Study No. 100630

4,4'–ビス (クロロメチル) –1,1'–ビフェニルのラットを用いる経口投与による反復投与毒性・生殖発生毒性併合試験

最 終 報 告 書

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16. 要約

4,4'–ビス (クロロメチル) –1,1'–ビフェニルの Crl:CD (SD) 雌雄ラットを用いる経口投与による反復投与毒性・生殖発生毒性併合試験を行い，雌雄動物に対する一般毒性学的影響を検討するとともに，性腺機能，交尾行動，受胎，受胎産物の発達及び分娩などの雌雄動物の生殖行動に及ぼす影響について検討した.

投与量は，62.5，250 及び 1000 mg/kg/day とした．主試験群では 28 日間投与し，14 日間の回復期間を設けた．交配群では，交配前 14 日間，交配期間中，妊娠期間中及び哺育 4 日まで 42 – 46 日間投与した．媒体には 0.5 w/v%メチルセルロース溶液を用い，対照群には被験物質投与群と同容量の 0.5 w/v%メチルセルロース溶液を投与した.

使用動物数は，主試験群雄は対照群，62.5，250 及び 1000 mg/kg 群とも各 12 例とし，各群ともその半数を回復群とした．主試験群雌は，対照群と 1000 mg/kg 群で各 10 例，62.5 及び 250 mg/kg 群で各 5 例とし，対照群と 1000 mg/kg 群の各半数を回復群とした．主試験群とは別に生殖発生毒性を検討する交配群を設け，使用動物数は対照群，62.5，250 及び 1000 mg/kg 群とも雌親各 12 例とした.

1. 反復投与毒性

血液学的検査において，投与期間終了時に雄の 1000 mg/kg 群でプロトロンビン時間の延長がみられた.

血液生化学的検査において，投与期間終了時に雄の 1000 mg/kg 群で ALT の高値及びトリグリセライドの低値，雌の 1000 及び 250 mg/kg 群で A/G の高値がみられた．回復期間終了時には，雄の 1000 mg/kg 群で ALT の高値がみられた.

器官重量において，投与期間終了時に雄の 1000 及び 250 mg/kg 群で脾臓の絶対重量及び相対重量の低値あるいは低値傾向，雌の 1000 mg/kg 群で甲状腺の絶対重量及び相対重量の高値，肝臓の相対重量の高値，肝臓の絶対重量の高値傾向がみられた．回復期間終了時には，雄の 1000 mg/kg 群で肝臓の絶対重量及び相対重量の高値あるいは高値傾向がみられた.

上記以外には，被験物質に起因する変化はみられなかった.

2. 生殖発生毒性

被験物質に起因する変化はみられなかった.

以上のように，4,4'–ビス (クロロメチル) –1,1'–ビフェニルの無影響量は，雄では 250 mg/kg 投与で脾臓の絶対重量及び相対重量の低値あるいは低値傾向が認められたことから 62.5 mg/kg/day,

雌では 250 mg/kg 投与で A/G の高値が認められたことから 62.5 mg/kg/day と考えられる．生殖発生毒性学的な無影響量は，1000 mg/kg 投与で雌雄ともいずれの項目にも影響が認められなかったことから 1000 mg/kg/day と考えられる．児動物への無影響量は，1000 mg/kg 投与でいずれの項目にも影響が認められなかったことから 1000 mg/kg/day と考えられる．

17. 緒言

4,4'–ビス (クロロメチル) –1,1'–ビフェニル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，4,4'–ビス (クロロメチル) –1,1'–ビフェニルを雌雄ラットに経口投与し，反復投与による毒性影響を検討するとともに，性腺機能，交尾行動，受胎，受胎産物の発達及び分娩などの雌雄動物の生殖行動に及ぼす影響について検討した.

18. 方法

18.1. 被験物質及び媒体

18.1.1. 被験物質

被験物質 4,4'–ビス (クロロメチル) –1,1'–ビフェニル [別名: 4,4'–ビス (クロロメチル) ビフェニル，英語化学名: 4,4'-bis(chloromethyl)-1,1'-biphenyl，CAS No. 1667-10-3，官報公示整理番号 (化審法): 4-798，Fig. 1] は，化学式: $C_{14}H_{12}Cl_2$，分子量: 251.15，物性・性状: 白色の結晶性粉末，エタノール及びアセトンに溶け，水にほとんど溶けず，融点: 141.7℃である[1)]．当試験には，

入手したものを用いた [

純度 (GC): 99.8%]．入手後は，室温・遮光・気密・防湿の条件下で保管した.

被験物質の保管場所の温・湿度を以下に示した.

被験物質	保管場所	温度	湿度
4,4'–ビス (クロロメチル) –1,1'–ビフェニル (Lot No.: ILJ4E) (a)	被験物質保管室の保管庫	設定: 23°C 許容範囲: 18.0 – 28.0°C 実測値: 22.0 – 25.0°C	設定: 55% 許容範囲: 40.0 – 70.0% 実測値: 47.0 – 67.0%

(a) 2010 年 6 月 29 日 (被験物質入手日) – 2010 年 10 月 28 日 (投与期間終了日)

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.: ILJ4E) の品質試験成績から，使用期間中の安定性が確認された.

投与期間終了後，試験施設で保管する被験物質のサンプル (1.0000 g) を除いた残余被験物質は廃棄した.

18.1.2. 媒体 (0.5 w/v%メチルセルロース溶液) 調製に用いた物質

メチルセルロース (品名: メトローズ®SM-100，規格: 局方，Lot No.: 8015056，使用期限: 2011 年 1 月 29 日，製造元: 信越化学工業株式会社，保管条件: 室温) 及び注射用水 (規格: 局方，Lot No.: 9L70N，使用期限: 2014 年 12 月，製造元: 株式会社大塚製薬工場，保管条件: 室温) を用いた.

メチルセルロース及び注射用水の保管場所の温・湿度を以下に示した.

物質	保管場所	温度	湿度
メチルセルロース (Lot No.: 8015056) (a)	被験物質保管室の保管庫	設定: 23°C 許容範囲: 18.0 – 28.0°C 実測値: 22.5 – 25.0°C	設定: 55% 許容範囲: 40.0 – 70.0% 実測値: 48.0 – 59.8%
注射用水 (Lot No.: 9L70N) (a)	被験物質保管室	設定: 23°C 許容範囲: 18.0 – 28.0°C 実測値: 22.5 – 25.0°C	設定: 55% 許容範囲: 40.0 – 70.0% 実測値: 48.0 – 59.8%

(a) 2010 年 8 月 24 日 (試験開始日) – 2010 年 10 月 26 日 (最終調製日)

18.2. 投与検体

18.2.1. 投与検体の調製

18.2.1.1. 媒体 (0.5 w/v%メチルセルロース溶液)

広口瓶に所定容量の 70%の注射用水を入れた．メチルセルロースの必要量を秤量 (電子天秤: AT250 又は PB3002-S/FACT，メトラー・トレド株式会社) 後，広口瓶に加え，マグネチックスターラーで撹拌した．溶解後，メスシリンダーに移し，注射用水で所定量とした．適切なガラス容器に 0.5 w/v%メチルセルロース溶液を移した．0.5 w/v%メチルセルロース溶液は，冷蔵の条件下で保管し，調製後 8 日以内に使用した．

0.5 w/v%メチルセルロース溶液の保管場所の温度を以下に示した．

媒体	保管容器	保管場所	温度
0.5 w/v%メチルセルロース溶液 (a)	ガラス容器	被験物質保管室の冷蔵庫 (BMS-500F3，日本フリーザー株式会社)	設定: 4°C 許容範囲: 2.0 – 8.0°C 実測値: 2.3 – 6.3°C

(a) 2010 年 9 月 8 日 (初回調製日) – 2010 年 10 月 27 日 (最終使用日)

18.2.1.2. 投与検体

1) 0.5 w/v%メチルセルロース溶液

対照群投与液とした．本液は各投与群投与液の調製に使用した 0.5 w/v%メチルセルロース溶液 (以下，0.5 w/v%MC) を兼ねた．

2) 投与群投与液

最高濃度の投与検体を調製するために，4,4'–ビス (クロロメチル) –1,1'–ビフェニルは必要量 (純度による補正は実施しなかった) を秤取 (電子天秤: AT250 又は PB3002-S/FACT，メトラー・トレド株式会社) 後，メノウ乳鉢及びメノウ乳棒を用いて，0.5 w/v%MC で 200 mg/mL 懸濁液を調製した．50 及び 12.5 mg/mL 濃度の各投与検体は，200 mg/mL 濃度液を 0.5 w/v%MC で段階希釈し

て調製した.

18.2.2. 投与検体の安定性及び均一性並びに調製頻度

媒体として 0.5 w/v%MCを用いた調製検体の安定性及び均一性については, 1 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・気密 7 日間とその後，室温 (設定温度: 23°C)・遮光・気密で 6 時間まで問題がないことが確認されている[2)](Attachment 1).

各投与検体は，週 1 回以上の頻度で調製し，褐色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・遮光・気密の条件下で保管し，調製後 7 日以内に使用した.

投与検体の保管場所の温度を以下に示した.

投与検体	保管容器	保管場所	温度
0，12.5，50 及び 200 mg/mL 濃度液 (a)	褐色ディスポーザブルポリプロピレン製容器	被験物質保管室の冷蔵庫 (BMS-500F3，日本フリーザー株式会社)	設定: 4°C 許容範囲: 2.0 – 8.0°C 実測値: 2.3 – 6.3°C

(a) 2010 年 9 月 9 日 (初回調製日) – 2010 年 10 月 28 日 (投与期間終了日)

保管した各投与検体は，冷蔵庫から持ち出し後 5 時間 56 分以内に使用した.

18.2.3. 投与検体中の被験物質の濃度測定及び均一性の確認

主試験群雄及び交配群雌親の投与開始日 (投与 1 日) に使用した各投与検体中の被験物質濃度及び均一性を高速液体クロマトグラフ (Waters Corp.) を用いて測定した (各濃度とも上層，中層及び下層の 3 サンプル). その結果，被験物質濃度は表示濃度の 102.7 – 106.7%であり，設定値の範囲内 (100.0 ± 10.0%) であった. また，均一性は，CV 値が 1.2%以内であり，適正範囲内 (5.0%以内) であった (Attachment 2).

18.2.4. 残余投与検体の取り扱い

残余投与検体は，毎日，投与終了後に廃棄した.

18.3. 試験動物及び飼育条件

18.3.1. 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，日本チャールス・リバー株式会社 日野飼育センター) を用いた.

動物は，2010 年 8 月 25 日に主試験群として 7 週齢の雄 62 匹と雌 42 匹，交配群として 7 週齢の

雌親 62 匹を入手した．入手後 1 日の体重範囲は，主試験群雄が 198 – 227 g，主試験群雌が 163 – 196 g，交配群雌親が 167 – 198 g であった．

18.3.2. 検疫及び馴化

入手した動物には，検疫期間 (2010 年 8 月 25 日 – 30 日) と馴化期間 (主試験群雄: 2010 年 8 月 31 日 – 2010 年 9 月 12 日，主試験群雌: 2010 年 8 月 31 日 – 2010 年 9 月 13 日，交配群雌親: 2010 年 8 月 31 日 – 2010 年 9 月 12 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: PB3002 又は PB3002-S/FACT，メトラー・トレド株式会社) を入手後 1 日，入手後 5 日 (検疫終了日)，馴化 7 日及び馴化終了日，さらに交配群雌親は性周期観察を群分け日までの 14 日間 (1 日 1 回) 行った．検疫・馴化期間中の一般状態，体重推移及び性周期に異常が認められない動物を群分けした (Attachments 3-1 – 3-3, 4-1, 4-2, 5-1 – 5-3, 6-1 – 6-3, 7-1, 7-2, 8-1 – 8-3, and 9-1 – 9-3).

18.3.3. 群分け

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．ただし，個々の動物の体重が平均値の ±20%以内であるものを選んで群分けした．群分け日の体重範囲は，主試験群雄が 292 – 385 g，主試験群雌が 212 – 270 g，交配群雌親が 211 – 263 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用いなかった群分け残余雄，群分け残余雌及び群分け残余雌親は，群分け日に炭酸ガスにて安楽死させた．

18.3.4. 個体識別

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 桁) 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，交尾確認日 (交配群雌親のみ)，分娩日 (交配群雌親のみ)，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．詳細な観察 (FOB)，感覚応答検査及び握力測定は Blind で検査したため，これらの検査時には試験番号，入手年月日及び検疫・馴化動物番号を記入したラベルを取り付けた．

児動物の個体識別は，生後 4 日に黒色油性インクを用いて背に児動物番号 (下 2 桁) を記入して行った．

児動物の各ケージには，試験番号，投与量，動物番号 (母動物番号，児動物番号) 及び出生日を

記入し，群ごとに色分けしたラベルを哺育 4 日に取り付けた.

18.3.5. 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 3 号室) で飼育した.

動物飼育室の温・湿度を以下に示した.

動物飼育室	温度	湿度
E 棟 3 号室 (a)	設定: 23°C 許容範囲: 20.0 – 26.0°C 実測値: 22.5 – 24.8°C	設定: 55% 許容範囲: 40.0 – 70.0% 実測値: 40.7 – 60.4%

(a) 2010 年 8 月 25 日 (動物入手日) – 2010 年 10 月 29 日 (最終剖検日)

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．交配は，雄のケージ内で行った．交配群雌親は，妊娠 18 日にオートクレーブ処理した床敷を入れたプラスチック製ケージ (W: 310 × D: 360 × H: 175 mm) に個別に移し，自然分娩，哺育をさせた．交配群雌親は，哺育 4 日にステンレス製懸垂式ケージを用いて個別飼育した.

給水瓶，ステンレス製懸垂式ケージの受皿及びプラスチック製ケージの交換は 1 週間に 2 回以上行い，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.

交配群雌親の剖検終了日にモニター動物から採血した血液を用いて微生物モニタリング検査 (Mycoplasma spp., Clostridium piliforme, HVJ, MHV, Corynebacterium kutscheri 及び SDAV) を実施した．北山ラベス株式会社で実施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.

18.3.6. 飼料

動物には，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) を給餌器に入れ，自由に摂取させた．ただし，主試験群雌雄の剖検前日及び交配群雌親の剖検前日 (哺育 4 日) には午後 4 時頃から絶食させた．飼料中の汚染物質濃度は Eurofins Scientific Analytics，細菌数及び栄養成分量はオリエンタル酵母工業株式会社で分析した．分析値は，当試験施設で設定した基

準値の範囲内であった.

18.3.7. 飲料水

動物には，水道水を給水瓶に入れ自由に摂取させた．飲料水中の汚染物質濃度及び細菌数は，東西化学産業株式会社あるいは株式会社環境公害センターで約 6 箇月ごとに分析した．分析値は，当試験施設で設定した基準値の範囲内であった.

18.3.8. 床敷

床敷 (サンフレーク，日本チャールス・リバー株式会社) の微量金属及び汚染物質濃度は，Eurofins Scientific Analytics で約 6 箇月ごとに分析した．分析値は，当試験施設で設定した基準値の範囲内であった.

18.4. 投与経路，投与方法及び投与期間

18.4.1. 投与経路及び投与方法

4,4'–ビス (クロロメチル)–1,1'–ビフェニルは，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．投与操作時には，各投与検体をマグネチックスターラーで撹拌しながら注射筒に吸引した.

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 で算出した.

投与回数は 1 日 1 回とした.

主試験群では，詳細な観察 (FOB) 及び自発運動量測定を実施した場合を除いた投与時刻は午前 8 時 32 分 – 10 時 49 分，詳細な観察 (FOB) を実施した場合の投与時刻は午前 9 時 00 分 – 11 時 56 分，自発運動量測定を実施した場合の投与時刻は午前 9 時 00 分 – 午後 0 時 31 分であった.

交配群では，詳細な観察 (FOB) を実施した場合を除いた投与時刻は午前 8 時 30 分 – 10 時 54 分，詳細な観察 (FOB) を実施した場合の投与時刻は午前 9 時 00 分 – 午後 0 時 56 分であった.

投与開始日の週齢は雄，雌及び雌親とも 10 週齢であり，体重範囲は主試験群雄が 325 – 367 g，主試験群雌が 223 – 258 g，交配群雌親が 222 – 259 g であった.

18.4.2. 投与期間及び回復期間

投与期間は，OECD Guideline for Testing of Chemicals for Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG422, March 22, 1996) に従った.

主試験群雄では，交配前 14 日間とその後 14 日間の合計 28 日間とした．28 日間の投与後に，各群半数の動物について 14 日間の回復期間を設けた．

主試験群雌では，28 日間とした．28 日間の投与後に，対照群及び高用量群の半数の動物について 14 日間の回復期間を設けた．

交配群雌親では，交配前 14 日間，交配期間中 (1－4 日間)，妊娠期間中 (22 又は 23 日間) 及び哺育 4 日 (5 日間) までの毎日とした (42－46 日間)．

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．また，交配開始日を交配 0 日とした．

18.5. 群構成及び投与量

18.5.1. 主試験群

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 1000 mg/kg 群を雄 12 例と雌 10 例，250 及び 62.5 mg/kg 群を雄 12 例と雌 5 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 (0.5 w/v%MC)	0	0	白色	6[1]+6[2] (M01101 – M01112)	5[1]+5[2] (F01151 – F01160)
2 群	4,4'–ビス (クロロメチル) –1,1'–ビフェニル	62.5	12.5	茶色	6[1]+6[2] (M02201 – M02212)	5[1] (F02251 – F02255)
3 群	4,4'–ビス (クロロメチル) –1,1'–ビフェニル	250	50	青色	6[1]+6[2] (M03301 – M03312)	5[1] (F03351 – F03355)
4 群	4,4'–ビス (クロロメチル) –1,1'–ビフェニル	1000	200	紫色	6[1]+6[2] (M04401 – M04412)	5[1]+5[2] (F04451 – F04460)

[1] 投与期間終了時に剖検

[2] 回復期間終了時に剖検

18.5.2. 交配群

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，雌親 12 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)
					雌親
1群	対照 (0.5 w/v%MC)	0	0	白色	12 (F01161 – F01172)
2群	4,4'–ビス (クロロメチル) –1,1'–ビフェニル	62.5	12.5	茶色	12 (F02261 – F02272)
3群	4,4'–ビス (クロロメチル) –1,1'–ビフェニル	250	50	青色	12 (F03361 – F03372)
4群	4,4'–ビス (クロロメチル) –1,1'–ビフェニル	1000	200	紫色	12 (F04461 – F04472)

18.6. 投与量設定の理由

4,4'–ビス (クロロメチル) –1,1'–ビフェニルの投与量は，予備試験[3] (投与段階: 0，200，500 及び 1000 mg/kg，使用動物数: 各群雌雄各 5 例，投与期間: 14 日間) の結果から決定した．予備試験において，1000 mg/kg群の雄で体重の低値傾向及び摂餌量の有意な低値，1000 mg/kg群の雌でA/Gの有意な高値及び肝臓の相対重量の有意な高値がみられたのみであった．

そこで，当試験では，OECD Guideline for Testing of Chemicals for Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG422, March 22, 1996) で上限量としている 1000 mg/kg を高用量とし，以下公比 4 で 250 mg/kg を中間用量，62.5 mg/kg を低用量に設定した．

対照として媒体 (0.5 w/v%MC) のみを被験物質投与群と同容量投与する群を設けた．

18.7. 観察及び検査項目

18.7.1. 主試験群雌雄

18.7.1.1. 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 (投与後 54 – 137 分) の 1 日 2 回，回復期間中に 1 日 1 回及び剖検日に 1 回行った．

投与期間中に詳細な観察 (FOB) を実施した場合は，詳細な観察 (FOB) 終了後に投与後の一般状態を観察した．

自発運動量測定を実施した場合は，自発運動量測定終了後に投与後の一般状態を観察した．

18.7.1.2. 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 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)].

18.7.1.3. 摂餌量

摂餌量は，1 週間に 2 回 1 日量を測定した [雄の残量測定日: 投与 2，5，9 及び 12 日，回復 2，5，9 及び 12 日，雌の残量測定日: 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.

18.7.1.4. 摂水量

摂水量は，1 週間に 2 回 1 日量を測定した [雄の残量測定日: 投与 2，5，9 及び 12 日，回復 2，5，9 及び 12 日，雌の残量測定日: 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.

18.7.1.5. 詳細な観察 (FOB)

全例について，群分け日，投与 7，14，21 及び 27 日に下記の 1) – 3)の項目を観察した．群分け日の観察は，午後 0 時 36 分 – 午後 2 時 44 分までの間に実施した．投与期間中の観察は，投与後約 1 時間 (観察終了時刻: 投与後 58 – 68 分) に実施した．観察者はほぼ固定し，Blind で実施した.

1) 姿勢，眼瞼閉鎖状態，常同行動 (過度の身づくろい，反復旋回運動，噛み付き行動)，間代性痙攣及び強直性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，被毛の状態，粘膜の状態，流涙，流涎，立毛，瞳孔及び呼吸状態は手に持って観察した.
3) 排尿，排便，立ち上がり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，覚醒度，異常行動及び正向反射をオープンフィールド内で観察した.

18.7.1.6. 感覚応答検査

投与期間終了時剖検例について，投与27日の詳細な観察 (FOB) 終了後に瞳孔反射，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．検査者はほぼ固定し，Blindで実施し

た.

18.7.1.7. 握力測定

投与期間終了時剖検例について，投与 27 日の感覚応答検査終了後に CPU ゲージ (San Diego Instruments Inc.) を用いて，前肢及び後肢の握力を 5 回測定した．最高値と最低値を除いた中央の 3 測定値の平均値をその動物の握力値とした．測定者はほぼ固定し，Blind で実施した.

18.7.1.8. 自発運動量測定

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.

18.7.1.9. 尿検査

投与期間終了前 (投与 23 日，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 12 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．

項 目	測 定 方 法	使 用 機 器
尿量 (UV)[b]	重量測定及び尿比重より算出	電子天秤 PG2002-S 又は PB3002-S/FACT (メトラー・トレド株式会社)
色調[a]	外観判定	–
尿比重 (SG)[b]	屈折率	屈折型尿比重計 ユリペット-ⅡD (株式会社ニコン)
pH[a] 蛋白質[a] ブドウ糖[a] ケトン体[a] ビリルビン[a] 潜血[a] ウロビリノーゲン[a]	尿検査試験紙	尿化学分析装置 クリニテック アドバンタス (シーメンスヘルスケア・ダイアグノスティクス株式会社)
沈渣 (上皮細胞，赤血球，白血球，円柱，結晶)[a]	鏡検	顕微鏡 (オリンパス株式会社)

a) 新鮮尿

b) 24 時間尿

18.7.1.10. 血液学的検査

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 (麻酔時刻: 午前 9 時 30 分 – 10 時 57 分，採血時刻: 午前 9 時 38 分 – 11 時 10 分)，以下の血液学的検査を実施した．動物は，動物飼育室から移動後，1 時間以上経過してから採血した．プロトロンビン時間，活性化部分トロンボプラスチン時間及びフィブリノーゲン濃度は，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] して得た血漿を用いて測定した．測定後の残余血液は廃棄した．

項 目	測 定 方 法	使 用 機 器
赤血球数 (RBC)	シースフローDC 検出法	多項目自動血球分析装置 XT-2000iV (シスメックス株式会社)
ヘモグロビン量	SLS ヘモグロビン法	
ヘマトクリット値	赤血球パルス波高値検出法	
血小板数	シースフローDC 検出法	
平均赤血球容積 (MCV)	RBC 及び HCT より算出	
平均赤血球血色素量 (MCH)	RBC 及び HGB より算出	
平均赤血球血色素濃度 (MCHC)	HCT 及び HGB より算出	
白血球数 (WBC)	フローサイトメトリー法	
白血球分類		
網状赤血球比率		
プロトロンビン時間 (PT)	光散乱検出方式	全自動血液凝固測定装置 CA-530 (シスメックス株式会社)
活性化部分トロンボプラスチン時間 (APTT)		
フィブリノーゲン濃度		

18.7.1.11. 血液生化学的検査

血液学的検査用の血液と同時期に腹大動脈から採取した血液を遠心分離 [約 4°C，3000 rpm (約 1972×g)，15 分間，遠心機: CF 8DL，日立工機株式会社] して得た血清は，血液生化学的検査測定用血清 (0.6 mL) 1 本，血中ホルモン測定用血清 (0.3 mL) 3 本及び保管用血清 (0.3 mL) 4 本に分け

て分取した (小分けチューブ: Safe-Lock Tubes，1.5 mL，エッペンドルフ株式会社). 血中ホルモン測定用血清及び保管用血清は冷凍庫内に保管した.

血液生化学的検査測定用血清について，以下の血液生化学的検査を実施し，測定後の残余血清は廃棄した.

項 目	測 定 方 法	使 用 機 器
AST	MDH-UV 法 (JSCC 標準化対応法)	生化学自動分析装置 AU 400 (ベックマン・コールター・バイオメディカル株式会社)
ALT	LDH-UV 法 (JSCC 標準化対応法)	
ALP	p-ニトロフェニルリン酸基質法 (JSCC 標準化対応法)	
γ-GT	L-γ-グルタミル-3-カルボキシ-4-ニトロアニリド基質法 (JSCC 標準化対応法)	
総コレステロール	COD·HDAOS 法	
トリグリセライド	GPO·HDAOS 法 (グリセリン消去法)	
総蛋白	Biuret 法	
尿素窒素	ウレアーゼ·GlDH 法	
クレアチニン	クレアチニナーゼ·F-DAOS 法	
総ビリルビン	BOD 法	
ブドウ糖	ヘキソキナーゼ·G-6-PDH 法	
無機リン	PNP·XDH 法	
カルシウム (Ca)	o-CPC 法	
ナトリウム (Na)	イオン選択電極法	
カリウム (K)	イオン選択電極法	
塩素 (Cl)	イオン選択電極法	

項 目	測 定 方 法	使 用 機 器
アルブミン	蛋白分画値 (電気泳動法) と総蛋白値から算出	–
A/G	蛋白分画値 (電気泳動法)からの 算出	自動電気泳動装置 AES 320 (ベックマン・コールター・ バイオメディカル株式会社)

18.7.1.12. 血中ホルモンの測定

血中ホルモン測定用血清及び保管用血清の保管場所の温度を以下に示した.

サンプル	保管容器	保管場所	温度
血中ホルモン測定用血 清及び保管用血清 (a)	Safe-Lock Tubes, 1.5 mL (エッペンドル フ株式会社)	超低温フリーザー: ULT1786-9JD (Kendro Laboratory Products)	設定: -80°C 許容範囲: -90 – -70°C 実測値: -85 – -75°C

(a) 2010年10月11日 (初回採血日) – 2010年11月16日 (測定終了日)

投与期間終了時剖検例について, トリヨードサイロニン (T3), サイロキシン (T4) 及び甲状腺刺激ホルモン (TSH) を以下の方法で測定した. 二重測定とし, 2 測定値の平均値をその動物の値とした. 測定後の残余血清は廃棄した.

T3, T4及びTSH測定に使用した測定キットは, 使用前に事前評価し, 支障がないことを確認した.

保管用血清及び回復期間終了時剖検例の血中ホルモン測定用血清は, 再測定あるいは他のホルモン測定の必要がないことを確認後, 廃棄した.

項 目	測 定 方 法	使 用 機 器
トリヨードサイロニン (T3)	Mouse/Rat Triiodothyronine (T3) ELISA Kit (Calbiotech, Inc.)	マイクロプレートリーダー (POWERSCAN HT, DSファー マバイオメディカル株式会社) 解析ソフト (KC4, V3.4, DSフ ァーマバイオメディカル株式 会社)
サイロキシン (T4)	Mouse/Rat Thyroxine (T4) ELISA Kit (Calbiotech, Inc.)	
甲状腺刺激ホルモン (TSH)	Rodent TSH ELISA Test Kit (Endocrine Technologies, Inc.)	

18.7.1.13. 剖検及び器官重量の測定

上記の18.7.1.10.及び18.7.1.11.の項で採血した動物をさらに放血して安楽死させた後，剖検した.

雌は，剖検日を含む 4 日間 (1 日 1 回)，膣垢検査により性周期を観察し，剖検日の性周期を決定した.

雌の剖検日の性周期は病理組織学的検査のための参考とし，個別表のみ作成した.

脳，下垂体，唾液腺 (舌下腺，顎下腺)，甲状腺，胸腺，心臓，肝臓，脾臓，腎臓，副腎，精巣，精巣上体, 前立腺腹葉, 精嚢 (凝固腺を含む), 卵巣及び子宮は重量を測定した (電子天秤: AB204, メトラー・トレド株式会社). なお，下垂体及び甲状腺重量は，10 vol%中性緩衝ホルマリンで 1 晩固定後，測定した. 対器官は一括秤量した.

各器官重量を最終体重で除して相対重量も算出した.

18.7.1.14. 病理組織学的検査

心臓，肺，気管，肝臓，膵臓，舌下腺，顎下腺，食道，胃，十二指腸，空腸，回腸 (パイエル板を含む)，盲腸，結腸，直腸，胸腺，脾臓，下顎リンパ節，腸間膜リンパ節，腎臓，膀胱，精巣，精巣上体，前立腺腹葉，精嚢 (凝固腺を含む)，卵巣，子宮，膣，下垂体，副腎，甲状腺 (上皮小体を含む)，大脳，小脳，橋，脊髄，坐骨神経，眼球，ハーダー腺，胸骨 (骨髄を含む)，大腿骨 (骨髄を含む)，大腿直筋及び乳腺は，10 vol%中性緩衝ホルマリンで固定した. ただし，肺及び気管は 10 vol%中性緩衝ホルマリンを注入後，10 vol%中性緩衝ホルマリンに浸漬固定し，精巣及び精巣上体はブアン液で 2 – 3 時間固定後，10 vol%中性緩衝ホルマリンに再固定し，眼球はグルタールアルデヒド・ホルマリンで 1 晩固定後，10 vol%中性緩衝ホルマリンに再固定した.

対照群及び 1000 mg/kg 群の投与期間終了時に剖検した動物について，上記器官・組織の HE 染色組織標本を作製し，病理組織学的検査を実施した.

精巣については，PAS-ヘマトキシリン染色組織標本も作製したが，PAS-ヘマトキシリン染色組織標本での検査は必要ないと判断したため，病理組織学的検査は HE 染色組織標本にて行った.

切り出し後の器官・組織は，10 vol%中性緩衝ホルマリンで保管した.

18.7.2. 交配群雌親

18.7.2.1. 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 (投与後 60 – 138 分) の 1 日 2 回及び剖検日に 1 回行った.

投与期間中に詳細な観察 (FOB) を実施した場合は，詳細な観察 (FOB) 終了後に投与後の一般状態を観察した.

18.7.2.2. 体重

体重は，交配開始前，交配期間中及び交配期間終了後には1週間に2回 [測定日: 投与1，4，8，11，15 (交配開始日) 及び18日，妊娠期間中には妊娠0，7，14及び20日，哺育期間中には哺育0，4及び5日に測定した (電子天秤: PB3002，PG2002-S又はPB3002-S/FACT，メトラー・トレド株式会社).

18.7.2.3. 摂餌量

摂餌量は，交配開始前には 1 週間に 2 回 1 日量 (残量測定日: 投与 2，5，9 及び 12 日)，妊娠期間中には妊娠 2，9，16 及び 20 日に 1 日量，哺育期間中には哺育 2 日に 1 日量を測定した (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.

18.7.2.4. 摂水量

摂水量は，交配開始前には 1 週間に 2 回 1 日量 (残量測定日: 投与 2，5，9 及び 12 日)，妊娠期間中には妊娠 2，9，16 及び 20 日に 1 日量，哺育期間中には哺育 2 日に 1 日量を測定した (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.

18.7.2.5. 詳細な観察 (FOB)

全例について，群分け日，投与 7 及び 14 日，妊娠 1，8 及び 15 日，哺育 4 日に下記の 1) – 3)の項目を観察した．群分け日の観察は，午後 0 時 47 分 – 午後 2 時 51 分までの間に実施した．投与期間中の観察時刻は，投与後約 1 時間 (観察終了時刻: 投与後 61 – 70 分) に実施した．観察者はほぼ固定し，Blind で実施した.

1) 姿勢，眼瞼閉鎖状態，常同行動 (過度の身づくろい，反復旋回運動，噛み付き行動)，間代性痙攣及び強直性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，被毛の状態，粘膜の状態，流涙，流涎，立毛，瞳孔及び呼吸状態は手に持って観察した.
3) 排尿，排便，立ち上がり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，覚醒度，異常行動及び正向反射をオープンフィールド内で観察した.

18.7.2.6. 性周期観察

性周期観察は，投与開始日から交尾確認前日まで 1 日 1 回，膣垢を検査して行った.

18.7.2.7. 分娩状態の観察

母動物は自然分娩させ，分娩状態の異常 (衰弱，多量の出血，出産児の食殺など) の有無及び触診による分娩終了の確認を妊娠 21 日から妊娠 25 日まで 1 日 1 回 (午前 10 時頃) 行った. 午前 10 時頃に分娩が終了していた場合，その日を哺育 0 日とした.

18.7.2.8. 妊娠 25 日までに分娩しなかった雌親の剖検

妊娠 25 日の午前 10 時頃までに分娩しなかった雌親は，体重測定 (電子天秤: PB3002-S/FACT，メトラー・トレド株式会社) 後，ペントバルビタールナトリウム (40 mg/kg) の腹腔内投与による麻酔下で腹大動脈から放血して安楽死させた後に剖検し，妊娠の有無の確認を行った.

着床の認められなかった雌親は不妊動物とした.

膵臓，舌下腺，顎下腺，卵巣，子宮，膣及び乳腺は，10 vol%中性緩衝ホルマリンで固定し，保管した.

雌親の体重は参考値とし，個別表のみ作成した.

18.7.2.9. 哺育状態の観察

哺育状態 (乳頭発達，巣作り行動，授乳行動など) の異常の有無は，哺育 0 から 4 日まで 1 日 1 回観察した.

18.7.2.10.哺育 5 日の母動物の剖検及び器官重量の測定

母動物は, 哺育 5 日にペントバルビタールナトリウム (40 mg/kg) の腹腔内投与による麻酔下で腹大動脈から放血して安楽死させた後に剖検し，妊娠黄体数及び着床数の算定を行った.

卵巣及び子宮は重量を測定した (電子天秤: AB204，メトラー・トレド株式会社). 対器官は一括秤量した.

各器官重量を最終体重で除して相対重量も算出した.

18.7.2.11.哺育 5 日の母動物の病理組織学的検査

膵臓，舌下腺，顎下腺，卵巣，子宮，膣及び乳腺は，10 vol%中性緩衝ホルマリンで固定した.

対照群及び 1000 mg/kg 群の各 6 例 (動物番号の若い順) について，卵巣，子宮，膣及び乳腺の HE 染色組織標本を作製し，病理組織学的検査を実施した.

切り出し後の器官・組織は，10 vol%中性緩衝ホルマリンで保管した.

18.7.3. 親動物の生殖発生検査

2 週間投与された主試験群雄と交配群雌親を同用量群内で動物番号の若い順に 1 対 1 の組み合わせで同居交配させた.

交配期間は14日間を限度とし，交尾確認まで連続同居交配とした．ただし，交配開始後4日以内に全例が交尾した．交尾確認は毎朝ほぼ一定時刻に行い，膣栓又は膣垢内に精子を確認した雌親を交尾動物として，その日を妊娠0日とした.

18.7.4. 児動物

18.7.4.1. 出産時観察

出産時に総出産児数と性，死産児数，新生児数及び外表異常の有無を観察した.

死産児は, 体重を測定し (電子天秤: PB3002-S/FACT, メトラー・トレド株式会社), 剖検後, 10 vol% 中性緩衝ホルマリンで固定し，保管した.

分娩終了の観察時に不明な児動物は，死産児が母動物により喰殺されたものとし，死産児に含めた.

18.7.4.2. 一般状態

死亡の有無の確認及び一般状態の観察は，1 日 1 回行った.

観察時に不明な児動物は, 死亡した児動物が母動物により喰殺されたものとし, 死亡児に含めた.

18.7.4.3. 死亡児動物

死亡児動物は，体重を測定し (電子天秤: PB3002-S/FACT，メトラー・トレド株式会社)，剖検した.

児動物のその日の体重は参考値とし，個別表のみ作成した.

18.7.4.4. 体重

体重は，哺育 0 及び 4 日に測定した (電子天秤: PB3002-S/FACT，メトラー・トレド株式会社).

18.7.4.5. 哺育 4 日剖検

児動物は，哺育 4 日に 20%イソフルランによる麻酔下で腹大動脈から放血して安楽死させた後，剖検した.

18.7.5. 各種データの算出式

交尾率 (%) = (交尾成立動物数/同居動物数) × 100

受胎率 (%) = (受胎雌親数/交尾成立動物数) × 100

出産率 (%) = (新生児出産雌親数/受胎雌親数) × 100

妊娠期間 (日) = 分娩日 (哺育 0 日) − 交尾確認日

着床率 (%) = (着床数/妊娠黄体数) × 100

分娩率 (%) = (総出産児数/着床数) × 100

児の産出率 (%) = (哺育0日の新生児数/着床数) × 100

出生率 (%) = (哺育 0 日の新生児数/総出産児数) × 100

哺育4日の生存率 (%) = (哺育4日の生存児数/哺育0日の新生児数) × 100

性比 = 雄/雌

外表異常の出現率 (%) = (外表異常新生児数/新生児数) × 100

18.8. 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，Bartlett検定[4]及びF検定[4]は 5%，その他の検定は両側 5%及び 1%とした.

一般状態，尿検査での色調，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，剖検所見並びに病理組織学的所見について統計学的解析は行わなかった．不妊雌親の交尾後の一般状態，体重，摂餌量，摂水量及び詳細な観察 (FOB) は集計から除外した．児動物の項目は一腹の平均を 1 単位とし，児動物の体重は一腹の平均値と腹重量値を算出した.

a) 体重，摂餌量，摂水量，詳細な観察 (FOB) における排尿，排便，立ち上がり及び毛づくろい回数，握力，自発運動量，尿量，尿比重，血液学的検査，血液生化学的検査，血中ホルモン濃度 (T3，T4，TSH)，器官重量 (相対重量を含む)，発情回数，交尾所要日数，妊娠期間，妊娠黄体数，着床数，総出産児数，哺育 0 日の新生児数，死産児数及び哺育 4 日の生存児数については，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.

b) 着床率，分娩率，児の産出率，出生率，哺育 4 日の生存率，性比及び外表異常の出現率については，各群で平均値及び標準偏差を算出した.

次に，対照群と各被験物質投与群との間でSteel検定を実施した．

c) 回復期間中の雌の体重，摂餌量，摂水量，尿量，尿比重，血液学的検査，血液生化学的検査及び器官重量 (相対重量を含む) については，F検定により対照群と1000 mg/kg群との間で分散の一様性の検定を実施し，等分散の場合にはStudentのt検定[4]，不等分散の場合にはAspin-Welchのt検定[4]を実施した．

d) 詳細な観察 (FOB) (ただし，排尿，排便，立ち上がり及び毛づくろい回数を除く) 及び感覚応答検査については，各群で平均値及び範囲を算出した．次に，対照群と各被験物質投与群との間でSteel検定を実施した．

e) 交尾率，受胎率及び出産率については，対照群と各被験物質投与群との間でFisherの正確検定[7]を実施した．

Dunnett検定及びSteel検定には，統計パッケージSASのPROBMC関数[8]を使用した．

19. 試験結果

19.1. 反復投与毒性

19.1.1. 一般状態

19.1.1.1. 投与期間中雄 (Table 1; Appendices 1-1 – 1-4)

死亡例又は瀕死例は，いずれの群にも認められなかった．

いずれの群とも，一般状態の異常はみられなかった．

19.1.1.2. 投与期間中雌 (Table 2; Appendices 2-1 – 2-4)

死亡例又は瀕死例は，いずれの群にも認められなかった．

いずれの群とも，一般状態の異常はみられなかった．

19.1.1.3. 回復期間中雄 (Table 1; Appendices 1-1 – 1-4)

死亡例又は瀕死例は，いずれの群にも認められなかった．

いずれの群とも，一般状態の異常はみられなかった．

19.1.1.4. 回復期間中雌 (Table 2; Appendices 2-1 and 2-4)

死亡例又は瀕死例は，いずれの群にも認められなかった．

1000 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．

19.1.1.5. 交配群雌親 (Tables 3, 4, and 5; Appendices 3-1 – 3-4, 4-1 – 4-4, and 5-1 – 5-4)

死亡例，瀕死例，流産例又は早産例は，いずれの群にも認められなかった．

交配開始前及び交配期間中には，いずれの群とも一般状態の異常はみられなかった．

妊娠期間中には，1000 mg/kg 群で投与後に一過性の流涎が 1 例にみられたが，妊娠 15 日にのみ認められたものであることから，被験物質による影響とは考えられない．250 及び 62.5 mg/kg 群並びに対照群では，一般状態の異常はみられなかった．

哺育期間中には，いずれの群とも一般状態の異常はみられなかった．

19.1.2. 体重

19.1.2.1. 投与期間中雄 (Table 6; Fig. 2; Appendices 6-1 – 6-4)

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．

19.1.2.2. 投与期間中雌 (Table 7; Fig. 3; Appendices 7-1 – 7-4)

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.

19.1.2.3. 回復期間中雄 (Table 6; Fig. 2; Appendices 6-1 – 6-4)

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.

19.1.2.4. 回復期間中雌 (Table 7; Fig. 3; Appendices 7-1 and 7-4)

1000 mg/kg群では，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.

19.1.2.5. 交配群雌親 (Tables 8, 9, and 10; Fig. 4; Appendices 8-1 – 8-4, 9-1 – 9-4, and 10-1 – 10-4)

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.

19.1.3. 摂餌量

19.1.3.1. 投与期間中雄 (Table 11; Fig. 5; Appendices 11-1 – 11-4)

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.

19.1.3.2. 投与期間中雌 (Table 12; Fig. 6; Appendices 12-1 – 12-4)

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.

19.1.3.3. 回復期間中雄 (Table 11; Fig. 5; Appendices 11-1 – 11-4)

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.

19.1.3.4. 回復期間中雌 (Table 12; Fig. 6; Appendices 12-1 and 12-4)

1000 mg/kg群では，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.

19.1.3.5. 交配群雌親 (Tables 13, 14, and 15; Fig. 7; Appendices 13-1 – 13-4, 14-1 – 14-4, and 15-1 – 15-4)

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.

19.1.4. 摂水量

19.1.4.1. 投与期間中雄 (Table 16; Fig. 8; Appendices 16-1 – 16-4)

各投与群とも，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.

19.1.4.2. 投与期間中雌 (Table 17; Fig. 9; Appendices 17-1 – 17-4)

各投与群とも，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.

19.1.4.3. 回復期間中雄 (Table 16; Fig. 8; Appendices 16-1 – 16-4)

各投与群とも，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.

19.1.4.4. 回復期間中雌 (Table 17; Fig. 9; Appendices 17-1 and 17-4)

1000 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.

19.1.4.5. 交配群雌親 (Tables 18, 19, and 20; Fig. 10; Appendices 18-1 – 18-4, 19-1 – 19-4, and 20-1 – 20-4)

妊娠期間中には，250 mg/kg群では対照群と比べて妊娠2日に摂水量の有意な低値がみられたが，投与量に依存した変化ではないことから，毒性学的影響とは考えられない.

1000及び62.5 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.

19.1.5. 詳細な観察 (FOB)

19.1.5.1. 雄 (Table 21; Appendices 21-1 – 21-4)

62.5 mg/kg群では，対照群と比べて投与27日に立ち上がり回数の有意な高値がみられたが，一過性の変化であること及び投与量に依存した変化ではないことから，毒性学的影響とは考えられない.

1000及び250 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った.

19.1.5.2. 雌 (Table 22; Appendices 22-1 – 22-4)

各投与群とも，各測定日のいずれの項目にも異常はみられなかった.

19.1.5.3. 交配群雌親 (Table 23; Appendices 23-1 – 23-4)

1000 mg/kg群では，対照群と比べて妊娠15日に立ち上がり回数の有意な低値がみられたが，一過

性の変化であること，その他の観察項目に異常は認められないことから，毒性学的影響とは考えられない.

250及び62.5 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った.

19.1.6. 感覚応答

19.1.6.1. 投与期間終了時雄 (Table 24; Appendices 24-1 – 24-4)

いずれの群とも，各項目に異常はみられなかった.

19.1.6.2. 投与期間終了時雌 (Table 25; Appendices 25-1 – 25-4)

いずれの群とも，各項目に異常はみられなかった.

19.1.7. 握力

19.1.7.1. 投与期間終了時雄 (Table 26; Appendices 26-1 – 26-4)

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った.

19.1.7.2. 投与期間終了時雌 (Table 27; Appendices 27-1 – 27-4)

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った.

19.1.8. 自発運動量

19.1.8.1. 投与期間終了時雄 (Table 28; Appendices 28-1 – 28-4)

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.

19.1.8.2. 投与期間終了時雌 (Table 29; Appendices 29-1 – 29-4)

62.5 mg/kg 群では，対照群と比べて総歩行量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考えられない.

1000 及び 250 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.

19.1.9. 尿検査

19.1.9.1. 投与期間終了時雄 (Table 30; Appendices 30-1 – 30-4)

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.

19.1.9.2. 投与期間終了時雌 (Table 31; Appendices 31-1 – 31-4)

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.

19.1.9.3. 回復期間終了時雄 (Table 32; Appendices 32-1 – 32-4)

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.

19.1.9.4. 回復期間終了時雌 (Table 33; Appendices 33-1 and 33-2)

1000 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.

1000 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.

19.1.10. 血液学的検査

19.1.10.1. 投与期間終了時雄 (Table 34; Appendices 34-1 – 34-4)

1000 mg/kg群では，対照群と比べてプロトロンビン時間の有意な延長がみられた.

1000及び62.5 mg/kg群では，対照群と比べてリンパ球比率の有意な低値及び好中球比率の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試験施設の背景データの範囲 [リンパ球比率: 74.5 ± 7.9 (%)，好中球比率: 21.7 ± 7.1 (%); Attachment 10] 内の変化であることから，被験物質による影響とは考えられない.

250 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.

19.1.10.2. 投与期間終了時雌 (Table 35; Appendices 35-1 – 35-4)

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.

19.1.10.3. 回復期間終了時雄 (Table 36; Appendices 36-1 – 36-4)

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.

19.1.10.4. 回復期間終了時雌 (Table 37; Appendices 37-1 and 37-2)

1000 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.

19.1.11. 血液生化学的検査

19.1.11.1. 投与期間終了時雄 (Table 38; Appendices 38-1 – 38-4)

1000 mg/kg群では，対照群と比べてALTの有意な高値及びトリグリセライドの有意な低値がみられた.

1000 mg/kg群では，対照群と比べて総ビリルビンの有意な低値がみられたが，対照群との差はわずかであること及び試験施設の背景データのほぼ範囲 [総ビリルビン: 0.11 ± 0.01 (mg/dL); Attachment 12] 内の変化であることから，被験物質による影響とは考えられない.

250及び62.5 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.

19.1.11.2. 投与期間終了時雌 (Table 39; Appendices 39-1 – 39-4)

1000及び250 mg/kg群では，対照群と比べてA/Gの有意な高値がみられた.

1000 mg/kg群では，対照群と比べて総ビリルビンの有意な低値がみられたが，対照群との差はわずかであること及び試験施設の背景データのほぼ範囲 [総ビリルビン: 0.11 ± 0.01 (mg/dL); Attachment 13] 内の変化であることから，被験物質による影響とは考えられない.

62.5 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.

19.1.11.3. 回復期間終了時雄 (Table 40; Appendices 40-1 – 40-4)

1000 mg/kg群では，対照群と比べてALTの有意な高値がみられた.

250及び62.5 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.

19.1.11.4. 回復期間終了時雌 (Table 41; Appendices 41-1 and 41-2)

1000 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.

19.1.12. 血中ホルモン濃度

19.1.12.1. 投与期間終了時雄 (Table 42; Appendices 42-1 – 42-4)

各投与群とも，対照群と比べてT3，T4及びTSH濃度に有意差はみられなかった.

19.1.12.2. 投与期間終了時雌 (Table 43; Appendices 43-1 – 43-4)

各投与群とも，対照群と比べてT3，T4及びTSH濃度に有意差はみられなかった.

19.1.13. 剖検所見

19.1.13.1. 投与期間終了時雄 (Table 44; Appendices 44-1 – 44-4)

いずれの群とも，異常はみられなかった.

19.1.13.2. 投与期間終了時雌 (Table 45; Appendices 45-1 – 45-4)

いずれの群とも，異常はみられなかった.

19.1.13.3. 回復期間終了時雄 (Table 46; Appendices 46-1 – 46-4)

いずれの群とも，異常はみられなかった.

19.1.13.4. 回復期間終了時雌 (Table 47; Appendices 47-1 and 47-2)

1000 mg/kg群及び対照群では，異常はみられなかった.

19.1.13.5. 交配群雌親 (Table 48; Appendices 48-1 – 48-4)

いずれの群とも，異常はみられなかった.

19.1.14. 器官重量

19.1.14.1. 投与期間終了時雄 (Table 49; Appendices 49-1 – 49-4)

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.

1000 mg/kg群では，対照群と比べて有意差はないものの，脾臓の絶対重量及び相対重量の低値傾向がみられた．250 mg/kg群では，対照群と比べて脾臓の絶対重量及び相対重量の有意な低値がみられた.

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

19.1.14.2. 投与期間終了時雌 (Table 50; Appendices 50-1 – 50-4)

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.

1000 mg/kg群では，対照群と比べて甲状腺の絶対重量及び相対重量の有意な高値，肝臓の相対重量の有意な高値，有意差はないものの，肝臓の絶対重量の高値傾向がみられた.

62.5 mg/kg群では，対照群と比べて脳の絶対重量の有意な高値がみられたが，投与量に依存した変化ではないことから，被験物質による影響とは考えられない.

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

19.1.14.3. 回復期間終了時雄 (Table 51; Appendices 51-1 – 51-4)

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.

1000 mg/kg群では，対照群と比べて肝臓の相対重量の有意な高値及び絶対重量の高値傾向がみられた.

62.5 mg/kg群では，対照群と比べて心臓の絶対重量の有意な高値がみられたが，投与量に依存した変化ではないことから，被験物質による影響とは考えられない.

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

19.1.14.4. 回復期間終了時雌 (Table 52; Appendices 52-1 and 52-2)

剖検日の体重は，1000 mg/kg群では対照群と比べて有意差はみられなかった.

1000 mg/kg群では，対照群と比べて脾臓の絶対重量及び相対重量の有意な高値がみられたが，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考えられない.

19.1.14.5. 交配群雌親 (Table 53; Appendices 53-1 – 53-4)

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.

各投与群とも，対照群と比べて各器官の絶対重量及び相対重量に有意差はみられなかった.

19.1.15. 病理組織学的所見

19.1.15.1. 投与期間終了時雄 (Table 54; Appendices 54-1 and 54-2)

肺: 片側性の血管壁への鉱質沈着が1000 mg/kg群で1例にみられた.

脾臓: 髄外造血が1000 mg/kg群で1例にみられた.

腎臓: 片側性の尿細管の好塩基性変化が対照群で1例，片側性の嚢胞が対照群で1例にみられた.

眼球: 片側性の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.

その他には，1000 mg/kg群及び対照群では，心臓，気管，肝臓，膵臓，舌下腺，顎下腺，食道，胃，十二指腸，空腸，回腸，パイエル板，盲腸，結腸，直腸，胸腺，下顎リンパ節，腸管膜リン

パ節，膀胱，精巣，精巣上体，前立腺腹葉，精嚢，凝固腺，下垂体，副腎，甲状腺，上皮小体，大脳，小脳，橋，脊髄，坐骨神経，ハーダー腺，胸骨，大腿骨，胸骨骨髄，大腿骨骨髄，大腿直筋及び乳腺に異常はみられなかった．

19.1.15.2. 投与期間終了時雌 (Table 55; Appendices 55-1 and 55-2)

腎臓: 片側性の嚢胞が対照群で1例にみられた．

甲状腺: 異所性胸腺が1000 mg/kg群で1例にみられた．

眼球: 片側性の網膜異形成が1000 mg/kg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．

その他には，1000 mg/kg群及び対照群では，心臓，肺，気管，肝臓，膵臓，舌下腺，顎下腺，食道，胃，十二指腸，空腸，回腸，パイエル板，盲腸，結腸，直腸，胸腺，脾臓，下顎リンパ節，腸管膜リンパ節，膀胱，卵巣，子宮，膣，下垂体，副腎，上皮小体，大脳，小脳，橋，脊髄，坐骨神経，ハーダー腺，胸骨，大腿骨，胸骨骨髄，大腿骨骨髄，大腿直筋及び乳腺に異常はみられなかった．

19.1.15.3. 交配群雌親 (Table 56; Appendices 56-1 and 56-2)

子宮: 嚢胞が対照群で1例にみられた．

その他には，1000 mg/kg群及び対照群では，卵巣，膣及び乳腺に異常はみられなかった．

19.2. 生殖発生毒性

19.2.1. 親動物の生殖発生

19.2.1.1. 発情回数 (Table 57; Appendices 57-1 – 57-4)

各投与群とも，対照群と比べて交配開始前の投与期間 (14日間) の発情回数に有意差はみられなかった．

19.2.1.2. 交尾所要日数，交尾率，受胎雌数及び受胎率 (Table 57; Appendices 57-1 – 57-4)

いずれの群とも全例が交配開始後4日以内に交尾した．交尾率は，いずれの群とも100.0%であった．交尾所要日数は，各投与群とも対照群との間に有意差はみられなかった．

不受胎雌は，250 mg/kg群と対照群で各1例に認められた．受胎率は，各投与群とも対照群との間に有意差はみられなかった．

19.2.1.3. 妊娠期間 (Table 58; Appendices 58-1 – 58-4)

妊娠期間は，各投与群とも対照群と比べて有意差はみられなかった.

19.2.1.4. 妊娠黄体数，着床数及び着床率 (Table 58; Appendices 58-1 – 58-4)

各投与群とも，対照群と比べて妊娠黄体数，着床数及び着床率に有意差はみられなかった.

19.2.1.5. 出産率，分娩状態及び哺育状態 (Tables 58 and 59; Appendices 58-1 – 58-4 and 59-1 – 59-4)

出産率は，いずれの群とも100.0%であった.

分娩状態において，いずれの群とも異常はみられなかった.

哺育状態において，いずれの群とも異常はみられなかった.

19.2.2. 児動物

19.2.2.1. 総出産児数，死産児数，哺育 0 日の新生児数，哺育 0 日の性比，分娩率，児の産出率及び出生率 (Table 58; Appendices 58-1 – 58-4)

各投与群とも，対照群と比べて総出産児数，死産児数，哺育0日の新生児数，哺育0日の性比，分娩率，児の産出率及び出生率に有意差はみられなかった.

19.2.2.2. 児動物の一般状態，哺育 4 日の生存児数，哺育 4 日の性比，哺育 4 日の生存率及び外表異常 (Tables 58 and 60; Appendices 58-1 – 58-4 and 60-1 – 60-4)

各投与群とも，対照群と比べて哺育4日の生存児数，哺育4日の性比及び哺育4日の生存率に有意差はみられなかった.

新生児の外表異常は，いずれの群にもみられなかった.

児動物の一般状態において，いずれの群とも異常はみられなかった.

19.2.2.3. 児動物の体重 (Table 61; Fig. 11; Appendices 61-1 – 61-4)

62.5 mg/kg群では，対照群と比べて哺育0日の雄体重の有意な高値がみられたが，投与量に依存した変化ではないことから，被験物質による影響とは考えられない.

1000及び250 mg/kg群では，対照群と比べて哺育0及び4日の雌雄別平均体重，哺育0及び4日の一腹平均体重，哺育0及び4日の一腹合計体重に有意差はみられなかった.

19.2.2.4. 死産児及び死亡児動物の剖検所見 (Table 62; Appendices 62-1 – 62-4)

いずれの群とも，異常はみられなかった.

19.2.2.5. 児動物の哺育 4 日の剖検所見 (Table 63; Appendices 63-1 – 63-4)

いずれの群とも，異常はみられなかった.

20. 考察

4,4'–ビス (クロロメチル)–1,1'–ビフェニルのラットを用いる経口投与による反復投与毒性・生殖発生毒性併合試験を行い，雌雄動物に対する一般毒性学的影響を検討するとともに，性腺機能，交尾行動，受胎，受胎産物の発達及び分娩などの雌雄動物の生殖行動に及ぼす影響について検討した．投与量は，1000 mg/kg/dayを高用量とし，以下，250 mg/kg/dayを中間用量，62.5 mg/kg/dayを低用量に設定した．

反復投与による毒性については，死亡例又は瀕死例はいずれの群の雄，雌及び雌親にも認められなかった．

一般状態，体重，摂餌量及び摂水量には，雄，雌及び雌親とも被験物質に起因する変化はみられなかった．

詳細な観察 (FOB) には，雄，雌及び雌親とも被験物質に起因する変化はみられなかった．感覚応答，握力及び自発運動量には，投与期間終了時に雌雄とも被験物質に起因する変化はみられなかった．

尿検査には，投与期間終了時及び回復期間終了時に雌雄とも被験物質に起因する変化はみられなかった．

血液学的検査において，投与期間終了時に雄の 1000 mg/kg 群でプロトロンビン時間の有意な延長がみられたが，対照群との差はわずかであること及び試験施設の背景データの範囲 [20.2 ± 3.0 (sec) ; Attachment 10] 内であることから，軽微な変化と考えられる．回復期間終了時には被験物質に起因する変化は認められなかった．

血液生化学的検査において，投与期間終了時に雄の1000 mg/kg群でALTの有意な高値及びトリグリセライドの有意な低値，雌の1000及び250 mg/kg群でA/Gの有意な高値がみられた．また，雌の1000 mg/kg群で肝臓の相対重量の有意な高値及び絶対重量の高値傾向がみられたものの，雌雄の1000 mg/kg群での肝臓の病理組織学的検査において異常は認められないことから，軽微な変化と考えられる．なお，雄の1000 mg/kg群のALT及びトリグリセライド，雌の1000及び250 mg/kg群のA/Gは，試験施設の背景データのほぼ範囲 [雄のALT: 28.1 ± 3.9 (IU/L)，雄のトリグリセライド: 34.2 ± 13.0 (mg/dL); Attachment 12，雌のA/G: 1.33 ± 0.12; Attachment 13] 内であった．回復期間終了時には，雄の1000 mg/kg群でALTの有意な高値，肝臓の相対重量の有意な高値及び絶対重量の高値傾向がみられ，遅延性の肝毒性が生じた可能性がある．雌では，回復期間終了時には被験物質に起因する変化は認められなかった．

血中ホルモン (T3，T4 及び TSH) には，投与期間終了時に雌雄とも被験物質に起因する変化はみられなかった．

剖検において，投与期間終了時に雄，雌及び雌親並びに回復期間終了時に雌雄とも被験物質に起

因する変化はみられなかった.

器官重量において，投与期間終了時に雄の 1000 及び 250 mg/kg 群で脾臓の絶対重量及び相対重量の低値あるいは低値傾向，雌の 1000 mg/kg 群で甲状腺の絶対重量及び相対重量の有意な高値がみられた. 雄の 1000 mg/kg 群での脾臓の病理組織学的検査において異常は認められなかった. また，雌雄の 1000 mg/kg 群での甲状腺の病理組織学的検査において異常は認められないこと，投与期間終了時の T3，T4 及び TSH に影響は認められないこと，試験施設の背景データ [甲状腺絶対重量: 18.6 ± 2.4 (mg)，甲状腺相対重量: 6.9 ± 0.9 (mg%); Attachment 14] に比べてもわずかに高いのみであることから，軽微な変化と考えられる．回復期間終了時には，前述の雄の 1000 mg/kg 群で肝臓の相対重量の有意な高値及び絶対重量の高値傾向がみられたが，雌では被験物質に起因する変化はみられなかった．雌親では，投与期間終了時の器官重量に被験物質に起因する変化はみられなかった.

病理組織学的検査において，投与期間終了時には雄，雌及び雌親とも被験物質に起因する変化はみられなかった.

親動物の生殖発生毒性については，交配開始前の投与期間 (14日間) の発情回数，交尾率，交尾所要日数，受胎雌数，受胎率，妊娠期間，出産率，妊娠黄体数，着床数，着床率，分娩状態及び哺育状態には，被験物質に起因する変化はみられなかった.

児動物については，総出産児数，死産児数，哺育0日の新生児数，分娩率，児の産出率，出生率，性比，哺育4日の生存児数，哺育4日の生存率，一般状態，哺育0及び4日の体重，外表及び剖検所見には，被験物質に起因する変化はみられなかった.

以上のように，4,4'–ビス (クロロメチル) –1,1'–ビフェニルの無影響量は，雄では250 mg/kg投与で脾臓の絶対重量及び相対重量の低値あるいは低値傾向が認められたことから62.5 mg/kg/day，雌では250 mg/kg投与でA/Gの高値が認められたことから62.5 mg/kg/dayと考えられる．生殖発生毒性学的な無影響量は，1000 mg/kg投与で雌雄ともいずれの項目にも影響が認められなかったことから1000 mg/kg/dayと考えられる．児動物への無影響量は，1000 mg/kg投与でいずれの項目にも影響が認められなかったことから1000 mg/kg/dayと考えられる.

21. 文献

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Table 1. General clinical signs in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of males and general clinical 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	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	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	12	12	12
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	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	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	12	12
	250	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	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	12	12
	1000	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	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	12	12

Pre: Before administration, Post: after administration. (Continued)

Table 1. (Continued) General clinical signs in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of males and general clinical signs	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	
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	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	12	12	12	12
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	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	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	12	12	12	12
	250	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	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	12	12	12	12
	1000	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	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	12	12	12	12

Pre: Before administration, Post: after administration.

(Continued)

#: Start of pairing.

*: Day 1 of recovery.

Table 1. (Continued) General clinical signs in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of males and general clinical signs	Days of recovery												
			2	3	4	5	6	7	8	9	10	11	12	13	14	15
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
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	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
	250	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
	1000	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 clinical signs in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of females and general clinical 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	Pre	Post	Pre	Post
Control	0	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		Normal	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	250	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	1000	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		Normal	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Pre: Before administration, Post: after administration.

(Continued)

Table 2. (Continued) General clinical signs in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of females and general clinical signs	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	
Control	0	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		Normal	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	250	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	1000	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		Normal	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Pre: Before administration, Post: after administration.

*: Day 1 of recovery.

(Continued)

Table 2. (Continued) General clinical signs in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of females and general clinical signs	Days of recovery												
			2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control	0	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4,4'-bis(chloromethyl) -1,1'-biphenyl	1000	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Table 3. General clinical signs in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of females and general clinical 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	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	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	12	12	12
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	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	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
	250	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	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
	1000	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	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)

Table 3. (Continued) General clinical signs in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of females and general clinical signs	Days of administration							
			15#		16		17		18	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control	0	Number of females	12	12	9	9	7	7	3	3
		Normal	12	12	9	9	7	7	3	3
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	Number of females	12	12	9	9	8	8	4	4
		Normal	12	12	9	9	8	8	4	4
	250	Number of females	12	12	8	8	4	4	1	1
		Normal	12	12	8	8	4	4	1	1
	1000	Number of females	12	12	10	10	6	6	3	3
		Normal	12	12	10	10	6	6	3	3

Pre: Before administration, Post: after administration.
#: Start of pairing.

Table 4. General clinical signs in parental female rats (mating groups) during pregnancy in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of females and general clinical signs	Days of pregnancy																									
			0		1		2		3		4		5		6		7		8		9		10		11		12	
			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	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
		Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	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
		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
	250	Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
		Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
	1000	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
		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
		Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

(Continued)

Table 4. (Continued) General clinical signs in parental female rats (mating groups) during pregnancy in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of females and general clinical signs	Days of pregnancy																										Total[a)]
			13		14		15		16		17		18		19		20		21		22		23		24		25		
			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	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	1	1	0	0	0	0	0		11
		Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	1	1	-	-	-	-	-		-
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	2	2	0	0	0	0	0		12
		Normal	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	2	2	-	-	-	-	-		-
	250	Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	5	5	0	0	0	0	0		11
		Normal	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	5	5	-	-	-	-	-		-
	1000	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	1	1	0	0	0	0	0		12
		Normal	12	12	12	12	12	11	12	12	12	12	12	12	12	12	12	12	12	12	1	1	-	-	-	-	-		-
		Salivation	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-	-	-	-	-		1

Pre: Before administration, Post: after administration.

a): Number of females showing abnormal signs at least once between Days 0 and 25 of pregnancy.

Table 5. General clinical signs in parental female rats (mating groups) during lactation in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of females and general clinical signs	Days of lactation										
			0		1		2		3		4		5
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Control	0	Number of females	11	11	11	11	11	11	11	11	11	11	11
		Normal	11	11	11	11	11	11	11	11	11	11	11
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	Number of females	12	12	12	12	12	12	12	12	12	12	12
		Normal	12	12	12	12	12	12	12	12	12	12	12
	250	Number of females	11	11	11	11	11	11	11	11	11	11	11
		Normal	11	11	11	11	11	11	11	11	11	11	11
	1000	Number of females	12	12	12	12	12	12	12	12	12	12	12
		Normal	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

Table 6. Body weights of male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	12	12	12	12
Days of administration				
1	343 ± 12	343 ± 11	345 ± 11	343 ± 12
4	357 ± 14	356 ± 14	359 ± 17	355 ± 15
8	373 ± 20	373 ± 18	378 ± 19	374 ± 17
11	385 ± 21	386 ± 22	390 ± 21	386 ± 19
15	397 ± 22	398 ± 24	404 ± 25	396 ± 22
18	407 ± 24	407 ± 28	414 ± 24	407 ± 24
22	421 ± 24	420 ± 29	429 ± 28	422 ± 25
25	429 ± 24	431 ± 27	438 ± 29	430 ± 27
28	436 ± 25	435 ± 27	446 ± 29	436 ± 26
Number of males	6	6	6	6
Days of recovery				
1	425 ± 13	437 ± 25	435 ± 21	429 ± 34
4	439 ± 13	455 ± 24	448 ± 19	445 ± 38
8	452 ± 11	466 ± 22	460 ± 20	455 ± 38
11	463 ± 12	478 ± 21	473 ± 22	466 ± 40
14	471 ± 14	486 ± 20	478 ± 22	470 ± 36

Each value shows mean (g) ± S.D.

Table 7. Body weights of female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	10	5	5	10
Days of administration				
1	238 ± 9	240 ± 4	238 ± 7	236 ± 7
4	246 ± 10	248 ± 9	245 ± 8	244 ± 10
8	250 ± 9	252 ± 12	250 ± 9	250 ± 7
11	257 ± 10	261 ± 8	254 ± 12	255 ± 9
15	263 ± 11	268 ± 10	261 ± 14	262 ± 10
18	270 ± 14	272 ± 11	266 ± 17	264 ± 11
22	274 ± 17	278 ± 11	273 ± 18	270 ± 12
25	276 ± 16	282 ± 9	272 ± 16	274 ± 10
28	278 ± 16	285 ± 14	275 ± 18	278 ± 11
Number of females	5	0	0	5
Days of recovery				
1	282 ± 24	-	-	280 ± 9
4	290 ± 25	-	-	283 ± 8
8	292 ± 23	-	-	286 ± 8
11	294 ± 24	-	-	287 ± 9
14	291 ± 30	-	-	287 ± 11

Each value shows mean (g) ± S.D.

Table 8. Body weights of parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	12	12	12	12
Days of administration				
1	238 ± 11	237 ± 9	236 ± 8	237 ± 8
4	245 ± 12	243 ± 9	242 ± 8	243 ± 11
8	253 ± 13	247 ± 11	248 ± 8	251 ± 12
11	257 ± 15	251 ± 10	256 ± 10	256 ± 11
15	262 ± 15	255 ± 9	259 ± 10	260 ± 13
18	280 ± 14 (3)	266 ± 10 (4)	270 (1)	268 ± 22 (3)

Each value shows mean (g) ± S.D.
Figures in parentheses indicate number of females.

Table 9. Body weights of parental female rats (mating groups) during pregnancy in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	11	12	11	12
Days of pregnancy				
0	273 ± 16	263 ± 13	266 ± 6	267 ± 14
7	313 ± 18	298 ± 13	305 ± 11	300 ± 19
14	349 ± 19	333 ± 12	341 ± 13	336 ± 24
20	420 ± 29	407 ± 22	409 ± 19	412 ± 28

Each value shows mean (g) ± S.D.

Table 10. Body weights of parental female rats (mating groups) during lactation in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	11	12	11	12
Days of lactation				
0	328 ± 27	317 ± 25	324 ± 23	313 ± 39
4	344 ± 14	332 ± 10	340 ± 18	333 ± 30

Each value shows mean (g) ± S.D.

Table 11. Food consumption in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	12	12	12	12
Days of administration				
2	25 ± 4	25 ± 4	24 ± 3	24 ± 4
5	25 ± 3	24 ± 4	25 ± 2	25 ± 3
9	25 ± 3	26 ± 4	27 ± 2	26 ± 3
12	23 ± 2	24 ± 3	23 ± 3	23 ± 4
Number of males	6	6	6	6
Days of recovery				
2	25 ± 2	27 ± 3	26 ± 2	25 ± 3
5	24 ± 4	26 ± 1	25 ± 3	24 ± 2
9	22 ± 2	23 ± 2	24 ± 2	24 ± 2
12	24 ± 2	25 ± 2	24 ± 2	25 ± 2

Each value shows mean (g/day) ± S.D.

Table 12. Food consumption in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	10	5	5	10
Days of administration				
2	18 ± 3	17 ± 2	16 ± 4	15 ± 3
5	17 ± 3	16 ± 3	16 ± 3	16 ± 3
9	19 ± 4	18 ± 2	17 ± 3	18 ± 2
12	17 ± 3	18 ± 3	18 ± 4	19 ± 3
16	18 ± 4	19 ± 4	18 ± 4	19 ± 3
19	19 ± 3	22 ± 3	20 ± 3	19 ± 2
23	18 ± 2	19 ± 3	20 ± 3	19 ± 2
26	17 ± 4	17 ± 2	17 ± 4	15 ± 2
Number of females	5	0	0	5
Days of recovery				
2	16 ± 5	-	-	14 ± 3
5	20 ± 3	-	-	18 ± 4
9	20 ± 4	-	-	19 ± 4
12	19 ± 2	-	-	18 ± 1

Each value shows mean (g/day) ± S.D.

Table 13. Food consumption in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	12	12	12	12
Days of administration				
2	17 ± 2	15 ± 3	16 ± 3	17 ± 3
5	17 ± 2	18 ± 3	16 ± 2	17 ± 2
9	19 ± 3	19 ± 2	18 ± 3	19 ± 2
12	20 ± 3	20 ± 3	18 ± 3	20 ± 3

Each value shows mean (g/day) ± S.D.

Table 14. Food consumption in parental female rats (mating groups) during pregnancy in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	11	12	11	12
Days of pregnancy				
2	24 ± 3	21 ± 4	22 ± 4	22 ± 4
9	22 ± 4	24 ± 3	25 ± 3	24 ± 4
16	25 ± 3	24 ± 2	24 ± 3	24 ± 4
20	23 ± 3	22 ± 3	24 ± 3	24 ± 4

Each value shows mean (g/day) ± S.D.

Table 15. Food consumption in parental female rats (mating groups) during lactation in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	11	12	11	12
Days of lactation 2	27 ± 5	28 ± 7	25 ± 9	27 ± 6

Each value shows mean (g/day) ± S.D.

Table 16. Water consumption in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	12	12	12	12
Days of administration				
2	32 ± 4	32 ± 9	31 ± 7	30 ± 7
5	34 ± 4	34 ± 7	33 ± 6	36 ± 6
9	34 ± 4	33 ± 6	35 ± 4	35 ± 5
12	31 ± 6	34 ± 6	33 ± 5	34 ± 8
Number of males	6	6	6	6
Days of recovery				
2	40 ± 11	36 ± 7	41 ± 5	34 ± 8
5	37 ± 9	34 ± 5	35 ± 7	36 ± 11
9	35 ± 11	32 ± 7	36 ± 10	31 ± 8
12	40 ± 8	35 ± 7	39 ± 11	33 ± 8

Each value shows mean (g/day) ± S.D.

Table 17. Water consumption in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	10	5	5	10
Days of administration				
2	24 ± 4	23 ± 5	22 ± 5	20 ± 5
5	28 ± 6	26 ± 3	24 ± 4	25 ± 7
9	27 ± 6	26 ± 4	23 ± 4	24 ± 3
12	25 ± 4	25 ± 3	26 ± 3	28 ± 3
16	23 ± 5	26 ± 5	24 ± 6	25 ± 5
19	27 ± 4	29 ± 5	28 ± 3	27 ± 3
23	25 ± 3	25 ± 6	27 ± 1	26 ± 3
26	24 ± 7	24 ± 2	25 ± 3	21 ± 7
Number of females	5	0	0	5
Days of recovery				
2	21 ± 7	-	-	24 ± 8
5	27 ± 3	-	-	27 ± 7
9	26 ± 5	-	-	27 ± 4
12	26 ± 5	-	-	31 ± 6

Each value shows mean (g/day) ± S.D.

Table 18. Water consumption in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	12	12	12	12
Days of administration				
2	24 ± 6	21 ± 5	24 ± 4	25 ± 5
5	27 ± 5	26 ± 3	24 ± 5	26 ± 8
9	29 ± 5	27 ± 5	26 ± 7	26 ± 7
12	27 ± 4	27 ± 4	23 ± 7	30 ± 4

Each value shows mean (g/day) ± S.D.

Table 19. Water consumption in parental female rats (mating groups) during pregnancy in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	11	12	11	12
Days of pregnancy				
2	35 ± 5	31 ± 4	28 ± 7 *	33 ± 5
9	31 ± 8	32 ± 6	33 ± 5	35 ± 5
16	40 ± 7	37 ± 4	36 ± 4	42 ± 5
20	39 ± 6	39 ± 8	39 ± 7	40 ± 4

Each value shows mean (g/day) ± S.D.
Significantly different from the control group (*: $p<0.05$ by Dunnett's test).

Table 20. Water consumption in parental female rats (mating groups) during lactation in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	11	12	11	12
Days of lactation 2	44 ± 6	43 ± 11	38 ± 11	44 ± 8

Each value shows mean (g/day) ± S.D.

Table 21. Detailed clinical signs (FOB) in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		12	12	12	12
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)
Excessive grooming	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)
Repetitive circling	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)

Pre: Day of grouping. (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.
Excessive grooming	1: Not observed, 2: observed.
Repetitive circling	1: Not observed, 2: observed.

Table 21. (Continued) Detailed clinical signs (FOB) in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		12	12	12	12
Observation of animals in cages					
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)
Tonic 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)

Pre: Day of grouping. (Continued)

Findings were graded as follows

Biting behavior: 1: Not observed, 2: observed.

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

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

Table 21. (Continued) Detailed clinical signs (FOB) in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		12	12	12	12
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)

Pre: Day of grouping. (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.
Muscle tone	1: Decreased, 2: normal, 3: increased.
Fur conditions	1: Normal, 2: slightly soiled, 3: markedly soiled.

Table 21. (Continued) Detailed clinical signs (FOB) in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		12	12	12	12
Observation of animals on observer's palm					
Mucous membranes	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)
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)	1.0 (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)
Piloerection	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)

Pre: Day of grouping. (Continued)

Findings were graded as follows

Mucous membranes	1: Normal, 2: brown, 3: hemorrhage, 4: swelling.
Lacrimation	1: None, 2: mild, 3: marked.
Salivation	1: None, 2: mild, 3: marked.
Piloerection	1: None, 2: mild, 3: marked.

Table 21. (Continued) Detailed clinical signs (FOB) in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		12	12	12	12
Observation of animals on observer's palm					
Pupil size	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)
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)

Pre: Day of grouping. (Continued)

Findings were graded as follows

Pupil size 1: Mydriasis, 2: normal, 3: miosis.

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

Table 21. (Continued) Detailed clinical signs (FOB) in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		12	12	12	12
Open-field test					
Frequency of urination	Pre	0.4 ± 0.7	0.4 ± 0.9	0.5 ± 1.2	0.0 ± 0.0
Mean ± S.D.	Day 7	0.9 ± 2.3	0.3 ± 0.5	0.2 ± 0.6	0.1 ± 0.3
	Day 14	0.3 ± 0.7	0.3 ± 0.6	0.3 ± 0.5	0.2 ± 0.6
	Day 21	0.5 ± 0.7	0.5 ± 0.7	0.8 ± 1.1	0.3 ± 0.7
	Day 27	0.6 ± 0.5	0.5 ± 1.0	0.3 ± 0.5	0.3 ± 0.5
Frequency of defecation	Pre	1.3 ± 1.8	0.8 ± 1.3	0.8 ± 1.9	1.0 ± 1.5
Mean ± S.D.	Day 7	0.8 ± 1.4	2.1 ± 3.1	0.5 ± 1.7	2.1 ± 3.0
	Day 14	1.1 ± 1.8	1.3 ± 2.7	0.6 ± 1.2	1.3 ± 2.0
	Day 21	0.7 ± 0.9	1.4 ± 1.5	0.8 ± 1.1	0.9 ± 1.4
	Day 27	0.8 ± 1.2	1.5 ± 2.4	0.4 ± 1.0	0.7 ± 1.4
Frequency of rearing	Pre	2.3 ± 2.8	2.4 ± 2.7	2.9 ± 3.4	1.6 ± 2.6
Mean ± S.D.	Day 7	5.0 ± 3.4	4.4 ± 4.3	7.4 ± 4.2	5.1 ± 5.1
	Day 14	3.1 ± 3.1	6.5 ± 4.1	5.6 ± 4.0	2.9 ± 3.5
	Day 21	3.3 ± 3.4	5.1 ± 5.1	2.9 ± 2.7	2.4 ± 3.1
	Day 27	0.8 ± 1.1	3.3 ± 3.4 #	1.9 ± 2.2	2.5 ± 2.5
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	0.0 ± 0.0	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

Pre: Day of grouping. (Continued)

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

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

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

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

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

Table 21. (Continued) Detailed clinical signs (FOB) in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		12	12	12	12
Open-field test					
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)
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)

Pre: Day of grouping. (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.
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, 5: self-biting.

Table 21. (Continued) Detailed clinical signs (FOB) in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		12	12	12	12
Open-field test					
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)

Pre: Day of grouping.
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.

Table 22. Detailed clinical signs (FOB) in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		10	5	5	10
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)
Excessive grooming	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)
Repetitive circling	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)

Pre: Day of grouping.

(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.
Excessive grooming	1: Not observed, 2: observed.
Repetitive circling	1: Not observed, 2: observed.

Table 22. (Continued) Detailed clinical signs (FOB) in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		10	5	5	10
Observation of animals in cages					
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)
Tonic 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)

Pre: Day of grouping. (Continued)

Findings were graded as follows

Biting behavior: 1: Not observed, 2: observed.

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

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

Table 22. (Continued) Detailed clinical signs (FOB) in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		10	5	5	10
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)

Pre: Day of grouping. (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.
Muscle tone	1: Decreased, 2: normal, 3: increased.
Fur conditions	1: Normal, 2: slightly soiled, 3: markedly soiled.

Table 22. (Continued) Detailed clinical signs (FOB) in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		10	5	5	10
Observation of animals on observer's palm					
Mucous membranes	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)
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)	1.0 (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)
Piloerection	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)

Pre: Day of grouping. (Continued)

Findings were graded as follows

Mucous membranes	1: Normal, 2: brown, 3: hemorrhage, 4: swelling.
Lacrimation	1: None, 2: mild, 3: marked.
Salivation	1: None, 2: mild, 3: marked.
Piloerection	1: None, 2: mild, 3: marked.

Table 22. (Continued) Detailed clinical signs (FOB) in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		10	5	5	10
Observation of animals on observer's palm					
Pupil size	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)
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)

Pre: Day of grouping. (Continued)

Findings were graded as follows

Pupil size: 1: Mydriasis, 2: normal, 3: miosis.

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

Table 22. (Continued) Detailed clinical signs (FOB) in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		10	5	5	10
Open-field test					
Frequency of urination	Pre	0.1 ± 0.3	0.2 ± 0.4	0.4 ± 0.5	0.2 ± 0.4
Mean ± S.D.	Day 7	0.1 ± 0.3	0.6 ± 0.9	0.0 ± 0.0	0.1 ± 0.3
	Day 14	0.2 ± 0.4	0.8 ± 0.8	0.6 ± 0.9	0.4 ± 0.7
	Day 21	0.4 ± 0.5	0.4 ± 0.9	0.8 ± 1.3	0.0 ± 0.0
	Day 27	0.5 ± 0.7	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 0.8
Frequency of defecation	Pre	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.4	0.0 ± 0.0
Mean ± S.D.	Day 7	0.1 ± 0.3	0.2 ± 0.4	0.2 ± 0.4	0.3 ± 0.9
	Day 14	0.0 ± 0.0	0.0 ± 0.0	0.4 ± 0.9	0.0 ± 0.0
	Day 21	0.3 ± 0.9	0.0 ± 0.0	0.4 ± 0.9	0.0 ± 0.0
	Day 27	0.0 ± 0.0	0.0 ± 0.0	0.4 ± 0.9	0.0 ± 0.0
Frequency of rearing	Pre	7.5 ± 4.5	6.8 ± 5.0	6.8 ± 4.0	5.2 ± 3.0
Mean ± S.D.	Day 7	7.4 ± 5.9	4.2 ± 1.8	7.4 ± 5.2	5.6 ± 3.5
	Day 14	6.1 ± 5.9	7.6 ± 1.1	6.2 ± 4.9	4.6 ± 3.9
	Day 21	4.8 ± 3.5	5.8 ± 3.1	3.6 ± 2.3	7.1 ± 3.3
	Day 27	4.3 ± 5.3	6.2 ± 2.8	3.2 ± 4.5	4.2 ± 3.2
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	0.1 ± 0.3
	Day 21	0.0 ± 0.0	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

Pre: Day of grouping.

(Continued)

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

Table 22. (Continued) Detailed clinical signs (FOB) in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		10	5	5	10
Open-field test					
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)
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)

Pre: Day of grouping. (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.
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, 5: self-biting.

Table 22. (Continued) Detailed clinical signs (FOB) in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		10	5	5	10
Open-field test					
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)

Pre: Day of grouping.
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.

Table 23. Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
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)	
	Pregnancy 1	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 8	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 15	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Lactation 4	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping. (Continued)

Figures in brackets indicate number of females.

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.

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
Observation of animals in cages									
Excessive grooming	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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
Repetitive circling	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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping. (Continued)

Figures in brackets indicate number of females.

Findings were graded as follows

Excessive grooming 1: Not observed, 2: observed.

Repetitive circling 1: Not observed, 2: observed.

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
Observation of animals in cages									
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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping. (Continued)

Figures in brackets indicate number of females.

Findings were graded as follows

Biting behavior 1: Not observed, 2: observed.

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

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
Observation of animals in cages									
Tonic 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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping.

(Continued)

Figures in brackets indicate number of females.

Findings were graded as follows

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

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
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)	
	Pregnancy 1	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 8	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 15	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Lactation 4	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	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)	
	Pregnancy 1	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 8	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 15	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Lactation 4	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	

Pre: Day of grouping. (Continued)

Figures in brackets indicate number of females.

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.

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
Observation of animals on observer's palm									
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)	
	Pregnancy 1	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 8	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 15	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Lactation 4	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping. (Continued)

Figures in brackets indicate number of females.

Findings were graded as follows

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

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

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
Observation of animals on observer's palm									
Mucous membranes	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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping.

(Continued)

Figures in brackets indicate number of females.

Findings were graded as follows

Mucous membranes 1: Normal, 2: brown, 3: hemorrhage, 4: swelling.

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

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
Observation of animals on observer's palm									
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)		1.0 (1)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.1 (1-2)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
Piloerection	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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping. (Continued)

Figures in brackets indicate number of females.

Findings were graded as follows

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

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

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
Observation of animals on observer's palm									
Pupil size	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)	
	Pregnancy 1	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 8	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 15	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Lactation 4	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping. (Continued)

Figures in brackets indicate number of females.

Findings were graded as follows

Pupil size 1: Mydriasis, 2: normal, 3: miosis.

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

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		12	12	12	12
Open-field test					
Frequency of urination	Pre	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3
Mean ± S.D.	Day 7	0.1 ± 0.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Day 14	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.6	0.0 ± 0.0
	Pregnancy 1	0.4 ± 0.7 [11]	0.2 ± 0.6	0.1 ± 0.3 [11]	0.0 ± 0.0
	Pregnancy 8	0.1 ± 0.3 [11]	0.2 ± 0.6	0.1 ± 0.3 [11]	0.1 ± 0.3
	Pregnancy 15	0.0 ± 0.0 [11]	0.1 ± 0.3	0.3 ± 0.6 [11]	0.1 ± 0.3
	Lactation 4	0.0 ± 0.0 [11]	0.0 ± 0.0	0.2 ± 0.4 [11]	0.0 ± 0.0
Frequency of defecation	Pre	0.8 ± 1.9	0.8 ± 1.6	0.0 ± 0.0	0.1 ± 0.3
Mean ± S.D.	Day 7	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.0
	Day 14	0.1 ± 0.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Pregnancy 1	0.4 ± 1.2 [11]	0.7 ± 2.3	0.1 ± 0.3 [11]	0.3 ± 0.9
	Pregnancy 8	0.1 ± 0.3 [11]	0.2 ± 0.6	0.1 ± 0.3 [11]	0.0 ± 0.0
	Pregnancy 15	0.0 ± 0.0 [11]	0.1 ± 0.3	0.0 ± 0.0 [11]	0.0 ± 0.0
	Lactation 4	0.1 ± 0.3 [11]	0.1 ± 0.3	0.0 ± 0.0 [11]	0.0 ± 0.0

Pre: Day of grouping.

(Continued)

Figures in brackets indicate number of females.

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

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

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		12	12	12	12
Open-field test					
Frequency of rearing	Pre	5.6 ± 3.9	4.8 ± 3.8	6.4 ± 3.2	5.8 ± 4.0
Mean ± S.D.	Day 7	9.3 ± 2.3	7.1 ± 2.9	7.4 ± 2.9	6.5 ± 3.8
	Day 14	8.4 ± 4.4	7.8 ± 3.7	7.8 ± 4.1	7.8 ± 4.2
	Pregnancy 1	5.5 ± 3.4 [11]	6.9 ± 3.6	6.6 ± 3.5 [11]	4.1 ± 3.3
	Pregnancy 8	6.5 ± 3.7 [11]	6.7 ± 4.8	6.8 ± 4.7 [11]	5.2 ± 3.4
	Pregnancy 15	6.2 ± 3.4 [11]	6.2 ± 3.4	5.0 ± 3.3 [11]	2.9 ± 2.4 *
	Lactation 4	9.2 ± 3.5 [11]	10.1 ± 6.1	8.2 ± 5.2 [11]	8.7 ± 4.3
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	0.2 ± 0.6
	Day 14	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Pregnancy 1	0.0 ± 0.0 [11]	0.0 ± 0.0	0.1 ± 0.3 [11]	0.0 ± 0.0
	Pregnancy 8	0.0 ± 0.0 [11]	0.0 ± 0.0	0.0 ± 0.0 [11]	0.0 ± 0.0
	Pregnancy 15	0.0 ± 0.0 [11]	0.0 ± 0.0	0.0 ± 0.0 [11]	0.0 ± 0.0
	Lactation 4	0.0 ± 0.0 [11]	0.0 ± 0.0	0.0 ± 0.0 [11]	0.1 ± 0.3

Pre: Day of grouping. (Continued)

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

Figures in brackets indicate number of females.

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

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

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
Open-field test									
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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping. (Continued)

Figures in brackets indicate number of females.

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.

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
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)	
	Pregnancy 1	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 8	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Pregnancy 15	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	2.0 (2)	
	Lactation 4	2.0 (2)	[11]	2.0 (2)		2.0 (2)	[11]	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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping. (Continued)

Figures in brackets indicate number of females.

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, 5: self-biting.

Table 23. (Continued) Detailed clinical signs (FOB) in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control		4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg		0		62.5		250		1000	
Number of females		12		12		12		12	
Open-field test									
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)	
	Pregnancy 1	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 8	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Pregnancy 15	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	
	Lactation 4	1.0 (1)	[11]	1.0 (1)		1.0 (1)	[11]	1.0 (1)	

Pre: Day of grouping.
Figures in brackets indicate number of females.
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.

Table 24. Sensory reactivity of male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Pupillary reflex				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
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: Pupils completely dilated, 2: normal pupillary contraction observed, 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 25. Sensory reactivity of female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	5	5	5	5
Pupillary reflex				
Mean (range)	2.0 (2)	2.0 (2)	2.0 (2)	2.0 (2)
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: Pupils completely dilated, 2: normal pupillary contraction observed, 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 26. Grip strength of male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Forelimb	1685 ± 217	1548 ± 181	1644 ± 310	1747 ± 222
Hindlimb	275 ± 98	273 ± 112	298 ± 200	283 ± 85

Each value shows mean (g) ± S.D.

Table 27. Grip strength of female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	5	5	5	5
Forelimb	1025 ± 78	955 ± 47	1031 ± 74	922 ± 78
Hindlimb	301 ± 45	296 ± 49	292 ± 47	278 ± 9

Each value shows mean (g) ± S.D.

Table 28. Spontaneous motor activity of male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Ambulatory counts				
Minutes after administration				
70	400 ± 172	488 ± 338	378 ± 164	412 ± 104
80	292 ± 146	421 ± 293	262 ± 147	375 ± 228
90	106 ± 108	307 ± 273	215 ± 144	211 ± 239
100	188 ± 79	123 ± 139	129 ± 150	158 ± 263
110	61 ± 96	119 ± 157	96 ± 111	78 ± 153
120	32 ± 32	85 ± 110	2 ± 4	145 ± 165
Total	1078 ± 269	1543 ± 888	1080 ± 477	1378 ± 951
Vertical counts				
Minutes after administration				
70	45 ± 19	54 ± 30	45 ± 24	43 ± 17
80	34 ± 15	37 ± 31	23 ± 17	28 ± 18
90	12 ± 11	24 ± 20	21 ± 10	16 ± 19
100	20 ± 7	10 ± 10	11 ± 13	14 ± 22
110	8 ± 11	10 ± 14	7 ± 9	7 ± 13
120	4 ± 4	7 ± 6	0 ± 1	12 ± 13
Total	122 ± 24	141 ± 74	107 ± 51	121 ± 87

Each value shows mean ± S.D.

Table 29. Spontaneous motor activity of female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	5	5	5	5
Ambulatory counts				
Minutes after administration				
70	406 ± 50	604 ± 320	605 ± 191	412 ± 192
80	263 ± 182	527 ± 116	468 ± 251	226 ± 191
90	113 ± 105	357 ± 327	221 ± 209	101 ± 139
100	32 ± 70	187 ± 239	59 ± 113	193 ± 258
110	250 ± 170	338 ± 239	140 ± 236	220 ± 208
120	118 ± 116	179 ± 91	125 ± 145	181 ± 69
Total	1183 ± 366	2191 ± 626 *	1620 ± 732	1333 ± 324
Vertical counts				
Minutes after administration				
70	47 ± 9	55 ± 13	64 ± 11	36 ± 8
80	31 ± 21	45 ± 23	48 ± 21	25 ± 23
90	20 ± 25	32 ± 27	20 ± 17	14 ± 23
100	4 ± 6	17 ± 20	7 ± 14	20 ± 24
110	19 ± 11	25 ± 19	12 ± 17	24 ± 20
120	14 ± 13	17 ± 10	9 ± 13	21 ± 14
Total	135 ± 61	191 ± 45	161 ± 43	140 ± 63

Each value shows mean ± S.D.

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

Table 30. Urinary findings in male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Volume (mL): Mean ± S.D.	14.7 ± 4.8	21.4 ± 10.5	17.9 ± 8.6	18.5 ± 6.2
Specific gravity: Mean ± S.D.	1.049 ± 0.007	1.037 ± 0.015	1.044 ± 0.018	1.039 ± 0.010
Color				
Light yellow	6	6	6	6
pH				
7.5	0	0	0	2
8.0	1	1	1	0
8.5	5	5	5	4
Protein				
Trace	0	1	1	0
30 mg/dL	5	3	4	6
100 mg/dL	1	2	1	0
Glucose				
Negative	6	6	6	6
Ketone body				
Negative	0	0	1	0
Trace	1	3	1	2
Slight	5	3	4	4
Bilirubin				
Negative	6	5	6	6
Slight	0	1	0	0
Occult blood				
Negative	5	5	4	4
Trace	1	1	2	2
Urobilinogen				
0.1 E.U./dL	6	5	6	6
1.0 E.U./dL	0	1	0	0

(Continued)

Table 30. (Continued) Urinary findings in male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
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	2	4	4	3
Observed	4	2	2	3

Table 31. Urinary findings in female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	5	5	5	5
Volume (mL): Mean ± S.D.	9.8 ± 3.7	11.6 ± 6.7	12.8 ± 4.7	15.0 ± 8.6
Specific gravity: Mean ± S.D.	1.047 ± 0.012	1.046 ± 0.014	1.042 ± 0.015	1.035 ± 0.014
Color				
Light yellow	5	5	5	5
pH				
7.0	0	1	0	0
7.5	0	1	0	0
8.0	0	0	1	0
8.5	4	3	0	2
≥9.0	1	0	4	3
Protein				
Negative	4	2	3	1
Trace	1	2	2	1
30 mg/dL	0	1	0	3
Glucose				
Negative	5	5	5	5
Ketone body				
Negative	5	4	5	3
Trace	0	1	0	1
Slight	0	0	0	1
Bilirubin				
Negative	5	5	5	5
Occult blood				
Negative	5	4	5	4
Trace	0	1	0	1
Urobilinogen				
0.1 E.U./dL	5	5	5	5

(Continued)

Table 31. (Continued) Urinary findings in female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	5	5	5	5
Urinary sediments				
Epithelial cells				
0-20 cells/100 fields	5	5	5	5
Erythrocytes				
0-20 cells/100 fields	5	5	5	5
Leukocytes				
0-20 cells/100 fields	5	5	5	5
Casts				
Not observed	5	5	5	5
Crystals				
Not observed	5	4	4	3
Observed	0	1	1	2

Table 32. Urinary findings in male rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Volume (mL): Mean ± S.D.	13.0 ± 3.4	14.6 ± 5.4	14.7 ± 7.6	13.1 ± 6.4
Specific gravity: Mean ± S.D.	1.045 ± 0.011	1.048 ± 0.014	1.043 ± 0.011	1.055 ± 0.016
Color				
Light yellow	6	6	6	6
pH				
8.5	3	5	2	3
≥9.0	3	1	4	3
Protein				
Negative	0	1	0	0
Trace	1	1	1	1
30 mg/dL	0	2	2	4
100 mg/dL	5	2	3	1
Glucose				
Negative	6	6	6	6
Ketone body				
Negative	0	1	1	0
Trace	0	2	3	1
Slight	5	2	2	5
Moderate	1	1	0	0
Bilirubin				
Negative	6	6	6	6
Occult blood				
Negative	5	3	6	4
Trace	1	2	0	2
Marked	0	1	0	0
Urobilinogen				
0.1 E.U./dL	4	6	5	5
1.0 E.U./dL	2	0	1	1

(Continued)

Table 32. (Continued) Urinary findings in male rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
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	5	6	6
21-100 cells/100fields	0	1	0	0
Leukocytes				
0-20 cells/100 fields	6	6	6	6
Casts				
Not observed	6	6	6	6
Crystals				
Not observed	3	3	1	5
Observed	3	3	5	1

Table 33. Urinary findings in female rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl
mg/kg	0	1000
Number of females	5	5
Volume (mL): Mean ± S.D.	9.9 ± 3.2	16.0 ± 8.5
Specific gravity: Mean ± S.D.	1.049 ± 0.018	1.032 ± 0.007
Color		
Light yellow	5	5
pH		
7.5	0	1
8.0	1	1
8.5	4	3
Protein		
Negative	0	2
Trace	4	2
30 mg/dL	1	1
Glucose		
Negative	5	5
Ketone body		
Negative	4	4
Trace	1	1
Bilirubin		
Negative	5	5
Occult blood		
Negative	5	5
Urobilinogen		
0.1 E.U./dL	5	5

(Continued)

Table 33. (Continued) Urinary findings in female rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl
mg/kg	0	1000
Number of females	5	5
Urinary sediments		
Epithelial cells		
0-20 cells/100 fields	5	5
Erythrocytes		
0-20 cells/100 fields	5	5
Leukocytes		
0-20 cells/100 fields	5	5
Casts		
Not observed	5	5
Crystals		
Not observed	5	4
Observed	0	1

Table 34. Hematological findings in male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
RBC	(10^4/μL)	815 ± 25	811 ± 33	823 ± 25	811 ± 27
Hemoglobin	(g/dL)	15.1 ± 0.3	15.4 ± 0.6	15.4 ± 0.4	15.2 ± 0.7
Hematocrit	(%)	42.0 ± 0.9	42.9 ± 1.5	42.2 ± 0.9	42.1 ± 1.6
MCV	(fL)	51.6 ± 0.9	52.9 ± 0.7	51.4 ± 1.1	51.9 ± 1.6
MCH	(pg)	18.6 ± 0.3	19.0 ± 0.3	18.7 ± 0.5	18.8 ± 0.7
MCHC	(g/dL)	36.0 ± 0.2	35.9 ± 0.5	36.4 ± 0.4	36.2 ± 0.3
Platelet	(10^4/μL)	111.2 ± 9.4	108.5 ± 6.6	116.1 ± 14.6	114.4 ± 8.1
Reticulocyte	(%)	3.21 ± 0.28	2.93 ± 0.23	3.06 ± 0.35	3.15 ± 0.45
PT	(sec.)	17.6 ± 1.9	18.5 ± 1.3	19.0 ± 3.3	21.8 ± 3.6 *
APTT	(sec.)	21.6 ± 1.7	21.3 ± 1.5	21.6 ± 1.1	22.4 ± 1.1
Fibrinogen	(mg/dL)	197.0 ± 9.5	195.7 ± 7.9	198.4 ± 6.8	194.3 ± 6.3
WBC	(10^2/μL)	75.4 ± 10.9	61.1 ± 16.2	79.2 ± 12.9	58.8 ± 22.8
Differential leukocyte (%)					
Lymphocyte		80.9 ± 2.0	72.2 ± 6.3 *	76.1 ± 5.2	70.4 ± 6.4 **
Neutrophil		15.8 ± 1.9	24.4 ± 5.7 *	20.0 ± 5.5	26.0 ± 6.7 **
Eosinophil		1.4 ± 0.5	1.2 ± 0.6	1.3 ± 0.5	1.1 ± 0.5
Basophil		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0
Monocyte		2.0 ± 0.7	2.2 ± 0.5	2.6 ± 0.6	2.5 ± 0.9

Each value shows mean ± S.D.

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

Table 35. Hematological findings in female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		5	5	5	5
RBC	(10^4/μL)	757 ± 40	747 ± 44	762 ± 22	749 ± 41
Hemoglobin	(g/dL)	14.5 ± 0.5	14.0 ± 1.1	14.4 ± 0.6	14.1 ± 0.7
Hematocrit	(%)	39.7 ± 1.2	38.7 ± 3.1	39.7 ± 1.7	39.1 ± 1.5
MCV	(fL)	52.5 ± 2.5	51.8 ± 2.4	52.2 ± 2.5	52.2 ± 1.9
MCH	(pg)	19.2 ± 0.8	18.7 ± 0.8	18.9 ± 1.0	18.9 ± 0.5
MCHC	(g/dL)	36.5 ± 0.3	36.1 ± 0.5	36.2 ± 0.9	36.1 ± 0.5
Platelet	(10^4/μL)	108.4 ± 10.4	116.7 ± 28.1	103.9 ± 7.8	110.4 ± 7.4
Reticulocyte	(%)	2.84 ± 0.38	3.12 ± 0.56	3.04 ± 0.76	3.15 ± 0.26
PT	(sec.)	14.9 ± 0.6	15.0 ± 0.7	14.4 ± 0.6	14.7 ± 0.4
APTT	(sec.)	16.7 ± 0.4	16.7 ± 0.9	16.7 ± 1.0	16.6 ± 0.7
Fibrinogen	(mg/dL)	175.7 ± 10.0	188.8 ± 33.0	167.8 ± 10.3	156.0 ± 13.5
WBC	(10^2/μL)	32.0 ± 8.9	49.4 ± 14.2	36.1 ± 9.2	35.4 ± 18.8
Differential leukocyte (%)					
Lymphocyte		77.3 ± 5.3	78.4 ± 6.1	76.4 ± 5.4	77.7 ± 3.0
Neutrophil		18.2 ± 3.9	17.6 ± 6.0	19.4 ± 4.4	18.1 ± 1.9
Eosinophil		2.0 ± 0.7	1.7 ± 0.6	1.6 ± 0.6	1.5 ± 0.8
Basophil		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Monocyte		2.5 ± 1.2	2.3 ± 0.4	2.6 ± 1.0	2.7 ± 1.1

Each value shows mean ± S.D.

Table 36. Hematological findings in male rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
RBC	(10^4/μL)	813 ± 25	815 ± 26	813 ± 31	839 ± 37
Hemoglobin	(g/dL)	14.8 ± 0.7	14.8 ± 0.5	14.7 ± 0.4	15.1 ± 0.3
Hematocrit	(%)	41.0 ± 1.8	41.0 ± 1.1	40.8 ± 0.9	41.7 ± 0.6
MCV	(fL)	50.4 ± 1.7	50.3 ± 1.3	50.3 ± 2.0	49.8 ± 2.4
MCH	(pg)	18.2 ± 0.6	18.2 ± 0.4	18.2 ± 0.9	18.0 ± 0.6
MCHC	(g/dL)	36.1 ± 0.5	36.2 ± 0.3	36.1 ± 0.5	36.2 ± 0.5
Platelet	(10^4/μL)	113.0 ± 14.1	114.5 ± 6.0	110.1 ± 11.0	116.8 ± 9.0
Reticulocyte	(%)	3.66 ± 0.36	3.63 ± 0.79	3.20 ± 0.36	3.29 ± 0.12
PT	(sec.)	18.8 ± 3.0	19.3 ± 3.1	19.9 ± 2.0	18.4 ± 2.4
APTT	(sec.)	21.3 ± 1.7	20.9 ± 2.0	21.7 ± 1.0	21.8 ± 1.0
Fibrinogen	(mg/dL)	192.3 ± 13.9	197.9 ± 13.4	197.9 ± 5.3	193.3 ± 8.2
WBC	(10^2/μL)	77.1 ± 10.6	69.6 ± 15.3	63.3 ± 21.4	61.5 ± 10.8
Differential leukocyte (%)					
Lymphocyte		75.6 ± 8.8	71.6 ± 8.5	78.6 ± 5.2	76.6 ± 4.5
Neutrophil		20.5 ± 8.9	23.6 ± 7.8	17.2 ± 5.2	18.9 ± 4.3
Eosinophil		1.3 ± 0.7	1.5 ± 0.4	1.7 ± 0.3	1.8 ± 0.7
Basophil		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Monocyte		2.7 ± 0.4	3.3 ± 1.0	2.5 ± 0.8	2.7 ± 0.5

Each value shows mean ± S.D.

Table 37. Hematological findings in female rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl
mg/kg		0	1000
Number of females		5	5
RBC	(10^4/μL)	781 ± 25	795 ± 31
Hemoglobin	(g/dL)	14.8 ± 0.2	14.8 ± 0.6
Hematocrit	(%)	40.7 ± 1.0	40.9 ± 1.8
MCV	(fL)	52.1 ± 1.7	51.5 ± 1.2
MCH	(pg)	19.0 ± 0.5	18.7 ± 0.3
MCHC	(g/dL)	36.5 ± 0.5	36.3 ± 0.5
Platelet	(10^4/μL)	110.8 ± 3.4	124.0 ± 13.9
Reticulocyte	(%)	2.66 ± 0.40	2.70 ± 0.24
PT	(sec.)	14.8 ± 0.6	14.9 ± 0.9
APTT	(sec.)	17.0 ± 1.0	17.4 ± 0.7
Fibrinogen	(mg/dL)	168.3 ± 14.6	167.0 ± 15.7
WBC	(10^2/μL)	34.6 ± 5.9	37.4 ± 7.4
Differential leukocyte (%)			
Lymphocyte		78.7 ± 5.5	74.7 ± 5.5
Neutrophil		17.0 ± 5.6	20.4 ± 5.7
Eosinophil		1.7 ± 0.6	1.9 ± 0.6
Basophil		0.0 ± 0.0	0.0 ± 0.0
Monocyte		2.6 ± 0.3	3.0 ± 0.8

Each value shows mean ± S.D.

Table 38. Clinical biochemistry findings in male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
AST	(IU/L)	73.7 ± 9.9	70.6 ± 7.7	70.2 ± 4.8	80.8 ± 9.4
ALT	(IU/L)	26.7 ± 3.9	27.7 ± 3.5	26.2 ± 2.9	32.1 ± 4.2 *
ALP	(IU/L)	375.7 ± 94.8	377.6 ± 79.2	352.1 ± 44.4	397.4 ± 43.5
γ-GT	(IU/L)	0.43 ± 0.18	0.44 ± 0.08	0.50 ± 0.07	0.50 ± 0.14
Total protein	(g/dL)	5.58 ± 0.19	5.65 ± 0.18	5.64 ± 0.20	5.56 ± 0.09
Albumin	(g/dL)	2.89 ± 0.13	3.00 ± 0.15	2.93 ± 0.17	2.96 ± 0.09
A/G		1.07 ± 0.07	1.14 ± 0.14	1.09 ± 0.12	1.15 ± 0.07
Total bilirubin	(mg/dL)	0.11 ± 0.01	0.10 ± 0.01	0.11 ± 0.01	0.09 ± 0.01 **
Urea nitrogen	(mg/dL)	16.7 ± 1.9	17.6 ± 2.7	16.9 ± 2.0	15.7 ± 1.4
Creatinine	(mg/dL)	0.26 ± 0.01	0.27 ± 0.02	0.27 ± 0.02	0.26 ± 0.03
Glucose	(mg/dL)	127.9 ± 6.3	132.2 ± 11.4	130.7 ± 17.0	131.1 ± 5.6
Total cholesterol	(mg/dL)	57.2 ± 5.8	54.7 ± 12.6	47.8 ± 9.1	47.3 ± 8.7
Triglyceride	(mg/dL)	56.4 ± 21.7	42.0 ± 17.0	32.6 ± 8.2	28.5 ± 6.4 #
Na	(mEq/L)	144.3 ± 0.4	144.2 ± 0.9	143.4 ± 0.8	144.6 ± 0.4
K	(mEq/L)	3.99 ± 0.17	3.96 ± 0.23	3.96 ± 0.16	4.03 ± 0.16
Cl	(mEq/L)	105.8 ± 1.3	106.9 ± 1.1	105.4 ± 1.6	106.5 ± 1.3
Ca	(mg/dL)	9.9 ± 0.2	9.9 ± 0.3	10.0 ± 0.3	9.8 ± 0.2
Inorganic phosphorus	(mg/dL)	8.1 ± 0.3	7.6 ± 0.5	7.6 ± 0.4	8.0 ± 0.3

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 39. Clinical biochemistry findings in female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		5	5	5	5
AST	(IU/L)	70.9 ± 9.8	77.6 ± 12.4	78.0 ± 14.7	74.4 ± 12.6
ALT	(IU/L)	23.5 ± 1.3	29.0 ± 6.8	24.8 ± 4.3	24.6 ± 10.1
ALP	(IU/L)	210.1 ± 57.0	236.4 ± 19.6	178.4 ± 40.7	223.3 ± 159.4
γ-GT	(IU/L)	0.68 ± 0.15	1.00 ± 0.34	0.67 ± 0.15	0.65 ± 0.14
Total protein	(g/dL)	6.16 ± 0.42	5.97 ± 0.15	6.30 ± 0.60	6.37 ± 0.25
Albumin	(g/dL)	3.45 ± 0.27	3.36 ± 0.26	3.71 ± 0.35	3.83 ± 0.16
A/G		1.27 ± 0.05	1.30 ± 0.18	1.43 ± 0.07 #	1.50 ± 0.05 #
Total bilirubin	(mg/dL)	0.12 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.10 ± 0.01 *
Urea nitrogen	(mg/dL)	18.3 ± 2.7	17.2 ± 3.0	17.6 ± 3.4	15.8 ± 2.0
Creatinine	(mg/dL)	0.37 ± 0.05	0.38 ± 0.04	0.35 ± 0.03	0.34 ± 0.02
Glucose	(mg/dL)	114.0 ± 7.2	117.6 ± 12.2	116.0 ± 14.7	112.5 ± 10.0
Total cholesterol	(mg/dL)	68.3 ± 16.9	70.6 ± 6.1	59.5 ± 23.1	57.9 ± 7.6
Triglyceride	(mg/dL)	23.1 ± 12.2	24.4 ± 6.2	23.7 ± 13.3	22.1 ± 5.6
Na	(mEq/L)	142.4 ± 0.9	142.7 ± 0.4	143.1 ± 0.9	142.9 ± 1.3
K	(mEq/L)	3.92 ± 0.24	3.82 ± 0.32	3.76 ± 0.42	4.03 ± 0.22
Cl	(mEq/L)	108.7 ± 0.8	107.6 ± 0.8	107.2 ± 1.5	107.8 ± 1.5
Ca	(mg/dL)	9.8 ± 0.2	9.9 ± 0.1	10.1 ± 0.3	10.0 ± 0.1
Inorganic phosphorus	(mg/dL)	6.0 ± 0.7	6.2 ± 0.9	6.3 ± 0.7	5.3 ± 0.8

Each value shows mean ± S.D.
Significantly different from the control group (#: $p<0.05$ by Steel's test).
Significantly different from the control group (*: $p<0.05$ by Dunnett's test).

Table 40. Clinical biochemistry findings in male rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
AST	(IU/L)	91.6 ± 19.5	90.3 ± 7.1	82.0 ± 11.3	98.0 ± 11.6
ALT	(IU/L)	25.5 ± 1.7	29.6 ± 2.8	28.4 ± 4.4	33.7 ± 4.1 **
ALP	(IU/L)	359.5 ± 31.8	379.7 ± 31.6	364.6 ± 50.0	312.9 ± 40.4
γ-GT	(IU/L)	0.60 ± 0.18	0.66 ± 0.20	0.55 ± 0.11	0.57 ± 0.11
Total protein	(g/dL)	5.49 ± 0.21	5.53 ± 0.06	5.56 ± 0.11	5.49 ± 0.20
Albumin	(g/dL)	2.82 ± 0.10	2.84 ± 0.14	2.83 ± 0.11	2.80 ± 0.08
A/G		1.07 ± 0.11	1.05 ± 0.09	1.04 ± 0.09	1.05 ± 0.14
Total bilirubin	(mg/dL)	0.11 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.11 ± 0.01
Urea nitrogen	(mg/dL)	15.0 ± 1.5	14.8 ± 2.1	15.7 ± 2.3	15.1 ± 0.9
Creatinine	(mg/dL)	0.29 ± 0.04	0.29 ± 0.03	0.30 ± 0.04	0.28 ± 0.03
Glucose	(mg/dL)	95.5 ± 7.4	103.0 ± 9.9	100.3 ± 2.4	99.7 ± 13.1
Total cholesterol	(mg/dL)	50.7 ± 5.6	50.5 ± 7.8	56.6 ± 8.5	49.7 ± 7.0
Triglyceride	(mg/dL)	30.5 ± 13.4	36.6 ± 14.7	37.6 ± 6.3	38.4 ± 18.0
Na	(mEq/L)	143.7 ± 0.4	143.2 ± 1.2	143.5 ± 0.8	143.3 ± 1.2
K	(mEq/L)	4.27 ± 0.23	4.42 ± 0.15	4.29 ± 0.12	4.50 ± 0.21
Cl	(mEq/L)	107.6 ± 1.0	106.5 ± 1.0	107.5 ± 1.1	106.5 ± 1.6
Ca	(mg/dL)	9.4 ± 0.1	9.6 ± 0.2	9.5 ± 0.2	9.6 ± 0.2
Inorganic phosphorus	(mg/dL)	7.3 ± 0.8	7.9 ± 0.3	7.3 ± 0.5	8.2 ± 1.1

Each value shows mean ± S.D.

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

Table 41. Clinical biochemistry findings in female rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl
mg/kg		0	1000
Number of females		5	5
AST	(IU/L)	68.9 ± 8.8	73.5 ± 10.3
ALT	(IU/L)	23.4 ± 4.2	25.5 ± 3.6
ALP	(IU/L)	189.1 ± 64.0	163.8 ± 46.6
γ-GT	(IU/L)	0.50 ± 0.12	0.52 ± 0.16
Total protein	(g/dL)	6.66 ± 0.45	6.47 ± 0.36
Albumin	(g/dL)	3.93 ± 0.43	3.64 ± 0.19
A/G		1.44 ± 0.18	1.29 ± 0.09
Total bilirubin	(mg/dL)	0.13 ± 0.00	0.12 ± 0.01
Urea nitrogen	(mg/dL)	17.4 ± 2.0	15.8 ± 1.5
Creatinine	(mg/dL)	0.39 ± 0.02	0.35 ± 0.04
Glucose	(mg/dL)	111.9 ± 16.4	104.3 ± 11.8
Total cholesterol	(mg/dL)	74.2 ± 7.8	61.4 ± 14.4
Triglyceride	(mg/dL)	23.4 ± 11.8	20.3 ± 7.9
Na	(mEq/L)	141.6 ± 1.1	142.8 ± 0.9
K	(mEq/L)	3.98 ± 0.23	3.99 ± 0.25
Cl	(mEq/L)	107.7 ± 0.9	106.8 ± 1.4
Ca	(mg/dL)	10.0 ± 0.3	10.1 ± 0.2
Inorganic phosphorus	(mg/dL)	5.3 ± 0.7	5.7 ± 0.6

Each value shows mean ± S.D.

Table 42. Hormone concentrations in the serum of male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
T3	(ng/mL)	1.093 ± 0.095	1.177 ± 0.094	1.134 ± 0.130	1.089 ± 0.099
T4	(ng/mL)	41.1 ± 4.9	45.8 ± 4.4	46.1 ± 3.5	42.8 ± 3.9
TSH	(ng/mL)	0.800 ± 0.363	0.928 ± 0.521	0.983 ± 0.248	0.696 ± 0.199

Each value shows mean ± S.D.

Table 43. Hormone concentrations in the serum of female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		5	5	5	5
T3	(ng/mL)	1.082 ± 0.115	1.141 ± 0.235	1.118 ± 0.206	1.048 ± 0.191
T4	(ng/mL)	33.8 ± 0.5	32.2 ± 5.5	32.4 ± 4.2	33.6 ± 9.5
TSH	(ng/mL)	0.531 ± 0.450	0.389 ± 0.159	0.454 ± 0.499	0.934 ± 0.407

Each value shows mean ± S.D.

Table 44. Gross necropsy findings in male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Findings				
Normal	6	6	6	6

Table 45. Gross necropsy findings in female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	5	5	5	5
Findings				
Normal	5	5	5	5

Table 46. Gross necropsy findings in male rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of males	6	6	6	6
Findings				
Normal	6	6	6	6

Table 47. Gross necropsy findings in female rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl
mg/kg	0	1000
Number of females	5	5
Findings		
Normal	5	5

Table 48. Gross necropsy findings in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females on Day 5 of lactation	11	12	11	12
Findings				
Normal	11	12	11	12
Number of non-pregnant females	1	0	1	0
Findings				
Normal	1	-	1	-

Table 49. Organ weights of male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
Body weight	(g)	423 ± 26	412 ± 30	434 ± 28	418 ± 11
Brain	(g)	2.00 ± 0.06	2.09 ± 0.08	2.06 ± 0.05	2.04 ± 0.05
	(g%)	0.48 ± 0.03	0.51 ± 0.03	0.48 ± 0.04	0.49 ± 0.01
Pituitary	(mg)	14.6 ± 1.3	14.0 ± 2.2	14.6 ± 2.2	14.0 ± 1.5
	(mg%)	3.5 ± 0.4	3.4 ± 0.3	3.4 ± 0.4	3.4 ± 0.3
Salivary glands	(mg)	647 ± 48	683 ± 72	631 ± 55	677 ± 71
	(mg%)	153 ± 13	166 ± 15	146 ± 18	162 ± 14
Thyroids	(mg)	20.7 ± 1.4	20.8 ± 5.8	25.0 ± 4.9	24.4 ± 4.1
	(mg%)	4.9 ± 0.5	5.1 ± 1.7	5.8 ± 1.0	5.9 ± 1.0
Thymus	(mg)	361 ± 110	295 ± 50	374 ± 75	326 ± 67
	(mg%)	86 ± 27	71 ± 11	87 ± 18	78 ± 17
Heart	(g)	1.29 ± 0.13	1.27 ± 0.16	1.33 ± 0.08	1.27 ± 0.05
	(g%)	0.31 ± 0.04	0.31 ± 0.02	0.31 ± 0.02	0.30 ± 0.01
Liver	(g)	11.16 ± 1.03	11.10 ± 1.45	12.03 ± 1.10	11.75 ± 0.81
	(g%)	2.64 ± 0.13	2.69 ± 0.23	2.77 ± 0.13	2.82 ± 0.21
Spleen	(mg)	840 ± 62	717 ± 133	700 ± 69 *	709 ± 90
	(mg%)	200 ± 24	173 ± 24	161 ± 13 *	170 ± 22
Kidneys	(g)	2.82 ± 0.10	2.70 ± 0.32	2.73 ± 0.24	2.78 ± 0.17
	(g%)	0.67 ± 0.04	0.65 ± 0.03	0.64 ± 0.09	0.67 ± 0.04
Adrenals	(mg)	70.9 ± 6.0	60.5 ± 10.9	62.5 ± 15.3	59.6 ± 6.2
	(mg%)	16.8 ± 1.3	14.6 ± 2.0	14.4 ± 3.3	14.3 ± 1.4
Testes	(g)	3.23 ± 0.27	3.01 ± 0.30	3.23 ± 0.34	3.16 ± 0.24
	(g%)	0.77 ± 0.10	0.73 ± 0.05	0.75 ± 0.10	0.76 ± 0.05
Epididymides	(mg)	1183 ± 59	1091 ± 69	1078 ± 131	1071 ± 80
	(mg%)	281 ± 21	265 ± 6	249 ± 35	257 ± 18
Ventral prostate	(mg)	651 ± 69	546 ± 100	664 ± 117	564 ± 152
	(mg%)	155 ± 20	132 ± 23	153 ± 25	135 ± 35
Seminal vesicles	(g)	1.86 ± 0.13	1.84 ± 0.36	1.84 ± 0.41	1.91 ± 0.27
	(g%)	0.44 ± 0.04	0.45 ± 0.08	0.43 ± 0.10	0.46 ± 0.07

Each value shows mean ± S.D.

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

Table 50. Organ weights of female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		5	5	5	5
Body weight	(g)	259 ± 10	269 ± 13	258 ± 17	255 ± 6
Brain	(g)	1.90 ± 0.03	1.99 ± 0.04 #	1.89 ± 0.10	1.89 ± 0.09
	(g%)	0.73 ± 0.02	0.74 ± 0.05	0.73 ± 0.02	0.74 ± 0.04
Pituitary	(mg)	18.3 ± 1.5	20.9 ± 1.9	19.6 ± 3.8	19.5 ± 3.6
	(mg%)	7.1 ± 0.4	7.8 ± 0.9	7.5 ± 1.1	7.6 ± 1.2
Salivary glands	(mg)	399 ± 34	422 ± 35	409 ± 60	409 ± 43
	(mg%)	154 ± 7	157 ± 8	158 ± 20	160 ± 14
Thyroids	(mg)	16.7 ± 1.5	18.6 ± 2.8	19.2 ± 2.2	21.6 ± 3.0 *
	(mg%)	6.5 ± 0.6	7.0 ± 1.3	7.4 ± 0.8	8.5 ± 1.1 *
Thymus	(mg)	402 ± 100	349 ± 62	307 ± 81	351 ± 147
	(mg%)	155 ± 32	129 ± 19	118 ± 28	137 ± 56
Heart	(g)	0.81 ± 0.08	0.88 ± 0.06	0.87 ± 0.09	0.86 ± 0.07
	(g%)	0.31 ± 0.02	0.33 ± 0.03	0.34 ± 0.01	0.34 ± 0.02
Liver	(g)	6.66 ± 0.62	7.32 ± 0.45	7.33 ± 1.13	7.72 ± 1.02
	(g%)	2.57 ± 0.18	2.73 ± 0.22	2.83 ± 0.29	3.02 ± 0.35 *
Spleen	(mg)	536 ± 13	598 ± 184	506 ± 72	539 ± 93
	(mg%)	208 ± 6	224 ± 77	195 ± 17	211 ± 33
Kidneys	(g)	1.76 ± 0.18	1.82 ± 0.07	1.84 ± 0.10	1.85 ± 0.13
	(g%)	0.68 ± 0.07	0.68 ± 0.05	0.71 ± 0.04	0.72 ± 0.04
Adrenals	(mg)	70.7 ± 14.2	74.9 ± 4.2	71.9 ± 7.7	64.6 ± 10.0
	(mg%)	27.4 ± 5.8	28.0 ± 2.4	27.8 ± 1.7	25.3 ± 3.6
Ovaries	(mg)	80.9 ± 10.8	79.0 ± 11.4	83.0 ± 13.8	80.5 ± 9.7
	(mg%)	31.4 ± 4.8	29.5 ± 4.7	32.2 ± 5.4	31.6 ± 3.7
Uterus	(mg)	532 ± 159	621 ± 173	559 ± 169	647 ± 116
	(mg%)	205 ± 56	230 ± 58	218 ± 74	254 ± 46

Each value shows mean ± S.D.

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

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

Table 51. Organ weights of male rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of males		6	6	6	6
Body weight	(g)	443 ± 13	455 ± 22	449 ± 19	441 ± 35
Brain	(g)	2.08 ± 0.09	2.07 ± 0.09	2.06 ± 0.06	2.05 ± 0.07
	(g%)	0.47 ± 0.03	0.46 ± 0.02	0.46 ± 0.02	0.47 ± 0.04
Pituitary	(mg)	15.9 ± 2.1	15.4 ± 1.6	14.7 ± 1.3	15.6 ± 1.2
	(mg%)	3.6 ± 0.5	3.4 ± 0.2	3.3 ± 0.3	3.5 ± 0.3
Salivary glands	(mg)	707 ± 51	687 ± 70	687 ± 111	696 ± 31
	(mg%)	160 ± 15	151 ± 19	153 ± 26	159 ± 14
Thyroids	(mg)	22.5 ± 4.4	23.0 ± 4.9	22.9 ± 7.1	23.0 ± 3.6
	(mg%)	5.1 ± 1.0	5.1 ± 1.1	5.1 ± 1.5	5.3 ± 1.1
Thymus	(mg)	364 ± 48	367 ± 34	355 ± 64	339 ± 48
	(mg%)	82 ± 11	81 ± 10	79 ± 18	77 ± 6
Heart	(g)	1.35 ± 0.10	1.50 ± 0.08 *	1.37 ± 0.10	1.33 ± 0.12
	(g%)	0.30 ± 0.02	0.33 ± 0.01	0.31 ± 0.04	0.30 ± 0.02
Liver	(g)	10.25 ± 0.54	11.36 ± 0.90	10.92 ± 0.72	11.46 ± 1.59
	(g%)	2.32 ± 0.09	2.50 ± 0.14	2.43 ± 0.13	2.60 ± 0.20 *
Spleen	(mg)	798 ± 62	795 ± 136	791 ± 117	751 ± 91
	(mg%)	181 ± 16	174 ± 26	177 ± 29	171 ± 21
Kidneys	(g)	2.78 ± 0.14	2.87 ± 0.18	2.81 ± 0.15	2.96 ± 0.28
	(g%)	0.63 ± 0.03	0.63 ± 0.05	0.63 ± 0.05	0.68 ± 0.06
Adrenals	(mg)	58.4 ± 5.0	58.6 ± 12.8	53.9 ± 5.5	60.0 ± 13.0
	(mg%)	13.2 ± 1.2	12.8 ± 2.5	12.0 ± 1.3	13.5 ± 2.1
Testes	(g)	3.19 ± 0.28	3.23 ± 0.20	3.21 ± 0.19	3.28 ± 0.17
	(g%)	0.72 ± 0.05	0.71 ± 0.03	0.72 ± 0.06	0.75 ± 0.07
Epididymides	(mg)	1241 ± 73	1200 ± 50	1234 ± 35	1172 ± 85
	(mg%)	280 ± 11	264 ± 8	275 ± 16	268 ± 35
Ventral prostate	(mg)	694 ± 95	590 ± 76	598 ± 74	700 ± 139
	(mg%)	157 ± 20	131 ± 20	133 ± 17	158 ± 21
Seminal vesicles	(g)	2.13 ± 0.41	2.14 ± 0.34	2.19 ± 0.43	1.90 ± 0.45
	(g%)	0.48 ± 0.08	0.48 ± 0.09	0.49 ± 0.09	0.43 ± 0.11

Each value shows mean ± S.D.

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

Table 52. Organ weights of female rats on termination of recovery period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl	
mg/kg		0	1000	
Number of females		5	5	
Body weight	(g)	276 ± 25	267 ± 9	
Brain	(g)	1.93 ± 0.07	1.98 ± 0.05	
	(g%)	0.70 ± 0.07	0.74 ± 0.02	
Pituitary	(mg)	20.0 ± 2.0	18.9 ± 2.7	
	(mg%)	7.2 ± 0.6	7.1 ± 1.1	
Salivary glands	(mg)	441 ± 27	446 ± 25	
	(mg%)	160 ± 14	167 ± 6	
Thyroids	(mg)	21.7 ± 1.8	21.0 ± 3.2	
	(mg%)	7.9 ± 0.5	7.8 ± 1.1	
Thymus	(mg)	269 ± 59	333 ± 75	
	(mg%)	99 ± 28	125 ± 32	
Heart	(g)	0.88 ± 0.09	0.90 ± 0.07	
	(g%)	0.32 ± 0.03	0.34 ± 0.03	
Liver	(g)	7.01 ± 0.97	7.08 ± 0.60	
	(g%)	2.53 ± 0.17	2.64 ± 0.15	
Spleen	(mg)	472 ± 46	575 ± 41	$$
	(mg%)	171 ± 19	216 ± 20	$$
Kidneys	(g)	1.82 ± 0.13	1.86 ± 0.11	
	(g%)	0.66 ± 0.04	0.69 ± 0.04	
Adrenals	(mg)	65.6 ± 9.6	71.9 ± 7.6	
	(mg%)	23.8 ± 3.8	26.9 ± 2.5	
Ovaries	(mg)	85.5 ± 14.2	90.7 ± 15.3	
	(mg%)	31.3 ± 6.4	34.0 ± 5.9	
Uterus	(mg)	524 ± 108	553 ± 94	
	(mg%)	189 ± 27	206 ± 29	

Each value shows mean ± S.D.

Significantly different from the control group ($$: $p<0.01$ by Student's t-test).

Table 53. Organ weights of parental female rats (mating groups) on Day 5 of lactation in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group		Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg		0	62.5	250	1000
Number of females		11	12	11	12
Body weight	(g)	310 ± 16	303 ± 12	307 ± 17	299 ± 27
Ovaries	(mg)	114.9 ± 14.2	115.9 ± 13.3	113.1 ± 9.4	115.6 ± 13.8
	(mg%)	37.1 ± 4.2	38.4 ± 4.9	36.9 ± 2.7	38.8 ± 4.8
Uterus	(mg)	682 ± 108	659 ± 53	611 ± 110	638 ± 103
	(mg%)	221 ± 41	218 ± 17	200 ± 39	214 ± 32

Each value shows mean ± S.D.

Table 54. Histopathological findings in male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control						4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg	0						1000					
Grade	N[a)]	A[b)]	±	+	2+	3+	N[a)]	A[b)]	±	+	2+	3+
Findings												
Heart	[6][c)]						[6]					
Lung	[6]						[6]					
Mineralization, vascular wall, lateral	6	0	0	0	0	0	5	1	1	0	0	0
Trachea	[6]						[6]					
Liver	[6]						[6]					
Pancreas	[6]						[6]					
Sublingual gland	[6]						[6]					
Submandibular gland	[6]						[6]					
Esophagus	[6]						[6]					
Stomach	[6]						[6]					
Duodenum	[6]						[6]					
Jejunum	[6]						[6]					
Ileum	[6]						[6]					
Peyer's patch	[6]						[6]					
Cecum	[6]						[6]					
Colon	[6]						[6]					
Rectum	[6]						[6]					
Thymus	[6]						[6]					
Spleen	[6]						[6]					
Hematopoiesis, extramedullary	6	0	0	0	0	0	5	1	1	0	0	0
Mandibular lymph node	[6]						[6]					
Mesenteric lymph node	[6]						[6]					
Kidney	[6]						[6]					
Basophilic change, renale tubule, lateral	5	1	1	0	0	0	6	0	0	0	0	0
Cyst, lateral	5	1	1	0	0	0	6	0	0	0	0	0
Urinary bladder	[6]						[6]					

a): No abnormality detected. (Continued)

b): Abnormality detected.

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

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

Table 54. (Continued) Histopathological findings in male rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control						4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg	0						1000					
Grade	N[a)]	A[b)]	±	+	2+	3+	N[a)]	A[b)]	±	+	2+	3+
Findings												
Testis	[6][c)]						[6]					
Epididymis	[6]						[6]					
Ventral prostate	[6]						[6]					
Seminal vesicle	[6]						[6]					
Coagulating gland	[6]						[6]					
Pituitary	[6]						[6]					
Adrenal	[6]						[6]					
Thyroid	[6]						[6]					
Parathyroid	[6]						[6]					
Cerebrum	[6]						[6]					
Cerebellum	[6]						[6]					
Pons	[6]						[6]					
Spinal cord	[6]						[6]					
Sciatic nerve	[6]						[6]					
Eyeball	[6]						[6]					
Retinal dysplasia, lateral	5	1	1	0	0	0	6	0	0	0	0	0
Harderian gland	[6]						[6]					
Sternal bone	[6]						[6]					
Femoral bone	[6]						[6]					
Sternal bone marrow	[6]						[6]					
Femoral bone marrow	[6]						[6]					
Muscle (rectus femoris)	[6]						[6]					
Mammary gland	[6]						[6]					

a): No abnormality detected.
b): Abnormality detected.
c): Number in brackets is number of males examined.
Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Table 55. Histopathological findings in female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control						4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg	0						1000					
Grade	N[a)]	A[b)]	±	+	2+	3+	N[a)]	A[b)]	±	+	2+	3+
Findings												
Heart	[5][c)]						[5]					
Lung	[5]						[5]					
Trachea	[5]						[5]					
Liver	[5]						[5]					
Pancreas	[5]						[5]					
Sublingual gland	[5]						[5]					
Submandibular gland	[5]						[5]					
Esophagus	[5]						[5]					
Stomach	[5]						[5]					
Duodenum	[5]						[5]					
Jejunum	[5]						[5]					
Ileum	[5]						[5]					
Peyer's patch	[5]						[5]					
Cecum	[5]						[5]					
Colon	[5]						[5]					
Rectum	[5]						[5]					
Thymus	[5]						[5]					
Spleen	[5]						[5]					
Mandibular lymph node	[5]						[5]					
Mesenteric lymph node	[5]						[5]					
Kidney	[5]						[5]					
Cyst, lateral	4	1	1	0	0	0	5	0	0	0	0	0
Urinary bladder	[5]						[5]					

a): No abnormality detected. (Continued)

b): Abnormality detected.

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

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

Table 55. (Continued) Histopathological findings in female rats on termination of administration period in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control						4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg	0						1000					
Grade	N[a)]	A[b)]	±	+	2+	3+	N[a)]	A[b)]	±	+	2+	3+
Findings												
Ovary	[5][c)]						[5]					
Uterus	[5]						[5]					
Vagina	[5]						[5]					
Pituitary	[5]						[5]					
Adrenal	[5]						[5]					
Thyroid	[5]						[5]					
Ectopic, thymic tissue	5	0	0	0	0	0	4	1	1	0	0	0
Parathyroid	[5]						[5]					
Cerebrum	[5]						[5]					
Cerebellum	[5]						[5]					
Pons	[5]						[5]					
Spinal cord	[5]						[5]					
Sciatic nerve	[5]						[5]					
Eyeball	[5]						[5]					
Retinal dysplasia, lateral	5	0	0	0	0	0	4	1	1	0	0	0
Harderian gland	[5]						[5]					
Sternal bone	[5]						[5]					
Femoral bone	[5]						[5]					
Sternal bone marrow	[5]						[5]					
Femoral bone marrow	[5]						[5]					
Muscle (rectus femoris)	[5]						[5]					
Mammary gland	[5]						[5]					

a): No abnormality detected.
b): Abnormality detected.
c): Number in brackets is number of females examined.
Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Table 56. Histopathological findings in parental female rats (mating groups) on Day 5 of lactation in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control						4,4'-bis(chloromethyl)-1,1'-biphenyl					
mg/kg	0						1000					
Grade	N[a)]	A[b)]	±	+	2+	3+	N[a)]	A[b)]	±	+	2+	3+
Findings												
Ovary	[6][c)]						[6]					
Uterus	[6]						[6]					
Cyst	5	1	1	0	0	0	6	0	0	0	0	0
Vagina	[6]						[6]					
Mammary gland	[6]						[6]					

a): No abnormality detected.
b): Abnormality detected.
c): Number in brackets is number of females examined.
Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Table 57. Reproductive performance of parental male and female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of females	12	12	12	12
Number of estrous cases before pairing (14 days) (Mean ± S.D.)	3.3 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	3.4 ± 0.5
Number of pairs	12	12	12	12
Number of pairs with successful copulation	12	12	12	12
Copulation index (%) [a)]	100.0	100.0	100.0	100.0
Number of conceiving days				
Mean ± S.D.	2.6 ± 1.2	2.8 ± 1.2	2.1 ± 1.0	2.6 ± 1.1
Conceiving days 1-5	12	12	12	12
Conceiving days ≧6	0	0	0	0
Number of pregnant females	11	12	11	12
Fertility index (%) [b)]	91.7	100.0	91.7	100.0

a): (Number of pairs with successful copulation/number of pairs)×100.

b): (Number of pregnant females/number of pairs with successful copulation)×100.

Table 58. Observation of pups in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of dams	11	12	11	12
Length of gestation (days)	22.1 ± 0.3	22.2 ± 0.4	22.5 ± 0.5	22.1 ± 0.3
Pregnancy days = 21	0	0	0	0
Pregnancy days = 22	10	10	6	11
Pregnancy days ≧ 23	1	2	5	1
Corpora lutea	15.5 ± 2.0	15.8 ± 2.0	14.2 ± 2.8	15.8 ± 1.6
Implantation scars	14.5 ± 2.0	14.7 ± 1.8	12.5 ± 3.4	14.6 ± 1.2
Implantation index (%) [a]	93.6 ± 5.7	92.8 ± 5.7	86.7 ± 13.9	92.9 ± 5.4
Gestation index (%) [b]	100.0	100.0	100.0	100.0
Pups born	13.5 ± 2.9	13.2 ± 2.9	12.0 ± 3.8	14.0 ± 1.3
Stillbirths	0.3 ± 0.6	0.3 ± 0.6	0.1 ± 0.3	0.1 ± 0.3
Live pups born	13.2 ± 2.9	12.9 ± 2.8	11.9 ± 3.8	13.9 ± 1.3
Sex ratio at birth [c]	0.91 ± 0.42	1.32 ± 0.89	0.85 ± 0.52	1.56 ± 1.20
(Total male/total female)	67/78	81/74	59/72	92/75
Delivery index (%) [d]	91.8 ± 13.3	88.8 ± 12.6	94.8 ± 7.7	96.1 ± 6.4
Birth index (%) [e]	90.0 ± 13.3	87.2 ± 12.0	94.1 ± 7.5	95.5 ± 6.3
Live birth index (%) [f]	98.1 ± 4.6	98.4 ± 4.1	99.2 ± 2.5	99.4 ± 1.9
Live pups on Day 4 of lactation	13.2 ± 2.9	12.8 ± 2.8	11.7 ± 3.7	13.8 ± 1.3
Sex ratio on Day 4 of lactation [c]	0.91 ± 0.42	1.33 ± 0.90	0.88 ± 0.56	1.59 ± 1.23
(Total male/total female)	67/78	80/73	59/70	91/74
Viability index (%) [g]	100.0 ± 0.0	98.8 ± 2.9	98.7 ± 2.8	98.9 ± 2.7
External abnormalities (%) [h]	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

Each value shows mean ± S.D. per dam.

a): (Number of implantation scars/number of corpora lutea)×100.
b): (Number of dams having live pups/number of pregnant dams)×100.
c): Number of male pups/number of female pups.
d): (Number of pups born/number of implantation scars)×100.
e): (Number of live pups born/number of implantation scars)×100.
f): (Number of live pups born/number of pups born)×100.
g): (Number of live pups on Day 4 of lactation/number of live pups born)×100.
h): (Number of pups with external abnormalities/number of live pups)×100.

Table 59. Delivery conditions and nursing conditions of dams in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of dams and delivery conditions/nursing conditions	Delivery conditions	Nursing conditions				
				Days of lactation				
				0	1	2	3	4
Control	0	Number of dams	11	11	11	11	11	11
		Normal	11	11	11	11	11	11
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	Number of dams	12	12	12	12	12	12
		Normal	12	12	12	12	12	12
	250	Number of dams	11	11	11	11	11	11
		Normal	11	11	11	11	11	11
	1000	Number of dams	12	12	12	12	12	12
		Normal	12	12	12	12	12	12

Table 60. General clinical signs in pups in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	mg/kg	Number of punps and general clinical signs	Days of lactation				
			0	1	2	3	4
Control	0	Number of pups	148	145	145	145	145
		Normal	145	145	145	145	145
		Death	3	0	0	0	0
4,4'-bis(chloromethyl) -1,1'-biphenyl	62.5	Number of pups	158	155	153	153	153
		Normal	155	153	153	153	153
		Death	3	2	0	0	0
	250	Number of pups	132	131	131	131	129
		Normal	131	131	131	129	129
		Death	1	0	0	2	0
	1000	Number of pups	168	167	166	166	165
		Normal	167	166	166	165	165
		Death	1	1	0	1	0

Table 61. Body weights of pups in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of dams	11	12	11	12
Male weight				
Days of lactation				
0	6.7 ± 0.5	7.0 ± 0.3 #	7.1 ± 0.7 (10)	6.5 ± 0.3
4	10.9 ± 1.9	11.1 ± 0.9	11.2 ± 1.5 (10)	9.9 ± 1.1
Female weight				
Days of lactation				
0	6.5 ± 0.4	6.7 ± 0.4	6.9 ± 0.8	6.3 ± 0.3
4	10.3 ± 1.3	10.6 ± 0.9	11.0 ± 2.4	9.6 ± 1.2
Mean pup weight				
Days of lactation				
0	6.6 ± 0.4	6.8 ± 0.3	7.1 ± 0.8	6.4 ± 0.3
4	10.6 ± 1.5	10.9 ± 0.8	11.3 ± 2.2	9.8 ± 1.1
Litter weight				
Days of lactation				
0	86.0 ± 16.2	88.1 ± 19.7	83.0 ± 24.4	89.3 ± 8.8
4	135.8 ± 19.0	137.5 ± 28.4	127.1 ± 33.3	133.1 ± 10.3

Each value shows mean (g) ± S.D. per dam.
Significantly different from the control group (#: $p<0.05$ by Steel's test).
Figures in parentheses indicate number of dams.

Table 62. Gross necropsy findings in stillbirths and dead pups in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of stillbirths	2	0	0	1
Normal	2	-	-	1
Number of dead pups	0	0	1	0
Normal	-	-	1	-

Table 63. Gross necropsy findings in pups in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration

Group	Control	4,4'-bis(chloromethyl)-1,1'-biphenyl		
mg/kg	0	62.5	250	1000
Number of dams	11	12	10	12
Number of male pups	67	80	59	91
Normal	67	80	59	91
Number of dams	11	12	11	12
Number of female pups	78	73	70	74
Normal	78	73	70	74

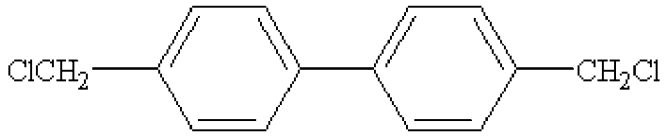

Fig. 1. Chemical structure of 4,4'-bis(chloromethyl)-1,1'-biphenyl.

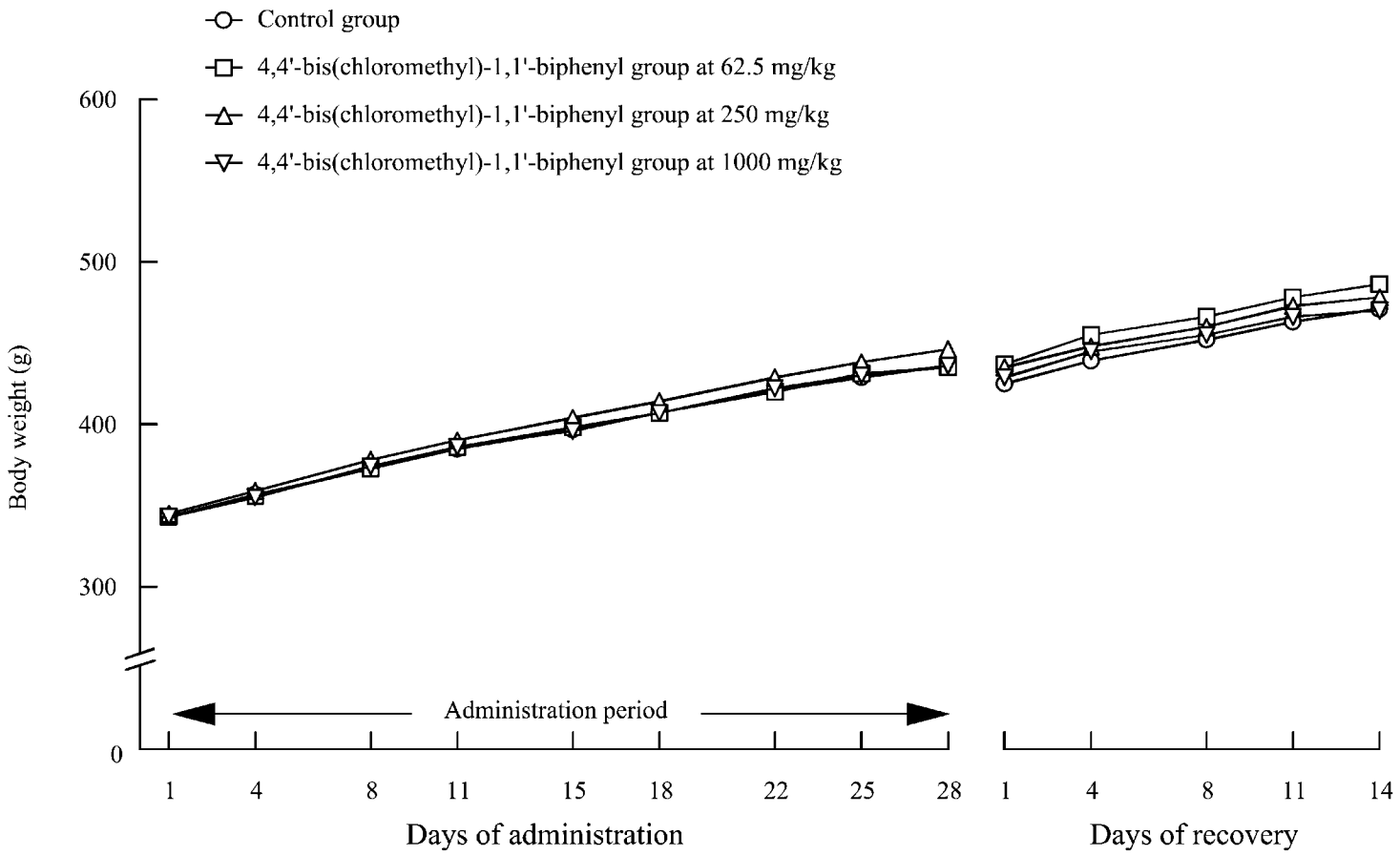

Fig. 2. Body weights of male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.

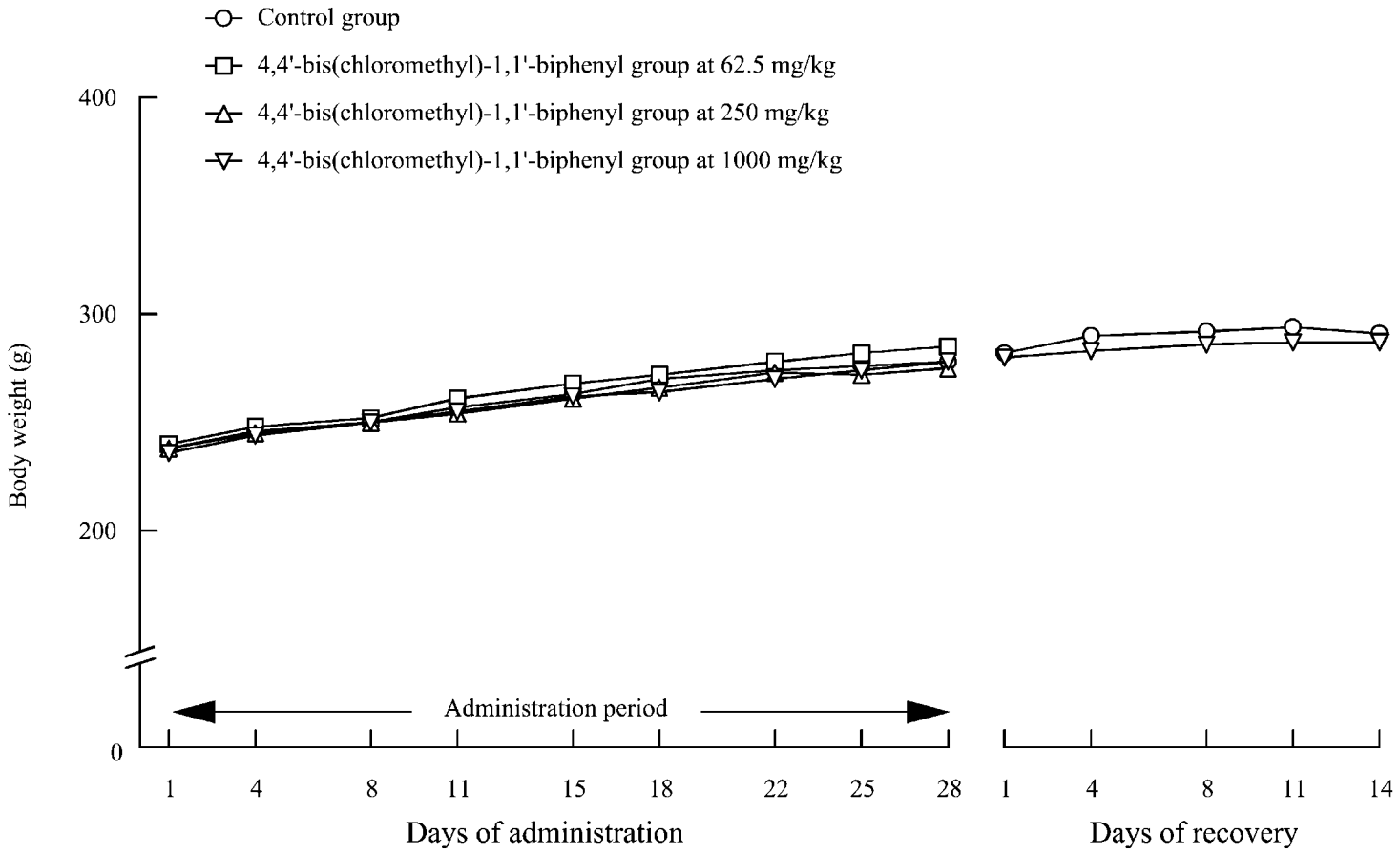

Fig. 3. Body weights of female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.

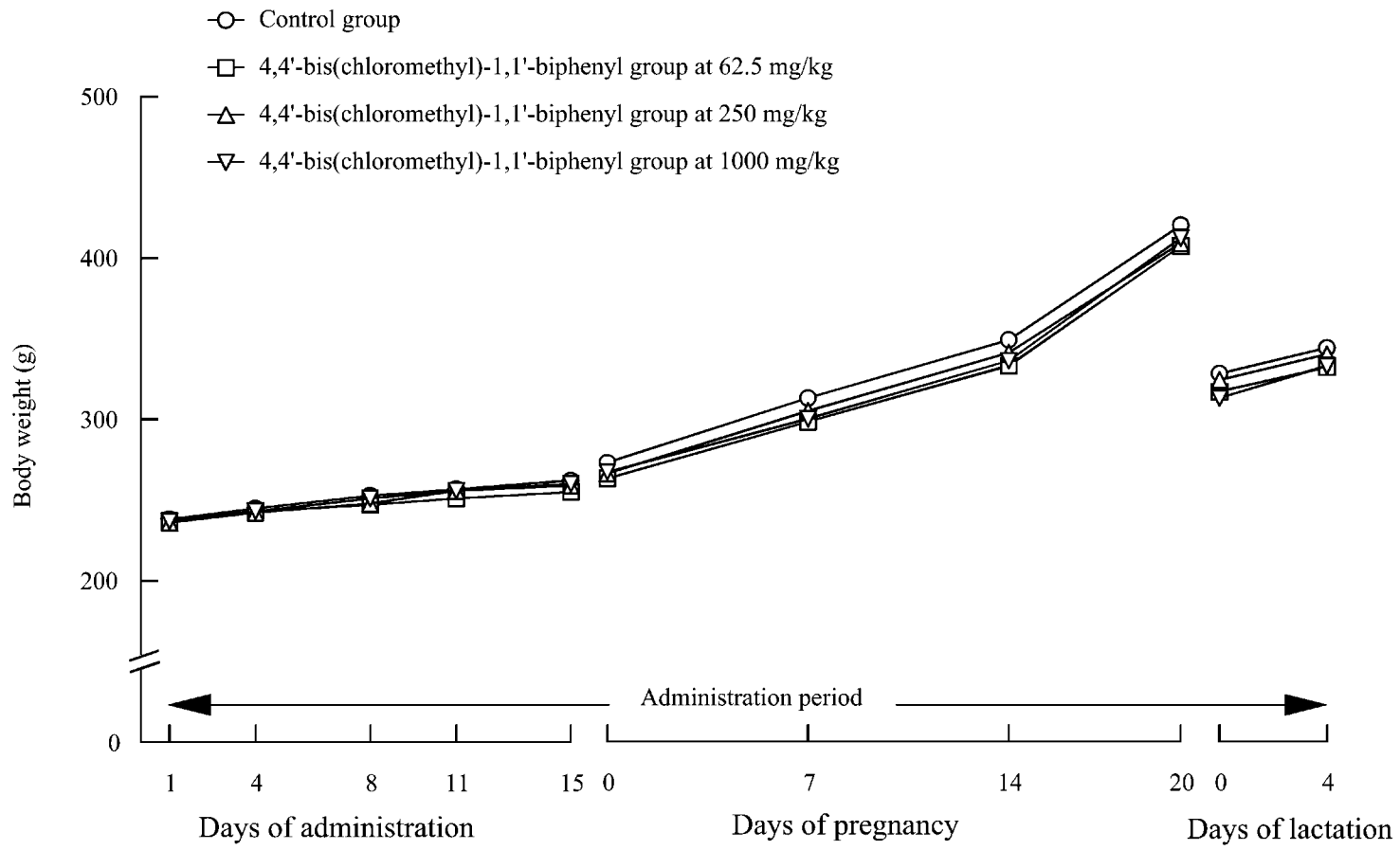

Fig. 4. Body weights of parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.

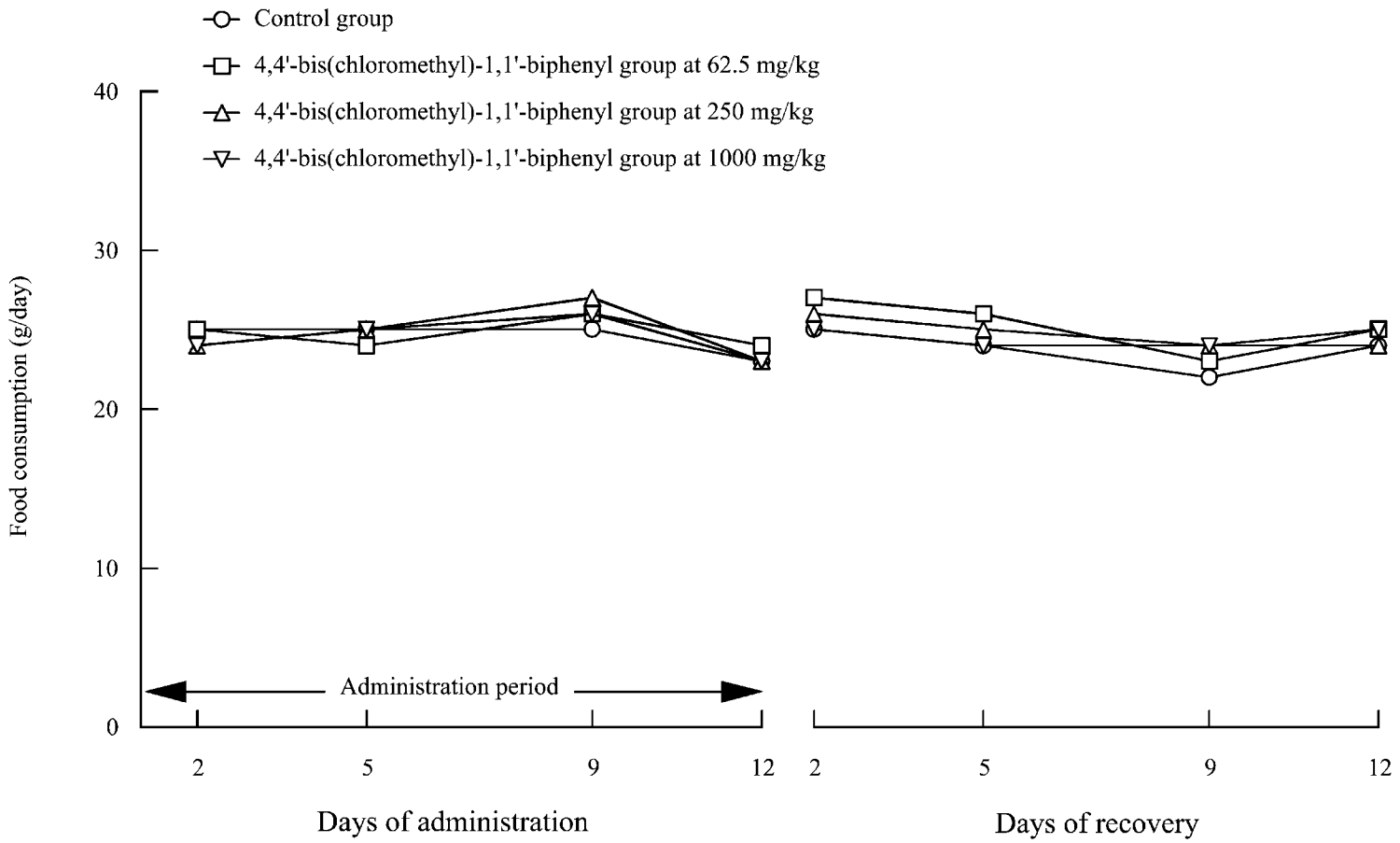

Fig. 5. Food consumption in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.

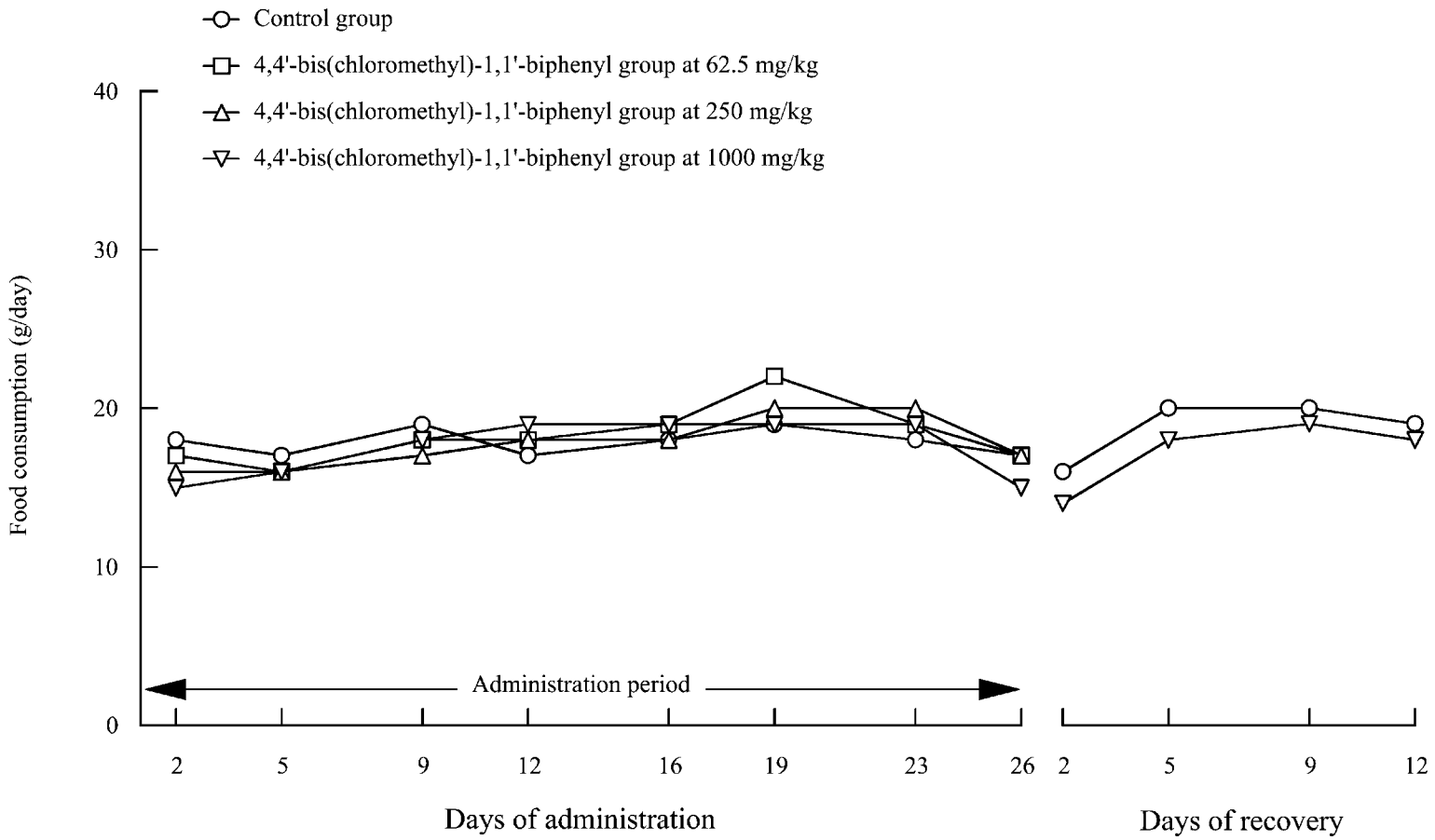

Fig. 6. Food consumption in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.

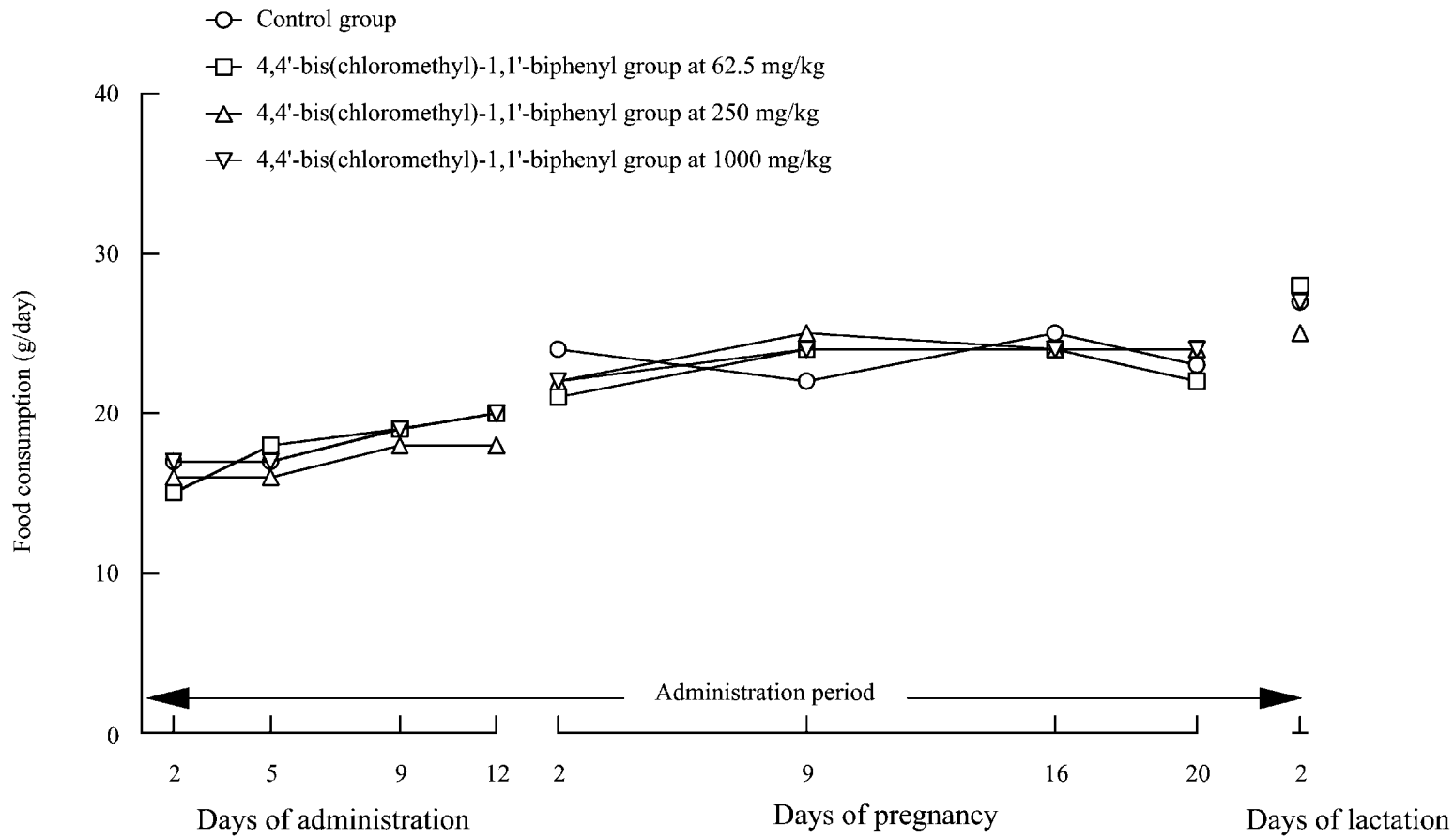

Fig. 7. Food consumption in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.

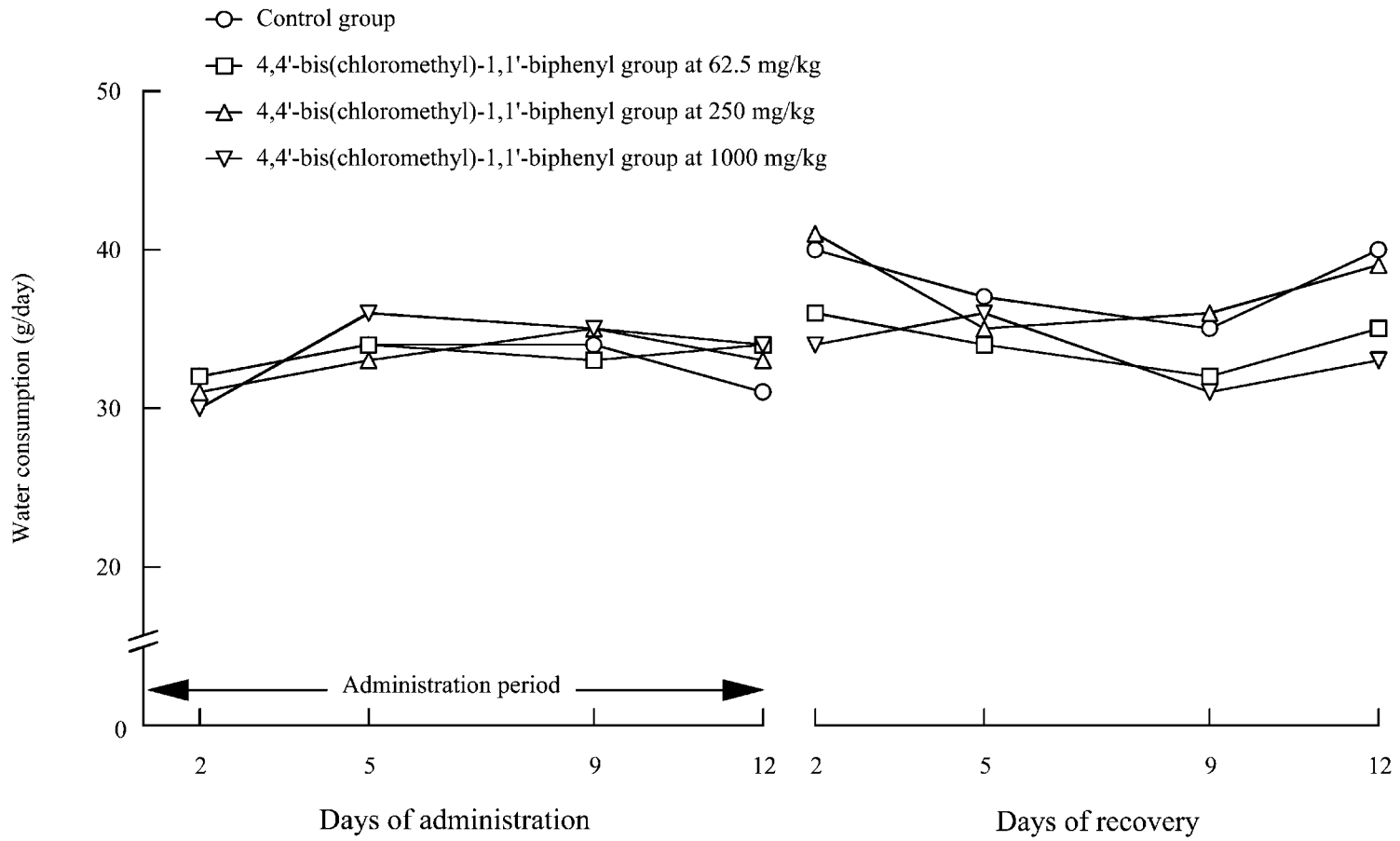

Fig. 8. Water consumption in male rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.

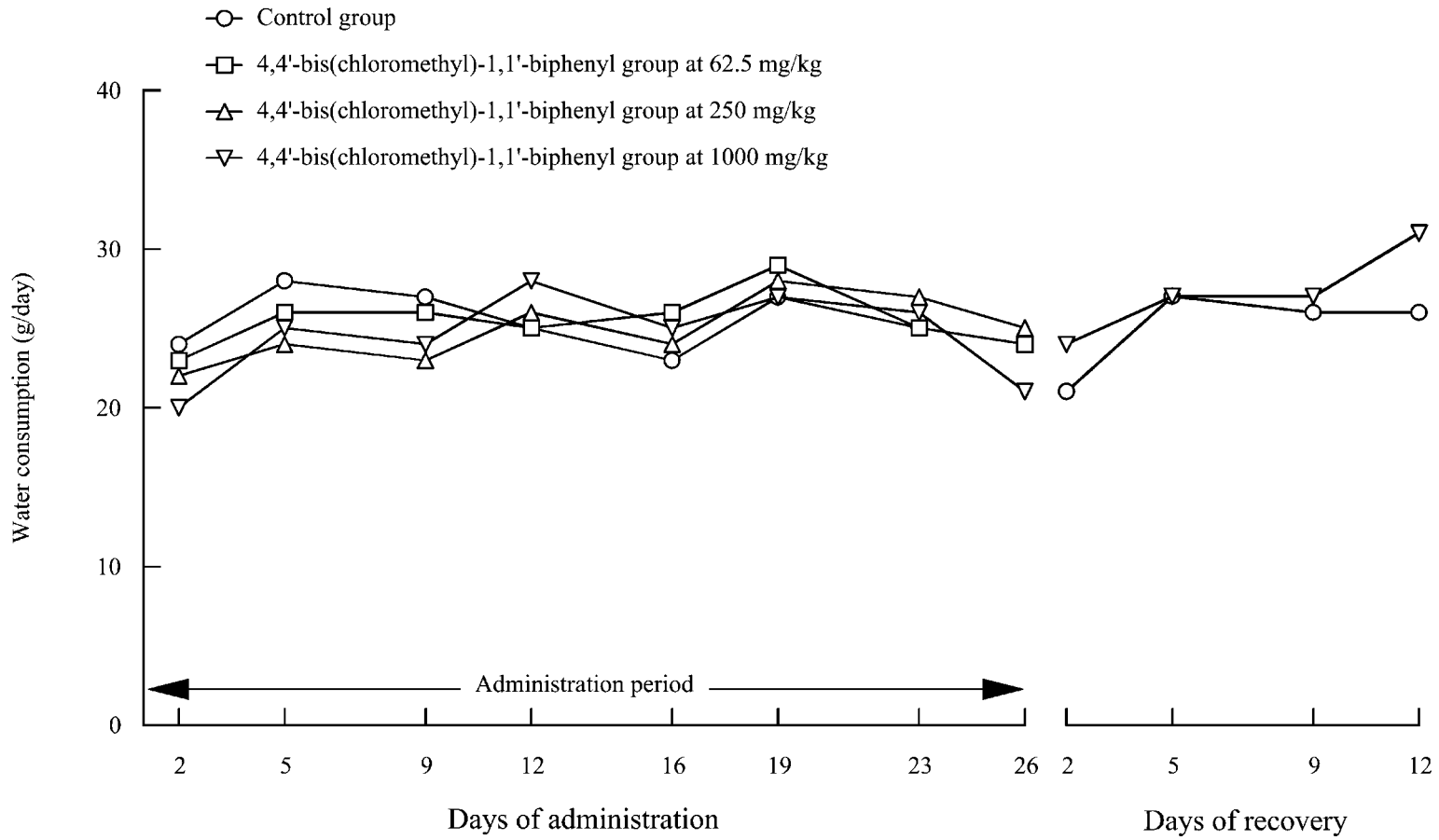

Fig. 9. Water consumption in female rats in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.

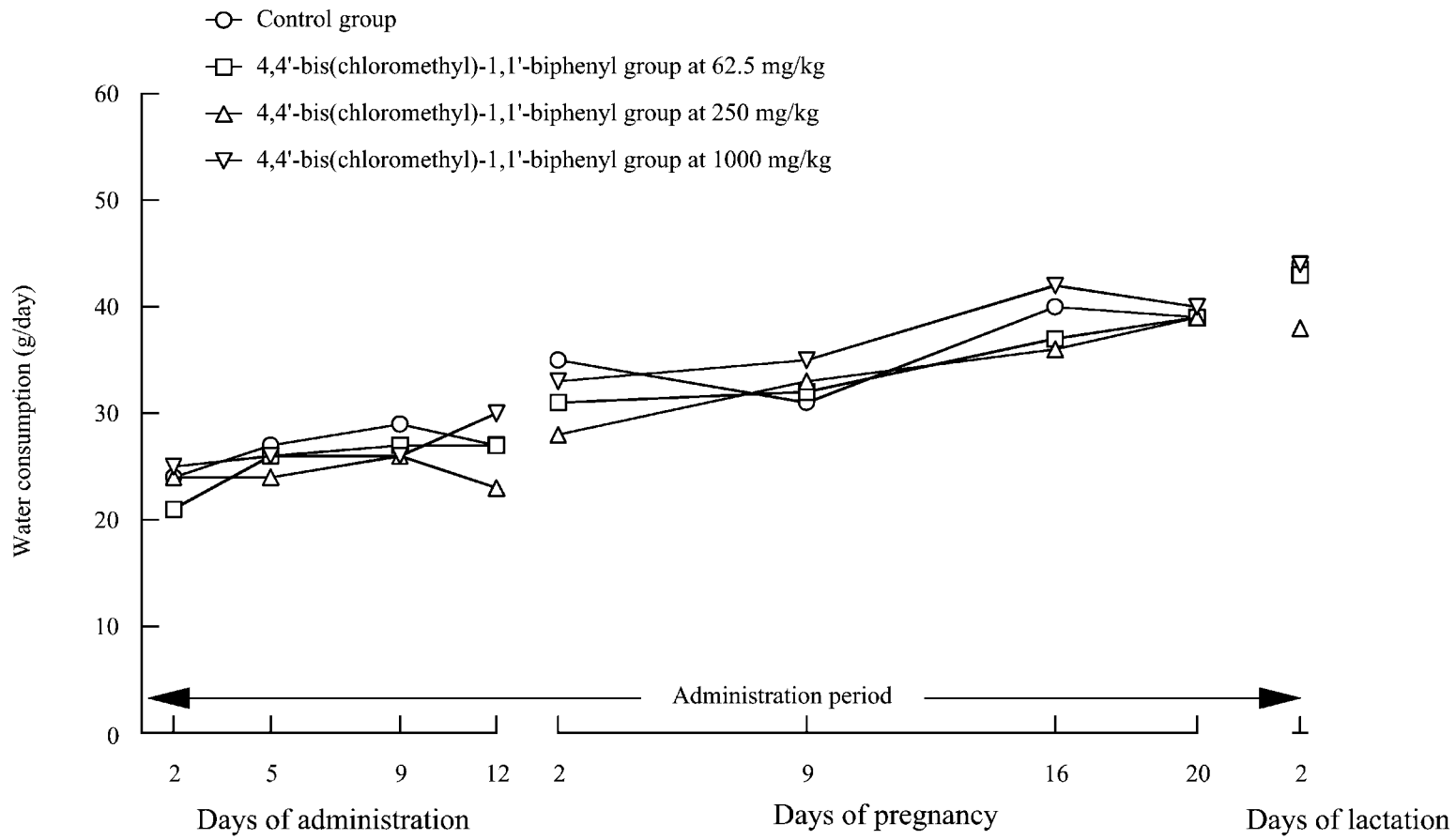

Fig. 10. Water consumption in parental female rats (mating groups) in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.

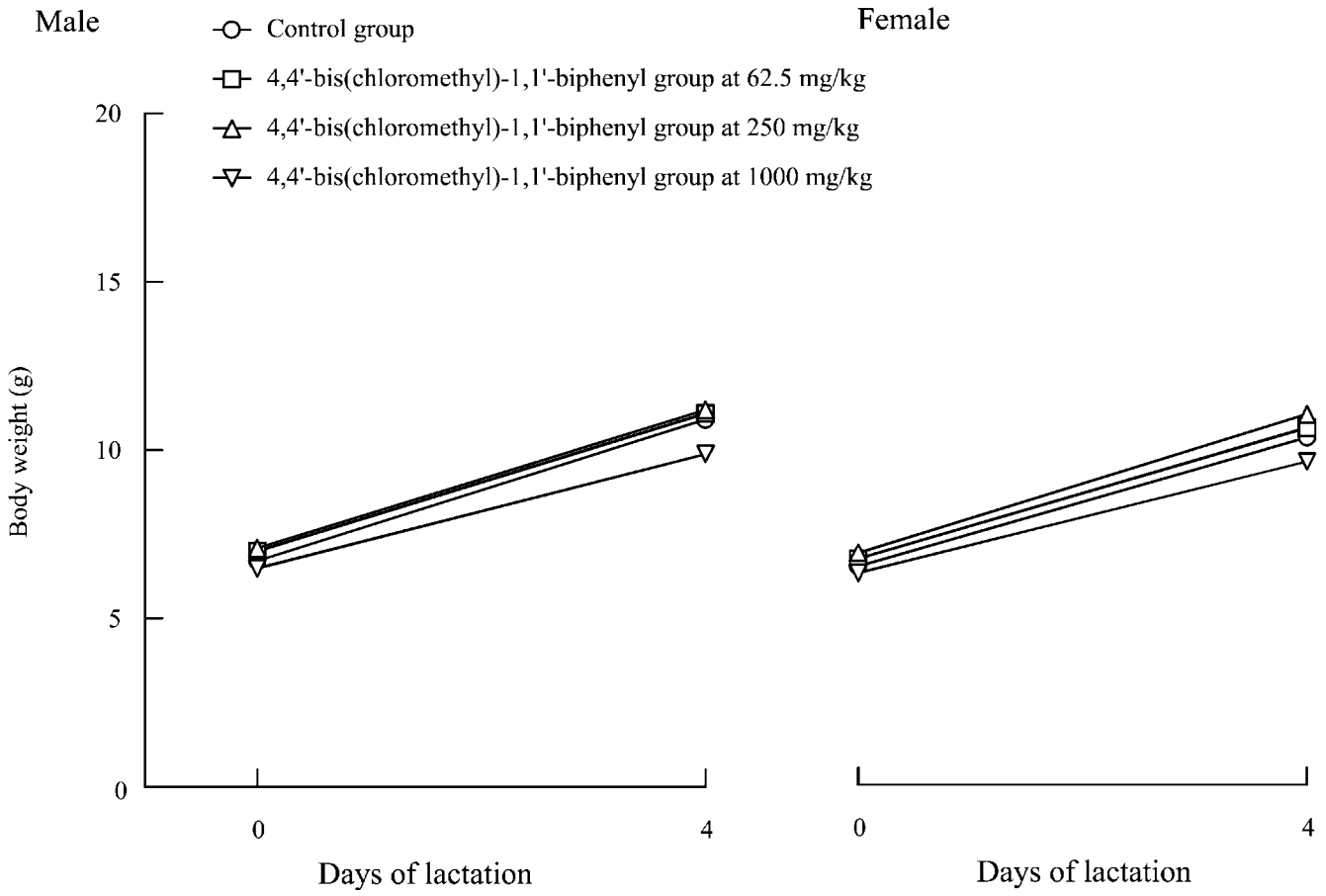

Fig. 11. Body weights of pups in combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of 4,4'-bis(chloromethyl)-1,1'-biphenyl by oral administration.