113.1	0.15	0.32	0.22	0.07

(Continued)

Appendix 26-1. (Continued) Individual blood chemical findings in female rats on termination of administration period

<u>Control group</u>						
Female No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
F01151	0.13	14.7	0.26	127.5	58.2	13.5
F01152	0.11	13.6	0.28	117.2	58.7	47.1
F01153	0.11	14.6	0.26	134.3	59.1	26.7
F01154	0.13	9.9	0.20	115.2	67.9	17.7
F01155	0.09	11.5	0.23	119.4	58.3	36.3
F01156	0.13	15.8	0.20	129.8	69.0	29.2
Number of females	6	6	6	6	6	6
Mean	0.12	13.4	0.24	123.9	61.9	28.4
S.D.	0.02	2.2	0.03	7.7	5.1	12.3

(Continued)

Appendix 26-1. (Continued) Individual blood chemical findings in female rats on termination of administration period

<u>Control group</u>		Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
F01151		141.3	3.84	103.9	9.8	6.9
F01152		142.4	3.82	105.0	9.4	6.4
F01153		140.6	3.86	105.3	9.9	6.6
F01154		146.2	3.90	108.3	9.6	6.5
F01155		143.6	4.35	107.8	9.1	7.2
F01156		144.0	4.08	106.7	10.2	6.4
Number of females		6	6	6	6	6
Mean		143.0	3.98	106.2	9.7	6.7
S.D.		2.0	0.21	1.7	0.4	0.3

Appendix 26-2. Individual blood chemical findings in female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg							
Female No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
F02251	89.5	24.9	403.0	0.81	5.79	3.32	1.35
F02252	74.8	23.4	436.4	0.75	5.22	2.88	1.23
F02253	67.9	20.4	320.5	0.96	5.22	3.01	1.36
F02254	83.0	21.9	370.6	1.18	5.22	2.86	1.21
F02255	99.7	31.7	343.7	0.83	4.91	2.73	1.25
F02256	102.4	29.4	286.6	1.05	5.08	2.88	1.30
Number of females	6	6	6	6	6	6	6
Mean	86.2	25.3	360.1	0.93	5.24	2.95	1.28
S.D.	13.6	4.4	54.8	0.16	0.30	0.20	0.06
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 26-2. (Continued) Individual blood chemical findings in female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Female No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
F02251	0.12	12.5	0.28	127.8	81.1	35.1
F02252	0.12	13.6	0.21	116.8	82.8	25.3
F02253	0.11	13.0	0.26	126.0	60.9	25.9
F02254	0.11	18.0	0.27	106.7	47.6	23.6
F02255	0.13	17.4	0.27	104.8	44.5	18.0
F02256	0.12	17.2	0.24	113.5	79.7	9.8
Number of females	6	6	6	6	6	6
Mean	0.12	15.3	0.26	115.9	66.1	23.0
S.D.	0.01	2.5	0.03	9.6	17.5	8.5
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 26-2. (Continued) Individual blood chemical findings in female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg					
Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
F02251	141.9	4.22	106.8	9.8	6.8
F02252	142.4	4.13	106.8	9.3	7.5
F02253	143.0	4.14	105.4	9.3	6.9
F02254	142.9	4.53	105.8	9.6	7.7
F02255	142.9	4.48	107.7	9.3	7.6
F02256	142.7	4.54	106.8	9.2	7.6
Number of females	6	6	6	6	6
Mean	142.6	4.34	106.6	9.4	7.4
S.D.	0.4	0.20	0.8	0.2	0.4
Significance	NS	*	NS	NS	NS
Statistical method	STL	DU	STL	DU	DU

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 26-3. Individual blood chemical findings in female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg							
Female No.	AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
F03351	79.1	21.7	367.8	0.95	5.68	3.33	1.42
F03352	82.1	28.5	267.2	0.97	5.67	3.19	1.28
F03353	88.0	26.6	400.4	0.93	5.55	3.10	1.27
F03354	92.5	18.5	310.2	0.62	5.79	3.57	1.60
F03355	87.4	24.1	250.1	0.80	5.74	3.43	1.48
F03356	63.9	20.8	331.2	0.88	6.08	3.54	1.40
Number of females	6	6	6	6	6	6	6
Mean	82.2	23.4	321.2	0.86	5.75	3.36	1.41
S.D.	10.1	3.8	57.7	0.13	0.18	0.19	0.12
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 26-3. (Continued) Individual blood chemical findings in female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Female No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
F03351	0.12	17.7	0.27	120.1	26.9	14.4
F03352	0.12	16.8	0.22	130.4	40.9	14.3
F03353	0.13	16.9	0.25	103.8	70.9	28.8
F03354	0.09	19.5	0.23	138.0	62.9	38.2
F03355	0.14	17.5	0.26	110.5	44.8	19.1
F03356	0.14	13.8	0.22	105.7	52.5	22.1
Number of females	6	6	6	6	6	6
Mean	0.12	17.0	0.24	118.1	49.8	22.8
S.D.	0.02	1.9	0.02	13.9	15.8	9.3
Significance	NS	#	NS	NS	NS	NS
Statistical method	DU	STL	DU	DU	DU	DU

Significantly different from the control group (#: p<0.05 by Steel's test).

(Continued)

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 26-3. (Continued) Individual blood chemical findings in female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
F03351	141.9	4.10	108.6	9.6	7.4
F03352	143.4	4.48	108.9	9.4	6.7
F03353	142.7	3.99	106.7	9.4	7.4
F03354	143.8	4.34	107.8	9.4	7.9
F03355	143.2	4.64	109.3	9.5	7.5
F03356	141.7	4.40	107.8	9.6	7.2
Number of females	6	6	6	6	6
Mean	142.8	4.33	108.2	9.5	7.4
S.D.	0.8	0.24	0.9	0.1	0.4
Significance	NS	NS	NS	NS	NS
Statistical method	STL	DU	STL	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 26-4. Individual blood chemical findings in female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg							
Female No.	AST IU/L	ALT IU/L	ALP IU/L	γ -GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
F04451	74.8	26.8	1465.9 a)	1.08	5.87	3.50	1.48
F04452	76.6	25.1	334.3	1.25	5.12	2.87	1.27
F04453	81.4	23.2	1209.7 a)	1.29	5.69	3.40	1.48
F04454	71.3	26.4	587.7	1.32	5.71	3.29	1.36
F04455	86.7	25.8	892.9	1.42	5.40	3.08	1.33
F04456	61.5	23.8	793.7	1.37	5.70	3.43	1.51
Number of females	6	6	6	6	6	6	6
Mean	75.4	25.2	880.7	1.29	5.58	3.26	1.41
S.D.	8.7	1.4	410.6	0.12	0.27	0.24	0.10
Significance	NS	NS	NS	**	NS	NS	NS
Statistical method	DU	DU	STL	DU	DU	DU	DU

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

(Continued)

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

a): Obtained in the scheduled measurement (1st measurement); the value, which is abnormally higher than that in other animals, was confirmed to be correct in the 2nd measurement.

Appendix 26-4. (Continued) Individual blood chemical findings in female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Female No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
F04451	0.18	26.3 a)	0.20	91.8	67.8	56.0
F04452	0.13	13.2	0.25	95.9	35.3	19.5
F04453	0.13	20.6 a)	0.24	101.8	56.9	34.3
F04454	0.11	14.9	0.19	135.2	53.6	36.9
F04455	0.13	27.2 a)	0.20	117.2	49.0	34.6
F04456	0.11	15.8	0.19	127.7	70.5	53.4
Number of females	6	6	6	6	6	6
Mean	0.13	19.7	0.21	111.6	55.5	39.1
S.D.	0.03	6.0	0.03	17.8	12.9	13.6
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	STL	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

a): Obtained in the scheduled measurement (1st measurement); the value, which is abnormally higher than that in other animals, was confirmed to be correct in the 2nd measurement.

Appendix 26-4. (Continued) Individual blood chemical findings in female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
F04451	141.1	3.75	100.0	9.7	8.8
F04452	143.5	4.57	104.9	8.8	8.2
F04453	139.3	4.31	104.8	9.3	7.6
F04454	144.7	4.26	108.2	9.5	8.5
F04455	142.6	4.57	107.2	8.9	9.8
F04456	144.5	4.35	107.4	9.4	9.5
Number of females	6	6	6	6	6
Mean	142.6	4.30	105.4	9.3	8.7
S.D.	2.1	0.30	3.0	0.4	0.8
Significance	NS	NS	NS	NS	**
Statistical method	STL	DU	STL	DU	DU

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 27-1. Individual blood chemical findings in male rats on termination of recovery period

Control group		AST IU/L	ALT IU/L	ALP IU/L	γ -GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
M01107	77.1	22.5	522.0	0.15	5.67	2.95	1.08	
M01108	101.7	24.3	448.6	0.90	5.97	2.96	0.98	
M01109	89.3	29.5	410.6	0.88	5.90	2.87	0.95	
M01110	95.5	27.9	450.9	0.70	5.45	2.80	1.06	
M01111	79.1	25.8	321.6	0.71	5.72	2.92	1.05	
M01112	108.3	25.3	495.9	0.61	5.52	2.72	0.97	
Number of males	6	6	6	6	6	6	6	
Mean	91.8	25.9	441.6	0.66	5.71	2.87	1.02	
S.D.	12.4	2.5	70.6	0.27	0.20	0.09	0.05	

(Continued)

Appendix 27-1. (Continued) Individual blood chemical findings in male rats on termination of recovery period

Control group

Male No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
M01107	0.10	14.4	0.24	107.4	37.8	33.4
M01108	0.09	15.7	0.23	138.5	33.8	21.9
M01109	0.09	15.2	0.23	120.5	66.6	41.4
M01110	0.12	15.6	0.26	110.6	62.5	56.4
M01111	0.14	17.6	0.24	106.4	54.7	53.6
M01112	0.14	16.6	0.25	94.1	52.3	50.0
Number of males	6	6	6	6	6	6
Mean	0.11	15.9	0.24	112.9	51.3	42.8
S.D.	0.02	1.1	0.01	15.1	13.1	13.3

(Continued)

Appendix 27-1. (Continued) Individual blood chemical findings in male rats on termination of recovery period

Control group		Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
Male No.						
M01107		143.6	4.48	103.3	9.3	7.9
M01108		144.1	4.62	103.8	9.6	7.9
M01109		145.0	4.27	104.6	9.3	7.1
M01110		143.8	4.43	103.6	9.1	8.3
M01111		143.0	4.48	102.7	9.7	8.0
M01112		144.1	4.57	103.5	9.4	8.2
Number of males		6	6	6	6	6
Mean		143.9	4.48	103.6	9.4	7.9
S.D.		0.7	0.12	0.6	0.2	0.4

Appendix 27-2. Individual blood chemical findings in male rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Male No.	AST IU/L	ALT IU/L	ALP IU/L	γ -GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
M04407	75.0	25.9	445.0	1.01	6.12	3.13	1.05
M04408	92.8	28.6	395.8	0.71	5.83	3.16	1.18
M04409	85.0	29.9	483.7	1.09	5.72	2.92	1.04
M04410	85.1	24.7	456.9	0.77	5.74	2.96	1.06
M04411	93.9	29.9	408.3	0.74	5.77	2.86	0.98
M04412	82.5	23.2	396.6	0.86	5.74	2.98	1.08
Number of males	6	6	6	6	6	6	6
Mean	85.7	27.0	431.1	0.86	5.82	3.00	1.07
S.D.	7.0	2.8	36.3	0.16	0.15	0.12	0.07
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

(Continued)

TT: Analysis by Student's t-test.

Appendix 27-2. (Continued) Individual blood chemical findings in male rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg						
Male No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
M04407	0.14	15.7	0.22	148.6	73.9	41.5
M04408	0.14	11.5	0.24	112.0	62.8	93.4
M04409	0.14	15.0	0.22	115.5	73.4	41.0
M04410	0.11	13.7	0.24	109.6	52.9	53.7
M04411	0.13	17.9	0.26	108.9	78.0	89.5
M04412	0.12	13.8	0.23	116.5	88.0	70.2
Number of males	6	6	6	6	6	6
Mean	0.13	14.6	0.24	118.5	71.5	64.9
S.D.	0.01	2.2	0.02	15.1	12.2	23.2
Significance	NS	NS	NS	NS	†	NS
Statistical method	TT	TT	TT	TT	TT	TT

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

(Continued)

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Appendix 27-2. (Continued) Individual blood chemical findings in male rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Male No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
M04407	142.6	4.28	102.4	9.7	8.0
M04408	144.9	4.24	103.8	9.7	7.9
M04409	145.6	4.31	104.1	9.4	8.3
M04410	144.9	4.41	103.9	9.5	8.2
M04411	145.9	4.34	104.8	9.7	7.9
M04412	146.5	4.21	105.3	10.0	7.8
Number of males	6	6	6	6	6
Mean	145.1	4.30	104.1	9.7	8.0
S.D.	1.4	0.07	1.0	0.2	0.2
Significance	NS	†	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Appendix 28-1. Individual blood chemical findings in female rats on termination of recovery period

<u>Control group</u>		AST IU/L	ALT IU/L	ALP IU/L	γ -GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
F01157		92.0	23.5	316.9	0.88	5.81	3.21	1.24
F01158		72.8	22.7	312.7	0.79	5.97	3.24	1.18
F01159		58.8	24.2	287.9	1.01	6.34	3.44	1.19
F01160		74.9	22.7	252.7	0.83	6.02	3.46	1.35
F01161		76.7	20.5	376.2	1.28	5.70	3.11	1.20
F01162		112.8	19.8	244.3	1.48	6.08	3.29	1.18
Number of females		6	6	6	6	6	6	6
Mean		81.3	22.2	298.5	1.05	5.99	3.29	1.22
S.D.		18.7	1.7	48.4	0.28	0.22	0.14	0.07

(Continued)

Appendix 28-1. (Continued) Individual blood chemical findings in female rats on termination of recovery period

<u>Control group</u>						
Female No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
F01157	0.18	13.2	0.24	111.7	62.5	16.4
F01158	0.14	15.7	0.27	111.6	76.3	21.2
F01159	0.15	19.1	0.31	128.9	77.7	17.0
F01160	0.15	16.2	0.26	107.3	80.5	9.2
F01161	0.12	19.0	0.26	124.3	57.6	22.8
F01162	0.13	18.6	0.31	103.9	73.8	10.5
Number of females	6	6	6	6	6	6
Mean	0.15	17.0	0.28	114.6	71.4	16.2
S.D.	0.02	2.4	0.03	9.8	9.2	5.5

(Continued)

Appendix 28-1. (Continued) Individual blood chemical findings in female rats on termination of recovery period

<u>Control group</u>		Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
Female No.						
F01157		143.6	4.02	106.9	9.6	7.2
F01158		143.4	4.42	106.0	9.5	8.2
F01159		142.3	4.02	104.7	9.5	6.9
F01160		142.3	4.49	105.7	9.6	8.1
F01161		142.9	4.54	104.9	9.5	8.2
F01162		143.7	3.96	106.6	9.4	8.1
Number of females		6	6	6	6	6
Mean		143.0	4.24	105.8	9.5	7.8
S.D.		0.6	0.27	0.9	0.1	0.6

Appendix 28-2. Individual blood chemical findings in female rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Female No.	AST IU/L	ALT IU/L	ALP IU/L	γ -GTP IU/L	Total protein g/dL	Albumin g/dL	A/G
F04457	77.3	21.4	173.3	0.88	5.95	3.33	1.27
F04458	69.5	18.4	176.2	0.97	6.60	3.81	1.36
F04459	74.8	27.0	220.3	0.92	5.46	2.78	1.04
F04460	72.7	22.9	268.6	1.36	5.39	2.89	1.16
F04461	72.0	18.9	302.6	0.99	5.49	2.96	1.17
F04462	158.4 a)	81.6	266.3	1.06	6.60	3.68	1.26
Number of females	6	6	6	6	6	6	6
Mean	87.5	31.7	234.6	1.03	5.92	3.24	1.21
S.D.	34.9	24.6	53.2	0.17	0.57	0.43	0.11
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	AW	TT	TT	TT	AW	TT

NS: Not significantly different from the control group.

(Continued)

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

a): Obtained in the scheduled measurement (1st measurement); the value, which is abnormally higher than that in other animals, was confirmed to be correct in the 2nd measurement.

Appendix 28-2. (Continued) Individual blood chemical findings in female rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Female No.	Total bilirubin mg/dL	Urea nitrogen mg/dL	Creatinine mg/dL	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL
F04457	0.12	17.2	0.24	97.2	67.3	12.6
F04458	0.12	17.1	0.22	117.2	78.2	17.3
F04459	0.13	18.9	0.25	113.0	55.2	18.3
F04460	0.13	20.0 a)	0.27	102.4	87.2	22.2
F04461	0.14	21.4 a)	0.29	113.1	72.2	21.5
F04462	0.14	19.2	0.26	100.7	70.3	8.5
Number of females	6	6	6	6	6	6
Mean	0.13	19.0	0.26	107.3	71.7	16.7
S.D.	0.01	1.7	0.02	8.2	10.7	5.3
Significance	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

(Continued)

TT: Analysis by Student's t-test.

a): Obtained in the scheduled measurement (1st measurement); the value, which is abnormally higher than that in other animals, was confirmed to be correct in the 2nd measurement.

Appendix 28-2. (Continued) Individual blood chemical findings in female rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Female No.	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	Inorganic phosphate mg/dL
F04457	143.9	4.12	106.6	9.6	6.8
F04458	143.8	3.91	106.5	9.8	6.5
F04459	144.2	4.35	106.6	9.4	7.9
F04460	144.7	4.33	105.7	9.3	8.1
F04461	142.8	3.91	104.5	9.6	7.8
F04462	143.4	4.29	105.7	10.0	7.3
Number of females	6	6	6	6	6
Mean	143.8	4.15	105.9	9.6	7.4
S.D.	0.7	0.20	0.8	0.3	0.6
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	AW	TT

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Appendix 29-1. Individual necropsy findings in male rats on termination of administration period

Control group	Male No.	Findings
	M01101	All organs and tissues
	M01102	All organs and tissues
	M01103	All organs and tissues
	M01104	All organs and tissues
	M01105	All organs and tissues
	M01106	All organs and tissues

Appendix 29-2. Individual necropsy findings in male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg		
Male No.	Findings	
M02201	All organs and tissues	Normal
M02202	All organs and tissues	Normal
M02203	All organs and tissues	Normal
M02204	All organs and tissues	Normal
M02205	Kidney Other organs and tissues	Dilatation, right pelvis Normal
M02206	All organs and tissues	Normal

Appendix 29-3. Individual necropsy findings in male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg		
Male No.	Findings	
M03301	Liver	Discoloration
	Other organs and tissues	Normal
M03302	All organs and tissues	Normal
M03303	All organs and tissues	Normal
M03304	All organs and tissues	Normal
M03305	All organs and tissues	Normal
M03306	All organs and tissues	Normal

Appendix 29-4. Individual necropsy findings in male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg		
Male No.	Findings	
M04401	Liver	Discoloration
	Other organs and tissues	Normal
M04402	Liver	Discoloration
	Other organs and tissues	Normal
M04403	Liver	Discoloration
	Other organs and tissues	Normal
M04404	Liver	Discoloration
	Other organs and tissues	Normal
M04405	Liver	Discoloration
	Other organs and tissues	Normal
M04406	Liver	Discoloration
	Other organs and tissues	Normal

Appendix 30-1. Individual necropsy findings in female rats on termination of administration period

Control group		
Female No.	Findings	
F01151	All organs and tissues	Normal
F01152	All organs and tissues	Normal
F01153	All organs and tissues	Normal
F01154	All organs and tissues	Normal
F01155	All organs and tissues	Normal
F01156	All organs and tissues	Normal

Appendix 30-2. Individual necropsy findings in female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Female No.	Findings
F02251	All organs and tissues
F02252	All organs and tissues
F02253	All organs and tissues
F02254	All organs and tissues
F02255	All organs and tissues
F02256	All organs and tissues

Appendix 30-3. Individual necropsy findings in female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg		
Female No.	Findings	
F03351	Liver	Discoloration
	Other organs and tissues	Normal
F03352	Liver	Discoloration
	Other organs and tissues	Normal
F03353	Liver	Discoloration
	Other organs and tissues	Normal
F03354	Liver	Discoloration
	Other organs and tissues	Normal
F03355	All organs and tissues	Normal
F03356	All organs and tissues	Normal

Appendix 30-4. Individual necropsy findings in female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Female No.	Findings	
F04451	Liver	Discoloration
	Other organs and tissues	Normal
F04452	Liver	Discoloration
	Other organs and tissues	Normal
F04453	Liver	Discoloration
	Other organs and tissues	Normal
F04454	Liver	Discoloration
	Other organs and tissues	Normal
F04455	Liver	Discoloration
	Other organs and tissues	Normal
F04456	Liver	Discoloration
	Other organs and tissues	Normal

Appendix 31-1. Individual necropsy findings in male rats on termination of recovery period

Control group	Male No.	Findings
	M01107	All organs and tissues
	M01108	All organs and tissues
	M01109	All organs and tissues
	M01110	All organs and tissues
	M01111	All organs and tissues
	M01112	All organs and tissues

Appendix 31-2. Individual necropsy findings in male rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Male No.	Findings
M04407	All organs and tissues
M04408	All organs and tissues
M04409	All organs and tissues
M04410	All organs and tissues
M04411	All organs and tissues
M04412	All organs and tissues

Appendix 32-1. Individual necropsy findings in female rats on termination of recovery period

Control group		
Female No.	Findings	
F01157	All organs and tissues	Normal
F01158	All organs and tissues	Normal
F01159	All organs and tissues	Normal
F01160	All organs and tissues	Normal
F01161	All organs and tissues	Normal
F01162	All organs and tissues	Normal

Appendix 32-2. Individual necropsy findings in female rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Female No.	Findings
F04457	All organs and tissues
F04458	All organs and tissues
F04459	All organs and tissues
F04460	All organs and tissues
F04461	All organs and tissues
F04462	All organs and tissues

Appendix 33-1. Individual organ weights of male rats on termination of administration period

Control group

Male No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
M01101	336	2.12	0.63	13.0	3.9	568	169	24.0	7.1	402	120	1.20	0.36	10.73	3.19	917	273
M01102	387	2.01	0.52	17.5	4.5	653	169	24.0	6.2	628	162	1.48	0.38	12.33	3.19	791	204
M01103	335	1.88	0.56	13.8	4.1	643	192	18.0	5.4	370	110	1.28	0.38	9.86	2.94	623	186
M01104	343	2.12	0.62	11.9	3.5	592	173	27.7	8.1	399	116	1.47	0.43	9.65	2.81	639	186
M01105	372	2.03	0.55	12.6	3.4	706	190	24.3	6.5	352	95	1.32	0.35	13.22	3.55	602	162
M01106	367	2.06	0.56	13.7	3.7	502	137	33.0	9.0	679	185	1.27	0.35	11.48	3.13	691	188
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	357	2.04	0.57	13.8	3.9	611	172	25.2	7.1	472	131	1.34	0.38	11.21	3.14	711	200
S.D.	22	0.09	0.04	2.0	0.4	72	20	5.0	1.3	143	35	0.11	0.03	1.40	0.25	122	38

(Continued)

Appendix 33-1. (Continued) Individual organ weights of male rats on termination of administration period

Male No.	Kidneys		Adrenals		Testes		Epididymides	
	(g)	(g%)	(mg)	(mg%)	(g)	(g%)	(mg)	(mg%)
M01101	2.60	0.77	54.1	16.1	2.98	0.89	873	260
M01102	2.78	0.72	71.2	18.4	3.13	0.81	776	201
M01103	2.64	0.79	51.3	15.3	3.45	1.03	922	275
M01104	2.66	0.78	55.6	16.2	3.10	0.90	867	253
M01105	2.96	0.80	66.3	17.8	2.73	0.73	780	210
M01106	2.81	0.77	46.9	12.8	2.62	0.71	768	209
Number of males	6	6	6	6	6	6	6	6
Mean	2.74	0.77	57.6	16.1	3.00	0.85	831	235
S.D.	0.13	0.03	9.3	2.0	0.30	0.12	65	32

Appendix 33-2. Individual organ weights of male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Male No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
M02201	376	2.13	0.57	14.9	4.0	641	170	30.4	8.1	486	129	1.39	0.37	12.60	3.35	714	190
M02202	365	1.97	0.54	12.8	3.5	646	177	20.8	5.7	555	152	1.38	0.38	12.36	3.39	776	213
M02203	314	2.13	0.68	13.6	4.3	557	177	20.8	6.6	490	156	1.28	0.41	10.03	3.19	493	157
M02204	365	2.02	0.55	14.3	3.9	596	163	17.2	4.7	562	154	1.41	0.39	12.35	3.38	730	200
M02205	382	2.01	0.53	16.6	4.3	532	139	15.1	4.0	546	143	1.24	0.32	11.73	3.07	732	192
M02206	375	1.95	0.52	14.4	3.8	595	159	21.6	5.8	514	137	1.31	0.35	12.20	3.25	595	159
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	363	2.04	0.57	14.4	4.0	595	164	21.0	5.8	526	145	1.34	0.37	11.88	3.27	673	185
S.D.	25	0.08	0.06	1.3	0.3	45	14	5.3	1.4	33	11	0.07	0.03	0.95	0.13	107	23
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	STL	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 33-2. (Continued) Individual organ weights of male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Male No.	Kidneys		Adrenals		Testes		Epididymides	
	(g)	(g%)	(mg)	(mg%)	(g)	(g%)	(mg)	(mg%)
M02201	2.77	0.74	76.4	20.3	3.18	0.85	838	223
M02202	2.85	0.78	74.5	20.4	3.21	0.88	926	254
M02203	2.53	0.81	51.9	16.5	2.93	0.93	815	260
M02204	2.93	0.80	59.2	16.2	3.49	0.96	845	232
M02205	3.01	0.79	43.2	11.3	3.15	0.82	929	243
M02206	2.60	0.69	65.2	17.4	2.93	0.78	890	237
Number of males	6	6	6	6	6	6	6	6
Mean	2.78	0.77	61.7	17.0	3.15	0.87	874	242
S.D.	0.19	0.05	12.9	3.3	0.21	0.07	48	14
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 33-3. Individual organ weights of male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Male No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
M03301	393	2.03	0.52	13.0	3.3	577	147	20.3	5.2	637	162	1.51	0.38	13.27	3.38	716	182
M03302	357	2.03	0.57	13.1	3.7	612	171	32.5	9.1	418	117	1.42	0.40	11.86	3.32	650	182
M03303	386	2.01	0.52	16.1	4.2	649	168	21.0	5.4	404	105	1.29	0.33	12.48	3.23	701	182
M03304	388	1.90	0.49	16.5	4.3	671	173	23.6	6.1	747	193	1.28	0.33	12.85	3.31	604	156
M03305	342	2.04	0.60	12.2	3.6	589	172	25.7	7.5	413	121	1.12	0.33	10.72	3.13	601	176
M03306	346	2.03	0.59	11.8	3.4	586	169	18.7	5.4	401	116	1.24	0.36	11.32	3.27	610	176
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	369	2.01	0.55	13.8	3.8	614	167	23.6	6.5	503	136	1.31	0.36	12.08	3.27	647	176
S.D.	23	0.05	0.04	2.0	0.4	38	10	5.0	1.6	150	34	0.14	0.03	0.96	0.09	51	10
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	STL	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 33-3. (Continued) Individual organ weights of male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Male No.	Kidneys		Adrenals		Testes		Epididymides	
	(g)	(g%)	(mg)	(mg%)	(g)	(g%)	(mg)	(mg%)
M03301	2.96	0.75	55.1	14.0	3.31	0.84	863	220
M03302	2.70	0.76	61.8	17.3	3.16	0.89	883	247
M03303	3.01	0.78	59.5	15.4	3.28	0.85	827	214
M03304	2.81	0.72	66.2	17.1	3.17	0.82	779	201
M03305	2.39	0.70	54.2	15.8	2.93	0.86	790	231
M03306	2.77	0.80	50.7	14.7	3.34	0.97	817	236
Number of males	6	6	6	6	6	6	6	6
Mean	2.77	0.75	57.9	15.7	3.20	0.87	827	225
S.D.	0.22	0.04	5.7	1.3	0.15	0.05	41	17
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 33-4. Individual organ weights of male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Male No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen		
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)	
M04401	361	2.12	0.59	16.7	4.6	654	181	27.3	7.6	682	189	1.29	0.36	14.75	4.09	637	176	
M04402	317	2.01	0.63	19.3	6.1	462	146	18.8	5.9	609	192	1.18	0.37	13.56	4.28	596	188	
M04403	374	2.25	0.60	14.4	3.9	532	142	17.0	4.5	560	150	1.12	0.30	16.58	4.43	799	214	
M04404	380	1.96	0.52	15.0	3.9	607	160	26.6	7.0	581	153	1.32	0.35	15.76	4.15	570	150	
M04405	332	2.06	0.62	15.7	4.7	531	160	15.6	4.7	552	166	1.21	0.36	13.86	4.17	650	196	
M04406	370	1.98	0.54	17.6	4.8	598	162	18.3	4.9	486	131	1.36	0.37	16.50	4.46	702	190	
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
Mean	356	2.06	0.58	16.5	4.7	564	159	20.6	5.8	578	164	1.25	0.35	15.17	4.26	659	186	
S.D.	25	0.11	0.04	1.8	0.8	69	14	5.0	1.3	65	24	0.09	0.03	1.31	0.15	82	21	
Significance	NS	NS	NS	*	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	**	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	DU	STL	DU	DU	DU	DU	DU	DU	DU	

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

(Continued)

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 33-4. (Continued) Individual organ weights of male rats on termination of administration period

Male No.	Kidneys		Adrenals		Testes		Epididymides	
	(g)	(g%)	(mg)	(mg%)	(g)	(g%)	(mg)	(mg%)
M04401	3.20	0.89	59.1	16.4	2.92	0.81	780	216
M04402	3.11	0.98	53.3	16.8	3.23	1.02	837	264
M04403	3.24	0.87	81.4	21.8	2.99	0.80	877	234
M04404	3.12	0.82	78.5	20.7	3.49	0.92	708	186
M04405	3.00	0.90	67.1	20.2	3.24	0.98	896	270
M04406	3.69	1.00	62.8	17.0	2.98	0.81	786	212
Number of males	6	6	6	6	6	6	6	6
Mean	3.23	0.91	67.0	18.8	3.14	0.89	814	230
S.D.	0.24	0.07	11.0	2.3	0.22	0.10	70	32
Significance	**	**	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 34-1. Individual organ weights of female rats on termination of administration period

Control group																	
Female No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
F01151	210	1.76	0.84	12.9	6.1	337	160	14.8	7.0	339	161	0.84	0.40	5.92	2.82	406	193
F01152	213	1.98	0.93	12.9	6.1	398	187	18.5	8.7	441	207	0.72	0.34	6.84	3.21	442	208
F01153	200	1.81	0.91	12.0	6.0	391	196	14.5	7.3	441	221	0.76	0.38	5.78	2.89	430	215
F01154	189	1.80	0.95	13.0	6.9	361	191	13.6	7.2	309	163	0.75	0.40	6.48	3.43	415	220
F01155	209	1.82	0.87	18.1	8.7	390	187	19.3	9.2	301	144	0.78	0.37	6.61	3.16	384	184
F01156	201	1.82	0.91	12.9	6.4	436	217	16.9	8.4	653	325	0.76	0.38	5.94	2.96	505	251
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	204	1.83	0.90	13.6	6.7	386	190	16.3	8.0	414	204	0.77	0.38	6.26	3.08	430	212
S.D.	9	0.08	0.04	2.2	1.0	34	18	2.3	0.9	133	66	0.04	0.02	0.44	0.23	42	23

(Continued)

Appendix 34-1. (Continued) Individual organ weights of female rats on termination of administration period

Control group Female No.	Kidneys		Adrenals		Ovaries	
	(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)
F01151	1.60	0.76	71.0	33.8	87.0	41.4
F01152	1.72	0.81	60.2	28.3	73.3	34.4
F01153	1.71	0.86	74.8	37.4	82.7	41.4
F01154	1.66	0.88	55.9	29.6	75.2	39.8
F01155	1.83	0.88	75.2	36.0	83.0	39.7
F01156	1.57	0.78	66.6	33.1	79.7	39.7
Number of females	6	6	6	6	6	6
Mean	1.68	0.83	67.3	33.0	80.2	39.4
S.D.	0.09	0.05	7.9	3.5	5.2	2.6

Appendix 34-2. Individual organ weights of female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Female No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
F02251	199	1.75	0.88	14.3	7.2	420	211	19.0	9.5	503	253	0.72	0.36	5.81	2.92	357	179
F02252	225	1.90	0.84	17.7	7.9	432	192	15.1	6.7	572	254	0.83	0.37	7.46	3.32	601	267
F02253	196	1.72	0.88	16.1	8.2	414	211	14.3	7.3	473	241	0.66	0.34	5.79	2.95	416	212
F02254	213	1.86	0.87	13.0	6.1	421	198	16.5	7.7	478	224	0.78	0.37	6.34	2.98	504	237
F02255	224	1.87	0.83	17.0	7.6	452	202	19.9	8.9	362	162	0.84	0.38	7.25	3.24	667	298
F02256	221	1.90	0.86	12.7	5.7	455	206	17.3	7.8	480	217	0.77	0.35	6.92	3.13	512	232
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	213	1.83	0.86	15.1	7.1	432	203	17.0	8.0	478	225	0.77	0.36	6.60	3.09	510	238
S.D.	13	0.08	0.02	2.1	1.0	17	8	2.2	1.0	68	34	0.07	0.01	0.72	0.17	114	42
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	STL	DU	DU	DU	DU	DU	DU	STL	DU

NS: Not significantly different from the control group.

(Continued)

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 34-2. (Continued) Individual organ weights of female rats on termination of administration period

Female No.	Kidneys		Adrenals		Ovaries	
	(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)
F02251	1.44	0.72	56.2	28.2	85.9	43.2
F02252	1.90	0.84	65.4	29.1	79.2	35.2
F02253	1.58	0.81	61.1	31.2	72.5	37.0
F02254	1.72	0.81	68.8	32.3	84.7	39.8
F02255	1.90	0.85	79.0	35.3	105.4	47.1
F02256	1.62	0.73	65.8	29.8	100.9	45.7
Number of females	6	6	6	6	6	6
Mean	1.69	0.79	66.1	31.0	88.1	41.3
S.D.	0.18	0.06	7.7	2.6	12.7	4.8
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 34-3. Individual organ weights of female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg

Female No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
F03351	221	1.98	0.90	14.3	6.5	463	210	14.0	6.3	451	204	0.83	0.38	8.02	3.63	560	253
F03352	212	1.88	0.89	16.0	7.5	430	203	15.7	7.4	402	190	0.87	0.41	7.82	3.69	519	245
F03353	214	1.96	0.92	17.5	8.2	412	193	17.8	8.3	467	218	0.80	0.37	7.43	3.47	458	214
F03354	224	1.98	0.88	16.1	7.2	383	171	15.3	6.8	326	146	0.82	0.37	7.57	3.38	453	202
F03355	196	1.90	0.97	15.4	7.9	375	191	24.7	12.6	335	171	0.72	0.37	6.20	3.16	412	210
F03356	232	1.81	0.78	16.2	7.0	431	186	15.3	6.6	487	210	0.81	0.35	8.51	3.67	530	228
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	217	1.92	0.89	15.9	7.4	416	192	17.1	8.0	411	190	0.81	0.38	7.59	3.50	489	225
S.D.	12	0.07	0.06	1.0	0.6	33	14	3.9	2.4	69	27	0.05	0.02	0.78	0.21	56	20
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	*	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	STL	DU	DU	DU	DU	DU	DU	STL	DU

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

(Continued)

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 34-3. (Continued) Individual organ weights of female rats on termination of administration period

Female No.	Kidneys		Adrenals		Ovaries	
	(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)
F03351	1.94	0.88	78.6	35.6	91.1	41.2
F03352	1.76	0.83	73.1	34.5	90.8	42.8
F03353	1.67	0.78	66.9	31.3	81.9	38.3
F03354	2.02	0.90	72.0	32.1	92.7	41.4
F03355	1.71	0.87	69.3	35.4	79.8	40.7
F03356	1.78	0.77	62.0	26.7	93.0	40.1
Number of females	6	6	6	6	6	6
Mean	1.81	0.84	70.3	32.6	88.2	40.8
S.D.	0.14	0.05	5.7	3.4	5.8	1.5
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 34-4. Individual organ weights of female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Female No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
F04451	217	1.81	0.83	13.1	6.0	412	190	17.2	7.9	564	260	0.86	0.40	10.11	4.66	413	190
F04452	223	1.86	0.83	15.0	6.7	455	204	19.0	8.5	387	174	0.80	0.36	9.94	4.46	375	168
F04453	208	1.89	0.91	15.6	7.5	386	186	16.4	7.9	457	220	0.75	0.36	8.58	4.13	341	164
F04454	204	1.87	0.92	18.7	9.2	346	170	18.5	9.1	423	207	0.75	0.37	8.54	4.19	384	188
F04455	199	1.87	0.94	16.0	8.0	359	180	14.8	7.4	417	210	0.78	0.39	9.17	4.61	332	167
F04456	203	1.74	0.86	16.6	8.2	319	157	18.5	9.1	376	185	0.77	0.38	7.75	3.82	323	159
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	209	1.84	0.88	15.8	7.6	380	181	17.4	8.3	437	209	0.79	0.38	9.02	4.31	361	173
S.D.	9	0.06	0.05	1.8	1.1	49	16	1.6	0.7	68	30	0.04	0.02	0.90	0.32	35	13
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	**	#	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU	STL	DU	DU	DU	DU	DU	DU	STL	DU

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

(Continued)

Significantly different from the control group (#: p<0.05 by Steel's test).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

STL: Analysis by Steel's test.

Appendix 34-4. (Continued) Individual organ weights of female rats on termination of administration period

Female No.	Kidneys		Adrenals		Ovaries	
	(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)
F04451	1.96	0.90	70.0	32.3	75.4	34.7
F04452	2.25	1.01	89.1	40.0	98.1	44.0
F04453	1.95	0.94	58.9	28.3	85.4	41.1
F04454	2.03	1.00	67.6	33.1	78.2	38.3
F04455	1.97	0.99	59.9	30.1	65.7	33.0
F04456	2.04	1.00	59.2	29.2	78.9	38.9
Number of females	6	6	6	6	6	6
Mean	2.03	0.97	67.5	32.2	80.3	38.3
S.D.	0.11	0.04	11.6	4.2	10.8	4.0
Significance	**	**	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Appendix 35-1. Individual organ weights of male rats on termination of recovery period

Control group

Male No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
M01107	449	2.15	0.48	16.9	3.8	676	151	22.4	5.0	459	102	1.45	0.32	11.84	2.64	968	216
M01108	454	2.21	0.49	16.4	3.6	684	151	29.6	6.5	455	100	1.48	0.33	13.51	2.98	781	172
M01109	403	1.94	0.48	13.4	3.3	598	148	17.4	4.3	330	82	1.30	0.32	12.42	3.08	691	171
M01110	450	2.07	0.46	14.6	3.2	628	140	20.5	4.6	656	146	1.48	0.33	11.54	2.56	767	170
M01111	428	2.10	0.49	13.9	3.2	722	169	23.1	5.4	400	93	1.58	0.37	10.88	2.54	727	170
M01112	452	2.16	0.48	16.8	3.7	765	169	24.2	5.4	479	106	1.60	0.35	11.03	2.44	872	193
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	439	2.11	0.48	15.3	3.5	679	155	22.9	5.2	463	105	1.48	0.34	11.87	2.71	801	182
S.D.	20	0.09	0.01	1.6	0.3	61	12	4.1	0.8	109	22	0.11	0.02	0.98	0.26	102	19

(Continued)

Appendix 35-1. (Continued) Individual organ weights of male rats on termination of recovery period

Male No.	Kidneys		Adrenals		Testes		Epididymides	
	(g)	(g%)	(mg)	(mg%)	(g)	(g%)	(mg)	(mg%)
M01107	3.09	0.69	56.7	12.6	3.24	0.72	1044	233
M01108	3.08	0.68	66.7	14.7	2.94	0.65	1022	225
M01109	2.59	0.64	53.4	13.3	3.10	0.77	1029	255
M01110	2.91	0.65	62.4	13.9	3.23	0.72	1068	237
M01111	3.09	0.72	64.0	15.0	3.25	0.76	1148	268
M01112	2.99	0.66	57.3	12.7	3.27	0.72	1127	249
Number of males	6	6	6	6	6	6	6	6
Mean	2.96	0.67	60.1	13.7	3.17	0.72	1073	245
S.D.	0.19	0.03	5.1	1.0	0.13	0.04	53	16

Appendix 35-2. Individual organ weights of male rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Male No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
M04407	397	1.99	0.50	15.2	3.8	683	172	25.0	6.3	436	110	1.42	0.36	11.24	2.83	624	157
M04408	436	2.07	0.47	16.1	3.7	643	147	28.5	6.5	469	108	1.43	0.33	11.67	2.68	806	185
M04409	422	2.08	0.49	13.9	3.3	586	139	22.1	5.2	645	153	1.50	0.36	10.97	2.60	697	165
M04410	436	2.01	0.46	16.7	3.8	700	161	25.2	5.8	456	105	1.44	0.33	11.42	2.62	683	157
M04411	452	1.99	0.44	16.2	3.6	646	143	21.1	4.7	559	124	1.42	0.31	13.54	3.00	815	180
M04412	434	2.02	0.47	18.6	4.3	734	169	18.9	4.4	461	106	1.45	0.33	12.73	2.93	833	192
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	430	2.03	0.47	16.1	3.8	665	155	23.5	5.5	504	118	1.44	0.34	11.93	2.78	743	173
S.D.	19	0.04	0.02	1.6	0.3	52	14	3.4	0.9	81	19	0.03	0.02	1.00	0.17	86	15
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

(Continued)

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Appendix 35-2. (Continued) Individual organ weights of male rats on termination of recovery period

Male No.	Kidneys		Adrenals		Testes		Epididymides	
	(g)	(g%)	(mg)	(mg%)	(g)	(g%)	(mg)	(mg%)
M04407	2.64	0.66	61.0	15.4	2.78	0.70	987	249
M04408	2.74	0.63	66.9	15.3	2.73	0.63	812	186
M04409	2.86	0.68	58.7	13.9	3.18	0.75	1142	271
M04410	3.17	0.73	65.4	15.0	3.39	0.78	1149	264
M04411	2.91	0.64	59.6	13.2	3.08	0.68	964	213
M04412	2.94	0.68	72.5	16.7	3.32	0.76	1195	275
Number of males	6	6	6	6	6	6	6	6
Mean	2.88	0.67	64.0	14.9	3.08	0.72	1042	243
S.D.	0.18	0.04	5.3	1.2	0.27	0.06	146	36
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	AW	TT

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Appendix 36-1. Individual organ weights of female rats on termination of recovery period

Control group																	
Female No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
F01157	248	1.88	0.76	16.0	6.5	411	166	20.1	8.1	504	203	0.91	0.37	6.49	2.62	509	205
F01158	232	1.93	0.83	12.0	5.2	419	181	18.2	7.8	451	194	0.82	0.35	6.67	2.88	417	180
F01159	268	1.85	0.69	17.5	6.5	544	203	15.0	5.6	417	156	0.90	0.34	7.54	2.81	612	228
F01160	234	1.74	0.74	16.7	7.1	393	168	12.9	5.5	350	150	0.91	0.39	6.95	2.97	422	180
F01161	232	1.93	0.83	12.4	5.3	349	150	19.9	8.6	296	128	0.77	0.33	5.61	2.42	366	158
F01162	221	1.82	0.82	19.7	8.9	424	192	15.1	6.8	550	249	0.89	0.40	5.96	2.70	524	237
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	239	1.86	0.78	15.7	6.6	423	177	16.9	7.1	428	180	0.87	0.36	6.54	2.73	475	198
S.D.	17	0.07	0.06	3.0	1.4	65	19	3.0	1.3	95	44	0.06	0.03	0.69	0.20	90	31

(Continued)

Appendix 36-1. (Continued) Individual organ weights of female rats on termination of recovery period

Control group Female No.	Kidneys		Adrenals		Ovaries	
	(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)
F01157	1.77	0.71	69.8	28.1	94.7	38.2
F01158	1.56	0.67	64.8	27.9	70.0	30.2
F01159	1.73	0.65	68.0	25.4	111.4	41.6
F01160	1.92	0.82	78.0	33.3	87.3	37.3
F01161	1.80	0.78	58.5	25.2	67.7	29.2
F01162	1.62	0.73	71.6	32.4	88.0	39.8
Number of females	6	6	6	6	6	6
Mean	1.73	0.73	68.5	28.7	86.5	36.1
S.D.	0.13	0.06	6.6	3.4	16.2	5.1

Appendix 36-2. Individual organ weights of female rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Female No.	Body weight (g)	Brain		Pituitary		Salivary glands		Thyroids		Thymus		Heart		Liver		Spleen	
		(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(mg)	(mg%)	(g)	(g%)	(g)	(g%)	(mg)	(mg%)
F04457	219	1.82	0.83	15.5	7.1	425	194	18.8	8.6	416	190	0.77	0.35	5.92	2.70	480	219
F04458	206	1.81	0.88	14.0	6.8	362	176	18.2	8.8	299	145	0.78	0.38	6.14	2.98	372	181
F04459	245	1.92	0.78	16.8	6.9	506	207	16.8	6.9	408	167	0.85	0.35	6.60	2.69	506	207
F04460	236	1.91	0.81	14.5	6.1	445	189	17.6	7.5	448	190	0.78	0.33	6.58	2.79	565	239
F04461	240	1.84	0.77	16.0	6.7	488	203	22.2	9.3	495	206	0.86	0.36	6.93	2.89	531	221
F04462	237	1.89	0.80	14.7	6.2	362	153	18.9	8.0	496	209	0.86	0.36	7.41	3.13	550	232
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	231	1.87	0.81	15.3	6.6	431	187	18.8	8.2	427	185	0.82	0.36	6.60	2.86	501	217
S.D.	15	0.05	0.04	1.0	0.4	61	20	1.9	0.9	73	24	0.04	0.02	0.54	0.17	70	21
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	AW	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

(Continued)

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Appendix 36-2. (Continued) Individual organ weights of female rats on termination of recovery period

Female No.	Kidneys		Adrenals		Ovaries	
	(g)	(g%)	(mg)	(mg%)	(mg)	(mg%)
F04457	1.50	0.68	65.9	30.1	72.5	33.1
F04458	1.56	0.76	50.7	24.6	56.3	27.3
F04459	1.72	0.70	84.4	34.4	95.1	38.8
F04460	1.72	0.73	62.0	26.3	80.6	34.2
F04461	1.91	0.80	59.1	24.6	81.7	34.0
F04462	1.77	0.75	57.1	24.1	77.8	32.8
Number of females	6	6	6	6	6	6
Mean	1.70	0.74	63.2	27.4	77.3	33.4
S.D.	0.15	0.04	11.6	4.1	12.7	3.7
Significance	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Appendix 37-1. Individual histopathological findings in male rats on termination of administration period

Control group	Male No.	Organ/Tissue	Findings
	M01101	All organs and tissues	No abnormality detected
	M01102	Eyeball	Dysplasia, retina, left: ±
		Other organs and tissues	No abnormality detected
	M01103	Jejunum	Mineralization, Peyer's patch: ±
		Other organs and tissues	No abnormality detected
	M01104	Kidney	Cast, hyaline, left: ±
		Other organs and tissues	No abnormality detected
	M01105	All organs and tissues	No abnormality detected
	M01106	Kidney	Cyst, left: ±
		Other organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight; +: mild; 2+: moderate; 3+: marked.

Examined the heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, thymus, spleen, mandibular lymph node, mesenteric lymph node, kidney, urinary bladder, testis, epididymis, seminal vesicle, prostate, pituitary, adrenal, thyroid, parathyroid, cerebrum, cerebellum, medulla oblongata, spinal cord, sciatic nerve, eyeball, Harderian gland, bone marrow (sternum and femur), bone (sternum and femur), and femur muscle.

Appendix 37-2. Individual histopathological findings in male rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg

Male No.	Organ/Tissue	Findings
M02201	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: ±
	Other organs and tissues	No abnormality detected
M02202	All organs and tissues	No abnormality detected
M02203	All organs and tissues	No abnormality detected
M02204	All organs and tissues	No abnormality detected
M02205	Kidney	Hydronephrosis, right: ±
	Other organs and tissues	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: ±
M02206	Other organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight; +: mild; 2+: moderate; 3+: marked.

Examined the liver, pancreas, thymus, and kidney.

Appendix 37-3. Individual histopathological findings in male rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg			
Male No.	Organ/Tissue	Findings	
M03301	Liver	Swelling, hepatocyte, periportal: ±	
	Pancreas	Decreased, zymogen granules: ±	
	Other organs and tissues	No abnormality detected	
M03302	Liver	Swelling, hepatocyte, periportal: ±	
	Liver	Microgranuloma: ±	
	Pancreas	Decreased, zymogen granules: ±	
	Kidney	Cast, hyaline, left: ±	
M03303	Other organs and tissues	No abnormality detected	
	Liver	Swelling, hepatocyte, periportal: ±	
	Pancreas	Decreased, zymogen granules: ±	
M03304	Other organs and tissues	No abnormality detected	
	Liver	Swelling, hepatocyte, periportal: ±	
	Pancreas	Decreased, zymogen granules: ±	
M03305	Kidney	Cast, hyaline, right: ±	
	Other organs and tissues	No abnormality detected	
	Liver	Microgranuloma: ±	
M03306	Pancreas	Decreased, zymogen granules: ±	
	Other organs and tissues	No abnormality detected	
	Liver	Swelling, hepatocyte, periportal: ±	
	Pancreas	Decreased, zymogen granules: ±	
	Other organs and tissues	No abnormality detected	

Grade of histopathological findings: ±: slight; +: mild, 2+: moderate, 3+: marked.

Examined the liver, pancreas, thymus, and kidney.

Appendix 37-4. Individual histopathological findings in male rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg

Male No.	Organ/Tissue	Findings
M04401	Liver	Swelling, hepatocyte, periportal: +
	Liver	Microgranuloma: ±
	Pancreas	Decreased, zymogen granules: +
	Thymus	Starry sky appearance: ±
	Kidney	Swelling, proximal tubule: ±
	Other organs and tissues	No abnormality detected
M04402	Liver	Swelling, hepatocyte, periportal: +
	Liver	Microgranuloma: ±
	Pancreas	Decreased, zymogen granules: +
	Kidney	Swelling, proximal tubule: ±
	Other organs and tissues	No abnormality detected
M04403	Liver	Swelling, hepatocyte, periportal: 2+
	Liver	Microgranuloma: ±
	Pancreas	Decreased, zymogen granules: +
	Thymus	Starry sky appearance: ±
	Kidney	Swelling, proximal tubule: ±
M04404	Other organs and tissues	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: +
	Pancreas	Decreased, zymogen granules: +
	Thymus	Starry sky appearance: ±
	Kidney	Swelling, proximal tubule: ±
M04405	Other organs and tissues	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: +
	Pancreas	Decreased, zymogen granules: +
	Thymus	Starry sky appearance: ±
	Kidney	Swelling, proximal tubule: ±
M04406	Kidney	Cast, hyaline, left: ±
	Other organs and tissues	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: 2+
	Liver	Microgranuloma: ±
	Pancreas	Decreased, zymogen granules: +
	Kidney	Swelling, proximal tubule: ±
	Other organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight; +: mild, 2+: moderate, 3+: marked.

Examined the heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, thymus, spleen, mandibular lymph node, mesenteric lymph node, kidney, urinary bladder, testis, epididymis, seminal vesicle, prostate, pituitary, adrenal, thyroid, parathyroid, cerebrum, cerebellum, medulla oblongata, spinal cord, sciatic nerve, eyeball, Harderian gland, bone marrow (sternum and femur), bone (sternum and femur), and femur muscle.

Appendix 38-1. Individual histopathological findings in female rats on termination of administration period

Control group	Female No.	Organ/Tissue	Findings
	F01151	All organs and tissues	No abnormality detected
	F01152	Kidney	Hydronephrosis, right: ±
		Thyroid	Ectopic, thymic tissue: ±
		Other organs and tissues	No abnormality detected
	F01153	All organs and tissues	No abnormality detected
	F01154	Thyroid	Ectopic, thymic tissue: ±
		Other organs and tissues	No abnormality detected
	F01155	All organs and tissues	No abnormality detected
	F01156	All organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Examined the heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, thymus, spleen, mandibular lymph node, mesenteric lymph node, kidney, urinary bladder, ovary, uterus, vagina, pituitary, adrenal, thyroid, parathyroid, cerebrum, cerebellum, medulla oblongata, spinal cord, sciatic nerve, eyeball, Harderian gland, bone marrow (sternum and femur), bone (sternum and femur), femur muscle, and mammary gland.

Appendix 38-2. Individual histopathological findings in female rats on termination of administration period

1,4-dichlorobutane group at 12 mg/kg		
Female No.	Organ/Tissue	Findings
F02251	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: ±
	Other organs and tissues	No abnormality detected
F02252	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: ±
	Other organs and tissues	No abnormality detected
F02253	All organs and tissues	No abnormality detected
F02254	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: ±
	Other organs and tissues	No abnormality detected
F02255	Liver	Swelling, hepatocyte, periportal: ±
	Liver	Microgranuloma: ±
	Pancreas	Decreased, zymogen granules: ±
F02256	Other organs and tissues	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: ±
	Other organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Examined the liver, pancreas, thymus, and kidney.

Appendix 38-3. Individual histopathological findings in female rats on termination of administration period

1,4-dichlorobutane group at 60 mg/kg		
Female No.	Organ/Tissue	Findings
F03351	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: +
	Other organs and tissues	No abnormality detected
F03352	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: +
	Other organs and tissues	No abnormality detected
F03353	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: +
	Other organs and tissues	No abnormality detected
F03354	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: +
	Kidney	Swelling, proximal tubule: ±
F03355	Other organs and tissues	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: +
F03356	Other organs and tissues	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: ±
	Pancreas	Decreased, zymogen granules: +
	Other organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Examined the liver, pancreas, thymus, and kidney.

Appendix 38-4. Individual histopathological findings in female rats on termination of administration period

1,4-dichlorobutane group at 300 mg/kg		
Female No.	Organ/Tissue	Findings
F04451	Liver	Swelling, hepatocyte, periportal: +
	Liver	Microgranuloma: ±
	Pancreas	Decreased, zymogen granules: +
	Thymus	Starry sky appearance: ±
	Kidney	Swelling, proximal tubule: ±
	Other organs and tissues	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: +
F04452	Pancreas	Decreased, zymogen granules: +
	Kidney	Swelling, proximal tubule: ±
	Other organs and tissues	No abnormality detected
	Lung	Mineralization, vascular wall, left: ±
F04453	Liver	Swelling, hepatocyte, periportal: +
	Pancreas	Decreased, zymogen granules: +
	Kidney	Swelling, proximal tubule: ±
	Other organs and tissues	No abnormality detected
F04454	Lung	Mineralization, vascular wall, left: ±
	Liver	Swelling, hepatocyte, periportal: +
	Pancreas	Decreased, zymogen granules: +
	Kidney	Swelling, proximal tubule: ±
	Other organs and tissues	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: +
	Pancreas	Microgranuloma: ±
F04455	Thymus	Decreased, zymogen granules: +
	Kidney	Starry sky appearance: ±
	Other organs and tissues	Swelling, proximal tubule: ±
	Liver	No abnormality detected
	Liver	Swelling, hepatocyte, periportal: +
	Pancreas	Microgranuloma: ±
	Thymus	Decreased, zymogen granules: +
F04456	Kidney	Starry sky appearance: ±
	Other organs and tissues	Swelling, proximal tubule: ±
	Liver	No abnormality detected
	Pancreas	Swelling, hepatocyte, periportal: +
373	Kidney	Decreased, zymogen granules: +
	Other organs and tissues	Swelling, proximal tubule: ±
	Liver	No abnormality detected

Grade of histopathological findings: ±: slight; +: mild, 2+: moderate, 3+: marked.

Examined the heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, thymus, spleen, mandibular lymph node, mesenteric lymph node, kidney, urinary bladder, ovary, uterus, vagina, pituitary, adrenal, thyroid, parathyroid, cerebrum, cerebellum, medulla oblongata, spinal cord, sciatic nerve, eyeball, Harderian gland, bone marrow (sternum and femur), bone (sternum and femur), femur muscle, and mammary gland.

Appendix 39-1. Individual histopathological findings in male rats on termination of recovery period

Control group		
Male No.	Organ/Tissue	Findings
M01107	All organs and tissues	No abnormality detected
M01108	All organs and tissues	No abnormality detected
M01109	All organs and tissues	No abnormality detected
M01110	All organs and tissues	No abnormality detected
M01111	All organs and tissues	No abnormality detected
M01112	All organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Examined the liver, pancreas, thymus, and kidney.

Appendix 39-2. Individual histopathological findings in male rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg

Male No.	Organ/Tissue	Findings
M04407	All organs and tissues	No abnormality detected
M04408	Kidney	Cyst, left: ±
	Other organs and tissues	No abnormality detected
M04409	All organs and tissues	No abnormality detected
M04410	All organs and tissues	No abnormality detected
M04411	All organs and tissues	No abnormality detected
M04412	All organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Examined the liver, pancreas, thymus, and kidney.

Appendix 40-1. Individual histopathological findings in female rats on termination of recovery period

Control group			
Female No.	Organ/Tissue	Findings	
F01157	Kidney	Cyst, left: ±	
	Other organs and tissues	No abnormality detected	
F01158	All organs and tissues	No abnormality detected	
F01159	All organs and tissues	No abnormality detected	
F01160	All organs and tissues	No abnormality detected	
F01161	All organs and tissues	No abnormality detected	
F01162	All organs and tissues	No abnormality detected	

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Examined the liver, pancreas, thymus, and kidney.

Appendix 40-2. Individual histopathological findings in female rats on termination of recovery period

1,4-dichlorobutane group at 300 mg/kg		
Female No.	Organ/Tissue	Findings
F04457	All organs and tissues	No abnormality detected
F04458	All organs and tissues	No abnormality detected
F04459	Liver	Swelling, hepatocyte, periportal: ±
	Other organs and tissues	No abnormality detected
F04460	Liver	Swelling, hepatocyte, periportal: ±
	Other organs and tissues	No abnormality detected
F04461	All organs and tissues	No abnormality detected
F04462	All organs and tissues	No abnormality detected

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Examined the liver, pancreas, thymus, and kidney.

Stability of 1,4-dichlorobutane in test preparations (Study No. 095127)

Test article (Lot No.) : 1,4-dichlorobutane (Lot No. [REDACTED])
 Vehicle : Corn oil
 Form : Solution
 Method : GC
 Date of analysis : July 15, 2008 and July 23, 2008
 Testing facility : Hashima Laboratory, Nihon Bioresearch Inc.

Results

Concentration of analyte (mg/mL)	Storage period	Measured concentrations (mg/mL)			Mean concentration (mg/mL)	Recovery rate ²⁾ (%)	Stability ³⁾ (%)
		1st	2nd	3rd			
2	Initial	1.835	1.808	1.817	1.820	91.0	-
	8 days after preparation ¹⁾	1.832	1.814	1.826	1.824	91.2	100.2
20	Initial	19.16	19.80	19.68	19.55	97.8	-
	8 days after preparation ¹⁾	20.19	20.34	20.34	20.29	101.5	103.8
200	Initial	203.1	203.4	203.1	203.2	101.6	-
	8 days after preparation ¹⁾	205.5	204.3	206.3	205.4	102.7	101.1

1) Stored at room temperature (set at 23 °C; values by actual measurement: 22.3 – 22.7°C), lightproof and airtight conditions for 6 hours after being stored under refrigerated (set at 4 °C; values by actual measurement: 3.7 – 6.2°C), lightproof and airtight conditions for 8 days.

2) Acceptable range: within ±10% of the prescribed concentrations.

3) Acceptable range: not less than 90%.

GLP:

This study was conducted in compliance with the OECD Guidelines for Safety Studies on Chemicals (OECD GLP Standards) and the Standards for Testing Facilities for Implementation of Studies of Novel Chemical Substances.

Concentrations of 1,4-dichlorobutane
in dosing preparations at the start of administration in male rats

Test article (Lot No.): 1,4-dichlorobutane (Lot No. [REDACTED])
Vehicle: Corn oil
Date of preparation: October 3, 2008
Form: Solution
Method: GC
Date of analysis: October 6, 2008
Testing facility: Hashima Laboratory, Nihon Bioresearch Inc.

Results

Concentration of 1,4-dichlorobutane (mg/mL)	Measured concentrations (mg/mL)				Recovery rate (%)
	1st	2nd	3rd	Mean	
2.4	2.280	2.261	2.259	2.267	94.5
12	12.35	12.24	12.23	12.27	102.3
60	60.56	60.92	60.93	60.80	101.3

The concentration of each preparation was within the acceptable range ($100 \pm 10\%$).

GLP:

This study was conducted in compliance with the OECD Guidelines for Safety Studies on Chemicals (OECD GLP Standards) and the Standards for Testing Facilities for Implementation of Studies of Novel Chemical Substances.

Concentrations of 1,4-dichlorobutane
in dosing preparations at the end of administration in female rats

Test article (Lot No.): 1,4-dichlorobutane (Lot No. [REDACTED])
Vehicle: Corn oil
Date of preparation: October 30, 2008
Form: Solution
Method: GC
Date of analysis: October 30, 2008
Testing facility: Hashima Laboratory, Nihon Bioresearch Inc.

Results

Concentration of 1,4-dichlorobutane (mg/mL)	Measured concentrations (mg/mL)				Recovery rate (%)
	1st	2nd	3rd	Mean	
2.4	2.312	2.305	2.310	2.309	96.2
12	12.18	12.15	12.24	12.19	101.6
60	61.54	61.56	61.71	61.60	102.7

The concentration of each preparation was within the acceptable range ($100 \pm 10\%$).

GLP:

This study was conducted in compliance with the OECD Guidelines for Safety Studies on Chemicals (OECD GLP Standards) and the Standards for Testing Facilities for Implementation of Studies of Novel Chemical Substances.

Attachment 4-1. General signs in male rats during quarantine and acclimatization

Quarantine/ acclimatization male No.	Male No.	Quarantine period					
		24-Sep-08 Day 0	25-Sep-08 Day 1	26-Sep-08 Day 2	27-Sep-08 Day 3	28-Sep-08 Day 4	29-Sep-08 Day 5
M00001	EG,MA	N	N	N	N	N	N
M00002	M03304	N	N	N	N	N	N
M00003	M03302	N	N	N	N	N	N
M00004	M01110	N	N	N	N	N	N
M00005	M01109	N	N	N	N	N	N
M00006	M03305	N	N	N	N	N	N
M00007	M03301	N	N	N	N	N	N
M00008	M01102	N	N	N	N	N	N
M00009	M01108	N	N	N	N	N	N
M00010	M02204	N	N	N	N	N	N
M00011	M04410	N	N	N	N	N	N
M00012	M02205	N	N	N	N	N	N
M00013	M04407	N	N	N	N	N	N
M00014	EG,MA	N	N	N	N	N	N
M00015	M04403	N	N	N	N	N	N
M00016	M04409	N	N	N	N	N	N
M00017	M04402	N	N	N	N	N	N
M00018	EG	N	N	N	N	N	N
M00019	M02206	N	N	N	N	N	N
M00020	M01112	N	N	N	N	N	N
M00021	M01111	N	N	N	N	N	N
M00022	M04404	N	N	N	N	N	N
M00023	M03306	N	N	N	N	N	N
M00024	EG	N	N	N	N	N	N
M00025	EG	N	N	N	N	N	N

EG: Excluded from grouping because body weight was extremely different from the mean.

(Continued)

MA: Monitor animal.

N: Normal.

Attachment 4-1. (Continued) General signs in male rats during quarantine and acclimatization

Quarantine/ acclimatization male No.	Male No.	Acclimatization period						
		30-Sep-08 Day 1	01-Oct-08 Day 2	02-Oct-08 Day 3	03-Oct-08 Day 4	04-Oct-08 Day 5	05-Oct-08 Day 6	06-Oct-08 Day 7 #
M00001	EG,MA	N	N	N	N	N	N	N
M00002	M03304	N	N	N	N	N	N	N
M00003	M03302	N	N	N	N	N	N	N
M00004	M01110	N	N	N	N	N	N	N
M00005	M01109	N	N	N	N	N	N	N
M00006	M03305	N	N	N	N	N	N	N
M00007	M03301	N	N	N	N	N	N	N
M00008	M01102	N	N	N	N	N	N	N
M00009	M01108	N	N	N	N	N	N	N
M00010	M02204	N	N	N	N	N	N	N
M00011	M04410	N	N	N	N	N	N	N
M00012	M02205	N	N	N	N	N	N	N
M00013	M04407	N	N	N	N	N	N	N
M00014	EG,MA	N	N	N	N	N	N	N
M00015	M04403	N	N	N	N	N	N	N
M00016	M04409	N	N	N	N	N	N	N
M00017	M04402	N	N	N	N	N	N	N
M00018	EG	N	N	N	N	N	N	N
M00019	M02206	N	N	N	N	N	N	N
M00020	M01112	N	N	N	N	N	N	N
M00021	M01111	N	N	N	N	N	N	N
M00022	M04404	N	N	N	N	N	N	N
M00023	M03306	N	N	N	N	N	N	N
M00024	EG	N	N	N	N	N	N	N
M00025	EG	N	N	N	N	N	N	N

#: Day of grouping.

EG: Excluded from grouping because body weight was extremely different from the mean.

MA: Monitor animal.

N: Normal.

Attachment 4-2. General signs in male rats during quarantine and acclimatization

Quarantine/ acclimatization male No.	Male No.	Quarantine period					
		24-Sep-08 Day 0	25-Sep-08 Day 1	26-Sep-08 Day 2	27-Sep-08 Day 3	28-Sep-08 Day 4	29-Sep-08 Day 5
M00026	M01101	N	N	N	N	N	N
M00027	EG	N	N	N	N	N	N
M00028	M01103	N	N	N	N	N	N
M00029	M04412	N	N	N	N	N	N
M00030	M04401	N	N	N	N	N	N
M00031	M04411	N	N	N	N	N	N
M00032	EG	N	N	N	N	N	N
M00033	M02203	N	N	N	N	N	N
M00034	M04405	N	N	N	N	N	N
M00035	M01105	N	N	N	N	N	N
M00036	M01106	N	N	N	N	N	N
M00037	M03303	N	N	N	N	N	N
M00038	M04408	N	N	N	N	N	N
M00039	M04406	N	N	N	N	N	N
M00040	M02201	N	N	N	N	N	N
M00041	M02202	N	N	N	N	N	N
M00042	M01107	N	N	N	N	N	N
M00043	EG	N	N	N	N	N	N
M00044	M01104	N	N	N	N	N	N
Number of males		44	44	44	44	44	44
N		44	44	44	44	44	44

EG: Excluded from grouping because body weight was extremely different from the mean.

(Continued)

N: Normal.

Attachment 4-2. (Continued) General signs in male rats during quarantine and acclimatization

Quarantine/ acclimatization male No.	Male No.	Acclimatization period						
		30-Sep-08 Day 1	01-Oct-08 Day 2	02-Oct-08 Day 3	03-Oct-08 Day 4	04-Oct-08 Day 5	05-Oct-08 Day 6	06-Oct-08 Day 7 #
M00026	M01101	N	N	N	N	N	N	N
M00027	EG	N	N	N	N	N	N	N
M00028	M01103	N	N	N	N	N	N	N
M00029	M04412	N	N	N	N	N	N	N
M00030	M04401	N	N	N	N	N	N	N
M00031	M04411	N	N	N	N	N	N	N
M00032	EG	N	N	N	N	N	N	N
M00033	M02203	N	N	N	N	N	N	N
M00034	M04405	N	N	N	N	N	N	N
M00035	M01105	N	N	N	N	N	N	N
M00036	M01106	N	N	N	N	N	N	N
M00037	M03303	N	N	N	N	N	N	N
M00038	M04408	N	N	N	N	N	N	N
M00039	M04406	N	N	N	N	N	N	N
M00040	M02201	N	N	N	N	N	N	N
M00041	M02202	N	N	N	N	N	N	N
M00042	M01107	N	N	N	N	N	N	N
M00043	EG	N	N	N	N	N	N	N
M00044	M01104	N	N	N	N	N	N	N
Number of males		44	44	44	44	44	44	44
	N	44	44	44	44	44	44	44

#: Day of grouping.

EG: Excluded from grouping because body weight was extremely different from the mean.

N: Normal.

Attachment 5-1. General signs in female rats during quarantine and acclimatization

Quarantine/ acclimatization female No.	Female No.	Quarantine period					
		24-Sep-08 Day 0	25-Sep-08 Day 1	26-Sep-08 Day 2	27-Sep-08 Day 3	28-Sep-08 Day 4	29-Sep-08 Day 5
F00001	F01152	N	N	N	N	N	N
F00002	F01151	N	N	N	N	N	N
F00003	F02251	N	N	N	N	N	N
F00004	F04459	N	N	N	N	N	N
F00005	F02255	N	N	N	N	N	N
F00006	F04457	N	N	N	N	N	N
F00007	EG	N	N	N	N	N	N
F00008	F04461	N	N	N	N	N	N
F00009	EG	N	N	N	N	N	N
F00010	F04462	N	N	N	N	N	N
F00011	F01156	N	N	N	N	N	N
F00012	F01158	N	N	N	N	N	N
F00013	F01157	N	N	N	N	N	N
F00014	F04458	N	N	N	N	N	N
F00015	F02253	N	N	N	N	N	N
F00016	F01161	N	N	N	N	N	N
F00017	F03354	N	N	N	N	N	N
F00018	EG	N	N	N	N	N	N
F00019	F01155	N	N	N	N	N	N
F00020	F01154	N	N	N	N	N	N
F00021	F04455	N	N	N	N	N	N
F00022	F01153	N	N	N	N	N	N
F00023	EG	N	N	N	N	N	N
F00024	F03353	N	N	N	N	N	N
F00025	F04452	N	N	N	N	N	N

EG: Excluded from grouping because body weight was extremely different from the mean.

(Continued)

N: Normal.

Attachment 5-1. (Continued) General signs in female rats during quarantine and acclimatization

Quarantine/ acclimatization female No.	Female No.	Acclimatization period								
		30-Sep-08	01-Oct-08	02-Oct-08	03-Oct-08	04-Oct-08	05-Oct-08	06-Oct-08	07-Oct-08	08-Oct-08
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9 #
F00001	F01152	N	N	N	N	N	N	N	N	N
F00002	F01151	N	N	N	N	N	N	N	N	N
F00003	F02251	N	N	N	N	N	N	N	N	N
F00004	F04459	N	N	N	N	N	N	N	N	N
F00005	F02255	N	N	N	N	N	N	N	N	N
F00006	F04457	N	N	N	N	N	N	N	N	N
F00007	EG	N	N	N	N	N	N	N	N	N
F00008	F04461	N	N	N	N	N	N	N	N	N
F00009	EG	N	N	N	N	N	N	N	N	N
F00010	F04462	N	N	N	N	N	N	N	N	N
F00011	F01156	N	N	N	N	N	N	N	N	N
F00012	F01158	N	N	N	N	N	N	N	N	N
F00013	F01157	N	N	N	N	N	N	N	N	N
F00014	F04458	N	N	N	N	N	N	N	N	N
F00015	F02253	N	N	N	N	N	N	N	N	N
F00016	F01161	N	N	N	N	N	N	N	N	N
F00017	F03354	N	N	N	N	N	N	N	N	N
F00018	EG	N	N	N	N	N	N	N	N	N
F00019	F01155	N	N	N	N	N	N	N	N	N
F00020	F01154	N	N	N	N	N	N	N	N	N
F00021	F04455	N	N	N	N	N	N	N	N	N
F00022	F01153	N	N	N	N	N	N	N	N	N
F00023	EG	N	N	N	N	N	N	N	N	N
F00024	F03353	N	N	N	N	N	N	N	N	N
F00025	F04452	N	N	N	N	N	N	N	N	N

#: Day of grouping.

EG: Excluded from grouping because body weight was extremely different from the mean.

N: Normal.

Attachment 5-2. General signs in female rats during quarantine and acclimatization

Quarantine/ acclimatization female No.	Female No.	Quarantine period					
		24-Sep-08 Day 0	25-Sep-08 Day 1	26-Sep-08 Day 2	27-Sep-08 Day 3	28-Sep-08 Day 4	29-Sep-08 Day 5
F00026	EG	N	N	N	N	N	N
F00027	F04460	N	N	N	N	N	N
F00028	F04456	N	N	N	N	N	N
F00029	F04454	N	N	N	N	N	N
F00030	F01160	N	N	N	N	N	N
F00031	F03352	N	N	N	N	N	N
F00032	F01162	N	N	N	N	N	N
F00033	F02254	N	N	N	N	N	N
F00034	F04453	N	N	N	N	N	N
F00035	F04451	N	N	N	N	N	N
F00036	F03351	N	N	N	N	N	N
F00037	F02256	N	N	N	N	N	N
F00038	F03356	N	N	N	N	N	N
F00039	F03355	N	N	N	N	N	N
F00040	EG	N	N	N	N	N	N
F00041	F02252	N	N	N	N	N	N
F00042	EG	N	N	N	N	N	N
F00043	F01159	N	N	N	N	N	N
F00044	EG	N	N	N	N	N	N
Number of females		44	44	44	44	44	44
N		44	44	44	44	44	44

EG: Excluded from grouping because body weight was extremely different from the mean.

(Continued)

N: Normal.

Attachment 5-2. (Continued) General signs in female rats during quarantine and acclimatization

Quarantine/ acclimatization female No.	Female No.	Acclimatization period								
		30-Sep-08 Day 1	01-Oct-08 Day 2	02-Oct-08 Day 3	03-Oct-08 Day 4	04-Oct-08 Day 5	05-Oct-08 Day 6	06-Oct-08 Day 7	07-Oct-08 Day 8	08-Oct-08 Day 9 #
F00026	EG	N	N	N	N	N	N	N	N	N
F00027	F04460	N	N	N	N	N	N	N	N	N
F00028	F04456	N	N	N	N	N	N	N	N	N
F00029	F04454	N	N	N	N	N	N	N	N	N
F00030	F01160	N	N	N	N	N	N	N	N	N
F00031	F03352	N	N	N	N	N	N	N	N	N
F00032	F01162	N	N	N	N	N	N	N	N	N
F00033	F02254	N	N	N	N	N	N	N	N	N
F00034	F04453	N	N	N	N	N	N	N	N	N
F00035	F04451	N	N	N	N	N	N	N	N	N
F00036	F03351	N	N	N	N	N	N	N	N	N
F00037	F02256	N	N	N	N	N	N	N	N	N
F00038	F03356	N	N	N	N	N	N	N	N	N
F00039	F03355	N	N	N	N	N	N	N	N	N
F00040	EG	N	N	N	N	N	N	N	N	N
F00041	F02252	N	N	N	N	N	N	N	N	N
F00042	EG	N	N	N	N	N	N	N	N	N
F00043	F01159	N	N	N	N	N	N	N	N	N
F00044	EG	N	N	N	N	N	N	N	N	N
Number of females		44	44	44	44	44	44	44	44	44
	N	44	44	44	44	44	44	44	44	44

#: Day of grouping.

EG: Excluded from grouping because body weight was extremely different from the mean.

N: Normal.

Attachment 6-1. Body weights (g) of male rats during quarantine and acclimatization

Quarantine/ acclimatization male No.	Male No.	Quarantine period		Acclimatization period	
		25-Sep-08 Day 1	29-Sep-08 Day 5	06-Oct-08 Day 7 #	
M00001	EG,MA	86 L	127	182	
M00002	M03304	88	131	195	
M00003	M03302	91	128	195	
M00004	M01110	91	133	196	
M00005	M01109	90	127	194	
M00006	M03305	86 L	127	189	
M00007	M03301	93	125	197	
M00008	M01102	90	124	197	
M00009	M01108	90	124	183	
M00010	M02204	93	132	199	
M00011	M04410	88	126	192	
M00012	M02205	92	128	195	
M00013	M04407	90	127	185	
M00014	EG,MA	94	135 H	206	
M00015	M04403	90	132	198	
M00016	M04409	91	128	191	
M00017	M04402	91	130	193	
M00018	EG	90	127	178	
M00019	M02206	86 L	129	197	
M00020	M01112	91	129	194	
M00021	M01111	93	128	193	
M00022	M04404	94	131	190	
M00023	M03306	87	123	191	
M00024	EG	93	133	206	
M00025	EG	92	122 L	173 L	

#: Day of grouping.

MA: Monitor animal.

EG: Excluded from grouping because body weight was extremely different from the mean.

L: Minimum body weight.

H: Maximum body weight.

Attachment 6-2. Body weights (g) of male rats during quarantine and acclimatization

Quarantine/ acclimatization male No.	Male No.	Quarantine period		Acclimatization period	
		25-Sep-08 Day 1	29-Sep-08 Day 5	06-Oct-08 Day 7 #	
M00026	M01101	93	130	194	
M00027	EG	88	124	179	
M00028	M01103	92	130	196	
M00029	M04412	89	129	201	
M00030	M04401	92	131	196	
M00031	M04411	95 H	132	199	
M00032	EG	92	132	207 H	
M00033	M02203	89	123	184	
M00034	M04405	93	131	189	
M00035	M01105	93	131	197	
M00036	M01106	91	127	195	
M00037	M03303	91	129	201	
M00038	M04408	92	130	195	
M00039	M04406	94	133	194	
M00040	M02201	90	129	193	
M00041	M02202	93	131	194	
M00042	M01107	94	133	200	
M00043	EG	91	126	177	
M00044	M01104	91	127	188	
Number of males		44	44	44	
Mean		91	129	193	
S.D.		2	3	8	

#: Day of grouping.

EG: Excluded from grouping because body weight was extremely different from the mean.

H: Maximum body weight.

Attachment 7-1. Body weights (g) of female rats during quarantine and acclimatization

Quarantine/ acclimatization female No.	Female No.	Quarantine period		Acclimatization period	
		25-Sep-08 Day 1	29-Sep-08 Day 5	06-Oct-08 Day 7	08-Oct-08 Day 9 #
F00001	F01152	73	101	140	144
F00002	F01151	73	103	140	141
F00003	F02251	69	96	140	145
F00004	F04459	70	97	145	155
F00005	F02255	70	99	140	143
F00006	F04457	69	96	138	148
F00007	EG	68	93	129	132 L
F00008	F04461	70	102	146	148
F00009	EG	74	106	157	170
F00010	F04462	71	100	143	144
F00011	F01156	69	93	136	143
F00012	F01158	73	101	142	150
F00013	F01157	73	103	142	152
F00014	F04458	71	97	134	140
F00015	F02253	69	98	140	148
F00016	F01161	71	96	135	145
F00017	F03354	69	99	147	155
F00018	EG	74	109 H	168 H	179 H
F00019	F01155	73	102	140	150
F00020	F01154	74	101	141	150
F00021	F04455	64 L	97	135	146
F00022	F01153	65	97	138	143
F00023	EG	67	91 L	130	140
F00024	F03353	72	100	139	143
F00025	F04452	72	98	146	159

#: Day of grouping.

EG: Excluded from grouping because body weight was extremely different from the mean.

L: Minimum body weight.

H: Maximum body weight.

Attachment 7-2. Body weights (g) of female rats during quarantine and acclimatization

Quarantine/ acclimatization female No.	Female No.	Quarantine period		Acclimatization period	
		25-Sep-08 Day 1	29-Sep-08 Day 5	06-Oct-08 Day 7	08-Oct-08 Day 9 #
F00026	EG	68	94	124 L	137
F00027	F04460	71	99	145	151
F00028	F04456	73	100	144	153
F00029	F04454	69	98	145	155
F00030	F01160	74	102	143	155
F00031	F03352	70	100	143	151
F00032	F01162	74	101	139	146
F00033	F02254	68	97	138	145
F00034	F04453	72	98	140	149
F00035	F04451	71	101	148	155
F00036	F03351	74	106	141	151
F00037	F02256	72	100	141	149
F00038	F03356	72	102	145	154
F00039	F03355	72	93	135	144
F00040	EG	75 H	104	160	169
F00041	F02252	68	94	145	159
F00042	EG	75 H	105	152	165
F00043	F01159	75 H	103	149	159
F00044	EG	68	96	134	137
Number of females		44	44	44	44
Mean		71	99	142	150
S.D.		3	4	8	9

#: Day of grouping.

EG: Excluded from grouping because body weight was extremely different from the mean.

L: Minimum body weight.

H: Maximum body weight.

Background Data

Blood chemical findings			Crl:CD (SD) Male Rats 10 weeks				
Exam.item	Unit	N	Value				
			Mean	± S.D.	Min.	Max.	Range of 2S.D.
AST	IU/ L	30	83.7	± 14.2	58.2	130.0	55.3 - 112.1
ALT	IU/ L	30	28.3	± 8.3	16.9	56.9	11.7 - 44.9
ALP	IU/ L	30	612.8	± 123.7	380.4	904.0	365.4 - 860.2
T-Chol	mg/dL	30	56.6	± 13.0	31.4	81.2	30.6 - 82.6
TG	mg/dL	30	37.3	± 14.6	16.7	68.2	8.1 - 66.5
T-Bil	mg/dL	30	0.11	± 0.01	0.09	0.15	0.09 - 0.13
UN	mg/dL	30	15.4	± 1.8	12.4	20.6	11.8 - 19.0
CRE	mg/dL	30	0.23	± 0.03	0.18	0.29	0.17 - 0.29
IP	mg/dL	30	8.3	± 0.7	6.5	9.5	6.9 - 9.7
Ca	mg/dL	30	9.7	± 0.3	9.1	10.2	9.1 - 10.3
Glu	mg/dL	30	120.3	± 11.0	93.8	138.6	98.3 - 142.3
Na	mEq/L	30	143.0	± 1.1	140.6	144.9	140.8 - 145.2
K	mEq/L	30	4.21	± 0.26	3.77	4.80	3.69 - 4.73
Cl	mEq/L	30	104.8	± 1.1	101.6	106.7	102.6 - 107.0
TP	g/dL	30	5.54	± 0.22	5.05	5.95	5.10 - 5.98
A/G		30	1.09	± 0.09	0.89	1.21	0.91 - 1.27
alb	%	30	52.1	± 2.0	47.2	54.8	48.1 - 56.1
α_1 -glob	%	30	21.0	± 1.9	16.0	23.7	17.2 - 24.8
α_2 -glob	%	30	7.3	± 0.7	6.3	8.7	5.9 - 8.7
β -glob	%	30	15.2	± 1.2	12.7	18.0	12.8 - 17.6
γ -glob	%	30	4.5	± 0.9	3.2	6.8	2.7 - 6.3
Alb	g/dL	30	2.88	± 0.13	2.65	3.20	2.62 - 3.14

N: Number of animals.

Hashima Laboratory, Nihon Bioresearch Inc.

Prepared: 2007.08

信頼性保証陳述書

試験番号 : 502427

表題 : 1,4-ジクロロブタンのラットを用いる28日間反復経口投与毒性試験及び14日間回復試験

当試験が新規化学物質等に係る試験を実施する試験施設に関する基準について(平成15年11月21日, 薬食発第1121003号, 平成15・11・17製局第3号, 環保企発第031121004号, 平成20年7月4日最終改正) 及びOECD PRINCIPLES OF GOOD LABORATORY PRACTICE(OECD 化学物質の安全性試験の実施に関する基準, 1997年11月26日)に従って実施され, この最終報告書には試験の方法が正確に記載され, かつ生データが正確に反映されていることを保証する.

(調査の状況は, 別紙1~2のとおりである。)

2011年 9月 13日

株式会社日本バイオリサーチセンター 羽島研究所

信頼性保証部門責任者

別紙 1

調査項目	調査実施日			運営管理者及び試験責任者への報告日		
1. 試験計画書	2008年 9月 19日			2008年 9月 19日		
2. コンピュータプロトコール	2008年 9月 24日			2008年 9月 24日		
3. 動物の受け入れ	2008年 9月 24日			2008年 9月 24日		
4. 被験物質の管理	2008年 10月 3日			2008年 10月 7日		
5. 検体の調製	2008年 10月 3日			2008年 10月 7日		
6. 群分け及び個体識別	2008年 10月 6日			2008年 10月 7日		
7. 投与	2008年 10月 7日			2008年 10月 7日		
8. 動物飼育管理	2008年 10月 7日			2008年 10月 7日		
9. 体重測定・摂餌量測定・摂水量測定	2008年 10月 9日			2008年 10月 9日		
10. 一般状態観察	2008年 10月 9日			2008年 10月 9日		
11. 投与	2008年 10月 9日			2008年 10月 9日		
12. 行動機能(FOB)観察 (投与7日, 雌)	2008年 10月 15日			2008年 10月 15日		
13. 尿検査(投与期間終了前, 雄)	2008年 10月 29日			2008年 10月 30日		
	～ 10月 30日					
14. 自発運動量測定	2008年 11月 3日			2008年 11月 4日		
15. 感覚反応検査	2008年 11月 4日			2008年 11月 4日		
16. 握力測定	2008年 11月 4日			2008年 11月 4日		
17. 剖検・採血・器官重量測定 (投与期間終了時, 雄)	2008年 11月 4日			2008年 11月 4日		
18. 血液学検査(血漿分取・測定) [投与期間終了時, 雄]	2008年 11月 4日			2008年 11月 4日		
19. 血液生化学検査(血清分取・測定 ・保存用血清の保管) [投与期間終了時, 雄]	2008年 11月 4日			2008年 11月 4日		
20. 剖検・採血・器官重量測定 (投与期間終了時, 雌)	2008年 11月 6日			2008年 11月 10日		
21. 体重測定・摂餌量測定・摂水量測定	2008年 11月 7日			2008年 11月 10日		
22. 一般状態観察	2008年 11月 7日			2008年 11月 10日		
23. 動物飼育管理	2008年 11月 7日			2008年 11月 10日		
24. 尿検査(回復期間終了前, 雄)	2008年 11月 12日			2008年 11月 13日		
	～ 11月 13日					

別紙 2

調査項目	調査実施日	運営管理者及び試験責任者への報告日
25. 剖検・採血・器官重量測定 (回復期間終了時, 雄)	2008年 11月 18日	2008年 11月 21日
26. 剖検・採血・器官重量測定 (回復期間終了時, 雌)	2008年 11月 20日	2008年 11月 21日
27. 血液学検査 (血漿分取・測定) [回復期間終了時, 雌]	2008年 11月 20日	2008年 11月 21日
28. 血液生化学検査 (血清分取・測定 ・保存用血清の保管) [回復期間終了時, 雌]	2008年 11月 20日	2008年 11月 21日
29. 標本作製 (病理 : 切り出し)	2008年 12月 19日	2008年 12月 19日
30. 標本作製 (病理 : 薄切)	2009年 1月 22日	2009年 1月 22日
31. 生データ	2009年 3月 2日 ～ 3月 4日	2009年 3月 9日
32. 標本	2009年 3月 4日	2009年 3月 9日
33. 最終報告書 (一次案)	2009年 3月 4日 ～ 3月 6日	2009年 3月 9日
34. 生データ (再調査)	2009年 3月 16日	2009年 3月 16日
35. 最終報告書 (一次案) (再調査)	2009年 3月 16日	2009年 3月 16日
36. 最終報告書	2011年 9月 13日	2011年 9月 13日