最　終　報　告　書

（訂正版）

1,4-ジクロロブタンのラットを用いた
経口投与による簡易生殖発生毒性試験

試験番号：R-1113

作成日：2013 年 9 月 10 日

試験期間：2012 年 10 月 23 日-2013 年 3 月 25 日

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

試験委託者
厚生労働省医薬食品局審査管理課化学物質安全対策室
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〒151-0065　東京都渋谷区大山町 36-7

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1,4-ジクロロブタンのラットを用いた経口投与による簡易生殖発生毒性試験

（A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane）

2.3　試験目的

1,4-ジクロロブタンを、雄ラットに交配前 14 日間及び交配期間を通して剖検前日まで、雌ラットには交配前 14 日間及び交配期間並びに妊娠期間を通して授乳 3 日まで投与し、雌雄ラットに対する影響、特に性腺機能、交尾行動、受胎及び分娩などの生殖発生に及ぼす影響を概略的に検討することを目的とした。

2.4　試験委託者

厚生労働省　医薬食品局　審査管理課　化学物質安全対策室

〒100-8916　東京都千代田区霞が関 1-2-2

2.5　試験受託者

株式会社ボゾリサーチセンター

〒151-0065　東京都渋谷区大山町 36-7

2.6　試験実施施設

株式会社ボゾリサーチセンター　御殿場研究所

〒412-0039　静岡県御殿場市かまど 1284

2.7　被験物質

名称	:	1,4-ジクロロブタン
CAS 番号	:	110-56-5
官報公示整理番号	:	(2)-61（化審法）
入手日	:	2012 年 10 月 4 日

2.8　試験日程

試験開始日	:	2012 年 10 月 23 日
動物入荷日	:	2012 年 10 月 24 日
被験物質出庫日	:	2012 年 11 月　6、 7 日

実験開始日（投与開始日）
: 2012 年 11 月 13 日
交配開始日 : 2012 年 11 月 27 日
分娩開始日 : 2012 年 12 月 19 日
母動物剖検開始日 : 2012 年 12 月 23 日
雄動物剖検日 : 2012 年 12 月 25 日
動物試験終了日 : 2013 年 1 月 2 日
実験終了日（病理組織学検査終了日）
: 2013 年 2 月 15 日
試験終了日 : 2013 年 3 月 25 日

2.9 試験責任者

株式会社ボゾリサーチセンター 御殿場研究所 研究部

[redacted]

2.10 試験担当者

試験主担当者 :
被験物質保存責任者 :
化学分析責任者 :
病理検査責任者 :
統計解析責任者 :

[redacted]

2.11 試験成績の信頼性に影響を及ぼしたと思われる環境要因あるいは予期し得ぬ事態並びに試験計画書に従わなかったこと

本試験において試験成績の信頼性に影響を及ぼしたと思われる環境要因あるいは予期し得ぬ事態は発生せず、試験は試験計画書に従って実施された。

2.12 資料保存

試験計画書原本（試験計画書変更書を含む）、記録文書、生データ、報告書類（最終報告書の原本を含む）及び標本（被験物質保存試料を含む）は株式会社ボゾリサーチセンター御殿場研究所の資料保存施設に最終報告書提出後 5 年間保存する。期間終了後の保存については、厚生労働省医薬食品局審査管理課化学物質安全対策室と株式会社ボゾリサーチセンター間で協議し、その処置を決定する。なお、長期保存に耐えられない腟垢標本は廃棄した。

2.13　試験責任者の記名・なつ印

[redacted]　2013 年 9 月 10 日 [redacted]

3. 要約

1,4-ジクロロブタンをコーン油で希釈し、2.4、12 及び 60 mg/kg/day の投与量で、1 群雌雄各 12 匹の Sprague-Dawley 系 SPF ラットに、雄には交配前 14 日間及び交配期間を通して剖検前日まで 42 日間、雌には交配前 14 日間及び交配期間並びに妊娠期間を通して分娩後 3 日まで（40~50 日間）1 日 1 回経口投与し、雌雄動物に対する影響、特に生殖発生毒性について概略的に検討した。なお、対照群には媒体であるコーン油を投与した。

3.1 雌雄動物に対する影響

60 mg/kg 投与群の雄において肝臓重量の増加が認められた。一方、雌の肝臓重量には被験物質投与の影響は認められず、雌雄ともに一般状態、体重、摂餌量、剖検並びに肝臓及び膵臓の病理組織学検査では、被験物質投与の影響を示唆する変化は認められなかった。

3.2 生殖発生に対する影響

性周期、交尾までに要した日数、交尾率、授精率及び受胎率並びに雌雄の生殖腺及び副生殖器に関する病理組織学検査では、被験物質投与の影響を示唆する変化は認められなかった。更に、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数、出生率及び性比に被験物質投与の影響を示唆する変化は認められず、哺育状態に異常はみられなかった。また、出生児の生後 4 日生存率及び生後 4 日の体重に被験物質投与の影響は認められず、出生児の外表に異常は認められなかった。しかし、60 mg/kg 投与群では分娩率（着床痕数に対する娩出された総児数の百分率）が低値な傾向を示し、着床後の胎生期における胚・胎児の生存性を低下させた可能性が示唆された。

これらの結果から、本試験条件下における 1,4-ジクロロブタンの無影響量は、雄については 12 mg/kg/ day、雌については 60 mg/kg/ day であり、雌雄動物の生殖機能及び母体機能に対しては顕著な影響を及ぼさないものの、出生児の発生に関し、その胎生期における生存性への影響を考慮して生殖発生に対する無影響量は 12 mg/kg/ day と推定された。

4. 緒言

厚生労働省医薬食品局審査管理課化学物質安全対策室の委託により、1,4-ジクロロブタンのラットを用いた経口投与による簡易生殖発生毒性試験を実施したので、その成績を報告する。なお、本試験は以下の基準を遵守し、ガイドライン等に準拠して実施した。

4.1 GLP 基準

- 「新規化学物質等に係る試験を実施する試験施設に関する基準」
  （平成 23 年 3 月 31 日付け薬食発第 0331008 号厚生労働省医薬食品局長、平成 23･03･29 製局第 6 号経済産業省製造産業局長、環保企発第 110331010 号環境省総合環境政策局長通知）

4.2 試験方法等に関する通知

- 「新規化学物質等に係る試験の方法について」
  （平成 23 年 3 月 31 日付け薬食発第 0331007 号厚生労働省医薬食品局長、平成 23･03･29 製局第 5 号、経済産業省製造産業局長、環保企発第 110331009 号環境省総合環境政策局長通知）
- 「OECD Guideline for Testing of Chemicals 421」
  （OECD 理事会：1995 年 7 月 27 日）

4.3 動物の福祉

- 「動物の愛護及び管理に関する法律」
  （昭和 48 年 10 月 1 日法律第 105 号、最終改正：平成 23 年 8 月 30 日法律第 105 号）
- 「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」
  （平成 18 年 4 月 28 日環境省告示第 88 号）
- 「動物実験の適正な実施に向けたガイドライン」
  （日本学術会議 平成 18 年 6 月 1 日）

なお、本試験は試験施設の動物実験委員会の承認を経て、試験施設が定める実験動物の管理及び福祉に関する指針（株式会社ボゾリサーチセンター動物実験指針）に従って実施した。

5. 試験材料及び方法

5.1 被験物質及び対照物質（媒体）

5.1.1 被験物質

以下に示す被験物質を試験に使用した。なお、使用した被験物質については試験施設において試験開始前に赤外吸収スペクトルの測定により特性が確認されている[1)]。

名称	:	1,4-ジクロロブタン
製造元	:	東京化成工業株式会社
ロット番号	:	DE6GA
化学式	:	$C_4H_8Cl_2$
構造式	:	
分子量	:	127.01
純度(GC)	:	99.8%(規格値：>98.0%）*
常温における性状	:	無色~ほとんど無色の透明液体**
引火点	:	53°C**
発火点	:	220°C**
沸点	:	155°C**
比重	:	1.1406
保存方法	:	冷暗所〔冷蔵庫内（許容温度：1~10°C、実測温度：4~7°C***）〕、密栓（密閉容器）
保存場所	:	御殿場研究所被験物質保存室及び第 2 研究棟 4 階被験物質調製室
取扱い上の注意	:	作業場の換気を十分に行い、マスク、保護眼鏡、保護手袋等の適切な保護具を着用し、直接の接触を防ぐ。取り扱い後は、手、顔等を良く洗い、うがいをする。
安定性	:	投与期間終了後、残余被験物質の赤外吸収スペクトルを確認した結果、実験実施前に確認した参照スペクトルとほぼ同様であり、投与期間を通して被験物質は安定であったと判断した。
残余被験物質の処理	:	被験物質 5 g を保存試料として保存し、動物試験及び分析終了後の残余は全て焼却処分した。

*：　製造元試験成績書に基づく
**：　製造元製品安全データーシートに基づく
***：　入手の後、動物試験終了までの間

5.1.2　対照物質（媒体）

名称	:	コーン油
規格	:	生化学用
製造元	:	和光純薬工業株式会社
ロット番号	:	WEN1861、WEK6144
保存方法	:	室温
保存場所	:	御殿場研究所第 2 研究棟 4 階被験物質調製室

なお、対照物質については、先に実施された「1,4-ジクロロブタンのラットを用いる 28 日間反復経口投与毒性試験及び 14 日間回復試験」[2)]において投与液の媒体として用いられたコーン油を陰性対照物質として選択した。

5.2　投与液

5.2.1　調製

濃度ごとに必要量の被験物質を秤取し、コーン油で規定濃度（0.48、2.4 及び 12 mg/mL）となるよう希釈した。

5.2.2　保存

調製後の被験物質投与液及び対照群の投与に使用するコーン油は、1 日使用分ごと褐色ガラス瓶に小分けして冷所（冷蔵庫内、許容温度範囲：1~10°C、実測温度範囲：3~9°C）に保存し、調製日を 0 日として調製後 7 日以内に使用した。

5.2.3　安定性

コーン油を媒体とする本被験物質の 0.36 及び 200 mg/mL 濃度の投与液について、冷所（冷蔵庫内、許容値：1~10°C）で 7 日間保存したのち、室温で 24 時間保存（冷所 7 日間 + 室温 24 時間）での安定性が確認されている。[1)]

5.2.4　濃度確認

雄の投与 1 及び 6 週の時点で計 2 回、各濃度の被験物質投与液について使用前にガスクロマトグラフ法により濃度を確認した。その結果、規定濃度に対する各投与液の測定濃度の割合は 90.4~100.8%であり、いずれも許容範囲内（表示値に対する割合：100.0±10.0%）であった。用いた標準物質、GC システム及び測定条件は以下の如くであった。

[標準物質]

被験物質の一部を標準物質として使用した。（保存場所：御殿場研究所生化学部標準物質保存場所及び被験物質保存室:実測温度:3~8°C）

[GC システム]

機器名及び型式		メーカー
GC	HP6890N	Agilent Technologies Inc.
インジェクタ	G2613A	
オートサンプラトレイ	G2614A	
データ処理ソフト	GC ChemStation G2070AJ	

[計算ソフト]

ソフト名	メーカー
Microsoft Office Excel 2003 SP3	Microsoft Corporation

[GC 測定条件]

カラム : DB-1（0.32 mm I.D.×30 m、膜厚 0.25 μm、Agilent Technologies Inc.）
キャリアガス : He
流量モード : コンスタントフローモード
流量 : 3.0 mL/min
注入口 : スプリット注入口
スプリット比 : 5:1
注入口温度 : 250°C
検出器 : Flame ionization detector（FID）
検出器温度 : 300°C
H2 流量 : 45 mL/min
Air 流量 : 450 mL/min
メイクアップガス（N2）流量 : 40 mL/min
オーブン温度 : 40°C（Hold 1 分）→ 80°C（10°C/min、Hold 2 分）
注入量 : 3 μL
測定順序 :

測定順序	測定回数	測定内容
1	3	標準溶液（システム適合性用）
2	3	標準溶液（定量用）
3~	各 1	測定実測試料

5.3 試験動物種及び系統の選択理由

毒性試験法ガイドラインによりげっ歯類を用いた試験が必要とされており、また、反復投与毒性試験、生殖発生毒性試験に広く用いられ、特性が良く知られており背景資料が豊富である系統を選択した。また、「1,4-ジクロロブタンのラットを用いる 28 日間反復経口投与毒性試験及び 14 日間回復試験」[2)]においても同系統のラットが使用されている。

5.4　試験動物

Sprague-Dawley 系 SPF ラット〔Crl:CD(SD)、日本チャールス・リバー株式会社、厚木飼育センター〕の雌雄各 62 匹をそれぞれ 8 週齢で入手[注)]し、入荷日を馴化 1 日として、3 日間の検疫期間を含む 20 日間、馴化飼育した。その間、一般状態を毎日 1 回観察し、体重を馴化 1、3、6、13 及び 20 日に測定した。更に、雌について腟垢を馴化 4~17 日の間採取し、多数の角化上皮細胞から成る腟垢像を発情の指標として 4~5 日の周期で回帰するものを正常とし、性周期異常の有無を調べた。その結果、体重推移には異常はみられず、馴化終了日の体重は、雄で 308~421 g（平均：379 g）、雌は 213~280 g（平均：245 g）であり、雌雄とも平均値±20%以内の体重範囲であった。しかし、一般状態において雄 1 例に外傷が認められ、雌 3 例の性周期に異常がみられたため、これらを除く個体より雌雄各 48 匹をそれぞれ選択して 10 週齢で試験に使用した。

注）：試験計画書に従い、動物発注数は雌雄各 60 匹であったが、実際には各 62 匹が納入された。

5.5　群分け

前項に記載された馴化中の観察、検査結果に基づいて選抜された雌雄各 48 匹は、群分け当日の体重を基に各群の平均体重ができるだけ均等となるよう各群に割付けた。個体の割付けはコンピュータを用いたブロック配置法及び無作為抽出法の組み合わせ（ブロック配置法で必要な群を構成し、試験群及び群内の個体番号を無作為に割当てた）で行った。群分けから除外された雄 14 匹と性周期異常の雌 3 匹は、群分け当日、動物管理責任者に移管して試験から除外した。残りの雌 11 匹は交配用予備動物として継続飼育したが、交配に用いなかったため、交配終了後、炭酸ガスにより安楽死させた。

5.6　飼育条件

動物は、温度 22~23°C（許容範囲：23±3°C）、相対湿度 45~57%（許容範囲：50±20%）、換気回数 10~15 回/1 時間、照明 1 日 12 時間（07:00~19:00）の動物飼育室（飼育室番号：910 号室）で、交配中を除いてブラケット式金属製網ケージ（W 254 × D 350 × H 170 mm：リードエンジニアリング株式会社）に個別に収容した。なお、妊娠 17 日以降は、床敷（ホワイトフレーク：日本チャールス・リバー株式会社、ロット番号：2012-4）を入れたプラスチック製エコンケージ（W340×D400×H185 mm：日本クレア株式会社）に 1 腹ごと収容した。飼料及び飲料水については、固形飼料 NMF（放射線滅菌、オリエンタル酵母工業株式会社、ロット番号：120919、121012）及び水道水（御殿場市営水道水）をステンレス製給餌器あるいは自動給水装置又は給水瓶を用いてそれぞれ自由に摂取させた。

5.7　飼料、飲料水及び床敷中の混入物質

飼料及び床敷中の混入物質等については、使用したロットについて Eurofins Scientific Analytics で実施された分析結果を入手し、飲料水については、水道法に準拠した水質の分析を芝浦セムテック株式会社に定期的（年 4 回）に依頼し、分析結果を入手した。これらの検査結果より飼料、飲料水及び床敷中の混入物質が試験成績に影響を与える可能性のないことを確認し、分析報告書の写しを保存した。

5.8　動物の識別

動物は、入荷時に固有の番号が刻印された小動物用耳標を装着して個体識別し、群分け後は、1000 の位が群、100 の位が性（0 番を雄、1 番を雌）、10 と 1 の位が個体番号を示す 4 桁の動物番号を設定した。飼育ケージには群ごとに色分けされ、試験番号、投与経路、投与量、性、動物番号、耳標番号、剖検予定日（雄）、交尾成立日（雌雄）及び分娩日（雌）を明記したラベルを表示した。

5.9　投与経路、投与期間及び投与回数とそれらの選択理由

投与経路は、ガイドラインに準じ経口投与を選択した。投与期間は、雄では交配前 14 日間、交配期間を通して剖検前日までの更に 14 日間の計 42 日間、雌では交配前 14 日間、交配期間及び妊娠期間を通して分娩後 3 日までとした。なお、本試験では、分娩母動物については 40~50 日間の投与期間となった。投与回数は反復投与試験で一般的に行われている 1 日 1 回とした。

5.10　投与方法

投与方法は、げっ歯類の経口投与に際して一般的な強制経口投与とし、投与液を 5 mL/kg 体重の投与容量で、胃ゾンデを用いて 1 日 1 回、08:56~12:13 の間に投与した。ただし、投与時に分娩中であった動物は分娩終了を待って、13:52~14:41 の間に投与した。対照群には媒体のみを同様に投与した。個体ごとの投与液量は、最近時の体重を基に算出した。

5.11　投与量及び群構成

投与量は 2.4、12 及び 60 mg/kg/day の 3 用量とし、対照群を加え 4 群構成とした。1 群当たりの動物数は雌雄各 12 匹とした。群構成表を次に示した。

群構成表

試験群	投与量 (mg/kg)	被験液濃度 (mg/mL)	投与容量 (mL/kg)	性	動物数	動物番号
対 照 群	0	0	5	雄 雌	12 12	1001~1012 1101~1112
低用量群	2.4	0.48	5	雄 雌	12 12	2001~2012 2101~2112
中用量群	12	2.4	5	雄 雌	12 12	3001~3012 3101~3112
高用量群	60	12	5	雄 雌	12 12	4001~4012 4101~4112

5.12　投与量の設定根拠

投与量は、先に実施された 28 日間反復経口投与毒性試験及び 14 日間回復試験 [2)]の結果に基づいて設定した。即ち、1,4-ジクロロブタンを 12、60 及び 300 mg/kg/day の投与量でラットに 28 日間反復投与した結果、各用量群において門脈周囲性の肝細胞腫大並びに膵臓のチモーゲン顆粒の減少が用量に依存してみられ、更に 60 mg/kg 以上の用量群の肝臓には退色と重量増加が認められ、これら肝臓の毒性変化に関連すると考えられる γ-GPT の高値が 300 mg/kg 投与群で認められた。このように当該試験では NOAEL が算定できなかったが、12 mg/kg 投与群の雄では、特定臓器の器質変化を認めた例数が少ないことから、簡易生殖毒性試験における投与量は、肝臓及び膵臓の明らかな組織学的変化が予想される 60 mg/kg を高用量とし、以下公比 5 で除して 12 及び 2.4 mg/kg をそれぞれ中及び低用量に設定した。

5.13　観察及び検査の方法

試験日の起算は、投与開始日を投与 1 日、投与 1 日から 7 日を投与 1 週、交尾成立日を妊娠 0 日、分娩終了日を哺育 0 日（生後 0 日）とした。

5.13.1　一般状態

全個体について、投与期間中は毎日 3 回（投与前、投与直後及び投与 1~3 時間後）、剖検日は午前中に 1 回、体外表、栄養状態、姿勢、行動及び排泄物の異常の有無を観察した。

5.13.2　体重

全個体について、雄は投与 1、8、15、22、29、36、42 日及び剖検日に、雌は投与 1、8、15 日、交配期間中週 1 回（火曜）、妊娠 0、7、14 及び 20 日、哺育 0 及び 4 日に体重を測定した。測定は、午後に分娩終了が確認された個体の哺育 0 日の体重を除いて、午前中の投与前に行なった。

5.13.3　摂餌量

全個体について、雄は投与 2、8、15、30、36 及び 43 日に、雌は投与 2、8 及び 15 日、妊娠 1、7、14 及び 20 日並びに哺育 2 及び 4 日に残餌量を測定し、前日の給餌量との差を 1 日摂餌量として算出した。給餌量及び残餌量ともに午前中の投与前に測定した。

5.13.4　膣垢検査

雌の全個体について、投与開始日から交尾が認められるまで毎日膣垢を採取し、交配前投与期間中は多数の角化上皮細胞から成る膣垢像を発情の指標とし、発情回数及び発情期から次の発情期までの日数（性周期）を調べた。交配期間中は膣垢内の精子の有無を調べた。

5.13.5　交配

交配前投与期間終了後、同一群内の雌雄を 1:1 で終夜同居させ、翌朝、膣栓形成あるいは膣垢中に精子を確認したものを交尾成立とみなした。交配開始日を 0 日と起算して交尾までに要した日数を求めた。予め同居期間は最長 14 日間と設定したが、交配開始後 10 日以内に全例で交尾が成立した。

5.13.6　分娩及び哺育

交尾が成立した雌動物は、妊娠 21 日以降 1 日 2 回（午前、午後）分娩の有無及びその終了を確認し、交尾成立日より分娩終了までの間を妊娠期間として 0.5 日単位で求めた。分娩が終了した母動物については、胎盤及び羊膜の処理及び生産児の状態を指標として分娩状態を観察した後、出生児を哺育させ、哺育 4 日に病理学検査に供した。授乳期間中は児集め、営巣及び授乳の状態等を指標として哺育状態を観察した。

5.13.7　出生児

生後 0 日に出生児数及び死産児数を数え、合わせて出産児数とした。出産児は口腔内を含む外表異常の有無を肉眼的に観察し、性別を判定して体重を測定した。死産児はブアン液で固定して保存した。哺育期間中は毎日 1 回、死亡児の有無を観察した。なお、死亡児は外表異常の有無を観察した後、ブアン液で固定して保存した。生存児は生後 4 日に性別を判定し、外表異常の有無を観察して体重を測定した後、炭酸ガスにより安楽死させた。なお、出生児の体重は個別に測定し、雌雄別に各腹の平均値を算出した。

5.13.8　病理学検査

1)　剖検及び器官重量

雌雄全個体について、最終投与翌日にイソフルラン麻酔下で腹大動脈切断により放血致死させた後、体外表並びに頭部、胸部及び腹部の器官・組織を肉眼的に検査する

とともに母動物の黄体数及び着床痕数を数えた。更に、肝臓、精巣、精巣上体、前立腺、精嚢（凝固腺含む）及び卵巣を摘出して重量（絶対重量）を測定し、剖検日の体重から体重 100 g 当たりの相対重量を算出した。なお、両側性の器官は左右別々に測定し、その合計値で評価した。

2) 病理組織学検査

全ての個体の肝臓、膵臓、精巣、精巣上体、前立腺、精嚢（凝固腺含む）、卵巣、子宮及び腟並びに肉眼的異常部位を個体識別部（耳標を装着した耳介）とともにリン酸緩衝 10 vol%ホルマリン液で固定した（ただし、精巣及び精巣上体はブアン液で固定した後、リン酸緩衝 10 vol%ホルマリン液に置換した）。個体識別部を除くこれらの器官は、パラフィン包埋した後、切片とし、ヘマトキシリン・エオジン（H・E）染色標本を作製し、肝臓及び膵臓については雌雄全例、生殖腺、副生殖器及び腟については対照群と高用量群を対象とし鏡検した。

5.14 統計解析

5.14.1 パラメータの算出

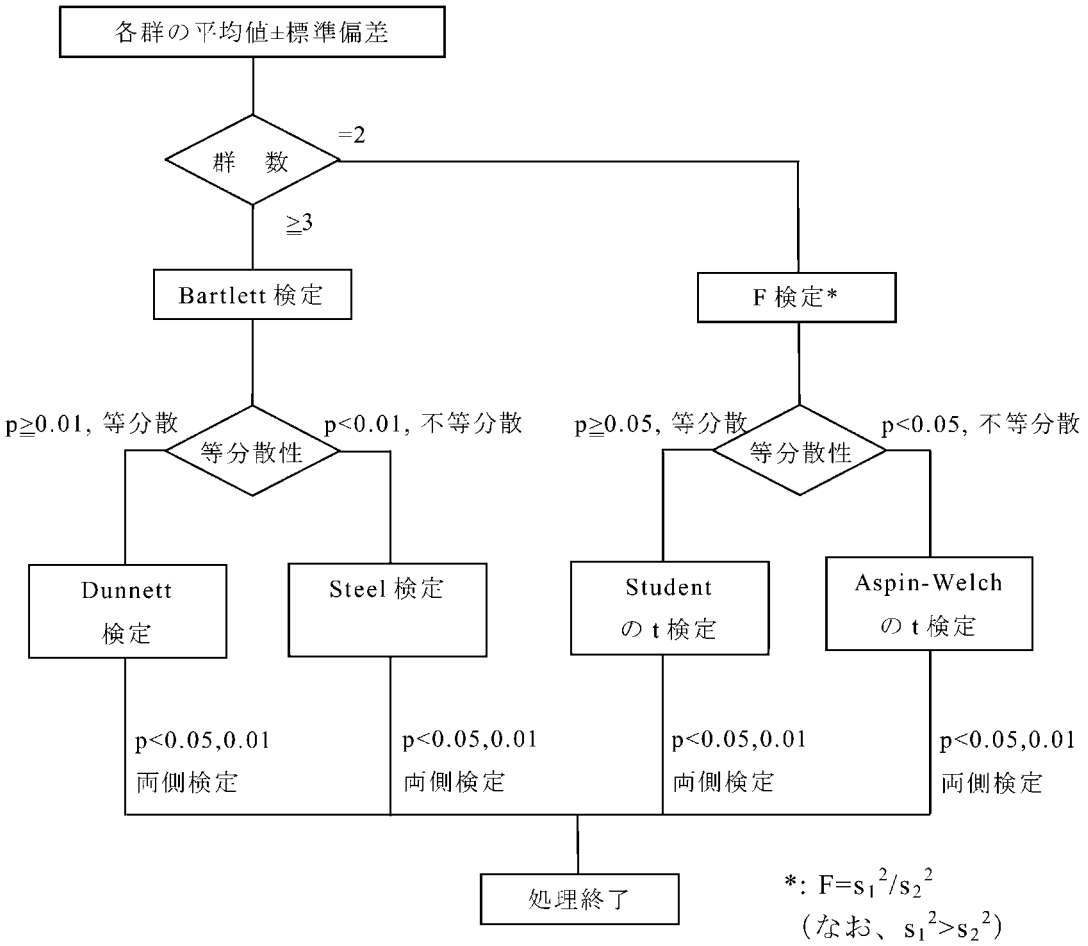
以下の式により交尾率、授精率、受胎率及び出産率を群ごとに、妊娠期間、分娩率、着床率、死産児率、外表異常率、出生率、生後 4 日生存率、生後 0 及び 4 日の性比を母動物ごとに算出した。

交尾率(%) =（交尾動物数/同居動物数）×100
授精率(%) =（雌を妊娠させた雄の数/交尾した雄の数）×100
受胎率(%) =（妊娠した雌の数/交尾した雌の数）×100
出産率(%) =（出生児出産雌数/妊娠雌数）×100
着床率(%) =（着床痕数/黄体数）×100
分娩率(%) =（出産児数/着床痕数）×100
死産児率(%) =（死産児数/出産児数）×100
外表異常率(%) =（外表異常児数/出産児数）×100
出生率(%) =（出生児数/出産児数）×100
生後 4 日生存率(%) =（生後 4 日の生存児数/出生児数）×100
生後 0 日（死産児含む）の性比 = 雄出産児数/出産児数
生後 0 日（出生児）の性比 = 雄出生児数/出生児数
生後 4 日の性比 = 生後 4 日の雄生存児数/生後 4 日の生存児数

5.14.2　検定

対照群と各用量群との差について統計学的有意性を以下の手順により検定した。

体重、体重増加量（雄：投与 1~42 日、雌：投与 1~15 日、妊娠 0~20 日及び哺育 0~4 日）、摂餌量、発情期像発現回数、性周期（発情周期）、交尾までに要した日数、妊娠期間、黄体数、着床痕数、生存児数、性比（生後 0 及び 4 日）及び器官重量は、群ごとに平均値及び標準偏差を求め、次に示す模式図の方法に従って検定した。なお、交配期間中の雌の体重は統計解析より除外した。



着床率、分娩率、出生率、死産児率、外表異常率及び生後 4 日生存率については、群ごとに平均値及び標準偏差を求め、Steel 検定（有意水準 0.05 及び 0.01、両側）を行った。

交尾率、授精率、受胎率及び出産率は、各群の交尾動物数、雌を妊娠させた雄動物数、妊娠雌動物数、出生児出産雌動物数より算出し、Fisher の直接確率計算法により検定（有意水準 0.05 及び 0.01、両側）を行った。

6. 試験結果

6.1 一般状態（Table 1-1~1-4、Appendix 1-1~1-16）

雌雄ともに投与期間を通して死亡はみられず、一般状態に異常は認められなかった。

6.2 体重（Fig. 1、2、Table 2-1~2-4、Appendix 2-1~2-16）

雌雄ともに投与期間を通して各測定日の体重に対照群と各用量群との間に有意な差は認められなかった。雌において 2.4 mg/kg 投与群の妊娠期間中の体重増加量が対照群と比べ有意な高値を示した。しかし、前述の如く、各測定日の体重には有意な差は認められず、12 及び 60 mg/kg 投与群の体重増加量は対照群と同程度であることから偶発的な変動と判断した。

6.3 摂餌量（Fig. 3、4、Table 3-1~3-4、Appendix 3-1~3-16）

雄では各用量群において投与 30 日の摂餌量が対照群に比べ有意な高値を示した。しかし、他の測定日には有意な差は認められず、一時的な変動であった。雌では、交配前、妊娠期間及び分娩後のいずれの摂餌量にも対照群と各用量群との間に有意な差は認められなかった。

6.4 器官重量（Table 4-1、4-2、Appendix 4-1~4-12）

60 mg/kg 投与群において、雄の肝臓の相対重量が対照群と比べ有意な高値を示し、絶対重量は有意な差は認められないものの対照群を上回る傾向を示した。雌の肝臓重量には絶対及び相対重量とも有意な差は認められなかった。精巣、精巣上体、前立腺、精嚢及び卵巣については絶対及び相対重量ともに対照群と各用量群との間に有意な差は認められなかった。

6.5 剖検所見（Table 5-1、5-2、Appendix 5-1~5-96）

肉眼的異常は 60 mg/kg 投与群の雄 1 例に横隔膜ヘルニア結節が、対照群の雄 1 例に肺の暗赤色巣が認められたのみであり、雌では異常は認められなかった。

6.6 病理組織学所見（Table 6-1、6-2、Appendix 5-1~5-96）

各群について検査した肝臓及び膵臓については、雄では肝臓の微小肉芽腫が対照群及び 2.4 mg/kg 投与群の各 2 例、12 及び 60 mg/kg 投与群の各 3 例、膵臓の細胞浸潤が 2.4 及び 12 mg/kg 投与群の各 1 例、雌では肝臓の微小肉芽腫が 12 mg/kg 投与群の 1 例、膵臓の限局性腺房細胞萎縮が 2.4 mg/kg 投与群の 1 例に認められた。対照群及び高用量群について検査した生殖腺及び副生殖器については、前立腺の細胞浸潤が対照群 7 例、60 mg/kg 投与群の 6 例に認められ、精巣上体の細胞浸潤が対照群の 1 例に認められた。これらの所見のいずれもその発生状況から偶発性変化と判断した。

6.7　性周期（Table 7、Appendix 6-1~6-4）

2 週間の観察期間中に対照群を含め各群の全例に 3 又は 4 回の発情がみられ、発情回数及び性周期ともに対照群と各用量群との間に有意な差は認められなかった。

6.8　交配成績（Table 8、Appendix 7-1~7-4）

対照群を含め各群の全例の雌雄で交尾が認められ、且つ、雌の全例が妊娠し、交尾に要した日数にも対照群と各用量群との間に有意な差は認められなかった。

6.9　分娩成績（Table 9、Appendix 8-1~8-4）

対照群を含め各群の全例が正常に分娩し、出産率、妊娠期間、黄体数、着床痕数、着床率、分娩率、死産児率及び出生児数には対照群と各用量群との間に有意な差は認められなかった。また、いずれの群においても出産児の外表に異常は認められなかった。しかし、統計学的な有意差は認められないものの 60 mg/kg 投与群の分娩率は対照群に比して低値な傾向を示した。

6.10　出生児の生存性（Table 10、Appendix 9-1~9-4）

出生率及び生後 4 日生存率ともに対照群と各用量群との間に有意な差は認められなかった。

6.11　出生児の性比（Table 11、Appendix 10-1~10-4）

出産児、出生児及び生後 4 日生存児の性比には対照群と各用量群との間に有意な差は認められなかった。

6.12　出生児の体重（Table 12、Appendix 11-1~11-4）

雌雄ともに出生日及び生後 4 日の体重には対照群と各用量群との間に有意な差は認められなかった。

6.13　死亡児の外表所見（Table 13、Appendix 12-1~12-4）

いずれの死亡児の外表にも異常は認められなかった。

6.14　出生児の生後 4 日外表所見（Table 14、Appendix 13-1~13-4）

対照群を含む各群とも出生児の外表に異常はみられなかった。

7. 考察

1,4-ジクロロブタンをコーン油で希釈し、2.4、12 及び 60 mg/kg/day の投与量で、Sprague-Dawley 系 SPF ラットの雄に交配前 14 日間及び交配期間を通して剖検前日まで、雌には交配前 14 日間及び交配期間並びに妊娠期間を通して哺育 3 日まで経口投与し、雌雄動物に対する影響、特に、雌雄動物の性腺機能、交尾行動、受胎及び分娩などの生殖発生に及ぼす影響を検討した。なお、対照群には媒体であるコーン油を投与した。

7.1 雌雄動物に対する影響

投与期間を通して死亡動物は発現せず、一般状態に異常は認められなかった。雌では、2.4 mg/kg 投与群において妊娠期間中の体重増加量が有意な高値を示し、雄では、各用量群において投与 30 日の摂餌量が一時的な高値を示した。しかし、体重増加量については 12 及び 60 mg/kg 投与群では変化は認められず、摂餌量については用量群間の比較において用量との関連性が認められず、一時的な変動であることからいずれも偶発的な変動と判断した。病理学検査では、60 mg/kg 投与群において雄の肝臓重量が増加傾向を示した。肝臓重量の増加は先に行われた同被験物質の 28 日間反復経口投与毒性試験及び 14 日間回復試験[2)]でもみられており、被験物質投与の影響と考えられた。一方、雌の肝臓重量には、被験物質投与の影響は認められず、雌雄ともに肝臓及び膵臓の病理組織学検査において被験物質投与に関連した組織変化は認められなかった。

7.2 生殖発生に対する影響

雌の性周期並びに雌雄動物の交尾までに要した日数、交尾率、授精率及び受胎率に被験物質投与の影響を示唆する変化は認められなかった。これら交配成績に加え、生殖器及び副生殖器に関する病理組織学検査では、被験物質投与に起因した変化は認められなかったことから、1,4-ジクロロブタンの 60 mg/kg/day 投与は、精子形成及び排卵などの性腺機能、交尾から受胎に至る雌雄動物の生殖機能に影響を及ぼさないと判断した。

妊娠動物はいずれの群においても正常に分娩し、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数、出生率及び性比に被験物質投与の影響を示唆する変化は認められず、哺育状態に異常はみられなかった。また、出生児に関し、生後 4 日生存率並びに出生日及び生後 4 日の体重に被験物質投与の影響は認められず、出生児の外表に異常は認められなかった。しかし、60 mg/kg 投与群の分娩率（77.3%）は、統計学的な有意差は認められないものの対照群（94.0%）に比して低値な傾向にあった。更に個体ごとの分娩率では、60 mg/kg 投与群の 7 例は対照群の最低値（85.7%）を下回り、この内、2 例の分娩率は 28.6 及び 29.4%と極めて低値であり、且つ、出生児数も対照群の最低値（8）を下回った。一方、前述の如く死産児率には被験物質投

与の影響は認められていないことから、1,4-ジクロロブタンの 60 mg/kg/day 投与は、妊娠維持、分娩及び哺育などの妊娠母体の機能並びに出生児に対して顕著な影響を及ぼさないが、着床後の胎生期における胚・胎児の生存性に影響を及ぼす可能性が示唆された。

これらの結果から、本試験条件下における 1,4-ジクロロブタンの無影響量は、雄については 12 mg/kg/ day、雌については 60 mg/kg/ day であり、雌雄動物の生殖機能及び母体機能に対しては顕著な影響を及ぼさないものの、出生児の発生に関し、その胎生期における生存性への影響を考慮して生殖発生に対する無影響量は 12 mg/kg/ day と推定された。

8. 文献

1) [redacted]: GC を用いた被験液中 1,4-Dichlorobutane 濃度測定法バリデーション及び安定性試験（媒体：コーン油）並びに IR を用いた特性及び安定性試験（株式会社ボゾリサーチセンター　御殿場研究所、試験番号：A-2541、2012 年）

2) [redacted]: 1,4-ジクロロブタンのラットを用いる 28 日間反復経口投与毒性試験及び 14 日間回復試験（株式会社日本バイオリサーチセンター 羽島研究所、試験番号：502427、2011 年）

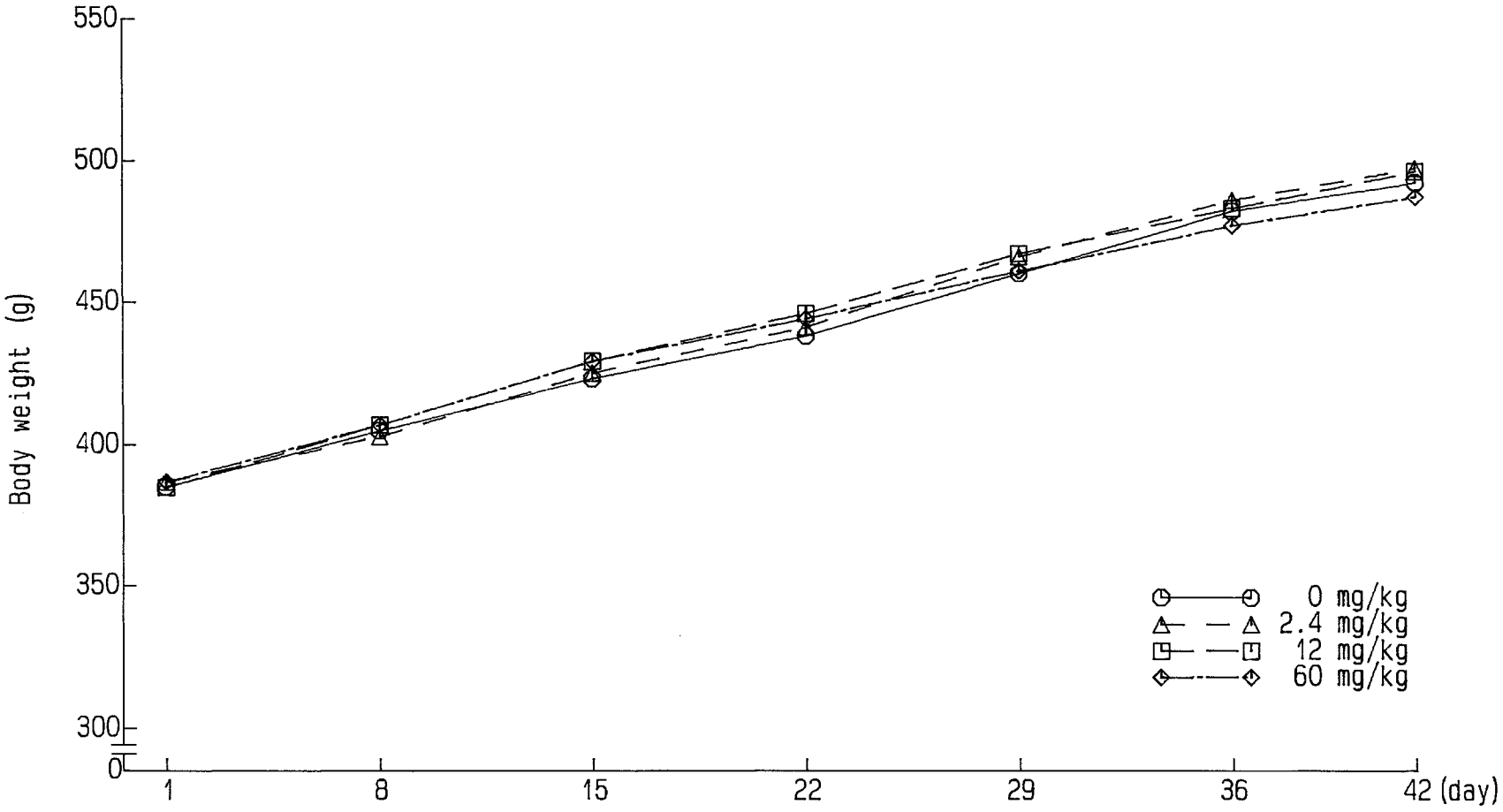


Fig.1 A reproduction/developmental toxicity screening test in rats treated orally with 1, 4-Dichlorobutane

Body weight of male rats

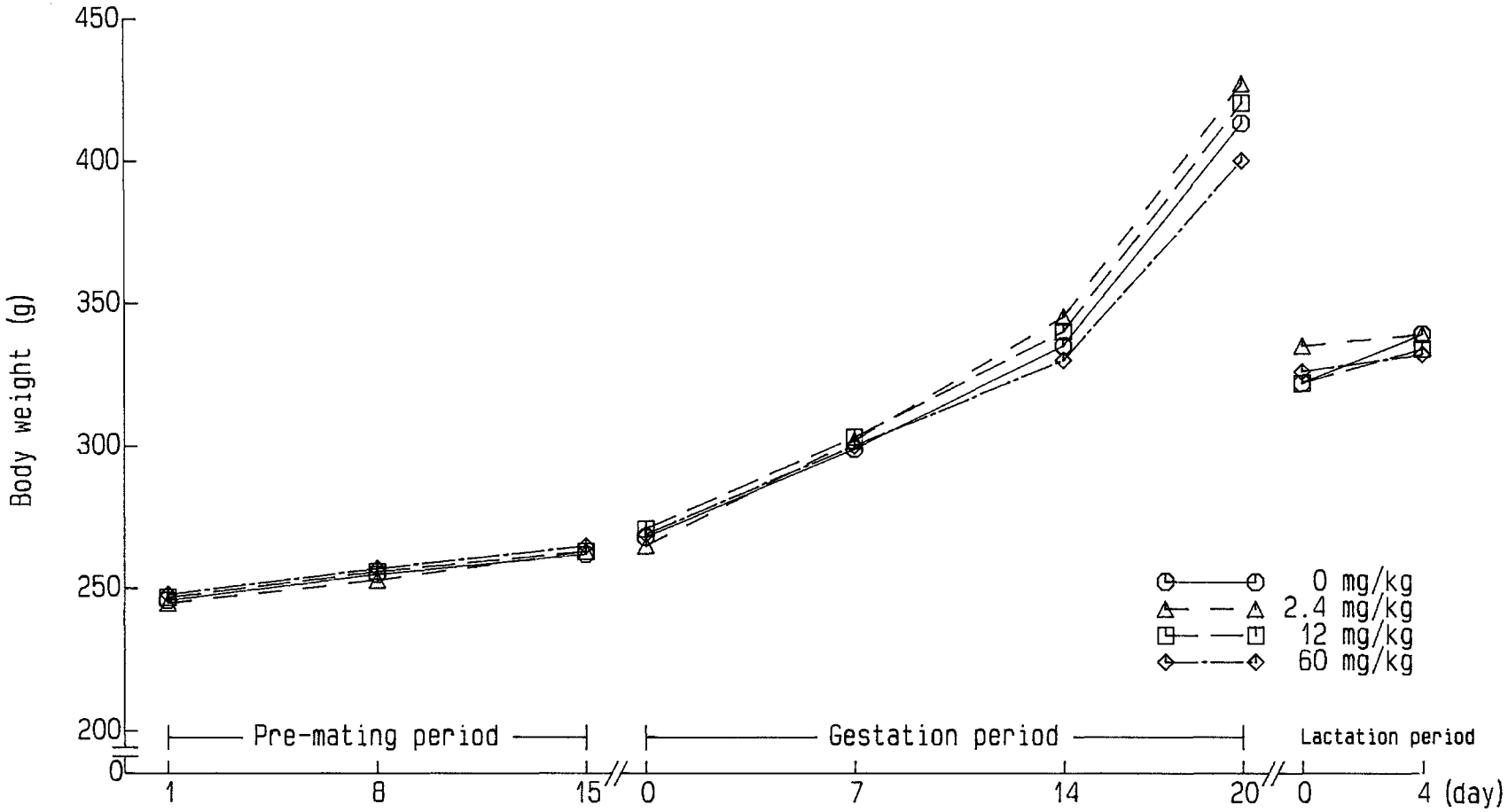


Fig.2 A reproduction/developmental toxicity screening test in rats treated orally with 1, 4-Dichlorobutane

Body weight of female rats

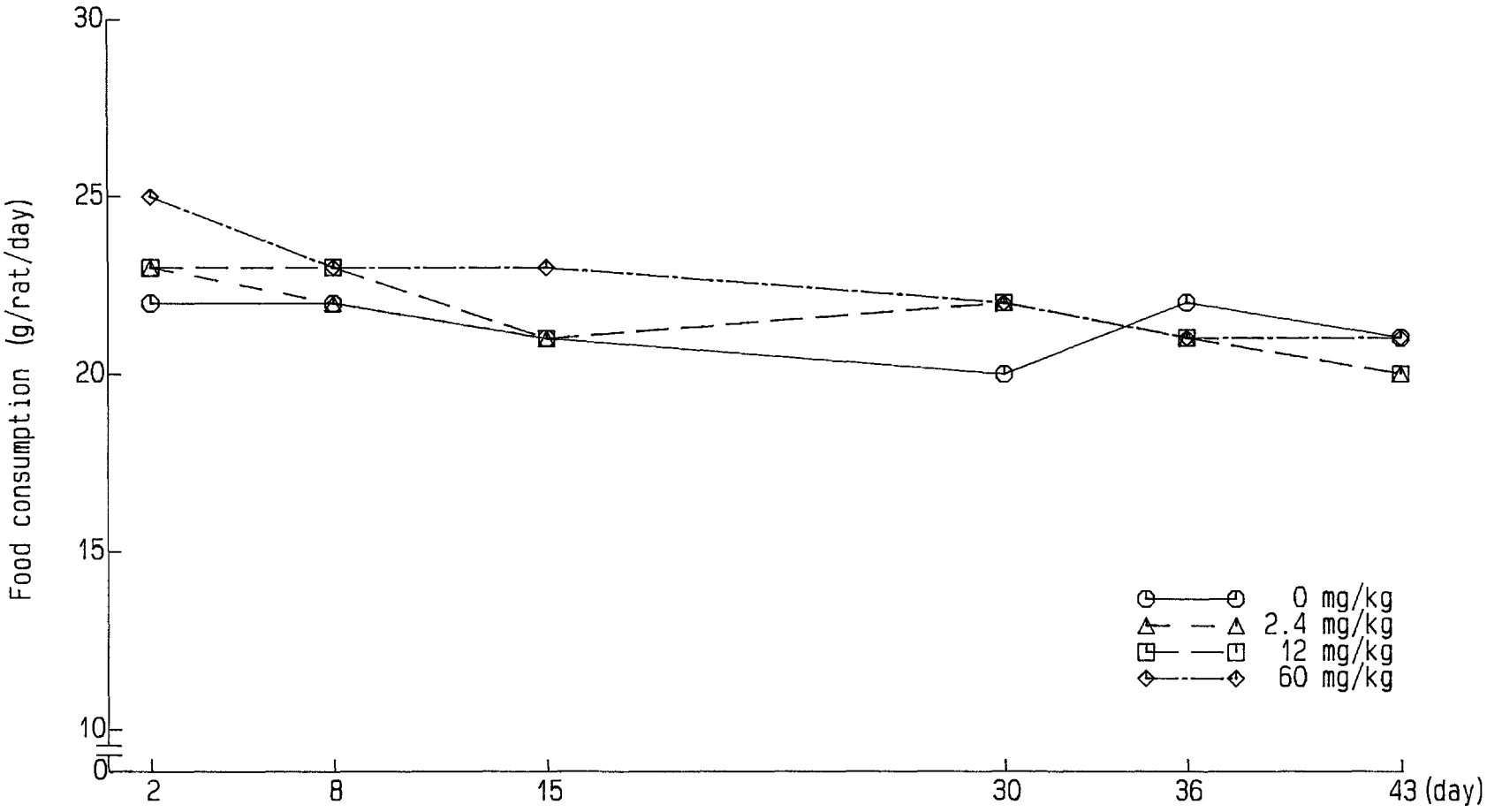


Fig.3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Food consumption of male rats

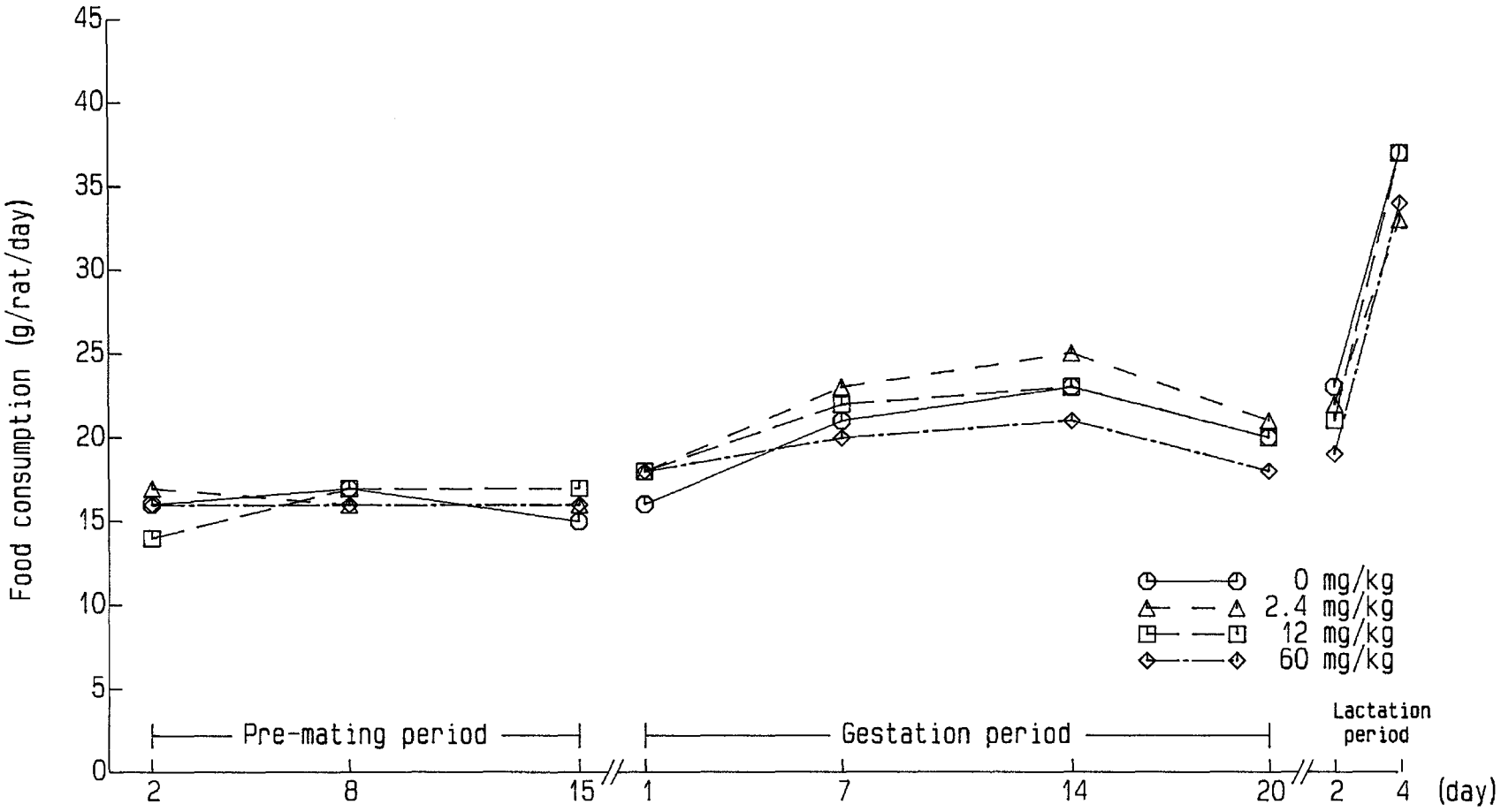


Fig.4 A reproduction/developmental toxicity screening test in rats treated orally with 1, 4-Dichlorobutane

Food consumption of female rats

Table 1-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Clinical signs in male rats

Dose mg/kg	Signs	Administration (day) 1-7	8-14	15-21	22-28	29-35	36-42	43a)
0	No. of animals	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0
2.4	No. of animals	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0
12	No. of animals	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0
60	No. of animals	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0

a): Day of necropsy

Table 1-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Clinical signs in female rats during the pre-mating period

Dose mg/kg	Signs	Administration (day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2.4	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
60	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Clinical signs in dams during the gestation period

Dose mg/kg	Signs	Administration 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
0	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	1	0
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2.4	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	2	0
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
12	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	1	0
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
60	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	0
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

a): Gestation day

Table 1-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Clinical signs in dams during the lactation period

Dose mg/kg	Signs	Administration 0	1	2	3	4a)
0	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
2.4	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
12	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
60	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0

a): Lactation day

Table 2-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Body weight of male rats

Dose mg/kg		Pre-mating period 1	8	15	Mating and post-mating periods 22	29	36	42a)	Gain 1-42
	No.	12	12	12	12	12	12	12	12
0	Mean	385	405	423	438	460	482	492	106
	S.D.	15	21	24	23	25	26	28	16
	No.	12	12	12	12	12	12	12	12
2.4	Mean	387	403	425	441	466	486	497	111
	S.D.	16	20	23	23	26	26	31	23
	No.	12	12	12	12	12	12	12	12
12	Mean	385	407	429	446	467	483	496	111
	S.D.	15	14	20	20	28	31	32	24
	No.	12	12	12	12	12	12	12	12
60	Mean	387	407	429	444	461	477	487	99
	S.D.	13	19	24	23	26	27	29	20

Unit: g
No.: No. of animals
a): Day of administration
No significant difference in any treated groups from control group

Table 2-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Body weight of female rats during the pre-mating period

Dose mg/kg		Day of administration 1	8	15	Gain 1-15
	No.	12	12	12	12
0	Mean	246	255	262	16
	S.D.	12	15	15	11
	No.	12	12	12	12
2.4	Mean	245	253	263	18
	S.D.	11	16	15	9
	No.	12	12	12	12
12	Mean	247	256	263	16
	S.D.	14	12	15	8
	No.	12	12	12	12
60	Mean	248	257	265	17
	S.D.	14	14	18	8

Unit: g
No.: No. of animals
No significant difference in any treated groups from control group

Table 2-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Body weight of dams during the gestation period

Dose mg/kg		Administration 0	7	14	20a)	Gain 0-20
	No.	12	12	12	12	12
0	Mean	268	299	335	413	145
	S.D.	18	16	16	19	7
	No.	12	12	12	12	12
2.4	Mean	265	302	345	427	162*
	S.D.	17	16	20	28	17ST
	No.	12	12	12	12	12
12	Mean	271	303	340	420	149
	S.D.	18	18	21	21	7
	No.	12	12	12	12	12
60	Mean	269	300	330	400	131
	S.D.	21	22	20	25	17

Unit: g
No.: No. of dams
a): Gestation day
*: $p<0.05$ (Significant difference from control group)
ST: Steel's test

Table 2-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Body weight of dams during the lactation period

Dose mg/kg		Administration 0	Administration 4a)	Gain 0-4
	No.	12	12	12
0	Mean	322	339	17
	S.D.	29	18	18
	No.	12	12	12
2.4	Mean	335	339	5
	S.D.	23	18	14
	No.	12	12	12
12	Mean	322	334	12
	S.D.	23	18	15
	No.	12	12	12
60	Mean	326	332	6
	S.D.	24	23	9

Unit: g
No.: No. of dams
a): Lactation day
No significant difference in any treated groups from control group

Table 3-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Food consumption of male rats

Dose mg/kg		Pre-mating period 2	8	15	Post-mating period 30	36a)	43b)
0	No.	12	12	12	12	12	12
	Mean	22	22	21	20	22	21
	S.D.	2	2	2	2	2	2
2.4	No.	12	12	12	12	12	12
	Mean	23	22	21	22*	21	20
	S.D.	2	2	2	2D	2	2
12	No.	12	12	12	12	12	12
	Mean	23	23	21	22*	21	20
	S.D.	3	2	2	2D	3	3
60	No.	12	12	12	12	12	12
	Mean	25	23	23	22*	21	21
	S.D.	2	3	3	2D	2	2

Unit: g/rat/day
No.: No. of animals
a): Day of administration
b): Day of necropsy
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 3-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Food consumption of female rats during the pre-mating period

Dose mg/kg		Day of administration 2	8	15
	No.	12	12	12
0	Mean	16	17	15
	S.D.	3	3	2
	No.	12	12	12
2.4	Mean	17	16	16
	S.D.	3	4	2
	No.	12	12	12
12	Mean	14	17	17
	S.D.	4	2	3
	No.	12	12	12
60	Mean	16	16	16
	S.D.	4	3	3

Unit: g/rat/day
No.: No. of animals
No significant difference in any treated groups from control group

Table 3-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Food consumption of dams during the gestation period

Dose mg/kg		Administration 1	7	14	20a)
	No.	12	12	12	12
0	Mean	16	21	23	20
	S.D.	4	2	2	2
	No.	12	12	12	12
2.4	Mean	18	23	25	21
	S.D.	3	3	3	3
	No.	12	12	12	12
12	Mean	18	22	23	20
	S.D.	2	3	3	3
	No.	12	12	12	12
60	Mean	18	20	21	18
	S.D.	4	3	3	3

Unit: g/rat/day
No.: No. of dams
a): Gestation day
No significant difference in any treated groups from control group

Table 3-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Food consumption of dams during the lactation period

Dose mg/kg		Administration 2	4a)
	No.	12	12
0	Mean	23	37
	S.D.	4	5
	No.	12	12
2.4	Mean	22	33
	S.D.	5	6
	No.	12	12
12	Mean	21	37
	S.D.	4	6
	No.	12	12
60	Mean	19	34
	S.D.	5	7

Unit: g/rat/day
No.: No. of dams
a): Lactation day
No significant difference in any treated groups from control group

Table 4-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Organ weight of male rats

	Dose mg/kg		Body weight g	Liver g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	0	No.	12	12	12	12	12	12
		Mean	495	16.52	3.18	1309	1.77	1.24
		S.D.	28	1.07	0.22	105	0.26	0.17
	2.4	No.	12	12	12	12	12	12
		Mean	500	16.89	3.15	1266	1.77	1.33
		S.D.	31	1.89	0.31	110	0.30	0.19
	12	No.	12	12	12	12	12	12
		Mean	497	16.12	3.05	1286	1.81	1.27
		S.D.	31	1.50	0.17	120	0.20	0.13
	60	No.	12	12	12	12	12	12
		Mean	490	17.44	3.08	1317	1.95	1.25
		S.D.	27	1.85	0.29	105	0.29	0.14
Relative	0	No.		12	12	12	12	12
		Mean		3.34	0.64	265	0.36	0.25
		S.D.		0.13	0.06	24	0.06	0.04
	2.4	No.		12	12	12	12	12
		Mean		3.37	0.63	254	0.35	0.27
		S.D.		0.26	0.06	26	0.06	0.03
	12	No.		12	12	12	12	12
		Mean		3.24	0.62	259	0.37	0.26
		S.D.		0.17	0.04	27	0.06	0.03
	60	No.		12	12	12	12	12
		Mean		3.56*	0.63	269	0.40	0.25
		S.D.		0.24D	0.06	17	0.05	0.03

No.: No. of animals
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 4-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Organ weight of female rats

	Dose mg/kg		Body weight g	Liver g(g/100g BW)	Ovary (R+L) mg(mg/100g BW)
Absolute	0	No.	12	12	12
		Mean	339	13.37	99.8
		S.D.	18	1.00	9.2
	2.4	No.	12	12	12
		Mean	339	13.15	104.2
		S.D.	18	1.07	16.3
	12	No.	12	12	12
		Mean	334	12.99	107.4
		S.D.	18	1.10	12.0
	60	No.	12	12	12
		Mean	332	13.43	107.2
		S.D.	23	1.67	12.7
Relative	0	No.		12	12
		Mean		3.95	29.5
		S.D.		0.24	3.1
	2.4	No.		12	12
		Mean		3.88	30.6
		S.D.		0.30	4.0
	12	No.		12	12
		Mean		3.89	32.1
		S.D.		0.31	2.7
	60	No.		12	12
		Mean		4.05	32.4
		S.D.		0.34	3.7

No.: No. of animals
No significant difference in any treated groups from control group

R-1113

Table 5-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Gross pathological findings

Organs	Sex:	M	M	M	M
	Dose(mg/kg):	0	2.4	12	60
Findings	Number:	12	12	12	12
Liver					
Hepatodiaphragmatic nodule		0	0	0	1
Lung(bronchus)					
Focus,dark red		1	0	0	0

M : Male

R-1113

Table 5-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Gross pathological findings

Organs	Sex:	F	F	F	F
	Dose(mg/kg):	0	2.4	12	60
Findings	Number:	12	12	12	12
All tissues					
Not remarkable		12	12	12	12

F : Female

Table 6-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Histopathological findings

Organs	Sex:	M	M	M	M
	Dose(mg/kg):	0	2.4	12	60
Findings	Number:	12	12	12	12
Epididymis					
Number examined		12	0	0	12
Not remarkable		11	0	0	12
Cell infiltration		1	0	0	0
minimal		1	0	0	0
Liver					
Number examined		12	12	12	12
Not remarkable		10	10	9	8
Hepatodiaphragmatic nodule		0	0	0	1
mild		0	0	0	1
Microgranuloma		2	2	3	3
minimal		2	2	3	3
Pancreas					
Number examined		12	12	12	12
Not remarkable		12	11	11	12
Cell infiltration		0	1	1	0
minimal		0	1	1	0
Prostate					
Number examined		12	0	0	12
Not remarkable		5	0	0	6
Cell infiltration		7	0	0	6
minimal		6	0	0	6
mild		1	0	0	0
Seminal vesicle(coagulating gland)					
Number examined		12	0	0	12
Not remarkable		12	0	0	12
Testis					
Number examined		12	0	0	12
Not remarkable		12	0	0	12

M : Male

Table 6-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Histopathological findings

Organs	Sex:	F	F	F	F
	Dose(mg/kg):	0	2.4	12	60
Findings	Number:	12	12	12	12
Liver					
Number examined		12	12	12	12
Not remarkable		12	12	11	12
Microgranuloma		0	0	1	0
minimal		0	0	1	0
Ovary					
Number examined		12	0	0	12
Not remarkable		12	0	0	12
Pancreas					
Number examined		12	12	12	12
Not remarkable		12	11	12	12
Atrophy,acinar,focal		0	1	0	0
minimal		0	1	0	0
Uterus					
Number examined		12	0	0	12
Not remarkable		12	0	0	12
Vagina					
Number examined		12	0	0	12
Not remarkable		12	0	0	12

F : Female

Table 7 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Estrous cycle in female rats during the pre-mating period

Dose mg/kg	No. of animals	Count of estrus 0	1	2	3	4	Mean±S.D.	Mean duration of cycles Mean±S.D.
0	12	0	0	0	3	9	3.8±0.5	4.2±0.5
2.4	12	0	0	0	5	7	3.6±0.5	4.1±0.3
12	12	0	0	0	2	10	3.8±0.4	4.1±0.1
60	12	0	0	0	7	5	3.4±0.5	4.4±0.5

No significant difference in any treated groups from control group

Table 8 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Mating and fertility of animals

	Male				Female			
Dose mg/kg	No. of males	Days until copulation Mean±S.D.	Copulation index (%) a)	Insemination index (%) b)	No. of females	Days until copulation Mean±S.D.	Copulation index (%) a)	Fertility index (%) c)
0	12	3.5±2.4	12/12(100.0)	12/12(100.0)	12	3.5±2.4	12/12(100.0)	12/12(100.0)
2.4	12	2.2±1.1	12/12(100.0)	12/12(100.0)	12	2.2±1.1	12/12(100.0)	12/12(100.0)
12	12	3.1±1.5	12/12(100.0)	12/12(100.0)	12	3.1±1.5	12/12(100.0)	12/12(100.0)
60	12	2.3±1.4	12/12(100.0)	12/12(100.0)	12	2.3±1.4	12/12(100.0)	12/12(100.0)

a): (No. of copulated animals / No. of mated animals)×100
b): (No. of males which impregnated females / No. of copulated males)×100
c): (No. of pregnant females / No. of copulated females)×100
No significant difference in any treated groups from control group

Table 9 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Delivery data on dams

Dose mg/kg		No. of pregnant females	No. of females with liveborns	Gestation index % a)	Gestation length in days	No. of corpora lutea	No. of implan-tation sites	Implan-tation index % b)	Delivery index % c)	No. of still-borns (%)d)	No. of live-borns	External e) abnor-malities(%)f)
	Total	12	12	100.0		173	169			1	158	0
0	Mean				22.1	14.4	14.1	98.0	94.0	(0.6)	13.2	(0.0)
	S.D.				0.2	2.1	1.8	3.9	5.2	(2.0)	1.9	(0.0)
	Total	12	12	100.0		193	180			0	164	0
2.4	Mean				22.0	16.1	15.0	93.4	91.1	(0.0)	13.7	(0.0)
	S.D.				0.5	2.0	2.9	14.6	7.5	(0.0)	3.1	(0.0)
	Total	12	12	100.0		187	185			3	174	0
12	Mean				22.0	15.6	15.4	99.0	95.9	(1.8)	14.5	(0.0)
	S.D.				0.3	1.4	1.4	2.5	6.4	(4.4)	1.6	(0.0)
	Total	12	12	100.0		188	183			1	140	0
60	Mean				22.1	15.7	15.3	97.4	77.3	(0.6)	11.7	(0.0)
	S.D.				0.4	1.4	1.4	4.2	25.4	(1.9)	3.8	(0.0)

a): (No. of females which delivered liveborns / No. of pregnant females)×100
b): (No. of implantation sites / No. of corpora lutea)×100
c): (No. of delivered pups / No. of implantation sites)×100
d): (No. of stillborns / No. of delivered pups)×100
e): No. of delivered pups with external abnormalities
f): (No. of delivered pups with external abnormalities / No. of delivered pups)×100
No significant difference in any treated groups from control group

Table 10 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Viability index of pups

Dose mg/kg		No. of dams	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of dams	No. of live pups Day 0	No. of live pups Day 4	Viability index on postnatal day 4 % b)
	Total	12	158	159		12	158	157	
0	Mean		13.2	13.3	99.4		13.2	13.1	99.4
	S.D.		1.9	1.9	2.0		1.9	1.9	2.0
	Total	12	164	164		12	164	160	
2.4	Mean		13.7	13.7	100.0		13.7	13.3	98.1
	S.D.		3.1	3.1	0.0		3.1	2.6	4.3
	Total	12	174	177		12	174	168	
12	Mean		14.5	14.8	98.2		14.5	14.0	97.0
	S.D.		1.6	1.3	4.4		1.6	1.1	6.9
	Total	12	140	141		12	140	135	
60	Mean		11.7	11.8	99.4		11.7	11.3	95.1
	S.D.		3.8	3.9	1.9		3.8	4.1	9.1

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100
No significant difference in any treated groups from control group

Table 11 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Sex ratio of pups

Dose mg/kg	No. of dams		Liveborns No. of males	Liveborns No. of females	Stillborns No. of males	Stillborns No. of females	Sex ratio of delivered pups a)	Sex ratio of liveborns b)	No. of dams	Postnatal day 4 No. of males	Postnatal day 4 No. of females	Sex ratio of live pups on day 4 c)
		Total	82	76	0	1				81	76	
0	12	Mean	6.8	6.3	0.0	0.1	0.51	0.51	12	6.8	6.3	0.51
		S.D.	2.3	1.6	0.0	0.3	0.13	0.13		2.3	1.6	0.13
		Total	94	70	0	0				92	68	
2.4	12	Mean	7.8	5.8	0.0	0.0	0.57	0.57	12	7.7	5.7	0.58
		S.D.	2.2	2.2	0.0	0.0	0.12	0.12		2.1	2.1	0.13
		Total	83	91	1	2				82	86	
12	12	Mean	6.9	7.6	0.1	0.2	0.48	0.48	12	6.8	7.2	0.49
		S.D.	1.4	2.2	0.3	0.4	0.11	0.12		1.4	2.0	0.11
		Total	76	64	0	1				72	63	
60	12	Mean	6.3	5.3	0.0	0.1	0.50	0.51	12	6.0	5.3	0.51
		S.D.	3.3	2.0	0.0	0.3	0.21	0.21		3.2	2.1	0.21

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4
No significant difference in any treated groups from control group

Table 12 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Body weight of pups

Dose mg/kg		Male 0	Male 4a)	Female 0	Female 4a)
0	No.	12	12	12	12
	Mean	6.8	10.4	6.4	9.9
	S.D.	0.3	0.4	0.3	0.3
2.4	No.	12	12	12	12
	Mean	6.6	10.2	6.3	9.5
	S.D.	0.7	1.8	0.6	1.7
12	No.	12	12	12	12
	Mean	6.5	10.0	6.1	9.4
	S.D.	0.4	0.8	0.4	0.7
60	No.	11b)	11	12	12
	Mean	6.6	10.2	6.4	9.9
	S.D.	0.8	1.3	0.8	1.6

Unit: g
No.: No. of dams
a): Postnatal day
b): Male pups were not born in one dam.
No significant difference in any treated groups from control group

Table 13 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Externally for gross abnormalities in dead pups

Dose (mg/kg)	0	2.4	12	60
Male				
No. of pups examined	1	1	0	2
No. of pups with abnormal findings	0	0	0	0
Female				
No. of pups examined	0	1	1	0
No. of pups with abnormal findings	0	0	0	0

Table 14 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Externally for gross abnormalities in pups on postnatal day 4

Dose (mg/kg)	0	2.4	12	60
Male				
No. of pups examined	81	92	82	72
No. of pups with abnormal findings	0	0	0	0
Female				
No. of pups examined	76	68	86	63
No. of pups with abnormal findings	0	0	0	0

Appendix 1-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in male rats
Dose (mg/kg): 0

Animal number	Administration (day) 1-7	8-14	15-21	22-28	29-35	36-42	43a)
1001	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in male rats
Dose (mg/kg): 2.4

Animal number	Administration (day) 1-7	8-14	15-21	22-28	29-35	36-42	43a)
2001	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-
2006	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-
2009	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-
2011	-	-	-	-	-	-	-
2012	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in male rats
Dose (mg/kg): 12

Animal number	Administration (day) 1-7	8-14	15-21	22-28	29-35	36-42	43a)
3001	-	-	-	-	-	-	-
3002	-	-	-	-	-	-	-
3003	-	-	-	-	-	-	-
3004	-	-	-	-	-	-	-
3005	-	-	-	-	-	-	-
3006	-	-	-	-	-	-	-
3007	-	-	-	-	-	-	-
3008	-	-	-	-	-	-	-
3009	-	-	-	-	-	-	-
3010	-	-	-	-	-	-	-
3011	-	-	-	-	-	-	-
3012	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in male rats
Dose (mg/kg): 60

Animal number	Administration (day) 1-7	8-14	15-21	22-28	29-35	36-42	43a)
4001	-	-	-	-	-	-	-
4002	-	-	-	-	-	-	-
4003	-	-	-	-	-	-	-
4004	-	-	-	-	-	-	-
4005	-	-	-	-	-	-	-
4006	-	-	-	-	-	-	-
4007	-	-	-	-	-	-	-
4008	-	-	-	-	-	-	-
4009	-	-	-	-	-	-	-
4010	-	-	-	-	-	-	-
4011	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-5 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in female rats during the pre-mating period
Dose (mg/kg): 0

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

-: No abnormal findings

Appendix 1-6 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in female rats during the pre-mating period
Dose (mg/kg): 2.4

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

-: No abnormal findings

Appendix 1-7 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in female rats during the pre-mating period
Dose (mg/kg): 12

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

-: No abnormal findings

Appendix 1-8 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in female rats during the pre-mating period
Dose (mg/kg): 60

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

-: No abnormal findings

Appendix 1-9 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in dams during the gestation period
Dose (mg/kg): 0

Dam number	Administration																						
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	

a): Gestation day
-: No abnormal findings
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-10 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in dams during the gestation period
Dose (mg/kg): 2.4

Dam number	Administration																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		

a): Gestation day
-: No abnormal findings
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-11 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in dams during the gestation period
Dose (mg/kg): 12

Dam number	Administration																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
3101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		

a): Gestation day
-: No abnormal findings
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-12 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in dams during the gestation period
Dose (mg/kg): 60

Dam number	Administration																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
4101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
4105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	

a): Gestation day
-: No abnormal findings
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-13 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in dams during the lactation period
Dose (mg/kg): 0

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

a): Lactation day
-: No abnormal findings

Appendix 1-14 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in dams during the lactation period
Dose (mg/kg): 2.4

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

a): Lactation day
-: No abnormal findings

Appendix 1-15 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in dams during the lactation period
Dose (mg/kg): 12

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

a): Lactation day
-: No abnormal findings

Appendix 1-16 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual clinical signs in dams during the lactation period
Dose (mg/kg): 60

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

a): Lactation day
-: No abnormal findings

Appendix 2-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of male rats
Dose (mg/kg): 0

Animal number	Pre-mating period 1	8	15	Mating and post-mating periods 22	29	36	42a)	Gain 1-42
1001	374	391	410	416	437	451	456	82
1002	401	423	440	461	493	521	526	125
1003	402	419	440	455	473	482	488	86
1004	383	409	423	440	456	479	497	114
1005	377	388	403	419	439	460	471	94
1006	411	442	466	472	504	529	538	127
1007	392	412	435	452	477	493	510	118
1008	379	392	407	432	454	483	499	120
1009	372	391	405	416	437	457	467	95
1010	364	376	389	407	425	451	452	88
1011	398	433	457	466	484	507	516	118
1012	372	383	406	420	446	470	481	109
Mean	385	405	423	438	460	482	492	106
S.D.	15	21	24	23	25	26	28	16

Unit: g
a): Day of administration

Appendix 2-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of male rats
Dose (mg/kg): 2.4

Animal number	Pre-mating period 1	8	15	Mating and post-mating periods 22	29	36	42a)	Gain 1-42
2001	397	421	452	477	501	519	543	146
2002	389	417	438	455	477	493	500	111
2003	380	376	398	419	442	459	467	87
2004	363	378	396	412	430	450	464	101
2005	407	420	452	452	492	513	526	119
2006	371	383	415	440	476	502	517	146
2007	390	403	429	436	451	463	457	67
2008	368	382	399	410	428	450	459	91
2009	412	429	446	465	494	520	539	127
2010	389	409	424	442	470	487	493	104
2011	375	388	400	419	443	476	491	116
2012	398	428	452	470	482	503	512	114
Mean	387	403	425	441	466	486	497	111
S.D.	16	20	23	23	26	26	31	23

Unit: g
a): Day of administration

Appendix 2-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of male rats
Dose (mg/kg): 12

Animal number	Pre-mating period 1	8	15	Mating and post-mating periods 22	29	36	42a)	Gain 1-42
3001	372	389	403	425	438	449	466	94
3002	375	399	424	443	464	482	493	118
3003	402	423	452	461	478	491	503	101
3004	369	399	412	426	441	459	473	104
3005	391	410	439	465	497	520	537	146
3006	415	435	469	488	520	546	562	147
3007	385	408	436	460	487	502	513	128
3008	383	412	433	441	462	470	487	104
3009	393	418	436	456	482	502	513	120
3010	396	406	415	428	440	449	455	59
3011	375	403	430	438	464	477	484	109
3012	361	382	403	422	427	449	462	101
Mean	385	407	429	446	467	483	496	111
S.D.	15	14	20	20	28	31	32	24

Unit: g
a): Day of administration

Appendix 2-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of male rats
Dose (mg/kg): 60

Animal number	Pre-mating period 1	8	15	Mating and post-mating periods 22	29	36	42a)	Gain 1-42
4001	384	399	416	429	441	461	470	86
4002	397	421	444	454	475	486	487	90
4003	401	434	469	478	500	527	535	134
4004	386	396	410	427	442	458	468	82
4005	382	404	430	447	468	485	495	113
4006	371	389	406	425	436	449	457	86
4007	398	425	452	474	492	512	532	134
4008	400	422	447	458	475	497	506	106
4009	378	387	402	419	426	441	451	73
4010	407	431	457	472	496	497	510	103
4011	375	392	417	421	444	462	473	98
4012	368	383	401	420	435	453	455	87
Mean	387	407	429	444	461	477	487	99
S.D.	13	19	24	23	26	27	29	20

Unit: g
a): Day of administration

Appendix 2-5 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of female rats during the pre-mating period
Dose (mg/kg): 0

Animal number	Day of administration 1	8	15	Gain 1-15
1101	235	251	272	37
1102	271	288	291	20
1103	232	245	255	23
1104	251	243	248	-3
1105	259	271	282	23
1106	239	246	260	21
1107	237	234	244	7
1108	251	254	253	2
1109	255	266	273	18
1110	243	250	252	9
1111	241	266	265	24
1112	235	240	249	14
Mean	246	255	262	16
S.D.	12	15	15	11

Unit: g

Appendix 2-6 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of female rats during the pre-mating period
Dose (mg/kg): 2.4

Animal number	Day of administration 1	8	15	Gain 1-15
2101	239	239	243	4
2102	245	264	280	35
2103	248	248	264	16
2104	262	273	277	15
2105	249	264	267	18
2106	246	247	258	12
2107	224	231	243	19
2108	247	247	263	16
2109	230	229	242	12
2110	248	262	265	17
2111	238	254	270	32
2112	264	282	287	23
Mean	245	253	263	18
S.D.	11	16	15	9

Unit: g

Appendix 2-7 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of female rats during the pre-mating period
Dose (mg/kg): 12

Animal number	Day of administration 1	8	15	Gain 1-15
3101	240	241	242	2
3102	242	257	269	27
3103	237	246	252	15
3104	243	247	248	5
3105	251	260	272	21
3106	236	256	261	25
3107	247	250	263	16
3108	224	239	244	20
3109	247	257	263	16
3110	268	266	286	18
3111	262	269	269	7
3112	269	281	289	20
Mean	247	256	263	16
S.D.	14	12	15	8

Unit: g

Appendix 2-8 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of female rats during the pre-mating period
Dose (mg/kg): 60

Animal number	Day of administration 1	8	15	Gain 1-15
4101	224	237	234	10
4102	242	241	254	12
4103	263	274	290	27
4104	261	267	262	1
4105	241	258	254	13
4106	229	245	251	22
4107	265	275	288	23
4108	251	265	267	16
4109	239	239	253	14
4110	252	259	275	23
4111	247	256	259	12
4112	264	270	293	29
Mean	248	257	265	17
S.D.	14	14	18	8

Unit: g

Appendix 2-9 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of dams during the gestation period
Dose (mg/kg): 0

Dam number	Administration 0	7	14	20a)	Gain 0-20
1101	255	290	328	411	156
1102	304	325	360	451	147
1103	259	285	324	405	146
1104	247	295	332	393	146
1105	293	318	349	438	145
1106	261	296	333	403	142
1107	248	276	306	387	139
1108	277	310	350	421	144
1109	279	299	327	410	131
1110	261	291	329	415	154
1111	283	322	358	431	148
1112	253	286	322	395	142
Mean	268	299	335	413	145
S.D.	18	16	16	19	7

Unit: g
a): Gestation day

Appendix 2-10 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of dams during the gestation period
Dose (mg/kg): 2.4

Dam number	Administration 0	7	14	20a)	Gain 0-20
2101	255	287	318	403	148
2102	285	323	364	463	178
2103	263	296	342	429	166
2104	287	326	370	452	165
2105	270	308	357	435	165
2106	264	297	330	404	140
2107	232	273	313	383	151
2108	266	313	366	462	196
2109	241	289	328	384	143
2110	265	300	350	446	181
2111	272	294	333	427	155
2112	282	319	364	438	156
Mean	265	302	345	427	162
S.D.	17	16	20	28	17

Unit: g
a): Gestation day

Appendix 2-11 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of dams during the gestation period
Dose (mg/kg): 12

Dam number	Administration 0	7	14	20a)	Gain 0-20
3101	248	281	316	402	154
3102	282	318	365	441	159
3103	253	292	336	405	152
3104	257	283	318	400	143
3105	280	312	347	427	147
3106	271	296	328	420	149
3107	270	291	322	401	131
3108	251	285	319	396	145
3109	264	302	337	413	149
3110	280	317	358	435	155
3111	292	322	353	439	147
3112	306	336	379	463	157
Mean	271	303	340	420	149
S.D.	18	18	21	21	7

Unit: g
a): Gestation day

Appendix 2-12 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of dams during the gestation period
Dose (mg/kg): 60

Dam number	Administration 0	7	14	20a)	Gain 0-20
4101	229	262	292	365	136
4102	248	286	310	350	102
4103	292	328	352	436	144
4104	287	318	346	412	125
4105	255	297	322	409	154
4106	257	275	312	390	133
4107	291	323	349	404	113
4108	275	305	335	408	133
4109	249	279	318	391	142
4110	281	311	338	384	103
4111	263	293	327	413	150
4112	296	328	361	432	136
Mean	269	300	330	400	131
S.D.	21	22	20	25	17

Unit: g
a): Gestation day

Appendix 2-13 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of dams during the lactation period
Dose (mg/kg): 0

Dam number	Administration 0	4a)	Gain 0-4
1101	327	332	5
1102	353	364	11
1103	290	329	39
1104	339	334	-5
1105	348	354	6
1106	322	329	7
1107	283	304	21
1108	324	356	32
1109	289	340	51
1110	307	327	20
1111	378	366	-12
1112	308	331	23
Mean	322	339	17
S.D.	29	18	18

Unit: g
a): Lactation day

Appendix 2-14 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of dams during the lactation period
Dose (mg/kg): 2.4

Dam number	Administration 0	Administration 4a)	Gain 0-4
2101	314	310	-4
2102	347	367	20
2103	352	356	4
2104	350	350	0
2105	329	339	10
2106	310	329	19
2107	287	308	21
2108	361	341	-20
2109	320	342	22
2110	334	328	-6
2111	350	342	-8
2112	362	358	-4
Mean	335	339	5
S.D.	23	18	14

Unit: g
a): Lactation day

Appendix 2-15 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of dams during the lactation period
Dose (mg/kg): 12

Dam number	Administration 0	4a)	Gain 0-4
3101	300	305	5
3102	365	365	0
3103	305	349	44
3104	288	317	29
3105	327	345	18
3106	306	329	23
3107	308	316	8
3108	321	320	-1
3109	315	326	11
3110	343	347	4
3111	333	351	18
3112	351	337	-14
Mean	322	334	12
S.D.	23	18	15

Unit: g
a): Lactation day

Appendix 2-16 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of dams during the lactation period
Dose (mg/kg): 60

Dam number	Administration 0	4a)	Gain 0-4
4101	293	291	-2
4102	318	322	4
4103	345	357	12
4104	360	351	-9
4105	328	329	1
4106	300	301	1
4107	352	358	6
4108	318	339	21
4109	298	315	17
4110	354	351	-3
4111	304	312	8
4112	341	354	13
Mean	326	332	6
S.D.	24	23	9

Unit: g
a): Lactation day

Appendix 3-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of male rats
Dose (mg/kg): 0

Animal number	Pre-mating period			Post-mating period		
	2	8	15	30	36a)	43b)
1001	21	20	21	17	21	18
1002	26	22	21	21	26	25
1003	24	25	19	18	19	19
1004	22	23	21	21	19	19
1005	19	21	18	20	22	22
1006	24	25	23	21	22	23
1007	23	24	22	20	20	21
1008	23	22	19	20	23	21
1009	20	20	19	19	18	20
1010	22	18	20	21	24	19
1011	23	26	25	21	22	18
1012	22	20	23	23	23	23
Mean	22	22	21	20	22	21
S.D.	2	2	2	2	2	2

Unit: g/rat/day
a): Day of administration
b): Day of necropsy

Appendix 3-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of male rats
Dose (mg/kg): 2.4

Animal number	Pre-mating period			Post-mating period		
	2	8	15	30	36a)	43b)
2001	26	24	25	24	23	22
2002	26	23	22	21	20	16
2003	20	17	18	20	19	17
2004	22	20	21	25	21	24
2005	25	21	23	25	18	19
2006	20	20	22	24	23	22
2007	20	20	23	20	18	17
2008	23	23	20	22	24	20
2009	20	22	17	23	19	19
2010	21	22	19	23	22	20
2011	23	25	21	22	22	20
2012	25	22	19	19	18	18
Mean	23	22	21	22	21	20
S.D.	2	2	2	2	2	2

Unit: g/rat/day
a): Day of administration
b): Day of necropsy

Appendix 3-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of male rats
Dose (mg/kg): 12

Animal number	Pre-mating period			Post-mating period		
	2	8	15	30	36a)	43b)
3001	20	20	19	19	16	20
3002	24	22	22	20	22	17
3003	25	21	22	24	19	17
3004	24	25	22	21	21	19
3005	20	25	22	23	25	25
3006	27	26	24	23	24	20
3007	24	23	21	25	22	24
3008	19	22	19	20	19	21
3009	24	23	23	25	23	19
3010	27	22	22	22	18	18
3011	22	25	21	23	22	22
3012	20	21	19	21	18	19
Mean	23	23	21	22	21	20
S.D.	3	2	2	2	3	3

Unit: g/rat/day
a): Day of administration
b): Day of necropsy

Appendix 3-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of male rats
Dose (mg/kg): 60

Animal number	Pre-mating period			Post-mating period		
	2	8	15	30	36a)	43b)
4001	22	18	19	20	20	21
4002	23	24	23	22	21	20
4003	24	26	26	25	24	24
4004	24	22	20	22	20	24
4005	23	23	22	22	23	18
4006	24	22	19	21	19	21
4007	28	25	25	25	22	23
4008	27	22	24	21	24	22
4009	24	23	21	23	20	22
4010	23	29	27	22	17	21
4011	25	22	26	24	23	21
4012	27	22	20	18	22	18
Mean	25	23	23	22	21	21
S.D.	2	3	3	2	2	2

Unit: g/rat/day
a): Day of administration
b): Day of necropsy

Appendix 3-5 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of female rats during the pre-mating period
Dose (mg/kg): 0

Animal number	Day of administration 2	8	15
1101	17	18	19
1102	19	20	16
1103	14	17	16
1104	17	12	14
1105	16	18	16
1106	16	14	16
1107	18	12	16
1108	15	14	11
1109	18	17	15
1110	10	16	16
1111	18	22	12
1112	9	18	15
Mean	16	17	15
S.D.	3	3	2

Unit: g/rat/day

Appendix 3-6 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of female rats during the pre-mating period
Dose (mg/kg): 2.4

Animal number	Day of administration 2	8	15
2101	16	15	12
2102	18	19	19
2103	18	11	19
2104	11	19	19
2105	17	21	14
2106	18	12	13
2107	16	15	17
2108	20	18	18
2109	18	10	14
2110	11	20	16
2111	18	18	17
2112	20	17	17
Mean	17	16	16
S.D.	3	4	2

Unit: g/rat/day

Appendix 3-7 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of female rats during the pre-mating period
Dose (mg/kg): 12

Animal number	Day of administration 2	8	15
3101	11	17	17
3102	19	20	19
3103	9	16	14
3104	11	15	15
3105	13	18	18
3106	11	18	18
3107	18	15	15
3108	16	17	15
3109	11	18	18
3110	20	12	23
3111	15	19	12
3112	15	19	16
Mean	14	17	17
S.D.	4	2	3

Unit: g/rat/day

Appendix 3-8 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of female rats during the pre-mating period
Dose (mg/kg): 60

Animal number	Day of administration 2	8	15
4101	15	15	12
4102	16	12	17
4103	21	13	19
4104	18	20	16
4105	10	19	15
4106	9	17	16
4107	19	19	14
4108	20	17	13
4109	18	16	19
4110	16	13	18
4111	17	16	15
4112	18	19	23
Mean	16	16	16
S.D.	4	3	3

Unit: g/rat/day

Appendix 3-9 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of dams during the gestation period
Dose (mg/kg): 0

Dam number	Administration 1	7	14	20a)
1101	13	17	21	19
1102	13	21	24	20
1103	18	20	20	18
1104	19	24	24	19
1105	15	20	21	24
1106	8	19	18	17
1107	18	20	21	18
1108	13	20	23	19
1109	18	22	23	21
1110	17	22	25	21
1111	21	25	26	21
1112	13	22	24	22
Mean	16	21	23	20
S.D.	4	2	2	2

Unit: g/rat/day
a): Gestation day

Appendix 3-10 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of dams during the gestation period
Dose (mg/kg): 2.4

Dam number	Administration 1	7	14	20a)
2101	16	22	18	18
2102	23	26	26	22
2103	18	21	26	23
2104	16	28	26	21
2105	13	24	27	15
2106	16	18	21	17
2107	18	22	21	20
2108	21	22	30	25
2109	19	22	25	22
2110	18	25	27	23
2111	20	22	22	24
2112	18	24	28	22
Mean	18	23	25	21
S.D.	3	3	3	3

Unit: g/rat/day
a): Gestation day

Appendix 3-11 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of dams during the gestation period
Dose (mg/kg): 12

Dam number	Administration 1	7	14	20a)
3101	17	22	22	20
3102	19	27	27	23
3103	16	20	24	21
3104	14	18	20	20
3105	17	24	21	24
3106	15	19	22	17
3107	17	18	20	17
3108	17	22	22	18
3109	18	23	26	20
3110	22	26	29	21
3111	22	25	22	19
3112	18	24	23	25
Mean	18	22	23	20
S.D.	2	3	3	3

Unit: g/rat/day
a): Gestation day

Appendix 3-12 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of dams during the gestation period
Dose (mg/kg): 60

Dam number	Administration 1	7	14	20a)
4101	15	20	21	14
4102	20	18	21	16
4103	21	24	14	18
4104	16	22	21	18
4105	18	21	23	24
4106	17	18	21	18
4107	18	23	21	18
4108	14	20	20	23
4109	20	16	25	18
4110	15	20	22	17
4111	11	19	22	15
4112	25	24	23	22
Mean	18	20	21	18
S.D.	4	3	3	3

Unit: g/rat/day
a): Gestation day

Appendix 3-13 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of dams during the lactation period
Dose (mg/kg): 0

Dam number	Administration 2	4a)
1101	23	32
1102	16	31
1103	23	45
1104	19	31
1105	21	45
1106	18	35
1107	27	37
1108	26	42
1109	28	44
1110	18	35
1111	23	32
1112	29	38
Mean	23	37
S.D.	4	5

Unit: g/rat/day
a): Lactation day

Appendix 3-14 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of dams during the lactation period
Dose (mg/kg): 2.4

Dam number	Administration 2	4a)
2101	20	34
2102	29	39
2103	22	37
2104	17	35
2105	24	36
2106	27	33
2107	24	35
2108	18	27
2109	28	37
2110	17	18
2111	18	29
2112	16	32
Mean	22	33
S.D.	5	6

Unit: g/rat/day
a): Lactation day

Appendix 3-15 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of dams during the lactation period
Dose (mg/kg): 12

Dam number	Administration 2	4a)
3101	20	37
3102	22	29
3103	26	42
3104	23	40
3105	16	40
3106	19	38
3107	22	33
3108	19	35
3109	23	45
3110	22	33
3111	27	46
3112	12	29
Mean	21	37
S.D.	4	6

Unit: g/rat/day
a): Lactation day

Appendix 3-16 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual food consumption of dams during the lactation period
Dose (mg/kg): 60

Dam number	Administration 2	4a)
4101	20	32
4102	9	21
4103	19	47
4104	19	34
4105	14	28
4106	23	31
4107	18	36
4108	27	45
4109	24	37
4110	15	28
4111	13	28
4112	23	36
Mean	19	34
S.D.	5	7

Unit: g/rat/day
a): Lactation day

Appendix 4-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of male rats
Dose (mg/kg): 0

	Animal number	Body weight g	Liver g(g/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)
	1001	457	16.13	1.74	1.76	3.50	720	662	1382
	1002	535	18.25	1.59	1.54	3.13	663	712	1375
	1003	491	16.77	1.71	1.74	3.45	734	730	1464
	1004	498	16.53	1.56	1.58	3.14	613	597	1210
	1005	477	14.98	1.66	1.69	3.35	665	655	1320
	1006	539	17.84	1.66	1.68	3.34	727	736	1463
	1007	514	16.68	1.65	1.65	3.30	691	676	1367
Absolute	1008	497	16.03	1.58	1.52	3.10	655	601	1256
	1009	466	16.73	1.49	1.42	2.91	664	607	1271
	1010	458	14.66	1.54	1.56	3.10	627	633	1260
	1011	520	17.60	1.39	1.39	2.78	583	538	1121
	1012	487	16.04	1.49	1.52	3.01	613	605	1218
	Mean	495	16.52	1.59	1.59	3.18	663	646	1309
	S.D.	28	1.07	0.10	0.12	0.22	49	60	105
	1001		3.53	0.38	0.39	0.77	158	145	302
	1002		3.41	0.30	0.29	0.59	124	133	257
	1003		3.42	0.35	0.35	0.70	149	149	298
	1004		3.32	0.31	0.32	0.63	123	120	243
	1005		3.14	0.35	0.35	0.70	139	137	277
	1006		3.31	0.31	0.31	0.62	135	137	271
	1007		3.25	0.32	0.32	0.64	134	132	266
Relative	1008		3.23	0.32	0.31	0.62	132	121	253
	1009		3.59	0.32	0.30	0.62	142	130	273
	1010		3.20	0.34	0.34	0.68	137	138	275
	1011		3.38	0.27	0.27	0.53	112	103	216
	1012		3.29	0.31	0.31	0.62	126	124	250
	Mean		3.34	0.32	0.32	0.64	134	131	265
	S.D.		0.13	0.03	0.03	0.06	12	12	24

Appendix 4-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of male rats
Dose (mg/kg): 0

	Animal number	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	1001	2.00	1.47
	1002	1.30	1.09
	1003	1.34	0.96
	1004	2.06	1.40
	1005	1.54	1.09
	1006	1.85	1.36
	1007	1.98	1.08
	1008	2.04	1.36
	1009	1.64	1.07
	1010	1.73	1.37
	1011	1.77	1.35
	1012	1.93	1.32
	Mean	1.77	1.24
	S.D.	0.26	0.17
Relative	1001	0.44	0.32
	1002	0.24	0.20
	1003	0.27	0.20
	1004	0.41	0.28
	1005	0.32	0.23
	1006	0.34	0.25
	1007	0.39	0.21
	1008	0.41	0.27
	1009	0.35	0.23
	1010	0.38	0.30
	1011	0.34	0.26
	1012	0.40	0.27
	Mean	0.36	0.25
	S.D.	0.06	0.04

Appendix 4-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of male rats
Dose (mg/kg): 2.4

	Animal number	Body weight g	Liver g(g/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)
	2001	542	19.55	1.62	1.74	3.36	607	624	1231
	2002	500	17.72	1.34	1.34	2.68	546	528	1074
	2003	473	16.14	1.31	1.37	2.68	598	585	1183
	2004	471	16.21	1.67	1.68	3.35	656	645	1301
	2005	531	18.78	1.40	1.49	2.89	594	598	1192
	2006	521	18.16	1.75	1.74	3.49	724	704	1428
	2007	457	13.08	1.48	1.49	2.97	608	617	1225
Absolute	2008	463	15.96	1.42	1.46	2.88	612	622	1234
	2009	549	18.46	1.69	1.60	3.29	632	610	1242
	2010	493	14.96	1.73	1.70	3.43	726	703	1429
	2011	495	18.20	1.58	1.58	3.16	608	620	1228
	2012	508	15.43	1.76	1.81	3.57	711	712	1423
	Mean	500	16.89	1.56	1.58	3.15	635	631	1266
	S.D.	31	1.89	0.17	0.15	0.31	57	54	110
	2001		3.61	0.30	0.32	0.62	112	115	227
	2002		3.54	0.27	0.27	0.54	109	106	215
	2003		3.41	0.28	0.29	0.57	126	124	250
	2004		3.44	0.35	0.36	0.71	139	137	276
	2005		3.54	0.26	0.28	0.54	112	113	224
	2006		3.49	0.34	0.33	0.67	139	135	274
	2007		2.86	0.32	0.33	0.65	133	135	268
Relative	2008		3.45	0.31	0.32	0.62	132	134	267
	2009		3.36	0.31	0.29	0.60	115	111	226
	2010		3.03	0.35	0.34	0.70	147	143	290
	2011		3.68	0.32	0.32	0.64	123	125	248
	2012		3.04	0.35	0.36	0.70	140	140	280
	Mean		3.37	0.31	0.32	0.63	127	127	254
	S.D.		0.26	0.03	0.03	0.06	13	13	26

Appendix 4-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of male rats
Dose (mg/kg): 2.4

	Animal number	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	2001	1.99	1.46
	2002	1.85	1.20
	2003	1.37	1.23
	2004	1.38	1.18
	2005	1.74	1.49
	2006	1.52	1.37
	2007	2.21	1.28
	2008	1.70	1.36
	2009	2.00	1.68
	2010	2.03	1.36
	2011	1.40	1.45
	2012	2.08	0.91
	Mean	1.77	1.33
	S.D.	0.30	0.19
Relative	2001	0.37	0.27
	2002	0.37	0.24
	2003	0.29	0.26
	2004	0.29	0.25
	2005	0.33	0.28
	2006	0.29	0.26
	2007	0.48	0.28
	2008	0.37	0.29
	2009	0.36	0.31
	2010	0.41	0.28
	2011	0.28	0.29
	2012	0.41	0.18
	Mean	0.35	0.27
	S.D.	0.06	0.03

Appendix 4-5 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of male rats
Dose (mg/kg): 12

	Animal number	Body weight g	Liver g(g/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)
	3001	469	14.68	1.62	1.55	3.17	634	622	1256
	3002	495	16.02	1.49	1.48	2.97	581	561	1142
	3003	503	16.95	1.48	1.46	2.94	606	597	1203
	3004	476	16.10	1.52	1.51	3.03	738	687	1425
	3005	536	18.50	1.62	1.60	3.22	789	709	1498
	3006	565	17.67	1.47	1.47	2.94	580	561	1141
	3007	513	17.49	1.66	1.59	3.25	682	746	1428
Absolute	3008	488	15.18	1.60	1.60	3.20	644	629	1273
	3009	511	15.94	1.59	1.62	3.21	603	617	1220
	3010	454	13.42	1.32	1.37	2.69	607	606	1213
	3011	492	17.10	1.51	1.54	3.05	724	670	1394
	3012	466	14.39	1.49	1.47	2.96	627	608	1235
	Mean	497	16.12	1.53	1.52	3.05	651	634	1286
	S.D.	31	1.50	0.09	0.07	0.17	67	57	120
	3001		3.13	0.35	0.33	0.68	135	133	268
	3002		3.24	0.30	0.30	0.60	117	113	231
	3003		3.37	0.29	0.29	0.58	120	119	239
	3004		3.38	0.32	0.32	0.64	155	144	299
	3005		3.45	0.30	0.30	0.60	147	132	279
	3006		3.13	0.26	0.26	0.52	103	99	202
	3007		3.41	0.32	0.31	0.63	133	145	278
Relative	3008		3.11	0.33	0.33	0.66	132	129	261
	3009		3.12	0.31	0.32	0.63	118	121	239
	3010		2.96	0.29	0.30	0.59	134	133	267
	3011		3.48	0.31	0.31	0.62	147	136	283
	3012		3.09	0.32	0.32	0.64	135	130	265
	Mean		3.24	0.31	0.31	0.62	131	128	259
	S.D.		0.17	0.02	0.02	0.04	15	13	27

Appendix 4-6 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of male rats
Dose (mg/kg): 12

	Animal number	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	3001	2.02	1.18
	3002	1.64	1.29
	3003	1.87	1.24
	3004	1.88	1.32
	3005	1.50	1.18
	3006	1.95	1.34
	3007	1.78	1.16
	3008	1.56	1.10
	3009	1.77	1.51
	3010	1.98	1.23
	3011	1.62	1.22
	3012	2.17	1.52
	Mean	1.81	1.27
	S.D.	0.20	0.13
Relative	3001	0.43	0.25
	3002	0.33	0.26
	3003	0.37	0.25
	3004	0.39	0.28
	3005	0.28	0.22
	3006	0.35	0.24
	3007	0.35	0.23
	3008	0.32	0.23
	3009	0.35	0.30
	3010	0.44	0.27
	3011	0.33	0.25
	3012	0.47	0.33
	Mean	0.37	0.26
	S.D.	0.06	0.03

Appendix 4-7 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of male rats
Dose (mg/kg): 60

	Animal number	Body weight g	Liver g(g/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)
	4001	471	16.31	1.52	1.51	3.03	606	658	1264
	4002	496	17.97	1.52	1.53	3.05	682	669	1351
	4003	535	19.40	1.46	1.42	2.88	698	645	1343
	4004	475	17.13	1.34	1.33	2.67	672	614	1286
	4005	496	17.18	1.55	1.54	3.09	610	603	1213
	4006	468	16.67	1.42	1.44	2.86	631	663	1294
	4007	530	22.31	1.84	1.83	3.67	686	733	1419
Absolute	4008	504	17.69	1.43	1.44	2.87	791	775	1566
	4009	451	15.99	1.49	1.47	2.96	619	606	1225
	4010	513	16.58	1.73	1.84	3.57	656	707	1363
	4011	479	16.70	1.51	1.51	3.02	693	619	1312
	4012	461	15.36	1.64	1.65	3.29	591	577	1168
	Mean	490	17.44	1.54	1.54	3.08	661	656	1317
	S.D.	27	1.85	0.14	0.16	0.29	55	59	105
	4001		3.46	0.32	0.32	0.64	129	140	268
	4002		3.62	0.31	0.31	0.61	138	135	272
	4003		3.63	0.27	0.27	0.54	130	121	251
	4004		3.61	0.28	0.28	0.56	141	129	271
	4005		3.46	0.31	0.31	0.62	123	122	245
	4006		3.56	0.30	0.31	0.61	135	142	276
	4007		4.21	0.35	0.35	0.69	129	138	268
Relative	4008		3.51	0.28	0.29	0.57	157	154	311
	4009		3.55	0.33	0.33	0.66	137	134	272
	4010		3.23	0.34	0.36	0.70	128	138	266
	4011		3.49	0.32	0.32	0.63	145	129	274
	4012		3.33	0.36	0.36	0.71	128	125	253
	Mean		3.56	0.31	0.32	0.63	135	134	269
	S.D.		0.24	0.03	0.03	0.06	9	9	17

Appendix 4-8 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of male rats
Dose (mg/kg): 60

	Animal number	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	4001	1.82	1.09
	4002	1.77	1.27
	4003	1.77	1.04
	4004	2.18	1.29
	4005	1.76	1.33
	4006	1.60	1.00
	4007	2.29	1.29
	4008	2.41	1.28
	4009	1.59	1.28
	4010	2.25	1.44
	4011	2.18	1.41
	4012	1.74	1.28
	Mean	1.95	1.25
	S.D.	0.29	0.14
Relative	4001	0.39	0.23
	4002	0.36	0.26
	4003	0.33	0.19
	4004	0.46	0.27
	4005	0.35	0.27
	4006	0.34	0.21
	4007	0.43	0.24
	4008	0.48	0.25
	4009	0.35	0.28
	4010	0.44	0.28
	4011	0.46	0.29
	4012	0.38	0.28
	Mean	0.40	0.25
	S.D.	0.05	0.03

Appendix 4-9 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of female rats
Dose (mg/kg): 0

	Animal number	Body weight g	Liver g(g/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)
Absolute	1101	332	12.26	43.5	55.6	99.1
	1102	364	14.00	39.4	60.5	99.9
	1103	329	13.68	56.7	33.2	89.9
	1104	334	11.74	49.5	49.4	98.9
	1105	354	14.16	54.2	53.1	107.3
	1106	329	13.12	48.1	69.9	118.0
	1107	304	12.14	39.7	51.0	90.7
	1108	356	15.31	47.2	42.4	89.6
	1109	340	14.13	58.3	41.9	100.2
	1110	327	13.08	57.7	55.8	113.5
	1111	366	13.29	63.7	35.6	99.3
	1112	331	13.51	44.3	47.0	91.3
	Mean	339	13.37	50.2	49.6	99.8
	S.D.	18	1.00	7.9	10.5	9.2
Relative	1101		3.69	13.1	16.7	29.8
	1102		3.85	10.8	16.6	27.4
	1103		4.16	17.2	10.1	27.3
	1104		3.51	14.8	14.8	29.6
	1105		4.00	15.3	15.0	30.3
	1106		3.99	14.6	21.2	35.9
	1107		3.99	13.1	16.8	29.8
	1108		4.30	13.3	11.9	25.2
	1109		4.16	17.1	12.3	29.5
	1110		4.00	17.6	17.1	34.7
	1111		3.63	17.4	9.7	27.1
	1112		4.08	13.4	14.2	27.6
	Mean		3.95	14.8	14.7	29.5
	S.D.		0.24	2.2	3.3	3.1

Appendix 4-10 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of female rats
Dose (mg/kg): 2.4

	Animal number	Body weight g	Liver g(g/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)
Absolute	2101	310	12.58	38.0	35.2	73.2
	2102	367	15.50	66.5	51.9	118.4
	2103	356	12.87	44.8	55.7	100.5
	2104	350	12.34	59.5	51.6	111.1
	2105	339	14.28	69.3	55.0	124.3
	2106	329	13.82	36.2	51.2	87.4
	2107	308	12.05	37.6	41.1	78.7
	2108	341	11.76	45.2	67.5	112.7
	2109	342	13.61	50.1	67.2	117.3
	2110	328	13.48	58.4	50.6	109.0
	2111	342	13.29	60.6	53.6	114.2
	2112	358	12.27	61.6	41.7	103.3
	Mean	339	13.15	52.3	51.9	104.2
	S.D.	18	1.07	11.8	9.6	16.3
Relative	2101		4.06	12.3	11.4	23.6
	2102		4.22	18.1	14.1	32.3
	2103		3.62	12.6	15.6	28.2
	2104		3.53	17.0	14.7	31.7
	2105		4.21	20.4	16.2	36.7
	2106		4.20	11.0	15.6	26.6
	2107		3.91	12.2	13.3	25.6
	2108		3.45	13.3	19.8	33.0
	2109		3.98	14.6	19.6	34.3
	2110		4.11	17.8	15.4	33.2
	2111		3.89	17.7	15.7	33.4
	2112		3.43	17.2	11.6	28.9
	Mean		3.88	15.4	15.3	30.6
	S.D.		0.30	3.0	2.6	4.0

Appendix 4-11 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of female rats
Dose (mg/kg): 12

	Animal number	Body weight g	Liver g(g/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)
Absolute	3101	305	11.05	40.8	53.2	94.0
	3102	365	12.68	59.1	59.3	118.4
	3103	349	12.96	64.0	63.9	127.9
	3104	317	13.65	48.8	47.6	96.4
	3105	345	12.39	45.7	52.1	97.8
	3106	329	13.73	57.3	47.9	105.2
	3107	316	12.67	51.9	42.1	94.0
	3108	320	12.51	55.1	46.3	101.4
	3109	326	13.20	46.9	60.3	107.2
	3110	347	13.46	47.9	55.7	103.6
	3111	351	15.56	61.2	55.9	117.1
	3112	337	11.98	61.9	63.7	125.6
	Mean	334	12.99	53.4	54.0	107.4
	S.D.	18	1.10	7.4	7.1	12.0
Relative	3101		3.62	13.4	17.4	30.8
	3102		3.47	16.2	16.2	32.4
	3103		3.71	18.3	18.3	36.6
	3104		4.31	15.4	15.0	30.4
	3105		3.59	13.2	15.1	28.3
	3106		4.17	17.4	14.6	32.0
	3107		4.01	16.4	13.3	29.7
	3108		3.91	17.2	14.5	31.7
	3109		4.05	14.4	18.5	32.9
	3110		3.88	13.8	16.1	29.9
	3111		4.43	17.4	15.9	33.4
	3112		3.55	18.4	18.9	37.3
	Mean		3.89	16.0	16.2	32.1
	S.D.		0.31	1.9	1.8	2.7

Appendix 4-12 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual organ weight of female rats
Dose (mg/kg): 60

	Animal number	Body weight g	Liver g(g/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)
Absolute	4101	291	12.31	54.3	52.1	106.4
	4102	322	12.16	45.8	45.0	90.8
	4103	357	17.47	62.0	67.2	129.2
	4104	351	14.98	62.7	43.4	106.1
	4105	329	11.89	39.8	45.6	85.4
	4106	301	11.86	61.1	49.0	110.1
	4107	358	14.64	49.6	57.1	106.7
	4108	339	13.36	67.2	40.5	107.7
	4109	315	13.55	55.5	37.3	92.8
	4110	351	13.25	62.8	52.0	114.8
	4111	312	11.85	63.6	49.6	113.2
	4112	354	13.88	68.9	54.0	122.9
	Mean	332	13.43	57.8	49.4	107.2
	S.D.	23	1.67	8.9	8.0	12.7
Relative	4101		4.23	18.7	17.9	36.6
	4102		3.78	14.2	14.0	28.2
	4103		4.89	17.4	18.8	36.2
	4104		4.27	17.9	12.4	30.2
	4105		3.61	12.1	13.9	26.0
	4106		3.94	20.3	16.3	36.6
	4107		4.09	13.9	15.9	29.8
	4108		3.94	19.8	11.9	31.8
	4109		4.30	17.6	11.8	29.5
	4110		3.77	17.9	14.8	32.7
	4111		3.80	20.4	15.9	36.3
	4112		3.92	19.5	15.3	34.7
	Mean		4.05	17.5	14.9	32.4
	S.D.		0.34	2.7	2.2	3.7

Appendix 5-1(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1001 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-2(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1002 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-3(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1003 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

Lung(bronchus)	Focus,dark red: 1 present 2x2mm
Other tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, inflammatory ventral and dorsolateral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-4(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1004 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Following tissues : Not remarkable

Epididymis, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-5(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1005 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Epididymis	Cell infiltration: minimal, unilateral, interstitial mononuclear
Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-6(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1006 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-7(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1007 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-8(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1008 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-9(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1009 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-10(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1010 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-11(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1011 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-12(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1012 Male 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: mild, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-13(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2001 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-14(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2002 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-15(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2003 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-16(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2004 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-17(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2005 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal
Pancreas	Cell infiltration: minimal, interstitial mononuclear

Appendix 5-18(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2006 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-19(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2007 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-20(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2008 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-21(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2009 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-22(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2010 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Pancreas

Appendix 5-23(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2011 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-24(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2012 Male 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-25(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3001 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-26(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3002 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-27(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3003 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-28(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3004 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-29(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3005 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-30(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3006 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-31(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3007 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Pancreas

Appendix 5-32(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3008 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Pancreas	Cell infiltration: minimal, interstitial mononuclear

Following tissues : Not remarkable

Liver

Appendix 5-33(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3009 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Pancreas

Appendix 5-34(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3010 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-35(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3011 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Pancreas

Appendix 5-36(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3012 Male 12 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-37(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4001 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-38(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4002 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

Liver	Hepatodiaphragmatic nodule: 1 present 3x3x1mm
Other tissues	Not remarkable

Histopathology:

Liver	Hepatodiaphragmatic nodule: mild

Following tissues : Not remarkable

Epididymis, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-39(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4003 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-40(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4004 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal
Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-41(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4005 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-42(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4006 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-43(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4007 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, inflammatory dorsolateral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-44(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4008 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-45(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4009 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Epididymis, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-46(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4010 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Epididymis, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-47(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4011 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Prostate, Seminal vesicle(coagulating gland), Testis

Appendix 5-48(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4012 Male 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral

Following tissues : Not remarkable

Epididymis, Liver, Pancreas, Seminal vesicle(coagulating gland), Testis

Appendix 5-49(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1101 Female 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-50(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1102 Female 0 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-51(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1103 Female 0 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-52(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1104 Female 0 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-53(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1105 Female 0 mg/kg Day 51 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-54(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1106 Female 0 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-55(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1107 Female 0 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-56(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1108 Female 0 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-57(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1109 Female 0 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-58(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1110 Female 0 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-59(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1111 Female 0 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-60(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 1112 Female 0 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-61(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2101 Female 2.4 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-62(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2102 Female 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-63(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2103 Female 2.4 mg/kg Day 41 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-64(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2104 Female 2.4 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-65(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2105 Female 2.4 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-66(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2106 Female 2.4 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-67(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2107 Female 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-68(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2108 Female 2.4 mg/kg Day 42 End of administration period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Pancreas	Atrophy,acinar,focal: minimal

Following tissues : Not remarkable

Liver

Appendix 5-69(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2109 Female 2.4 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-70(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2110 Female 2.4 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-71(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2111 Female 2.4 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-72(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 2112 Female 2.4 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-73(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3101 Female 12 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-74(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3102 Female 12 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-75(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3103 Female 12 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-76(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3104 Female 12 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-77(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3105 Female 12 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-78(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3106 Female 12 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-79(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3107 Female 12 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-80(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3108 Female 12 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Following tissues : Not remarkable

Pancreas

Appendix 5-81(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3109 Female 12 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-82(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3110 Female 12 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-83(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3111 Female 12 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-84(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 3112 Female 12 mg/kg Day 47 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Pancreas

Appendix 5-85(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4101 Female 60 mg/kg Day 41 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-86(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4102 Female 60 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-87(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4103 Female 60 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-88(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4104 Female 60 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-89(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4105 Female 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-90(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4106 Female 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-91(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4107 Female 60 mg/kg Day 45 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-92(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4108 Female 60 mg/kg Day 46 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-93(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4109 Female 60 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-94(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4110 Female 60 mg/kg Day 42 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-95(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4111 Female 60 mg/kg Day 44 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 5-96(1/1) A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane

Individual gross and histopathological findings

Animal No. 4112 Female 60 mg/kg Day 43 End of administration period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Liver, Ovary, Pancreas, Uterus, Vagina

Appendix 6-1

A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual estrous cycle in female rats during the pre-mating period
Dose (mg/kg): 0

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles
1101	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0
1102	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
1103	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0
1104	D	P	E	M	D	P	E	M	D	D	P	E	M	D	P	3	4.5
1105	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0
1106	D	P	E	M	D	D	P	E	E	M	D	D	P	E	M	3	5.5
1107	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
1108	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
1109	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
1110	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
1111	E	M	D	P	E	M	D	D	P	E	M	D	D	P	E	4	4.7
1112	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
Mean																3.8	4.2
S.D.																0.5	0.5

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling

Appendix 6-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual estrous cycle in female rats during the pre-mating period
Dose (mg/kg): 2.4

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles
2101	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
2102	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0
2103	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
2104	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
2105	M	D	P	E	E	M	D	D	P	E	M	D	P	E	E	3	5.0
2106	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
2107	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0
2108	D	P	E	M	D	P	E	M	D	D	P	E	M	D	P	3	4.5
2109	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
2110	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
2111	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0
2112	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0
Mean																3.6	4.1
S.D.																0.5	0.3

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling

Appendix 6-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual estrous cycle in female rats during the pre-mating period
Dose (mg/kg): 12

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles
3101	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
3102	E	M	D	P	E	M	D	P	E	M	D	D	P	E	M	4	4.3
3103	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
3104	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
3105	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
3106	E	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.3
3107	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
3108	E	M	D	P	E	M	D	P	E	E	M	D	P	E	M	4	4.3
3109	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
3110	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
3111	P	E	M	D	D	P	E	M	D	P	E	M	D	P	E	4	4.3
3112	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
Mean																3.8	4.1
S.D.																0.4	0.1

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling

Appendix 6-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual estrous cycle in female rats during the pre-mating period
Dose (mg/kg): 60

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles
4101	E	M	D	D	P	E	M	D	P	E	M	D	D	P	E	4	4.7
4102	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
4103	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
4104	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
4105	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
4106	P	E	M	D	D	P	E	M	D	D	P	E	M	D	D	3	5.0
4107	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0
4108	M	D	P	E	E	M	D	P	E	E	M	D	D	P	E	3	5.5
4109	D	P	E	E	M	D	P	E	M	D	P	E	M	D	P	3	4.5
4110	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0
4111	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0
4112	M	D	P	E	M	D	D	P	E	M	D	P	E	M	D	3	4.5
Mean																3.4	4.4
S.D.																0.5	0.5

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling

Appendix 7-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual mating and fertility of animals
Dose (mg/kg): 0

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
1001	1101	C	2	P
1002	1102	C	4	P
1003	1103	C	2	P
1004	1104	C	1	P
1005	1105	C	10	P
1006	1106	C	4	P
1007	1107	C	1	P
1008	1108	C	4	P
1009	1109	C	4	P
1010	1110	C	3	P
1011	1111	C	4	P
1012	1112	C	3	P

C: Copulated P: Pregnant

Appendix 7-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual mating and fertility of animals
Dose (mg/kg): 2.4

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
2001	2101	C	4	P
2002	2102	C	2	P
2003	2103	C	1	P
2004	2104	C	3	P
2005	2105	C	4	P
2006	2106	C	1	P
2007	2107	C	2	P
2008	2108	C	1	P
2009	2109	C	1	P
2010	2110	C	3	P
2011	2111	C	2	P
2012	2112	C	2	P

C: Copulated P: Pregnant

Appendix 7-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual mating and fertility of animals
Dose (mg/kg): 12

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
3001	3101	C	3	P
3002	3102	C	3	P
3003	3103	C	3	P
3004	3104	C	3	P
3005	3105	C	3	P
3006	3106	C	3	P
3007	3107	C	1	P
3008	3108	C	3	P
3009	3109	C	3	P
3010	3110	C	1	P
3011	3111	C	4	P
3012	3112	C	7	P

C: Copulated P: Pregnant

Appendix 7-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual mating and fertility of animals
Dose (mg/kg): 60

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
4001	4101	C	1	P
4002	4102	C	1	P
4003	4103	C	1	P
4004	4104	C	4	P
4005	4105	C	3	P
4006	4106	C	2	P
4007	4107	C	4	P
4008	4108	C	5	P
4009	4109	C	1	P
4010	4110	C	1	P
4011	4111	C	3	P
4012	4112	C	2	P

C: Copulated P: Pregnant

Appendix 8-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Delivery data on dams
Dose (mg/kg): 0

Dam number	Gestation length in days	No. of corpora lutea	No. of implan-tation sites	Implan-tation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnor-malities(%)e)
1101	22.0	14	14	100.0	100.0	0(0.0)	14	0(0.0)
1102	22.0	15	15	100.0	86.7	0(0.0)	13	0(0.0)
1103	22.0	15	14	93.3	100.0	0(0.0)	14	0(0.0)
1104	22.0	9	9	100.0	88.9	0(0.0)	8	0(0.0)
1105	22.0	16	16	100.0	93.8	0(0.0)	15	0(0.0)
1106	22.5	17	15	88.2	93.3	0(0.0)	14	0(0.0)
1107	22.0	14	14	100.0	100.0	0(0.0)	14	0(0.0)
1108	22.0	14	14	100.0	100.0	0(0.0)	14	0(0.0)
1109	22.0	17	16	94.1	93.8	0(0.0)	15	0(0.0)
1110	22.5	15	15	100.0	93.3	1(7.1)	13	0(0.0)
1111	22.0	14	14	100.0	85.7	0(0.0)	12	0(0.0)
1112	22.0	13	13	100.0	92.3	0(0.0)	12	0(0.0)
Total		173	169			1	158	0
Mean	22.1	14.4	14.1	98.0	94.0	(0.6)	13.2	(0.0)
S.D.	0.2	2.1	1.8	3.9	5.2	(2.0)	1.9	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100

Appendix 8-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Delivery data on dams
Dose (mg/kg): 2.4

Dam number	Gestation length in days	No. of corpora lutea	No. of implan-tation sites	Implan-tation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnor-malities(%)e)
2101	22.0	16	16	100.0	87.5	0(0.0)	14	0(0.0)
2102	22.0	19	19	100.0	100.0	0(0.0)	19	0(0.0)
2103	21.5	15	15	100.0	86.7	0(0.0)	13	0(0.0)
2104	22.5	16	16	100.0	93.8	0(0.0)	15	0(0.0)
2105	22.0	18	18	100.0	94.4	0(0.0)	17	0(0.0)
2106	22.0	13	13	100.0	100.0	0(0.0)	13	0(0.0)
2107	22.0	14	14	100.0	78.6	0(0.0)	11	0(0.0)
2108	22.0	18	15	83.3	80.0	0(0.0)	12	0(0.0)
2109	23.0	16	8	50.0	100.0	0(0.0)	8	0(0.0)
2110	22.5	19	18	94.7	94.4	0(0.0)	17	0(0.0)
2111	21.5	15	15	100.0	93.3	0(0.0)	14	0(0.0)
2112	21.5	14	13	92.9	84.6	0(0.0)	11	0(0.0)
Total		193	180			0	164	0
Mean	22.0	16.1	15.0	93.4	91.1	(0.0)	13.7	(0.0)
S.D.	0.5	2.0	2.9	14.6	7.5	(0.0)	3.1	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100

Appendix 8-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Delivery data on dams
Dose (mg/kg): 12

Dam number	Gestation length in days	No. of corpora lutea	No. of implan-tation sites	Implan-tation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnor-malities(%)e)
3101	22.0	14	14	100.0	100.0	2(14.3)	12	0(0.0)
3102	22.0	15	15	100.0	93.3	0(0.0)	14	0(0.0)
3103	22.0	15	14	93.3	100.0	0(0.0)	14	0(0.0)
3104	22.0	17	16	94.1	100.0	0(0.0)	16	0(0.0)
3105	22.5	15	15	100.0	100.0	0(0.0)	15	0(0.0)
3106	22.0	17	17	100.0	100.0	0(0.0)	17	0(0.0)
3107	22.0	14	14	100.0	100.0	0(0.0)	14	0(0.0)
3108	22.0	15	15	100.0	86.7	0(0.0)	13	0(0.0)
3109	22.5	14	14	100.0	100.0	1(7.1)	13	0(0.0)
3110	22.0	16	16	100.0	87.5	0(0.0)	14	0(0.0)
3111	22.0	18	18	100.0	83.3	0(0.0)	15	0(0.0)
3112	21.5	17	17	100.0	100.0	0(0.0)	17	0(0.0)
Total		187	185			3	174	0
Mean	22.0	15.6	15.4	99.0	95.9	(1.8)	14.5	(0.0)
S.D.	0.3	1.4	1.4	2.5	6.4	(4.4)	1.6	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100

Appendix 8-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Delivery data on dams
Dose (mg/kg): 60

Dam number	Gestation length in days	No. of corpora lutea	No. of implan-tation sites	Implan-tation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnor-malities(%)e)
4101	21.5	15	14	93.3	100.0	0(0.0)	14	0(0.0)
4102	22.0	14	14	100.0	28.6	0(0.0)	4	0(0.0)
4103	22.5	18	17	94.4	100.0	0(0.0)	17	0(0.0)
4104	22.5	13	13	100.0	84.6	0(0.0)	11	0(0.0)
4105	21.5	16	16	100.0	81.3	0(0.0)	13	0(0.0)
4106	22.0	17	17	100.0	76.5	0(0.0)	13	0(0.0)
4107	22.0	15	15	100.0	60.0	0(0.0)	9	0(0.0)
4108	22.5	16	15	93.8	93.3	0(0.0)	14	0(0.0)
4109	22.5	16	14	87.5	92.9	0(0.0)	13	0(0.0)
4110	22.0	17	17	100.0	29.4	0(0.0)	5	0(0.0)
4111	22.5	15	15	100.0	100.0	1(6.7)	14	0(0.0)
4112	22.0	16	16	100.0	81.3	0(0.0)	13	0(0.0)
Total		188	183			1	140	0
Mean	22.1	15.7	15.3	97.4	77.3	(0.6)	11.7	(0.0)
S.D.	0.4	1.4	1.4	4.2	25.4	(1.9)	3.8	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100

Appendix 9-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual viability index of pups
Dose (mg/kg): 0

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups Day 0	No. of live pups Day 4	Viability index on postnatal day 4 % b)
1101	14	14	100.0	14	13	92.9
1102	13	13	100.0	13	13	100.0
1103	14	14	100.0	14	14	100.0
1104	8	8	100.0	8	8	100.0
1105	15	15	100.0	15	15	100.0
1106	14	14	100.0	14	14	100.0
1107	14	14	100.0	14	14	100.0
1108	14	14	100.0	14	14	100.0
1109	15	15	100.0	15	15	100.0
1110	13	14	92.9	13	13	100.0
1111	12	12	100.0	12	12	100.0
1112	12	12	100.0	12	12	100.0
Total	158	159		158	157	
Mean	13.2	13.3	99.4	13.2	13.1	99.4
S.D.	1.9	1.9	2.0	1.9	1.9	2.0

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 9-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual viability index of pups
Dose (mg/kg): 2.4

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups Day 0	No. of live pups Day 4	Viability index on postnatal day 4 % b)
2101	14	14	100.0	14	14	100.0
2102	19	19	100.0	19	17	89.5
2103	13	13	100.0	13	13	100.0
2104	15	15	100.0	15	15	100.0
2105	17	17	100.0	17	15	88.2
2106	13	13	100.0	13	13	100.0
2107	11	11	100.0	11	11	100.0
2108	12	12	100.0	12	12	100.0
2109	8	8	100.0	8	8	100.0
2110	17	17	100.0	17	17	100.0
2111	14	14	100.0	14	14	100.0
2112	11	11	100.0	11	11	100.0
Total	164	164		164	160	
Mean	13.7	13.7	100.0	13.7	13.3	98.1
S.D.	3.1	3.1	0.0	3.1	2.6	4.3

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 9-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual viability index of pups
Dose (mg/kg): 12

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups Day 0	No. of live pups Day 4	Viability index on postnatal day 4 % b)
3101	12	14	85.7	12	12	100.0
3102	14	14	100.0	14	14	100.0
3103	14	14	100.0	14	14	100.0
3104	16	16	100.0	16	15	93.8
3105	15	15	100.0	15	15	100.0
3106	17	17	100.0	17	16	94.1
3107	14	14	100.0	14	14	100.0
3108	13	13	100.0	13	13	100.0
3109	13	14	92.9	13	13	100.0
3110	14	14	100.0	14	14	100.0
3111	15	15	100.0	15	15	100.0
3112	17	17	100.0	17	13	76.5
Total	174	177		174	168	
Mean	14.5	14.8	98.2	14.5	14.0	97.0
S.D.	1.6	1.3	4.4	1.6	1.1	6.9

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 9-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual viability index of pups
Dose (mg/kg): 60

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups Day 0	No. of live pups Day 4	Viability index on postnatal day 4 % b)
4101	14	14	100.0	14	14	100.0
4102	4	4	100.0	4	3	75.0
4103	17	17	100.0	17	17	100.0
4104	11	11	100.0	11	9	81.8
4105	13	13	100.0	13	11	84.6
4106	13	13	100.0	13	13	100.0
4107	9	9	100.0	9	9	100.0
4108	14	14	100.0	14	14	100.0
4109	13	13	100.0	13	13	100.0
4110	5	5	100.0	5	5	100.0
4111	14	15	93.3	14	14	100.0
4112	13	13	100.0	13	13	100.0
Total	140	141		140	135	
Mean	11.7	11.8	99.4	11.7	11.3	95.1
S.D.	3.8	3.9	1.9	3.8	4.1	9.1

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 10-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual sex ratio of pups
Dose (mg/kg): 0

Dam number	Liveborns No. of males	Liveborns No. of females	Stillborns No. of males	Stillborns No. of females	Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4 No. of males	Postnatal day 4 No. of females	Sex ratio of live pups on day 4 c)
1101	6	8	0	0	0.43	0.43	5	8	0.38
1102	5	8	0	0	0.38	0.38	5	8	0.38
1103	11	3	0	0	0.79	0.79	11	3	0.79
1104	3	5	0	0	0.38	0.38	3	5	0.38
1105	9	6	0	0	0.60	0.60	9	6	0.60
1106	9	5	0	0	0.64	0.64	9	5	0.64
1107	8	6	0	0	0.57	0.57	8	6	0.57
1108	8	6	0	0	0.57	0.57	8	6	0.57
1109	7	8	0	0	0.47	0.47	7	8	0.47
1110	6	7	0	1	0.43	0.46	6	7	0.46
1111	4	8	0	0	0.33	0.33	4	8	0.33
1112	6	6	0	0	0.50	0.50	6	6	0.50
Total	82	76	0	1			81	76	
Mean	6.8	6.3	0.0	0.1	0.51	0.51	6.8	6.3	0.51
S.D.	2.3	1.6	0.0	0.3	0.13	0.13	2.3	1.6	0.13

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 10-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual sex ratio of pups
Dose (mg/kg): 2.4

Dam number	Liveborns No. of males	Liveborns No. of females	Stillborns No. of males	Stillborns No. of females	Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4 No. of males	Postnatal day 4 No. of females	Sex ratio of live pups on day 4 c)
2101	8	6	0	0	0.57	0.57	8	6	0.57
2102	8	11	0	0	0.42	0.42	7	10	0.41
2103	11	2	0	0	0.85	0.85	11	2	0.85
2104	9	6	0	0	0.60	0.60	9	6	0.60
2105	11	6	0	0	0.65	0.65	10	5	0.67
2106	8	5	0	0	0.62	0.62	8	5	0.62
2107	6	5	0	0	0.55	0.55	6	5	0.55
2108	8	4	0	0	0.67	0.67	8	4	0.67
2109	4	4	0	0	0.50	0.50	4	4	0.50
2110	9	8	0	0	0.53	0.53	9	8	0.53
2111	8	6	0	0	0.57	0.57	8	6	0.57
2112	4	7	0	0	0.36	0.36	4	7	0.36
Total	94	70	0	0			92	68	
Mean	7.8	5.8	0.0	0.0	0.57	0.57	7.7	5.7	0.58
S.D.	2.2	2.2	0.0	0.0	0.12	0.12	2.1	2.1	0.13

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 10-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual sex ratio of pups
Dose (mg/kg): 12

Dam number	Liveborns No. of males	Liveborns No. of females	Stillborns No. of males	Stillborns No. of females	Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4 No. of males	Postnatal day 4 No. of females	Sex ratio of live pups on day 4 c)
3101	7	5	1	1	0.57	0.58	7	5	0.58
3102	6	8	0	0	0.43	0.43	6	8	0.43
3103	6	8	0	0	0.43	0.43	6	8	0.43
3104	4	12	0	0	0.25	0.25	4	11	0.27
3105	6	9	0	0	0.40	0.40	6	9	0.40
3106	9	8	0	0	0.53	0.53	9	7	0.56
3107	7	7	0	0	0.50	0.50	7	7	0.50
3108	9	4	0	0	0.69	0.69	9	4	0.69
3109	8	5	0	1	0.57	0.62	8	5	0.62
3110	7	7	0	0	0.50	0.50	7	7	0.50
3111	6	9	0	0	0.40	0.40	6	9	0.40
3112	8	9	0	0	0.47	0.47	7	6	0.54
Total	83	91	1	2			82	86	
Mean	6.9	7.6	0.1	0.2	0.48	0.48	6.8	7.2	0.49
S.D.	1.4	2.2	0.3	0.4	0.11	0.12	1.4	2.0	0.11

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 10-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual sex ratio of pups
Dose (mg/kg): 60

Dam number	Liveborns No. of males	Liveborns No. of females	Stillborns No. of males	Stillborns No. of females	Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4 No. of males	Postnatal day 4 No. of females	Sex ratio of live pups on day 4 c)
4101	10	4	0	0	0.71	0.71	10	4	0.71
4102	2	2	0	0	0.50	0.50	2	1	0.67
4103	11	6	0	0	0.65	0.65	11	6	0.65
4104	9	2	0	0	0.82	0.82	7	2	0.78
4105	8	5	0	0	0.62	0.62	6	5	0.55
4106	6	7	0	0	0.46	0.46	6	7	0.46
4107	3	6	0	0	0.33	0.33	3	6	0.33
4108	6	8	0	0	0.43	0.43	6	8	0.43
4109	8	5	0	0	0.62	0.62	8	5	0.62
4110	0	5	0	0	0.00	0.00	0	5	0.00
4111	8	6	0	1	0.53	0.57	8	6	0.57
4112	5	8	0	0	0.38	0.38	5	8	0.38
Total	76	64	0	1			72	63	
Mean	6.3	5.3	0.0	0.1	0.50	0.51	6.0	5.3	0.51
S.D.	3.3	2.0	0.0	0.3	0.21	0.21	3.2	2.1	0.21

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 11-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of pups
Dose (mg/kg): 0

Dam number	Male 0	Male 4a)	Female 0	Female 4a)
1101	6.8	10.1	6.5	9.6
1102	7.2	10.4	6.8	10.0
1103	7.1	9.9	6.7	9.9
1104	6.5	11.2	6.0	10.5
1105	6.8	10.9	6.3	9.9
1106	6.4	10.1	6.0	9.4
1107	6.7	9.9	6.3	9.4
1108	6.8	10.6	6.3	9.6
1109	7.2	10.4	6.7	10.3
1110	7.2	10.5	6.7	9.8
1111	6.6	10.8	6.3	10.1
1112	6.2	10.5	5.8	10.0
Mean	6.8	10.4	6.4	9.9
S.D.	0.3	0.4	0.3	0.3

Unit: g
a): Postnatal day

Appendix 11-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of pups
Dose (mg/kg): 2.4

Dam number	Male 0	Male 4a)	Female 0	Female 4a)
2101	6.7	10.0	6.3	9.1
2102	5.7	8.8	6.1	9.3
2103	6.1	10.2	5.6	9.3
2104	7.1	9.8	6.6	9.3
2105	6.1	7.6	5.5	6.2
2106	6.8	10.2	6.2	9.3
2107	7.2	11.9	6.7	11.1
2108	6.9	11.1	6.5	11.0
2109	8.2	14.6	7.7	13.1
2110	6.5	9.7	6.1	8.8
2111	5.8	8.4	5.5	8.0
2112	6.4	10.1	6.4	9.9
Mean	6.6	10.2	6.3	9.5
S.D.	0.7	1.8	0.6	1.7

Unit: g
a): Postnatal day

Appendix 11-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of pups
Dose (mg/kg): 12

Dam number	Male 0	Male 4a)	Female 0	Female 4a)
3101	6.2	9.6	5.9	9.0
3102	6.6	10.1	6.0	9.6
3103	6.7	10.4	6.2	9.9
3104	6.0	9.0	5.8	9.2
3105	6.6	9.4	6.2	9.1
3106	6.0	9.3	5.5	8.3
3107	6.8	9.5	6.3	9.0
3108	6.8	9.9	6.5	9.5
3109	7.2	11.7	6.7	10.8
3110	6.8	10.7	6.2	9.5
3111	6.8	10.6	6.4	10.1
3112	5.7	9.3	5.2	8.5
Mean	6.5	10.0	6.1	9.4
S.D.	0.4	0.8	0.4	0.7

Unit: g
a): Postnatal day

Appendix 11-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual body weight of pups
Dose (mg/kg): 60

Dam number	Male 0	Male 4a)	Female 0	Female 4a)
4101	5.8	8.5	5.6	8.1
4102	8.3	11.8	8.0	11.7
4103	6.1	9.3	6.0	8.7
4104	6.7	10.7	6.6	10.3
4105	5.8	8.8	5.6	8.4
4106	7.0	10.8	5.9	9.2
4107	7.7	12.5	7.1	11.7
4108	6.9	10.2	6.3	9.3
4109	6.6	10.6	6.6	10.3
4110	b)		7.5	13.2
4111	6.3	8.9	6.1	8.1
4112	5.9	10.0	5.8	9.8
Mean	6.6	10.2	6.4	9.9
S.D.	0.8	1.3	0.8	1.6

Unit: g
a): Postnatal day
b): No male pups were born.

Appendix 12-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 0

Dam number	No. of pups examined Total (Male + Female)	Findings
1101	1 (1 + 0)	NAF
1102	0	
1103	0	
1104	0	
1105	0	
1106	0	
1107	0	
1108	0	
1109	0	
1110	0	
1111	0	
1112	0	

NAF: No abnormal findings

Appendix 12-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 2.4

Dam number	No. of pups examined Total (Male + Female)	Findings
2101	0	
2102	2 (1 + 1)	NAF
2103	0	
2104	0	
2105	0	
2106	0	
2107	0	
2108	0	
2109	0	
2110	0	
2111	0	
2112	0	

NAF: No abnormal findings

Appendix 12-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 12

Dam number	No. of pups examined Total (Male + Female)	Findings
3101	0	
3102	0	
3103	0	
3104	0	
3105	0	
3106	1 (0 + 1)	NAF
3107	0	
3108	0	
3109	0	
3110	0	
3111	0	
3112	0	

NAF: No abnormal findings

Appendix 12-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 60

Dam number	No. of pups examined Total (Male + Female)	Findings
4101	0	
4102	0	
4103	0	
4104	2 (2 + 0)	NAF
4105	0	
4106	0	
4107	0	
4108	0	
4109	0	
4110	0	
4111	0	
4112	0	

NAF: No abnormal findings

Appendix 13-1 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 0

Dam number	No. of pups examined Total	(Male	+	Female)	Findings
1101	13	(5	+	8)	NAF
1102	13	(5	+	8)	NAF
1103	14	(11	+	3)	NAF
1104	8	(3	+	5)	NAF
1105	15	(9	+	6)	NAF
1106	14	(9	+	5)	NAF
1107	14	(8	+	6)	NAF
1108	14	(8	+	6)	NAF
1109	15	(7	+	8)	NAF
1110	13	(6	+	7)	NAF
1111	12	(4	+	8)	NAF
1112	12	(6	+	6)	NAF

NAF: No abnormal findings

Appendix 13-2 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 2.4

Dam number	No. of pups examined Total	(Male	+	Female)	Findings
2101	14	(8	+	6)	NAF
2102	17	(7	+	10)	NAF
2103	13	(11	+	2)	NAF
2104	15	(9	+	6)	NAF
2105	15	(10	+	5)	NAF
2106	13	(8	+	5)	NAF
2107	11	(6	+	5)	NAF
2108	12	(8	+	4)	NAF
2109	8	(4	+	4)	NAF
2110	17	(9	+	8)	NAF
2111	14	(8	+	6)	NAF
2112	11	(4	+	7)	NAF

NAF: No abnormal findings

Appendix 13-3 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 12

Dam number	No. of pups examined Total	(Male	+	Female)	Findings
3101	12	(7	+	5)	NAF
3102	14	(6	+	8)	NAF
3103	14	(6	+	8)	NAF
3104	15	(4	+	11)	NAF
3105	15	(6	+	9)	NAF
3106	16	(9	+	7)	NAF
3107	14	(7	+	7)	NAF
3108	13	(9	+	4)	NAF
3109	13	(8	+	5)	NAF
3110	14	(7	+	7)	NAF
3111	15	(6	+	9)	NAF
3112	13	(7	+	6)	NAF

NAF: No abnormal findings

Appendix 13-4 A reproduction/developmental toxicity screening test in rats treated orally with 1,4-Dichlorobutane
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 60

Dam number	No. of pups examined Total	(Male	+	Female)	Findings
4101	14	(10	+	4)	NAF
4102	3	(2	+	1)	NAF
4103	17	(11	+	6)	NAF
4104	9	(7	+	2)	NAF
4105	11	(6	+	5)	NAF
4106	13	(6	+	7)	NAF
4107	9	(3	+	6)	NAF
4108	14	(6	+	8)	NAF
4109	13	(8	+	5)	NAF
4110	5	(0	+	5)	NAF
4111	14	(8	+	6)	NAF
4112	13	(5	+	8)	NAF

NAF: No abnormal findings