

最終報告書

1,2-メチレンジオキシベンゼンのラットを用いる 反復投与毒性・生殖発生毒性併合試験

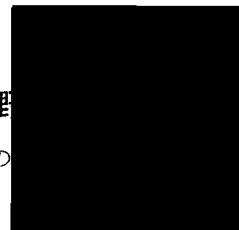
厚生労働省医薬食品局審査管理課 化学物質安全対策室 委託

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試験番号 R-12-012

被験物質 1,2-メチレンジオキシベンゼン

試験項目 反復投与毒性ならびに生殖発生毒性試験

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試験資料保管場所 秦野研究所資料保存室

被験物質保管場所 秦野研究所被験物質保存庫

保管期間 試験終了後 10 年間
その後の保管については試験委託者と協議する。

運営管理者 一般財団法人食品薬品安全センター 秦野研究所
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本試験は、「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 0331 第 7 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、環境企発第 110331009 号環境省総合環境政策局長通知)に準拠し、「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 0331 第 8 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、環境企発第 110331010 号環境省総合環境政策局長通知)を遵守して実施した。

2014 年 1 月 3 日

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投与観察

動物飼育管理

(検疫を含む)

尿検査

血液学検査

(採血を含む)

血液生化学検査

病理学検査

被験物質管理

検体調製

化学分析

目次

要約.....	6
1. 反復投与毒性および回復性	6
2. 生殖発生毒性	6
3. 無毒性量	6
試験目的	7
試験ガイドラインと GLP	7
動物愛護	7
材料と方法.....	8
1. 被験物質	8
2. 動物および飼育方法.....	8
3. 投与検体.....	9
1) 調製.....	9
2) 安定性試験	9
3) 含量試験	9
4. 投与量の設定および投与方法	9
5. 検査法	10
1) 親動物 (F ₀)	10
2) 出生児 (F ₁)	15
6. データの解析法.....	15
予見することができなかった試験の信頼性に影響を及ぼす疑いのある事態及び試験計画書に従わな かったこと	16
試験成績	16
1. 親動物.....	16
1) 一般状態	16
2) 詳細な症状観察	17
3) 体重.....	17
4) 摂餌量	18
5) 機能検査	18
6) 尿検査	19
7) 血液学検査	19
8) 血液生化学検査.....	20
9) 器官重量	20
10) 剖検所見	21

11) 病理組織学検査	22
2. 生殖能力	26
1) 性周期および交配成績	26
2) 出産率および妊娠期間	27
3) 分娩および哺育状態	27
4) 黄体数、着床数および着床率	27
3. 出生児	27
1) 生存	27
2) 体重	27
3) 出生児観察	27
考察	28
1. 反復投与毒性	28
2. 毒性の回復性	29
3. 生殖発生毒性	29
4. 無毒性量	30
参考文献	30
Annexes	31
Tables	35
Appendices	115

(最終ページ: 330 ページ)

信頼性保証書

要約

1,2-メチレンジオキシベンゼンの反復投与毒性・生殖発生毒性併合試験を化審法ガイドラインに従って実施した。被験物質をトウモロコシ油で希釈して 0、30、100 ならびに 300 mg/kg の用量で、Crl:CD (SD)ラット(各群とも雌雄各 12 匹)に強制経口投与した。雄は 42 日間投与した後に剖検し、雌は交配前 2 週間および妊娠期間を通して哺育 4 日まで 42～45 日間投与し、出生児は哺育 4 日、母動物は哺育 5 日に剖検した。また、0 および 300 mg/kg の用量に非交配雌(10 匹/群)を設け、42 日間投与した後に半数を剖検し、残りの半数と 0 および 300 mg/kg 群の雄 5 匹は、14 日間飼育して剖検した。

1. 反復投与毒性および回復性

300 mg/kg 群では立毛が雄 1 例、排便量の減少と腹臥位が交配雌 1 例、軟便または被毛の汚れなどが非交配雌 2 例で一過性に観察され他、耳介反射の低下が 100 mg/kg 以上の群の交配雌と 300 mg/kg 群の雄および非交配雌で、驚愕反応の低下が 300 mg/kg 群の雄および非交配雌で観察された。また、区画移動数の増加と立ち上がり回数の増加が 300 mg/kg 群の雄および非交配雌でみられた。体重増加抑制は 300 mg/kg 群の雄および非交配雌さらには妊娠雌でみられたが、摂餌量の低下は 300 mg/kg 群の交配雌および非交配雌で一過性に認められた。尿中カリウムイオン濃度の低下が 300 mg/kg 群の雄および非交配雌で、網状赤血球比率の増加、血中グルコース濃度の低下および無機リン濃度の増加が 300 mg/kg 群の雄で、血色素量の低下、血中総コレステロール、トリグリセライド、リン脂質および無機リン濃度の増加が 300 mg/kg 群の非交配雌で観察された。肝臓および腎臓重量の増加は 300 mg/kg 群の雄および非交配雌で認められ、肝臓の小葉中心性の肝細胞肥大とくもり硝子様変性が 100 mg/kg 以上の群の雄および分娩雌、さらには 300 mg/kg 群の非交配雌で、腎臓の近位尿細管の硝子滴(抗 α 2u-グロブリン陽性)が 30 mg/kg 以上の群の雄で観察された。

回復観察では、区画移動数の増加と腎臓重量の増加が 300 mg/kg 群の雄で、低体重が 300 mg/kg 群の非交配雌でみられた。

2. 生殖発生毒性

異常性周期、妊娠率の低下、妊娠期間の延長、さらには出生時死亡の増加などの分娩状態の不良が 300 mg/kg 群で観察された他、全哺育児が死亡した例が 100 mg/kg 以上の群でみられた。生児出産率(出產生児数/着床痕数)および出生率(出產生児数/産児数)の低下が 300 mg/kg 群、哺育 0 日の出生児体重の低下と新生児生存率(哺育 4 日の生児数/哺育 0 日の生児数)の低下が 100 mg/kg 以上の群で認められた。

3. 無毒性量

小葉中心性の肝細胞の肥大とくもり硝子様変性が 100 mg/kg 群の雌雄で、耳介反射の低下が 100 mg/kg 群の雌で観察されたことから雌雄動物の反復投与毒性に対する無毒性量(NOAE)は

30 mg/kg/day と判断された。なお、近位尿細管の硝子滴が 30 mg/kg 群の雄で観察されたことから、雄動物の反復投与毒性に対する無作用量(NOEL)は 30 mg/kg/day 未満と判断された。

哺育 0 日の出生児体重と新生児生存率の低下が 100 mg/kg 群でみられたことから、生殖発生毒性に対する無毒性量は 30 mg/kg/day と判断された。

試験目的

雌雄ラットの交配前(2 週間)および交配期間中(最長 2 週間)、ならびに雄では交配期間終了後 2 週間、雌では妊娠期間を通して周産期(哺育 4 日まで)に 1,2-メチレンジオキシベンゼンを経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

試験ガイドラインと GLP

本試験は、「新規化学物質等に係る試験の方法について:以下、化審法ガイドライン」(平成 23 年 3 月 31 日付け、薬食発 0331 第 7 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、環境企発第 110331009 号環境省総合環境政策局長通知)に準拠し、「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 0331 第 8 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、環境企発第 110331010 号環境省総合環境政策局長通知)を遵守して実施した。

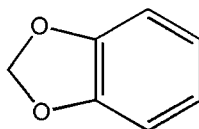
動物愛護

全ての実験操作は、「動物の愛護及び管理に関する法律」(昭和 48 年 10 月 1 日 法律第 105 号、平成 24 年 9 月 5 日 一部改正)、「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)および「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」(平成 18 年 6 月 1 日、科発第 0601001 号)を遵守し、「財団法人食品薬品安全センター・秦野研究所動物実験に関する指針」(平成 2 年 10 月 1 日、平成 22 年 10 月 1 日改正)に基づいて実施した。本試験における動物実験計画は、秦野研究所動物実験委員会の審査を受け、承認されている(動物実験承認番号:1120197A)。なお、承認された動物実験計画からの変更はなかった。

材料と方法

1. 被験物質

被験物質である 1,2-メチレンジオキシベンゼン(別名:1,3-ベンゾジオキソール、CAS No.274-09-9、分子式:C₇H₆O₂、分子量:122.12、性状:無色〜ごくうすい黄色の透明液体、無臭、融点:-10℃、沸点:172℃、比重:1.1873(20/20)、ロット番号:CRETG、純度:99.9%(GC)、Annex A、以下、1,2-MD)は、XXXXXXXXXXより購入し(被験物質入手:2012 年 7 月 3 日)、使用時まで冷蔵(実測値 3~7℃)、遮光、密閉で保管した。1,2-MD の構造式を次に示す。



被験物質の安定性については、実験開始前および実験終了後に秦野研究所にて赤外吸収スペクトルを測定し、スペクトルに変化がなかったことが確認されている(試験番号:M-12-021)。

2. 動物および飼育方法

日本チャールス・リバー厚木飼育センターより 8 週齢の Sprague-Dawley (SD) 系 [CrI:CD(SD)、SPF] ラット雄 55 匹、雌 83 匹を購入し、飼育室(18 号室)に収容した。入荷日も含めて 15 日間、検疫と飼育環境への馴化のため飼育した。その間毎日、動物の一般状態を観察し、入荷日(検疫 1 日)および検疫終了日に体重を測定した。検疫・馴化期間中は動物の尾に赤のフェルトペンで馴化番号を記し、飼育ケージに試験番号、性別および馴化番号を記入した動物カードを掛けて識別した。また、雌動物については、検疫 3 日から毎日、性周期を観察した。入荷動物の入荷時および検疫終了時の体重は下記の通りであった。

動物入荷日	:2012 年 9 月 24 日
入荷時体重	:雄 251.9~291.0 g、雌 184.6~219.3 g
検疫終了日	:2012 年 10 月 8 日
検疫終了時体重	:雄 347.0~434.8 g、雌 229.7~290.5 g

検疫・馴化期間中の一般状態および体重推移に試験実施に影響を及ぼすと判断される異常は認められなかった。なお、雌動物では、詳細な症状観察で挙尾または常同行動(後肢立ち)が観察された 3 匹と規則的な性周期の回帰が認められない 4 匹を除外し、体重別層化無作為抽出法により群分けを行った。群分けした動物には一連の動物番号を割り当て、フェルトペンで尾に動物番号を標識し、色彩の異なった動物カードに試験番号および動物番号を記入して飼育ケージに掛けた。群分けから棄却した雄動物 7 匹、雌動物 15 匹(性周期の結果により除外した例を含む)は全て余剰動物とし、雌 12 匹は他目的に転用し、その他の動物は他の目的に転用予定がなかったため、安楽死させた。

動物は許容温度 21.0～25.0℃、許容湿度 40.0～75.0%、換気設定約 15 回/時間、明暗サイクル 12 時間(7 時～19 時)点灯、12 時間(19 時～7 時)消灯に設定された飼育室内で、金属製金網床ケージ(220w×270d×190h mm)に 1 匹ずつ(交配時は 2 匹)収容し、固型飼料(CE-2、日本クレア)と水道水(秦野市水道局給水)を自由に摂取させて飼育した(剖検前の絶食に関しては剖検の項を参照)。雌動物は分娩例全例について、妊娠 18 日から哺育 4 日までラット用プラスチック製繁殖ケージ(350w×400d×180h mm)に 1 匹ずつ収容し、床敷として紙パルプ製チップ(ペパークリーン、日本エスエルシー)を適宜供給した。飼育期間中の動物室の温度は 23.0～25.0℃、湿度は 41.5～73.5%であった。また、供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを確認した。

3. 投与検体

1) 調製

被験物質を秤量し、媒体(トウモロコシ油、製造元:ナカライテスク、製造番号:V2K9025)を加え攪拌混和させ、7.5 w/v%液を調製した。さらに 7.5 w/v%液を媒体によって希釈し、2.5 ならびに 0.75 w/v%液を段階的に調製した。調製した検体は冷蔵(実測値 2～12℃)・遮光下で保管し、安定性の保証期間内に使用した。

2) 安定性試験

投与に先立ち、0.75 および 7.5 w/v%(7.5 および 75 mg/mL)濃度の調製検体について、冷蔵(実測値 4～5℃)、遮光条件下における 8 日間の安定性を確認した(Annex B)。調製検体中の被験物質含量測定は Annex C、第 2 項に従った。

3) 含量試験

初回調製検体(調製日:2012 年 10 月 5 日)について、0.75、2.5 および 7.5 w/v%濃度の被験物質含量を測定した。その結果、平均含量は調製濃度の 99.7～100.0%であり、各測定値のばらつきはそれぞれ平均値の 98.6～101.8%で規定範囲内にあった(Annex D)。

調製検体中の被験物質含量測定は Annex C、第 2 項に従った。

4. 投与量の設定および投与方法

本試験の投与量は、本被験物質を用いて行った「1,2-メチレンジオキシベンゼンのラットを用いる反復投与毒性・生殖発生毒性併合試験(予備試験)」(試験番号:R-12-011)の結果をもとに設定した。なお、予備試験で使用した被験物質および媒体は本試験と同じロットを用いた。

予備試験では、当初、0(媒体、トウモロコシ油)、30、100 および 300 mg/kg の 1,2-MD を 8 週齢の雌雄各 3 匹の SD 系ラットに 14 日間、反復強制経口投与することを計画したが、投与 7 日までの観察において 300 mg/kg 群に毒性徴候が認められなかったことから、投与 8 日からは 30 mg/kg 群の動物に

500 mg/kg を投与した。その結果、500 mg/kg 群において翌日からよろめき歩行が観察され、雄 1 例、雌全例が 500 mg/kg の投与 4 日目までに死亡した。したがって、500 mg/kg は反復投与による最大耐量を凌駕する用量と判断された。300 mg/kg 群においては、雌雄とも初回投与直後の体重増加が抑制されたが、その後の体重推移に影響は認められず、血液学検査および血液生化学検査においても被験物質投与の影響を強く示唆する変化は認められなかった。しかしながら、100 および 300 mg/kg 群の雌では肝臓重量が用量依存的に増加し、300 mg/kg 群の雌では腎臓の相対重量の増加が観察されたことから、本試験においては、最高用量には死亡を引き起こさない 300 mg/kg を、中用量には用量相関性を明確にする 100 mg/kg を設定し、低用量には無毒性量(NOEL)が得られると期待される 30 mg/kg を設定した。

本試験では、雄動物は交配前 2 週間、交配期間を通して剖検前日まで(総投与回数 42 回)、雌動物は交配前 2 週間、交配期間、妊娠期間を通して分娩後の哺育 4 日まで(総投与回数 42～45 回)、交尾が確認されなかった雌は剖検前日まで(総投与回数 52 回)、分娩しない雌は剖検前日(妊娠 25 日相当日)まで、非交配雌の反復毒性を評価するために設定したサテライト群は投与 42 日まで、1 日 1 回、1 週 7 回、毎日 9 時～13 時の間(9 時 00 分～12 時 12 分)に投与した。投与容量は 4 mL/kg とし、雌雄とも最新の測定日の体重を基に投与液量を算出した。なお、対照群には媒体であるトウモロコシ油を同様に投与した。投与経路は化審法ガイドラインに拠り、ラット用胃管による強制経口投与とした。

本試験の群構成および動物番号を以下に示した。

群	投与物質	投与量 (mg/kg)	濃度 (w/v%)	投与容量 (mL/kg)	動物番号	
					雄	雌
対照群	トウモロコシ油 (媒体)	0	0	4	M01001～M01012*	F01001～F01012
低用量群	1,2-MD	30	0.75	4	M02013～M02024	F02013～F02024
中用量群	1,2-MD	100	2.5	4	M03025～M03036	F03025～F03036
高用量群	1,2-MD	300	7.5	4	M04037～M04048*	F04037～F04048
対照群 (サテライト群)	トウモロコシ油 (媒体)	0	0	4	-	F05049～F05058*
高用量群 (サテライト群)	1,2-MD	300	7.5	4	-	F06059～F06068*

*:雄の対照群および高用量群、雌のサテライト群の動物番号の大きい各5例は回復観察に供した。

5. 検査法

1) 親動物 (F₀)

① 一般状態の観察

全例について、飼育期間中は毎日 1 回、投与期間中は投与前後の毎日 2 回以上観察した。

② 回復および遅発毒性の観察

雄動物は対照群および高用量群のうち動物番号の大きい各 5 例を、雌動物はサテライト群の動物番

号の大きい各 5 例を最終投与翌日(回復 1 日)から 14 日間、毎日 1 回以上、一般状態を観察した。

③詳細な症状観察

全例について、検疫終了日、投与 8、15、24、30、36 および 42 日(分娩例は哺育 0 日から 4 日の間)、未交尾例は投与 49 日にも、回復期間中は回復 7 および 14 日にスコアリング法による詳細な症状観察を行った。観察は、いずれも 13 時～17 時の間(13 時 13 分～15 時 47 分)に行った。

まず、ケージ越しでの観察を行い、ケージから取り出す際に外表を観察し、作業台上での観察を行った。作業台上では、体位、姿勢、探索行動、立毛、眼裂、振戦、痙攣、呼吸数、歩行、常同行動、奇妙な行動、挙尾反応、身づくろい、発声、排尿、排便、接触に対する反応、撤去反射、耳介反射を観察した。

④機能検査

雄動物は、動物番号の若い各群 5 例について、投与 39 日に自発運動測定と握力測定を実施し、投与 42 日に詳細な症状観察に引き続いて刺激に対する感覚運動反応を検査した。分娩例は、投与期間が近接し、出来るだけ分娩から日数が経過した各群 5 例(高用量群は 1 例)、サテライト群は動物番号の若い各群 5 例について、投与最終週に自発運動測定、握力測定および刺激に対する感覚運動反応を検査した。なお、投与最終週に実施した自発運動測定および刺激に対する感覚運動反応で被験物質投与の影響が示唆されたことから、回復 11 日に自発運動測定、回復 14 日に刺激に対する感覚運動反応を検査した。

(1)刺激に対する感覚運動反応

プライエル反応、瞳孔反射、視覚定位、驚愕反応、後肢引込み反射、眼瞼(瞬目)反射、正向反射の有無を検査した。

(2)握力測定

小動物握力測定システムを用いて握力を測定した。各動物の前肢および後肢の握力をそれぞれ 5 回測定し、最高値および最低値を除外した 3 回の握力値の平均値を求めた。

(3)自発運動測定

自発運動量測定装置(SUPER-MEX、室町機器)を用いて、20 分間の自発運動量(区画移動数および立ち上がり回数)を計測し、計測値は 5 分毎に集計した。試験対象動物は、検査直前に別室の装置設置場所に運搬し、速やかに自発運動測定を開始した。

⑤体重測定

雄および雌動物のサテライト群は、投与 1(投与開始日)、3、7、14、21、28、35、42 日、回復 1、7、14 日および剖検日に測定した。雌動物は投与 1、3、7、14 日、妊娠 0、7、14、20 日および未分娩例は妊娠 26 日相当日、哺育 0、4 日および剖検日に測定し、未交尾例は投与 21、28、35、42、49 日および剖検日に測定した。

⑥摂餌量測定

雄および雌動物のサテライト群は、投与 1～2、7～8、14～15、29～30、35～36、41～42 日、回復 6～7、12～13 日に測定し、サテライト群は投与 21～22 日にも測定した。雌動物は投与 1～2、7～8、14～15 日および妊娠 0～1、7～8、14～15、20～21 日ならびに哺育 3～4 日に測定し、未交尾例は投与 29～30、35～36、41～42、48～49 日に測定した。

⑦尿検査

雄動物および雌動物のサテライト群を検査対象とし、投与37日の検査では各群5例、また、回復13日における検査では回復例全例を検査した。

投与37日の検査では当日の投与後に、回復13日の検査では一般状態の観察終了後に動物を代謝ケージに収容し、以下の項目について検査した。ただし、色調・濁度、試験紙による検査および尿沈渣は、採尿開始後約4～8時間の時点で採取した蓄尿で、その他の項目は約24時間の蓄尿で行った。

項目	測定法	使用機器
色調・濁度	視診	
pH・潜血・蛋白・糖・ケトン体	試験紙法	オーションイレブンAE-4020(アークレイ)
ウロビリノーゲン・ビリルビン	同上	同上
沈渣	鏡検	光学顕微鏡
尿量	計量	メスシリンダー等
比重	屈折法	デジタル臨床屈折計SU-202(エルマ販売)
ナトリウムイオン濃度	イオン電極法	全自動電解質分析装置EA05(エイアントティー)
カリウムイオン濃度	同上	同上
塩素イオン濃度	同上	同上

⑧性周期観察

全例の雌について、検疫 3 日から性周期を観察し、群分け後、投与開始以降も引き続きサテライト群を除く全例の膣スミア標本を作製し、各動物の同居後、交尾が確認されるまで性周期を観察した。また、群ごとの平均発情回帰日数(個体ごとの発情期から発情期までの日数の平均)および投与開始後に4あるいは5日間隔の性周期がそれ以外の性周期に変化した動物の頻度を群毎に算出した。なお、規則的に4～5日の間で性周期が回帰している動物は正常と判断した。

⑨交配

投与 15 日の 16 時 05 分より同群内の雌雄を 1 対 1 で同居させた。翌朝より毎朝、膣栓を確認し、同居中の雌の膣スミア標本を作製して鏡検した。膣内に膣栓あるいは膣スミア標本中に精子が確認された動物を交尾成立動物とし、この日を妊娠 0 日と起算して個別飼育に戻した。交配結果および妊娠の成否により、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数、交尾率[(交尾動物数/交配に用いた動物数)×100, %]、妊娠率[(妊娠動物数/交尾した雌動物数)×100, %]を算出した。

⑩妊娠・分娩・哺育状態の観察

交尾雌は全例を自然分娩させた。分娩の確認は、妊娠 21 日相当日から分娩が確認されるまで毎日、午前と午後に行い、15 時までには分娩が完了した例について、その日を哺育 0 日(分娩日)とした。分娩状態の直接観察は観察可能な動物について行い、直接観察できなかった動物についても、分娩後の一般状態および産児の状態から異常の有無を判断した。分娩後は、哺育状態を哺育 1～4 日の間、毎日観察した。分娩例については、妊娠期間(妊娠 0 日から分娩日までの日数)を求めた。また、剖検時には、妊娠黄体数と着床数を数え、着床率[(着床数/妊娠黄体数)×100, %]を算出した。

⑪採血

雄の投与終了時剖検では各群の動物番号が若い 5 例、回復 15 日における剖検では回復観察に供した全例について採血を行った。また、分娩雌の投与終了時剖検では、投与期間が近接した各群の 5 例(高用量群は 1 例)について採血を行った。サテライト群の投与終了時剖検では各群の動物番号が若い 5 例、回復 15 日における剖検では回復観察に供した全例について採血を行った。いずれも解剖前 18～24 時間絶食させた後、腹部後大静脈から以下の(1)、(2)、(3)の順に注射筒を換えて採血した。

- (1) 血液学検査用:抗凝固剤 EDTA-2K
- (2) 血液学検査用:抗凝固剤 クエン酸ナトリウム
- (3) 血液生化学検査用:抗凝固剤 ヘパリン

⑫血液学検査

採血対象動物について以下の項目を検査した。抗凝固剤としてクエン酸ナトリウムを用いて採取した血液から血漿を分離して、プロトロンビン時間および活性化部分トロンボプラスチン時間を測定し、その他の項目は抗凝固剤として EDTA-2K を用いて採取した血液で測定した。

項目	測定法	使用機器
赤血球数(RBC)	電気抵抗検出法	血液自動分析装置 XT-2000iV(シスメックス)
白血球数(WBC)	半導体レーザを用いたフローサイトメトリー法	同上
白血球分類	同上	同上
網状赤血球比率(RET%)	同上	同上
血色素量(HGB)	SLSヘモグロビン法	同上
平均赤血球容積(MCV)	計算($HCT \times 1000 / RBC$)	同上
血小板数(PLT)	電気抵抗検出法	同上
ヘマトクリット値(HCT)	同上	同上
平均赤血球血色素量(MCH)	計算($HGB \times 1000 / RBC$)	同上
平均赤血球血色素濃度(MCHC)	計算($HGB \times 100 / HCT$)	同上
活性化部分トロンボプラスチン時間(APTT)	光散乱検出法	全自動血液凝固測定装置 CA-1000(シスメックス)
プロトロンビン時間(PT)	同上	同上

⑬血液生化学検査

採血対象動物について以下の項目を検査した。抗凝固剤としてヘパリンを用いて採取した血液から血漿を分離して測定した。なお、得られた血漿の一部は甲状腺機能に関するホルモン(T3、T4 および TSH)測定用として凍結保存(-70℃以下)したが、甲状腺の病理学検査およびその他全ての検査項目の結果から、本被験物質は甲状腺機能に影響を及ぼさないと判断されたため、甲状腺ホルモン測定は実施しなかった。

項目	測定法	使用機器
総蛋白濃度(TP)	ビウレット法	自動分析装置 JCA-BM6010(日本電子)
アルブミン濃度(rALB)	BCG法	同上
グルコース濃度(Glc)	ヘキソキナーゼ・G-6-PDH法	同上
総コレステロール濃度(TC)	コレステロールオキシダーゼ・HMMPS法	同上
トリグリセリド濃度(TG)	GPO・HMMPS法、グリセリン消去法	同上

項目	測定法	使用機器
リン脂質濃度 (PL)	コリンオキシダーゼ・DAOS法	自動分析装置 JCA-BM6010(日本電子)
尿素窒素濃度 (BUN)	ウレアーゼ・G6PDH法,ウレアーゼ律速系	同上
クレアチニン濃度 (cre)	Jaffé法	同上
γ-グルタミルトランスペプチダーゼ活性 (γ-GTP)	IFCC法	同上
アルカリフォスファターゼ活性 (ALP)	GSCC法	同上
アスパラギン酸アミトランスフェラーゼ活性 (AST)	IFCC法	同上
アラニンアミトランスフェラーゼ活性 (ALT)	IFCC法	同上
乳酸脱水素酵素活性 (LDH)	JSCC標準化対応法	同上
カルシウム濃度 (Ca)	OCPC法	同上
総ビリルビン濃度 (tbil)	酵素法	同上
無機リン濃度 (IP)	モリブデン酸直接法	同上
胆汁酸濃度 (TBA)	酵素サイクリング法	同上
A/G比	計算 (rALB/(TP- rALB))	同上
ナトリウムイオン濃度 (Na)	イオン電極法	全自動電解質分析装置 EA05(エイアントディー)
カリウムイオン濃度 (K)	同上	同上
塩素イオン濃度 (Cl)	同上	同上

⑭剖検および器官重量

雌雄動物は、以下の時期にペントバルビタールにて麻酔し剖検した。採血対象動物はペントバルビタールナトリウム麻酔下で採血した後に剖検し、これ以外の動物はペントバルビタールナトリウム麻酔下で放血致死させ、剖検した。

対象動物	解剖時期	屠殺前の絶食
雄		
投与終了時剖検例	投与 42 日の翌日	18～24 時間絶食
回復観察例	回復 15 日	18～24 時間絶食
雌		
分娩例	哺育 4 日の翌日	18～24 時間絶食
交尾したが分娩しなかった例(未分娩)	妊娠26日相当日	実施せず
交尾が確認されなかった例(未交尾)	投与52日の翌日	実施せず
サテライト群(投与終了時剖検例)	投与42日の翌日	18～24 時間絶食
サテライト群(回復観察例)	回復15日	18～24 時間絶食
全哺育児が死亡した例	全哺育児が死亡した日	実施せず
死亡動物	死亡確認日	実施せず

全例について、脳、甲状腺および上皮小体、胸腺、心臓、肝臓、腎臓、脾臓、副腎、精巣、精巣上体、前立腺(腹側葉)および精嚢(凝固腺を含む)、卵巣、子宮の重量を測定した。また、全例の脳、脊髄、下垂体、眼球(ハーダー腺)、顎下腺および舌下腺、気管、甲状腺および上皮小体、胸腺、心臓、肺および気管支、肝臓、腎臓、脾臓、膵臓、副腎、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、下顎リンパ節、腸間膜リンパ節、精巣、精巣上体、前立腺、精嚢および凝固腺、卵巣、子宮、膣、膀胱、大腿骨および大腿骨骨髓、骨格筋、坐骨神経および乳腺を採取し、保存した。死亡動物以外の肺および気管支は 15 cm 水柱以下の圧力で、気管内に 10%中性緩衝ホルマリン溶液 5 mL 以下を注入し固定してから摘出

して同固定液に保存した。精巣および精巣上体はブアン液に固定（長期保存は 10%中性緩衝ホルマリン溶液）し、その他の器官・組織は 10%中性緩衝ホルマリン溶液に固定した。

なお、未分娩、未交尾および全哺育児が死亡した例の器官重量値は評価対象から除外し、剖検所見についても、哺育 4 日の翌日に剖検した分娩雌とは分けて評価した。

⑮病理組織学検査

剖検した動物のうち、雄およびサテライト群の投与終了時剖検では対照群ならびに高用量群の動物番号が若い各 5 例、分娩雌の投与終了時剖検では採血を行った対照群の 5 例ならびに高用量群の 1 例について、組織学検査対象器官（保存した器官・組織のうち乳腺は除く）のヘマトキシリン・エオジン（HE）標本作製し、病理組織学検査を実施した。

死亡動物および全哺育児が死亡した例についても同様に、病理組織学検査を実施した。また、剖検時に異常がみられた器官・組織に関しても同様に HE 標本作製し、病理組織学検査を実施した。

なお、投与期間終了時の剖検例で被験物質投与の影響が疑われた器官については、低および中用量群の 5 例と回復期間終了時の剖検例についても病理組織学検査を実施した。また、投与終了時剖検例のうち対照群の 1 例（動物番号:M01001）および 300 mg/kg 群の 1 例（動物番号:M04037）の腎臓については、 α_{2u} -グロブリン免疫組織染色（ABC 法）を実施した。

2) 出生児 (F_1)

①出生児の観察

哺育 0 日に生存児数および死亡児数を雌雄別に数えて、性別および外表奇形の有無を観察し、分娩率[(産児数/着床痕数) × 100, %]、生児出産率[(出產生児数/着床痕数) × 100, %]、出産率[(生児出産雌数/妊娠動物数) × 100, %]および出生率[(出產生児数/産児数) × 100, %]を算出した。また、哺育 0～4 日まで、毎日、一般状態を観察し、生存児数と死亡児数を雌雄別に数え、新生児生存率[(哺育 4 日の生児数/哺育 0 日の生児数) × 100, %]を算出した。生存児については、哺育 0 および 4 日に個別の体重を測定し、腹ごとに雌雄別の平均体重を算出するとともに、哺育 0 日および 4 日における性比[(雄生児数/総生児数) × 100, %]を算出した。

②剖検

死亡児は外表奇形の有無を観察して剖検し、10%中性緩衝ホルマリン溶液に固定して保存した。生存児は哺育 4 日に外表奇形の有無を観察してセボフルラン吸入麻酔下に放血致死させて剖検し、内部器官の異常の有無を観察した。

6. データの解析法

性周期の変化した動物の頻度、交尾率、受胎率ならびに出生児の形態異常の出現頻度については Fisher の直接確率検定を行った（有意水準:5%）。被験物質投与群の病理組織学検査所見のうち、グレード分けしたデータは Mann-Whitney の U 検定により、また陽性グレードの合計値は Fisher の直接確率の片側検定により対照群との間の有意差検定を行った（有意水準:5%）。

その他の定量的検査のデータは、個体ごとに得られた値あるいは litter ごとの平均値を 1 標本とし、サテライト群内あるいはその他の群内で比較した。その際、解析の対象が 2 群の場合には、まず F 検定を行い、有意差が認められなければ Student's-t 検定を行った。F 検定において有意差が認められた場合は、Aspin-Welch 検定を行った。解析の対象が 3 群以上の場合は、先ず、Bartlett の方法により各群の分散の一様性について検定(有意水準:5%)を行った。分散が一樣であった場合には、一元配置型の分散分析(有意水準:5%)を行い、群間に有意性が認められた場合は、Dunnett 法により多重比較を行った(有意水準:5%)。一方、いずれかの群で分散が 0 となった場合および分散が一樣でなかった場合には、Kruskal-Wallis の順位検定(有意水準:5%)を行い、群間に有意性が認められた場合には、Dunnett 型の検定法により多重比較を行った(有意水準:5%)。

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

2012 年 10 月 4 日の 11:00～14:26 に受変電設備の定期点検のために停電し、それに伴い動物飼育室内の照明が明期に消え、同日の 11:00～14:30 に空調が停止した。しかし、いずれの動物の一般状態にも上述事象に起因したと考えられる変化は認められず、また、温湿度(23.0～25.0℃、58.5～73.5%)は許容範囲内であったことから、試験への影響はないと判断した。

2012 年 10 月 26 日の 10:21～10:37(16 分間)、14:15～14:16(1 分間)および 16:02～16:07(5 分間)に本館電灯用回路が停電し、本館の動物飼育室内の照明が消えた。しかし、いずれの動物の一般状態、性周期等に上述事象に起因したと考えられる変化は認められず、消灯は短時間であったことから、試験への影響はないと判断した。

齧歯類自発運動量測定法の標準操作手順書には、「測定用ケージへの動物の収容は、乱数表を用いて、無作為に実施する」と記載されていたが、試験では乱数表を用いず、動物番号の若い順に測定用ケージへ収容した。しかし、各測定用ケージの精度管理(センサー感度)の測定値を確認し、装置間のばらつきはないと判断されたことから、試験成績へ影響はないと判断した。

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

試験成績

1. 親動物

1) 一般状態 (Table 1-1～Table 4, Appendix 1-1-1～Appendix 4-4)

雄では死亡動物は観察されなかった。300 mg/kg 群の雄 1 例(動物番号:M04046)で投与 25 および 26 日に立毛が観察された以外に、異常は認められなかった。

雌では対照群の 1 例(動物番号:F01011)が妊娠 22 日に死亡したが、被験物質投与群に死亡動物

は観察されなかった。生存雌では 300 mg/kg 群において投与 7 日から 10 日の間に排便量の減少と腹臥位が交配雌 1 例(動物番号:F04045)、軟便が非交配雌 1 例(動物番号:F06062)、被毛の汚れおよび下腹部の汚れが非交配雌 1 例(動物番号:F06063)で観察された。その他、哺育期間中の 100 mg/kg 群の 1 例(動物番号:F03028)に膈口出血と下腹部の汚れが観察され、この例では全哺育児が哺育 4 日までに死亡した。

雌雄とも回復観察中に一般状態の異常は認められなかった。

2) 詳細な症状観察 (Table 5～Table 6-2, Appendix 5-1～Appendix 6-2-2)

投与期間中の雄では、300 mg/kg 群の 10 例で投与 24、30、36 または 42 日に耳介反射の低下が観察された。また、同群の 1 例(動物番号:M04039)で投与 24 日に異常歩行(腰高歩行)が、1 例(動物番号:M04046)で投与 24 日に一般状態の観察でも認められた立毛が観察された。その他、100 mg/kg 群の 1 例(動物番号:M03031)で投与 24 日に挙尾が観察されたが、対照群の非交配雌(動物番号:F05049、F05052)にもみられた変化であり、用量に依存したものではなかった。その他の検査項目には、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。

回復期間中の雄では、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。

投与期間中の交配雌では、100 mg/kg 群の 4 例および 300 mg/kg の 12 例で投与 8、24、30、36、42、49 日または哺育期間中に耳介反射の低下が観察された。300 mg/kg 群の 1 例(動物番号:F04045)で投与 8 日に、一般状態の観察でも認められた腹臥位(うずくまり姿勢)と自発運動の低下が観察された。また、100 mg/kg 群の 1 例(動物番号:F03028)で哺育期間中に、一般状態の観察でも認められた被毛の汚れが観察された。

投与期間中の非交配雌では、300 mg/kg の 9 例で投与 24、30、36 または 42 日に耳介反射の低下が観察された。また、300 mg/kg 群の 1 例(動物番号:F06063)で投与 15 日に、一般状態の観察でも認められた被毛の汚れが観察された。その他の検査項目には、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。

回復期間中の非交配雌では、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) 体重 (Table 7-1～Table 10, Appendix 7-1-1～Appendix 10-4)

投与期間中の雄では、投与 3 日から 300 mg/kg 群の体重が低値を示し、投与 7、21、28 および 35 日の値が対照群と比較して有意に低下した。回復期間中の雄の体重では、対照群と 300 mg/kg 群との間に有意差は認められなかった。

投与期間中の交配雌では、投与開始から 300 mg/kg 群の体重が対照群より低値で推移したが、有意差は認められなかった。投与期間中の非交配群では、投与開始から 300 mg/kg 群で体重増加抑制がみられ、投与 7 日から投与 42 日までの体重が対照群と比較して有意に低下した。回復期間中の非交配雌では、300 mg/kg 群の回復 1 日から回復 14 日までの体重が対照群と比較して有意に低下した。

妊娠期間中の雌では、300 mg/kg 群の体重が低値を示し、妊娠 7、14 および 20 日の値が対照群と比

較して有意に低下した。哺育期間中の雌では、300 mg/kg 群の哺育 0 日の体重が対照群と比較して低値を示したが、100 mg/kg 以下の群の体重には、対照群との差はなかった。

4) 摂餌量 (Table 11-1～Table 14, Appendix 11-1-1～Appendix 14-4)

投与期間中の雄では、300 mg/kg 群の投与 41～42 日の摂餌量が対照群と比較して有意に増加した。回復期間中の雄でも、300 mg/kg 群の回復 6～7 日の値が対照群と比較して有意に増加した。

投与期間中の交配雌では、300 mg/kg 群の投与 7～8 日の摂餌量が対照群と比較して有意に低下した。投与期間中の非交配雌では、投与 7～8 日の値が対照群と比較して有意に低下した。回復期間中の非交配雌では、対照群と比較して有意差なかった。

妊娠期間中の摂餌量には、被験物質投与の影響を示唆する有意な変化は認められなかった。哺育期間中の雌では、100 mg/kg 以上の群で哺育 3～4 日の摂餌量が対照群より低値を示したが、これは被験物質による新生児生存率の低下に伴う変化と推定される。

5) 機能検査

① 刺激に対する感覚運動反応 (Table 15～Table 16-2, Appendix 15-1～Appendix 16-2-4)

投与期間中の雄では、驚愕反応の低下した動物が 300 mg/kg 群の 1 例に認められた。回復期間中の雄では、驚愕反応を含むいずれの検査でも異常を示した動物は認められなかった。

投与期間中の分娩雌では、いずれの検査でも異常を示した動物は認められなかった。投与期間中の非交配雌では、驚愕反応の低下した動物が 300 mg/kg 群の 1 例に認められた。回復期間中の非交配雌では、驚愕反応を含むいずれの検査でも異常を示した動物は認められなかった。

② 握力測定 (Table 17～Table 19, Appendix 17～Appendix 19)

投与最終週に実施した前肢および後肢の握力測定では、非交配雌を含む雌雄に、被験物質投与の影響は認められなかった。

③ 自発運動量測定 (Table 20～Table 22, Appendix 20-1～Appendix 22-2)

投与期間中の雄では、300 mg/kg 群の開始 20 分の区画移動数および立ち上がり回数が対照群と比較して有意に増加した。

回復期間中の雄でも、300 mg/kg 群の開始 20 分の区画移動数が対照群と比較して有意に増加したが、同群の立ち上がり回数には対照群との差はなかった。

投与期間中の分娩雌では、300 mg/kg 群の 1 例で区画移動数および立ち上がり回数が対照群に比較して増加する傾向がみられたが、100 mg/kg 以下の群の自発運動量には対照群との差は認められなかった。

投与期間中の非交配雌では、300 mg/kg 群の区画移動数および立ち上がり回数が対照群に比較して有意に増加し、その差は、開始から時間が経過するほど顕著であった。回復期間中の非交配雌では、開始 5 分の立ち上がり回数が 300 mg/kg 群で有意に減少したが、対照群に比較して自発運動が増加する傾向は認められなかった。

6) 尿検査 (Table 23-1～Table 24-2, Appendix 23-1-1～Appendix 24-2-2)

投与期間中の雄では、被験物質投与群のカリウムイオン濃度が用量に依存して低下傾向を示し、300 mg/kg 群の値が対照群と比較して有意に低下した。その他の検査項目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。

回復期間中の雄では、被験物質投与の影響を示唆する尿の変化は観察されなかった。

投与期間中の非交配雌では、300 mg/kg 群のカリウムイオン濃度が対照群と比較して有意に低下したが、その他の検査項目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。

回復期間中の非交配雌では、被験物質投与の影響を示唆する尿の変化は観察されなかった。

7) 血液学検査 (Table 25-1～Table 26-3, Appendix 25-1-1～Appendix 26-3-2)

①雄動物

投与期間終了時の雄では、300 mg/kg 群の網状赤血球比率(平均 4.20%)が対照群と比較して有意に増加し、背景データの範囲(下表参照)を上回った。その他、300 mg/kg 群のプロトロンビン時間(平均 13.7sec)が有意に短縮したが、背景データの範囲(下表参照)内であり、延長とは逆の変化であることから被験物質の影響ではないと判断した。回復期間終了時の雄では、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。

雄(投与終了時)	試験数*	サンプル数	平均	平均±2SD
網状赤血球比率	6	30	2.87	2.31-3.43
PT	6	30	16.7	13.3-20.0

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:トウモロコシ油)を使用

②雌動物

投与期間終了時の分娩雌では 30 mg/kg 群の好酸球比率が対照群と比較して有意に低下したが、用量に依存した変化ではなく、その他の検査項目に影響を示唆する変化は認められなかった。

非交配雌では、300 mg/kg 群の血色素量が対照群と比較して有意に低下したが、その他の検査項目に被験物質投与の影響を示唆する有意な変化は認められなかった。

回復期間終了時の非交配雌では、300 mg/kg 群の MCH(平均 18.3 pg)が対照群と比較して有意に低下したが、背景データの範囲(下表参照)内であったことから偶発的な変化と判断した。

非交配雌(回復終了時)	試験数*	サンプル数	平均	平均±2SD
MCH	6	30	18.5	17.5-19.4

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:トウモロコシ油)を使用

8) 血液生化学検査 (Table 27-1～Table 28-3, Appendix 27-1-1～Appendix 28-3-2)

①雄動物

投与期間終了時の雄では、300 mg/kg 群のグルコース濃度が対照群と比較して有意に低下し、無機リン濃度が有意に増加した。

回復期間終了時の雄では、300 mg/kg 群の A/G 比 (平均 1.42) が対照群と比較して有意に低下し、5 例中 1 例 (動物番号: M04044) の値 (1.27) が背景データの範囲 (下表参照) を明らかに下回った。

雄(回復終了時)	試験数*	サンプル数	平均	平均±2SD
A/G 比	6	30	1.66	1.43-1.88

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群 (媒体: トウモロコシ油) を使用

②雌動物

投与期間終了時の分娩雌では、300 mg/kg 群の 1 例に LDH の高値が認められたが、100 mg/kg 以下の群に被験物質投与の影響を示唆する変化は観察されなかった。

投与期間終了時の非交配雌では、300 mg/kg 群の総コレステロール、トリグリセライド、リン脂質および無機リンの各濃度が対照群と比較して有意に増加した。その他、同群のクレアチニン濃度および塩素イオン濃度が対照群と比較して有意に低下したが、対照群との差はごくわずかであることから、被験物質投与の影響とは考えなかった。

回復期間終了時の非交配雌では、300 mg/kg 群の A/G 比 (平均 1.79) とカルシウム濃度 (平均 9.1 mg/dL) が対照群と比較して有意に低下したが、いずれも背景データの範囲 (下表参照) 内の変化であった。

非交配雌(回復終了時)	試験数*	サンプル数	平均	平均±2SD
A/G 比	6	30	2.04	1.63-2.46
血中カルシウム濃度	6	30	9.4	9.0-9.8

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群 (媒体: トウモロコシ油) を使用

9) 器官重量 (Table 29-1～Table 30-3, Appendix 29-1-1～Appendix 30-3-2)

①雄動物

投与期間終了時の雄では、300 mg/kg 群の肝臓および腎臓の重量が高値を示し、肝臓の絶対および相対重量と腎臓の相対重量が対照群と比較して有意に増加した。その他、300 mg/kg 群の体重低下に伴う変化と考えられる相対重量の有意な増加が、脳および心臓で認められた。雄性生殖器の重量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。

回復期間終了時の雄では、300 mg/kg 群の腎臓の相対重量 (平均 6.852 mg/g) が対照群と比較して有意に増加し、背景データ (下表参照) の範囲を上回った。その他、300 mg/kg 群の左精巣の絶対重量が対照群と比較して有意に低下したが、左右の合計値に有意差は認められなかった。

雄(回復終了時)	試験数*	サンプル数	平均	平均±2SD
腎臓の相対重量	6	30	6.159	5.946-6.371

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:トウモロコシ油)を使用

②雌動物

投与期間終了時の分娩雌では、300 mg/kg 群の 1 例に肝臓重量の増加が認められた。その他、100 mg/kg 群の卵巢および副腎の各重量が低値を示し、右卵巢の絶対重量と右副腎の相対重量が対照群と比較して有意に低下したが、用量に依存した変化ではなかった。

投与期間終了時の非交配雌では、300 mg/kg 群の肝臓および腎臓の重量が高値を示し、肝臓の絶対および相対重量と腎臓の相対重量が対照群と比較して有意に増加した。その他、300 mg/kg 群の体重低下に伴う変化と考えられる相対重量の有意な増加が心臓で認められたが、雌性生殖器の重量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。

回復期間終了時の非交配雌では、体重低下に伴う変化と考えられる脳、肝臓および腎臓の相対重量の有意な増加が 300 mg/kg 群に認められた。

10) 剖検所見 (Table 31-1～Table 32-3, Appendix 31-1～Appendix 32-3)

①雄の投与終了時剖検例

投与 42 日の翌日に剖検した雄動物、対照群 7 例、30 mg/kg 群 12 例、100 mg/kg 群 12 例および 300 mg/kg 群 7 例の剖検所見は以下の通りである。

腎臓では、両側性の大型化が 300 mg/kg 群の 6 例にみられ、うち 1 例は表面が粗造であった。

肝臓では、大型化が 100 mg/kg 群の 1 例と 300 mg/kg 群の 5 例に認められた。

精巣では、両側性の小型化が 100 mg/kg 群の 2 例(動物番号:M03025、M03026)にみられ、うち 1 例は淡色化を呈していたが、300 mg/kg 群に精巣の異常は認められなかった。

②雄の回復観察例

回復 15 日に剖検した雄動物、対照群 5 例および 300 mg/kg 群 5 例に異常は認められなかった。

③分娩雌の投与終了時剖検例

哺育 4 日の翌日に剖検した雌動物、対照群 11 例、30 mg/kg 群 11 例、100 mg/kg 群 8 例および 300 mg/kg 群 1 例の剖検所見は以下の通りである。

肝臓では、大型化が 300 mg/kg 群の 1 例に認められた。

④不妊例、全哺育児が死亡した例および未交尾例

妊娠 26 日相当日に剖検した不妊例、30 mg/kg 群 1 例、100 mg/kg 群 2 例、300 mg/kg 群 4 例、および全哺育児が死亡した例、100 mg/kg 群 2 例、300 mg/kg 群 6 例、さらには未交尾例、300 mg/kg 群 1 例の剖検所見は以下の通りである。

不妊例では、肝臓の大型化が 300 mg/kg 群の 3 例に観察された他、脾臓の小型化が 300 mg/kg 群の 1 例に観察された。

全哺育児が死亡した例では、肝臓の大型化が 100 mg/kg 群の 1 例および 300mg/kg 群の 5 例に観察され、そのうち 100 mg/kg 群の 1 例では淡色化を伴っていた。また、胸腺の小型化が 300 mg/kg 群の 3 例に観察され、そのうち 1 例(動物番号:F04042)では脾臓の小型化が、1 例(動物番号:F04048)では十二指腸および空腸の壁肥厚が、残りの 1 例(動物番号:F04044)では副腎の大型化が観察された。その他、腎臓の大型化が 100 および 300 mg/kg 群の各 1 例に認められた。

未交尾例の 300 mg/kg 群の 1 例では、肝臓の大型化がみられた。

⑤サテライト群の投与終了時剖検例

投与 42 日の翌日に剖検した非交配雌、対照群 5 例および 300 mg/kg 群 5 例に異常は認められなかった。

⑥サテライト群の回復観察例

回復 15 日に剖検した非交配雌、対照群 5 例および 300 mg/kg 群 5 例に異常は認められなかった。

⑦雌の死亡例

妊娠 22 日に死亡した対照群の 1 例(動物番号:F01011)では、脾臓の小型化、胸腺の小型化、腺胃粘膜に暗色点、前胃粘膜の菲薄化が観察された。

11)病理組織学検査 (Table 33-1～Table 34-3, Appendix 33-1～Appendix 34-3)

①雄の投与終了時剖検例

投与終了時剖検例のうち、対照群および 300 mg/kg 群の 5 例について病理組織学検査を実施し、さらに被験物質の影響が疑われた下垂体、甲状腺、肝臓、腎臓および副腎については、30 および 100 mg/kg 群の 5 例についても病理組織学検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以下の通りである。

下垂体では、限局性のリンパ球浸潤と好塩基性細胞の空胞化が 300 mg/kg 群の各 1 例にみられたが、100 mg/kg 以下の群に異常は認められなかった。

甲状腺では、対照群を含む全ての群で各群 1 例に鰓後体遺残が観察されたが、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。

肺では、300 mg/kg 群の 3 例に肺胞の泡沫細胞の集簇が観察されたが、対照群の 1 例にもみられた軽度な変化であった。その他、動脈壁にごく軽度の鉍質沈着が 300 mg/kg 群の 1 例で認められた。

肝臓では、小葉中心性の肝細胞の肥大とくもり硝子様変性が 100 mg/kg 以上の群で観察され、肝細胞肥大の頻度および程度は、100 mg/kg 以上の群で対照群と比較して有意に増加した。肝臓の小肉芽腫は対照群を含む全ての群で認められ、100 mg/kg 群のみで頻度および程度が対照群と比較して有意に増加した。門脈周囲性の肝細胞の脂肪化は対照群および被験物質投与群で散見されたが、対照群と比較して程度および頻度の差はなかった。その他、小葉中心性の肝細胞の空胞化が 30 mg/kg 群の 2 例および 300 mg/kg 群の 1 例で認められたが、軽度な変化であった。

脾臓では、間質にリンパ球浸潤が 300 mg/kg 群の 2 例にみられ、そのうち 1 例は限局性の出血を伴っていたが、いずれもごく軽度な変化であった。

脾臓では対照群と 300 mg/kg 群の全例に髄外造血および褐色色素の沈着が観察されたが、対照群と 300 mg/kg 群との間で程度の差はなかった。

腎臓では、近位尿細管に硝子滴が 30 mg/kg 以上の群で観察され、100 mg/kg 以上の群で頻度および程度が対照群と比較して有意に増加した。また、皮質の好塩基性尿細管は対照群を含む各群でみられ、300 mg/kg 群の頻度が対照群と比較して有意に増加した。その他、30 mg/kg 群の 2 例にみられた硝子円柱は用量に依存した変化ではなく、300 mg/kg 群の 2 例にみられた髄質の鉍質沈着は、対照群の 1 例にもみられた変化であった。なお、近位尿細管の硝子滴については、免疫組織化学的に $\alpha 2\mu$ -グロブリンであることを確認した。

副腎では、球状帯細胞の肥大が 300 mg/kg 群の 2 例にみられたが、100 mg/kg 以下の群では認められなかった。その他、束状帯細胞の脂肪滴の増加が 300 mg/kg 群の 4 例に観察されたが、同様の変化は 100 mg/kg 以下の群にも認められ、対照群と比較して頻度および程度に差はなかった。

精巣では、剖検時に両側性の小型化がみられた 100 mg/kg 群の 2 例(動物番号:M03025、M03026)に精細管の萎縮が観察され、その頻度が対照群と比較して有意に増加したが、300 mg/kg 群に同様の所見はみられなかった。

前立腺では、リンパ球浸潤が 300 mg/kg 群の 1 例にみられたが、同様の変化は対照群の 3 例にも認められた。

ハーダー腺では、間質にリンパ球浸潤が 300 mg/kg 群の 1 例にみられたが、ごく軽度の変化であった。

②雄の回復観察例

回復 15 日に剖検した対照群および 300 mg/kg 群の 5 例については、投与終了時の剖検例で被験物質の影響が疑われた下垂体、甲状腺、肝臓、腎臓および副腎について病理組織学検査を実施した。病理組織所見は、以下の通りである。

下垂体では、異常は認められなかった。

甲状腺では、対照群の 1 例および 300 mg/kg 群の 2 例に鰹後体遺残が観察されたが、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。

肝臓では、小葉中心性でごく軽度の肝細胞の肥大が 300 mg/kg 群の 1 例に観察されたが、300 mg/kg 群にくもり硝子様変性は認められなかった。その他、300 mg/kg 群において門脈周囲性の肝細胞の脂肪化、小肉芽腫および小葉中心性の肝細胞の空胞化が観察されたが、対照群にも観察され、程度および頻度とも対照群との差はなかった。

腎臓では、300 mg/kg 群において皮質の好塩基性尿細管、硝子円柱、間質にリンパ球浸潤、皮質または髄質に鉍質沈着が観察されたが、対照群にも観察され、程度および頻度とも対照群との差はなかった。なお、投与終了時にみられた近位尿細管の硝子滴は回復終了時には観察されなかった。

副腎では、束状帯細胞の脂肪滴の増加が対照群および 300 mg/kg 群の各 2 例に観察されたが、程度の差はなかった。

③分娩雌の投与終了時剖検例

哺育 4 日の翌日に剖検した対照群の 5 例および 300 mg/kg 群の 1 例について、病理組織学検査を

実施し、さらに被験物質の影響が疑われた下垂体、甲状腺、肝臓、腎臓、副腎、卵巣、子宮および膺については、30 および 100 mg/kg 群の 5 例についても病理組織学検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以下の通りである。

肝臓では、小葉中心性の肝細胞の肥大とくもり硝子様変性が 100 mg/kg 以上の群で観察され、肝細胞の肥大の頻度が 100 mg/kg 群で対照群と比較して有意に増加した。また、クッパー細胞の増殖が 30 mg/kg 群の 3 例および 100 mg/kg 群の 1 例でみられたが、いずれもごく軽度なものであった。その他、クッパー細胞の赤血球貪食像が 100 mg/kg 群の 1 例、門脈周囲性の肝細胞の脂肪化が対照群を含む 100 mg/kg 以下の投与群、小肉芽腫が対照群を含む全ての投与群で観察されたが、被験物質投与の影響を示唆する変化はなかった。

脾臓では、対照群の全例と 300 mg/kg 群の 1 例に髄外造血および褐色色素の沈着が観察されたが、対照群と 300 mg/kg 群との間で程度の差はなかった。

腎臓では、間質にリンパ球浸潤が 300 mg/kg 群の 1 例にみられたが、対照群にも認められたごく軽度な変化であった。

副腎では、球状帯細胞の肥厚が 300 mg/kg 群の 1 例にみられたが、対照群にも認められたごく軽度な変化であった。その他、限局性の静脈洞の拡張が 30 mg/kg 群の 1 例、束状帯細胞の脂肪滴の増加が 300 mg/kg 群の 1 例に観察されたが、いずれもごく軽度な変化であった。

卵巣では、黄体細胞の脂肪滴の増加が 100 および 300 mg/kg 群の各 1 例に認められた。

子宮では、異常は認められなかった。

膺では、上皮の粘膜細胞化が 100 mg/kg 群の 1 例に観察されたが、用量に依存した変化ではなかった。

大腿骨骨髓では、造血の亢進が 300 mg/kg 群の 1 例に認められたが、同様の変化は対照群でも観察された。

④全哺育児が死亡した例

哺育 4 日までに全哺育児が死亡した 100 mg/kg 群の 2 例および 300 mg/kg 群の 6 例について、病理組織検査を実施した。病理組織所見は、以下の通りである。

甲状腺では、異所性の胸腺組織が 300 mg/kg 群の 1 例に観察された他、対照群の分娩雌にも認められた鰓後体遺残が 300 mg/kg 群の 3 例に観察された。

上皮小体では、細胞質の空胞化が 300 mg/kg 群の 1 例に認められたが、ごく軽度な変化であった。

胸腺では、対照群の分娩雌でもみられた萎縮が 100 mg/kg 群の 2 例および 300 mg/kg 群の 6 例に認められた。

肝臓では、小葉中心性の肝細胞の肥大が 100 mg/kg 群の 2 例および 300 mg/kg 群の 6 例、くもり硝子様変性が 100 mg/kg 群の 1 例および 300 mg/kg 群の 4 例で観察され、肝細胞の肥大は 300 mg/kg 群で程度が増強される傾向がみられた。その他、門脈周囲性の肝細胞の脂肪化、髄外造血、小肉芽腫およびクッパー細胞の増加が散見されたが、いずれも対照群の分娩雌にみられた変化であった。

脾臓では、萎縮、髄外造血および褐色色素の沈着が 100 および 300 mg/kg 群に観察されたが、いず

れも対照群の分娩雌にみられた変化であった。

腎臓では、皮質の好塩基性尿細管が 100 および 300 mg/kg 群の各 2 例、硝子円柱が 100 mg/kg 群の 1 例、間質にリンパ球浸潤が 100 mg/kg 群の 2 例および 300 mg/kg 群の 1 例、尿細管上皮の空胞変性が 100 mg/kg 群の 1 例で観察されたが、いずれも軽度な変化であった。

副腎では、球状帯細胞の肥大が 100 mg/kg 群の 1 例および 300 mg/kg 群の 4 例、束状帯細胞の脂肪滴の増加が 100 mg/kg 群の 2 例および 300 mg/kg 群の 4 例に観察された。

卵巣では、黄体細胞の脂肪滴の増加が 100 mg/kg 群の 2 例および 300 mg/kg 群の 6 例で観察された。

子宮では、子宮内膜の出血または好中球浸潤が 100 mg/kg 群の 2 例および 300 mg/kg 群の 6 例で観察され、内腔上皮細胞の肥大が 300 mg/kg 群の 6 例、細胞残屑を伴った内腔上皮の空胞化が 100 mg/kg 群の 1 例および 300 mg/kg 群の 6 例に認められたが、いずれも分娩後の子宮にみられる変化と推察された。

膣では、上皮または固有層へ好中球浸潤が 100 mg/kg 群の 1 例および 300 mg/kg 群の 2 例、上皮の粘液細胞化が 100 mg/kg 群の 1 例および 300 mg/kg 群の 5 例に観察されたが、いずれも分娩後の膣に見られる変化と推察された。

ハーダー腺では、間質にリンパ球浸潤が 300 mg/kg 群の 3 例に観察されたが、対照群の分娩雌にもみられたごく軽度な変化であった。

大腿骨髄では、造血の亢進が 100 mg/kg 群の 2 例および 300 mg/kg 群の 6 例に認められたが、対照群の分娩雌にもみられた変化であった。

⑤非交配雌の投与終了時剖検例

非交配雌の投与終了時剖検例、対照群 5 例および 300 mg/kg 群 5 例の病理組織所見は以下の通りである。

甲状腺では、間質にリンパ球浸潤が 300 mg/kg 群の 1 例にみられたが、軽度な変化であった。

上皮小体では、細胞質のごく軽度な空胞化が 300 mg/kg 群の 1 例に認められたが、対照群の 1 例にもみられた。

胸腺では、萎縮が 300 mg/kg 群の 4 例に認められたが、対照群と比較して程度および頻度とも差がなかった。

肺では、肺胞内に泡沫細胞の集簇が 300 mg/kg 群の 1 例に観察されたが、ごく軽度な変化であった。

肝臓では、小葉中心性の肝細胞の肥大とくもり硝子様変性が 300 mg/kg 群で観察され、両所見の頻度および程度は対照群と比較して有意に増加した。その他、門脈周囲性の肝細胞の脂肪化と小肉芽腫が 300 mg/kg 群の全例で観察されたが、対照群と比較して程度および頻度の差はなかった。

脾臓では、褐色色素沈着および髄外造血が 300 mg/kg 投与群の全例で認められたが、対照群と比較して程度および頻度の差はなかった。

腎臓では、300 mg/kg 群で皮質の好塩基性尿細管が 3 例、硝子円柱が 2 例、間質のリンパ球浸潤が 2 例観察されたが、いずれも対照群で観察された所見であり、頻度および程度に対照群との差はなかった。その他、同群では皮質のごく軽度な鉍質沈着が 2 例に、皮質の嚢胞が 1 例のみに観察された。

副腎では、300 mg/kg 群で球状帯細胞の肥大が 2 例、束状帯細胞の脂肪滴の増加が 2 例観察されたが、い

いずれも対照群に観察された所見であり、頻度および程度に対照群との差はなかった。

卵巢では、閉鎖卵胞の増加が対照群の 1 例および 300 mg/kg 群の 2 例にみられ、そのうち 300 mg/kg 群の 1 例(動物番号:F06059)には黄体嚢胞が認められた。その他、卵胞嚢胞が 300 mg/kg 群の 1 例に観察されたが、対照群にもみられたごく軽度な変化であった。

子宮では、子宮腺の嚢胞状拡張が 300 mg/kg 群の 1 例(動物番号:F06059)にみられた他、発情前期にみられる子宮腔の拡張が対照群および 300 mg/kg 群の各 1 例に認められた。

膣では、粘膜固有層にリンパ球浸潤が 300 mg/kg 群の 1 例に観察されたが、ごく軽度な変化であった。

ハーダー腺では、間質にリンパ球浸潤が 300 mg/kg 群の 2 例に観察されたが、対照群の分娩雌にもみられたごく軽度な変化であった。

大腿骨骨髓では、造血の亢進が 300 mg/kg 群の 5 例(全例)に認められたが、対照群にもみられた軽度な変化であった。

⑥非交配雌の回復観察例

回復 15 日に剖検した対照群の 5 例および 300 mg/kg 群の 5 例については、投与終了時の剖検例で被験物質の影響が疑われた下垂体、甲状腺、肝臓、副腎、卵巢、子宮および膣について病理組織学検査を実施した。

甲状腺では、300 mg/kg 群の 2 例に鰓後体遺残が観察されたが、被験物質投与の影響を示唆する変化は観察されなかった。

肝臓では、門脈周囲性の肝細胞の脂肪化と小肉芽腫が 300 mg/kg 群の全例で観察されたが、対照群と比較して程度および頻度の差はなかった。また、限局性のごく軽度な壊死が 300 mg/kg 群の 1 例に認められたが、投与終了時にみられた小葉中心性の肝細胞の肥大とくもり硝子様変性は、回復終了時には観察されなかった。

子宮では、子宮腺の嚢胞状拡張と内腔の拡張が 300 mg/kg 群の 1 例(動物番号:F06064)に観察された。

下垂体、副腎、卵巢および膣では、異常は認められなかった。

2. 生殖能力

1)性周期および交配成績 (Table 35～Table 36, Appendix 35-1～Appendix 36-4)

投与開始後に不規則な異常性周期を示した動物が 300 mg/kg 群に 3 例(動物番号:F04039、F04040、F04045)みられ、同群の投与期間中の平均発情回帰日数が対照群と比較して有意に延長した。交尾率、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数には、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が、300 mg/kg 群の妊娠率が対照群に比較して有意に低下した。

2) 出産率および妊娠期間 (Table 37, Appendix 37-1～Appendix 37-4)

妊娠雌は全例が生児を出産し、出産率は各群とも 100%であった。300 mg/kg 群では 7 例中 4 例が妊娠 23 日に産出、同群の妊娠期間が対照群と比較して有意に延長した。

3) 分娩および哺育状態

300 mg/kg 群では、分娩状態が不良と判断された母動物が 7 例中 6 例みられ、いずれの例も出生児にミルクスポット(乳児の腹壁を透して胃内に貯留したミルクの白色斑)が観察されなかった。また、これらの母動物では、全哺育児が哺育 4 日までに死亡した。100 mg/kg 以下の群では分娩状態の異常は観察されなかったが、100 mg/kg 群の 10 例中 2 例では、全哺育児が哺育 4 日までに死亡した。

4) 黄体数、着床数および着床率 (Table 37, Appendix 37-1～Appendix 37-4)

黄体数、着床数および着床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。

3. 出生児

1) 生存 (Table 37, Appendix 37-1～Appendix 37-4)

300 mg/kg 群の産児数と分娩率が対照群と比較して低下し、同群の死亡児数が有意に増加した。また、300 mg/kg 群の出産生児数、生児出産率および出生率が対照群と比較して有意に低下し、100 mg/kg 以上の群の新生児生存率が対照群と比較して有意に低下した。その他、30 mg/kg 群の哺育 4 日の性比が対照群と比較して有意に低下したが、用量に依存した変化ではなかった。

2) 体重 (Table 38, Appendix 38-1～Appendix 38-4)

哺育 0 日では出生児体重が用量に依存して低下し、100 mg/kg 以上の群の体重が雌雄とも対照群と比較して有意に低下した。哺育 4 日では、300 mg/kg 群の 1 腹の出生児体重は雌雄とも低値を示したが、100 mg/kg 以下の群の出生児体重には対照群と比較して有意差は認められなかった。

3) 出生児観察 (Table 39～Table 40, Appendix 39-1～Appendix 39-4)

哺育 0 日の産児の形態観察では、30 mg/kg 群の雄 1 例(動物番号:F02017M05)に短尾が観察されたが、その他の産児に外表奇形は認められなかった。出生児の一般状態観察では、300 mg/kg 群の 42 例で哺育 0 日に哺乳不良が、同群の 4 例で哺育 0 日にチアノーゼが観察された。

死亡児および哺育 4 日の生存児の剖検では、被験物質投与の影響を示唆する外表奇形および内蔵異常は観察されなかった。

考察

雌雄ラットの交配前(2週間)および交配期間中、ならびに雄では交配期間終了後を通して計42日間、雌では妊娠期間を通して周産期(哺育4日まで)に1,2-メチレンジオキシベンゼンを経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

1. 反復投与毒性

一般状態観察では、被験物質投与による死亡例は認められなかったが、300 mg/kg 群において立毛が雄1例、排便量の減少と腹臥位が交配雌1例、軟便または被毛の汚れおよび下腹部の汚れが非交配雌2例に一過性に観察された。これらの症状は、投与量設定のための予備試験(試験番号:R-12-011)においても観察されていることから、被験物質投与により誘発された毒性影響と考えられる。詳細な症状観察では、耳介反射の低下が300 mg/kg 群の雄と100 mg/kg 以上の群の雌で認められ、機能検査では300 mg/kg 群の雄1例および非交配雌1例に驚愕反応の低下が観察されたことから、雄では300 mg/kg、雌では100 mg/kg の反復投与により、感覚反応の低下を来す可能性が示唆された。一方、自発運動測定では、300 mg/kg 群の雌雄に自発運動量が増加する傾向がみられたことから、被験物質の反復投与により活動性の亢進を誘発している可能性が示唆された。本被験物質の単回経口投与によるラットのLD₅₀値は580 mg/kgであり、中枢神経系の亢進と抑制の両方を示すことが報告¹⁾されている。

妊娠22日に死亡した対照群の1例(動物番号:F01011)については、剖検時に脾臓や胸腺の小型化、腺胃粘膜に暗色点などストレスに関連した変化は観察されたが、病理組織学検査からも誤投与の可能性を示唆する所見は認められなかった。

体重測定では、投与開始から300 mg/kg 群の雄および非交配雌で体重増加抑制が認められ、交配雌の妊娠期間中の体重も対照群より低値を示したことから、本被験物質には体重増加抑制作用があるものと推察される。しかしながら、300 mg/kg 群の雌では、投与7日の摂餌量が低下したものの、雄については摂餌量の低下は認められなかった。

投与終了時の器官重量測定では、肝臓重量の増加が300 mg/kg 群の雌雄で認められ、肝臓の病理組織学検査では、雌雄とも小葉中心性の肝細胞の肥大とくもり硝子様変性が100 mg/kg 以上の群で観察された。血液生化学検査では、肝毒性を示唆する酵素濃度の上昇等が認められていないことから、肝臓重量の増加は、被験物質投与による薬物代謝酵素の誘導に起因した生理的反応と判断した。なお、300 mg/kg 群の非交配雌の血液生化学検査でみられた総コレステロール、トリグリセライドおよびリン脂質濃度の上昇は、上記の酵素誘導に伴う蛋白合成の亢進が原因と推定される。投与終了時の雄では、腎臓重量の増加が300 mg/kg 群で認められ、腎臓の病理組織学検査では、近位尿細管の硝子滴が30 mg/kg 以上の群の雄で観察された。しかし、近位尿細管の硝子滴は、雄性ラットに特異的に発現する α_{2u} -グロブリン腎症^{2,3)}の特徴的な所見であり、本試験の雌では尿細管の硝子滴が認められていないこと、免疫組織化学的に α_{2u} -グロブリンが確認されたことから、本試験の雄でみられた硝子滴は α_{2u} -グロブリン

ン腎症によるものと考えられる。なお、300 mg/kg 群で好塩基性尿細管の頻度が増加したが、これは α_{2u} -グロブリン沈着による尿細管傷害に伴う再生像と推察される。しかしながら、腎臓重量の増加は 300 mg/kg 群の非交配雌でも認められ、尿中カリウムイオン濃度の低下、血中無機リン濃度の増加が 300 mg/kg 群の雄および非交配雌で認められていることから、腎機能が低下している可能性は否定できない。また、血中グルコース濃度の低下が 300 mg/kg 群の雄で認められたが、この変化は、投与量設定のための予備試験(試験番号:R-12-011)においても認められていることから、被験物質投与の影響と考えられる。

副腎の病理組織検査では、皮質球状帯細胞の肥大が 300 mg/kg 群の雄および非交配雌、さらには 100 mg/kg 以上の群の全哺育児が死亡した雌に観察され、前述の通り 300 mg/kg 群の雄および非交配雌で尿中カリウムイオン濃度が低下したことから、血圧やアルドステロン産生に被験物質投与の影響が及んだ可能性も考えられるが、皮質球状帯細胞の肥大は対照群の雌にも認められた変化であること、当該病変は体重低下などのストレスにより惹起される場合もあることから、毒性影響とは判断しなかった。

投与終了時の血液学検査では、網状赤血球比率の増加が 300 mg/kg 群の雄に認められた。同群の非交配雌においても血色素量の低下が認められていることから、被験物質投与により貧血傾向になったと考えられるが、その他の血液学的検査および病理組織学検査の結果に貧血を示唆する変化が認められなかったことから、その程度はごく軽度なものと推察される。

100 mg/kg 以上の群の全哺育児が死亡した例について実施した病理組織学検査では酵素誘導に起因したと推定される肝臓の変化がみられた以外に、卵巣の黄体細胞に脂肪滴の増加が認められた。同様の変化は、100 mg/kg 以上の分娩雌にも観察されていることから被験物質投与による内分泌系への影響が疑われた。しかしながら、下垂体、甲状腺、子宮および膣の病理組織学検査では、被験物質の内分泌系への影響を裏付ける変化を見出すことはできなかった。

2. 毒性の回復性

回復観察中の雌雄には、耳介反射の低下は認められず、驚愕反応の検査でも異常を示した動物は認められなかった。したがって、投与期間中にみられた感覚反応の低下は、投与終了後にすみやかに回復すると考えられた。一方、雄の区画移動数の増加や雌の低体重は回復観察中にも認められたことから、本試験期間内に回復性は確認できなかった。回復終了時の雄では 300 mg/kg 群の A/G 比が低下したが、明らかな低値を示した個体は 5 例中 1 例のみであり、他の指標も変動していないことから、被験物質投与による影響とは断言できなかった。

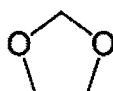
回復終了時には、腎臓の相対重量の増加が 300 mg/kg 群の雄に認められたが、病理組織学検査においては、投与終了時にみられた肝細胞の肥大、くもり硝子様変性および尿細管の硝子滴がほぼ消失したことから、酵素の誘導に起因した変化や α_{2u} -グロブリン腎症に関連した変化は、投与終了後に回復するものと考えられた。

3. 生殖発生毒性

300 mg/kg 群において、投与開始後に不規則な異常性周期を示した動物が 3 例みられ、同群の妊娠

率が有意に低下した。300 mg/kg 群の精巣および精巣上体の病理組織学検査では、被験物質投与の影響を示唆する所見が認められていないことから、妊娠率の低下は雌動物への影響に起因したものと推察される。さらに、300 mg/kg 群では妊娠期間が延長する傾向がみられ、分娩状態が不良と判断された母動物が 7 例中 6 例認められた。これらの母動物では、全哺育児が哺育 4 日までに死亡したことから、本被験物質は、母動物の妊娠期間、分娩および哺育にも悪影響を及ぼすと考えられた。

300 mg/kg 群では分娩状態の不良により出生時死亡が増加したことから、出産生児数が減少し、生児出産率および出生率が有意に低下した。また 100 mg/kg 以上の群において哺育 0 日の出生児体重が雌雄とも有意に低下し、新生児生存率も有意に低下した。100 mg/kg 群においても、10 例中 2 例の母動物で全哺育児が哺育 4 日までに死亡していることから、100 mg/kg 以上の用量では、新生児の発育および生存性に悪影響を及ぼすことが示された。類似の化学構造を持つ 1,3-ジオキソラン（下図参照）においても、ラットを用いた一世代生殖毒性試験⁴⁾において交尾率および分娩率の低下、死産児数の増加、児の生存率の低下が報告されている。



1,3-ジオキソランの構造式

4. 無毒性量

小葉中心性の肝細胞の肥大とくもり硝子様変性が 100 mg/kg 群の雌雄で、耳介反射の低下が 100 mg/kg 群の雌で観察されたことから雌雄動物の反復投与毒性に対する無毒性量 (NOAEL) は 30 mg/kg/day と判断された。なお、近位尿細管の硝子滴が 30 mg/kg 群の雄で観察されたことから、雄動物の反復投与毒性に対する無作用量 (NOEL) は 30 mg/kg/day 未満と判断された。

哺育 0 日の出生児体重と新生児生存率の低下が 100 mg/kg 群でみられたことから、生殖発生毒性に対する無毒性量は 30 mg/kg/day と判断された。

参考文献

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Annex A



試験成績書

2012年07月03日

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〒103-0023
東京都中央区日本橋本町4丁目10番
TEL: 03(5640)8860 FAX: 03(5640)8861

製品名: 1,2-Methylenedioxybenzene						
製品コード: M0658	等級: GR	製品ロット: CRETG	判定: 合格			
項目	結果		規格値			
純度(GC)	99.9 %		99.0 %以上			
比重 (20/20)	1.1873		1.1850 ~ 1.1890			
屈折率 n _{20/D}	1.5397		1.5380 ~ 1.5420			

Annex B

SOP/CHE/001

採用開始 2010年4月23日

安定性試験結果

試験番号	R - 12 - 012
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被験(対照)物質 : 1,2-メチレンジオキシベンゼン
 ロット番号 : CRETG
 媒体 : トウモロコシ油

調製年月日 : 2012年9月25日
 測定年月日 A : 2012年9月25日(調製後 0 日)
 B : 2012年10月3日(調製後 8 日)
 保管条件 : 冷蔵、遮光

調製濃度 (mg/mL)	A				B				
	試料 番号	測定濃度 (mg/mL)	含量 ^{a)} (%)	ばらつき ^{b)} (%)	試料 番号	測定濃度 (mg/mL)	含量 ^{a)} (%)	ばらつき ^{b)} (%)	残存率 ^{c)} (%)
7.50	1	7.356	98.1	100.8	7	7.747	103.3	105.6	106.2
	2	7.330	97.7	100.5	8	7.452	99.4	101.6	102.1
	3	7.205	96.1	98.7	9	6.812	90.8	92.8	93.4
	平均	7.297	97.3		平均	7.337	97.8		100.6
75.0	4	75.01	100.0	100.0	10	68.82	91.8	94.3	91.8
	5	74.69	99.6	99.6	11	74.85	99.8	102.6	99.8
	6	75.31	100.4	100.4	12	75.20	100.3	103.1	100.3
	平均	75.00	100.0		平均	72.95	97.3		97.3

a): 各測定時の測定濃度／調製濃度×100 b): 各測定時の測定濃度／各測定時の平均測定濃度×100
 c): 各測定時の測定濃度／初回の平均測定濃度×100

安定性の判定基準(溶液検体)
 各試料採取時点の平均含量がそれぞれ調製濃度の90.0～110.0%、また、各測定値のばらつきがそれぞれ平均値の90.0～110.0%以内であり、かつ、
 初回の測定平均値に対する各保管期間後の測定値の比(残存率)の平均値が90.0%以上を示す期間とする

Annex C

1. 被験物質原体の安定性の測定方法

① 使用機器

フーリエ変換赤外分光光度計 (FTIR-8300) 島津製作所

② 測定条件

測定方法 液膜法
波数範囲 4000～400 cm^{-1}

③ 測定方法

被験物質1、2滴を2枚の窓板(臭化カリウム)の間に挟み、測定する。対照は、測定雰囲気のパックグラウンド吸収とする。

2. 投与検体中の被験物質濃度測定法

① 試薬

蒸留水 (HPLC用) 和光純薬工業
アセトニトリル (HPLC用) 和光純薬工業
メタノール (HPLC用) 和光純薬工業
アセトン (HPLC用) 和光純薬工業

② 試液の調製(代表例)

1) 移動相

蒸留水及びアセトニトリルを1:1 (v/v)の割合で混合する。

③ 使用機器

電子天秤 (R200D) ザルトリウス
高速液体クロマトグラフ (HPLC) システム 島津製作所

主要構成: LC-10AS (ポンプ)、SIL-10A (オートインジェクタ)、CTO-10AS VP (カラムオーブン)、SPD-10A (検出器)、SCL-10A VP (システムコントローラ)、C-R7AまたはC-R7A plus (データ処理装置)

④ 標準溶液の調製

被験物質約50 mgを精密に量り、メタノールに溶解して正確に25 mLとする。この液1 mLを正確にとり、メタノールを加えて正確に10 mLとし、さらにこの液1 mLを正確にとり、メタノールを加えて正確に20 mLとして、標準原液(約10 $\mu\text{g/mL}$)とする。この標準原液1、2および4 mLを正確にとり、メタノールを加えてそれぞれ正確に20、10および10 mLとし、標準溶液(約0.5、2および4 $\mu\text{g/mL}$ 、各濃度 $n=1$)を調製する。

⑤ 試料溶液の調製

投与検体の1 mLを正確にとり、少なくとも50倍以上アセトンで希釈後、メタノールで適宜希釈し、検量線の範囲内となるように試料溶液を調製する。試料溶液は、投与検体の採取から $n=3$ で調製する。

⑥ 検量線の作成および投与検体中被験物質濃度の算出

試料溶液および標準溶液を高速液体クロマトグラフィーにより測定する。標準溶液は $n=3$ で測定し、得られた1,2-MDのピーク面積と調製濃度を基に、最小二乗法により検量線を作成する。試料溶液は、各 $n=1$ で測定し得られた1,2-MDのピーク面積から、先の検量線を用いて、試料溶液中の1,2-MDの濃度を求める。さらに、希釈係数を乗じて投与検体中の1,2-MD濃度を算出し、調製濃度に対する割合(含量、%)および各測定濃度の平均値に対するばらつき(%)を算出する。

⑦ HPLC 測定条件

検出器 紫外分光光度計(測定波長280 nm)
分析カラム CAPCELL PAK C18 UG120
(内径4.6 mm、長さ150 mm、粒子径5 μm 、資生堂)
移動相 蒸留水/アセトニトリル混液(1:1 v/v)
流量 1.0 mL/min
カラム設定温度 40°C
試料設定温度 室温
試料注入量 10 μL
オートインジェクタ洗浄液 アセトニトリル
システムの適合性 標準溶液(約2 $\mu\text{g/mL}$)を使用し、SOP/CHE/001に従って行う。

⑧ 数値の取り扱い

SOP/CHE/001に従う。

Annex D

SOP/CHE/001

採用開始 2010年4月23日

試験番号

R - 12 - 012

含 量 試 験 結 果

被験(対照)物質：1,2-メチレンジオキシベンゼン

調製年月日：2012年10月5日

ロット番号：CRETG

測定年月日：2012年10月5日

媒体：トウモロコシ油

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 $B/A \times 100$ (%)	平均含量 (%)	ばらつき $B/C \times 100$ (%)
13	7.50	7.434	7.483	99.1	99.8	99.3
14		7.414		98.9		99.1
15		7.603		101.4		101.6
16	25.0	24.85	24.93	99.4	99.7	99.7
17		25.38		101.5		101.8
18		24.57		98.3		98.6
19	75.0	74.44	75.01	99.3	100.0	99.2
20		75.36		100.5		100.5
21		75.23		100.3		100.3

含量の判定基準(溶液検体)平均含量が調製濃度の90.0～110.0%、各測定値のばらつきが平均値の90.0～110.0%以内とする。

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 1-1. General conditions of male rats

[illegible]

Pre: Before administration, Post: after administration.

[illegible]

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 1-2. General conditions of male rats at the recovery period

Group	Number of males and general conditions	Days of recovery period														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: corn oil)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
1,2-MD 300 mg/kg	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 2-1. General conditions of female rats

Group	Number of females and general conditions	Days of administration																																																							
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25							
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post								
Control (vehicle: corn oil)	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12						
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12				
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						
1,2-MD 30 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12				
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						
1,2-MD 100 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						
1,2-MD 300 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						

Pre: Before administration, Post: after administration.

Group	Number of females and general conditions	Days of administration																																																	
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43		44		45		46		47		48		49		50	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
1,2-MD 300 mg/kg	Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	General appearance, No abnormality	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	

Pre: Before administration, Post: after administration.

Group	Number of females and general conditions	Days of administration				
		51		52		53
		Pre	Post	Pre	Post	Pre
1,2-MD 300 mg/kg	Number of females	1	1	1	1	1
	General appearance, No abnormality	1	1	1	1	1

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 2-2. General conditions of female rats, satellite group

Group	Number of females and general conditions	Days of administration																																																		
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25		
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post			
Control (vehicle: corn oil)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	Fur, Hair, Coat, Soiled fur	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Anorectal region, Soiled perineal region	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
1,2-MD 300 mg/kg	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	9	9	8	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	Fur, Hair, Coat, Soiled fur	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Anorectal region, Soiled perineal region	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		

Pre: Before administration, Post: after administration.

Group	Number of females and general conditions	Days of administration																																																
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43														
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post													
Control (vehicle: corn oil)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5	
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
1,2-MD 300 mg/kg	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 2-3. General conditions of female rats at the recovery period

Group	Number of females and general conditions	Days of recovery period														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: corn oil)	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
1,2-MD 300 mg/kg	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 3. General conditions in dams during pregnancy

Group	Number of females and general conditions	Days of pregnancy																											
		0		1		2		3		4		5		6		7		8		9		10		11		12		13	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: corn oil)	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
1,2-MD 30 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
1,2-MD 100 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
1,2-MD 300 mg/kg	Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11

Pre: Before administration, Post: after administration.

Group	Number of females and general conditions	Days of pregnancy																								
		14		15		16		17		18		19		20		21		22		23		24		25		26
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: corn oil)	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	3	0	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
1,2-MD 30 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	1	1	1	1	1	1	1	1
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	1	1	1	1	1	1	1	1
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1,2-MD 100 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	2	2	2	2	2	2	2	2
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	2	2	2	2	2	2	2	2
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1,2-MD 300 mg/kg	Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4	4	4	4	4	4	4	4
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4	4	4	4	4	4	4	4
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 4. General conditions in dams during lactation

Group	Number of females and general conditions	Days of lactation										
		0		1		2		3		4		5
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: corn oil)	Number of females	7	7	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	7	7	11	11	11	11	11	11	11	11	11
	Anorectal region, Soiled perineal region	0	0	0	0	0	0	0	0	0	0	0
	Anorectal region, Vaginal hemorrhage	0	0	0	0	0	0	0	0	0	0	0
1,2-MD 30 mg/kg	Number of females	9	9	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	9	9	11	11	11	11	11	11	11	11	11
	Anorectal region, Soiled perineal region	0	0	0	0	0	0	0	0	0	0	0
	Anorectal region, Vaginal hemorrhage	0	0	0	0	0	0	0	0	0	0	0
1,2-MD 100 mg/kg	Number of females	7	7	10	10	10	10	10	10	10	8	8
	General appearance, No abnormality	7	7	10	10	9	9	10	10	10	8	8
	Anorectal region, Soiled perineal region	0	0	0	0	1	1	0	0	0	0	0
	Anorectal region, Vaginal hemorrhage	0	0	0	0	1	1	0	0	0	0	0
1,2-MD 300 mg/kg	Number of females	4	4	7	2	1	1	1	1	1	1	1
	General appearance, No abnormality	4	4	7	2	1	1	1	1	1	1	1
	Anorectal region, Soiled perineal region	0	0	0	0	0	0	0	0	0	0	0
	Anorectal region, Vaginal hemorrhage	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 5. Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery ^a	
				8	15	24	30	36	42	7	14
[Straub tail] Tail elevation	Control (vehicle: corn oil)	12	0 ^b	0	0	0	0	0	0	0	0
	1,2-MD 30 mg/kg	12	0	0	0	0	0	0	0		
	1,2-MD 100 mg/kg	12	0	0	0	1	0	0	0		
	1,2-MD 300 mg/kg	12	0	0	0	0	0	0	0	0	0
[Piloerection] Slight	Control (vehicle: corn oil)	12	0 ^b	0	0	0	0	0	0	0	0
	1,2-MD 30 mg/kg	12	0	0	0	0	0	0	0		
	1,2-MD 100 mg/kg	12	0	0	0	0	0	0	0		
	1,2-MD 300 mg/kg	12	0	0	0	1	0	0	0	0	0
[Abnormal gait] Reluctance to walk	Control (vehicle: corn oil)	12	0 ^b	0	0	0	0	0	0	0	0
	1,2-MD 30 mg/kg	12	0	0	0	0	0	0	0		
	1,2-MD 100 mg/kg	12	0	0	0	0	0	0	0		
	1,2-MD 300 mg/kg	12	0	0	0	1	0	0	0	0	0
[Pinna reflex] Hyporeflexia	Control (vehicle: corn oil)	12	0 ^b	0	0	0	0	0	0	0	0
	1,2-MD 30 mg/kg	12	0	0	0	0	0	0	0		
	1,2-MD 100 mg/kg	12	0	0	0	0	0	0	0		
	1,2-MD 300 mg/kg	12	0	0	0	5	8	8	8	0	0
[Urination] (frequency/30sec)	Control (vehicle: corn oil)	12	0 ^c	0	0	2	0	0	0	0	0
	1,2-MD 30 mg/kg	12	1	1	1	7	2	3	4		
	1,2-MD 100 mg/kg	12	1	0	1	2	1	3	1		
	1,2-MD 300 mg/kg	12	2	0	0	3	0	0	4	0	1
[Defecation] (frequency/30sec)	Control (vehicle: corn oil)	12	0 ^c	2	1	1	0	0	0	0	0
	1,2-MD 30 mg/kg	12	1	0	1	1	0	0	0		
	1,2-MD 100 mg/kg	12	0	0	1	1	0	0	0		
	1,2-MD 300 mg/kg	12	0	0	0	0	0	0	0	0	0

^a The recovery test was performed in 5 animals for each of the 0 and 300 mg/kg groups.

^b Values represent number of animals with the findings.

^c Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 6-1. Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						The lactation period	
				8	15	24	30	36	42		49
[Posture in home-cage]	Control (vehicle: corn oil)	12	0 ^a	0	0	0	0	0			0 (11)
Prone position	1,2-MD 30 mg/kg	12	0	0	0	0	0	0	0 (1)		0 (11)
or crouching position	1,2-MD 100 mg/kg	12	0	0	0	0	0	0	0 (1)		0 (10)
	1,2-MD 300 mg/kg	12	0	1	0	0	0	0	0 (5)	0 (1)	0 (4)
[Locomotor in home-cage]	Control (vehicle: corn oil)	12	0 ^a	0	0	0	0	0			0 (11)
Decrease in locomotor activity	1,2-MD 30 mg/kg	12	0	0	0	0	0	0	0 (1)		0 (11)
	1,2-MD 100 mg/kg	12	0	0	0	0	0	0	0 (1)		0 (10)
	1,2-MD 300 mg/kg	12	0	1	0	0	0	0	0 (5)	0 (1)	0 (4)
[Fur]	Control (vehicle: corn oil)	12	0 ^a	0	0	0	0	0			0 (11)
Soiled fur	1,2-MD 30 mg/kg	12	0	0	0	0	0	0	0 (1)		0 (11)
	1,2-MD 100 mg/kg	12	0	0	0	0	0	0	0 (1)		1 (10)
	1,2-MD 300 mg/kg	12	0	0	0	0	0	0	0 (5)	0 (1)	0 (4)
[Pinna reflex]	Control (vehicle: corn oil)	12	0 ^a	0	0	0	0	0			0 (11)
Hyporeflexia	1,2-MD 30 mg/kg	12	0	0	0	0	0	0	0 (1)		0 (11)
	1,2-MD 100 mg/kg	12	0	0	0	1	1	1	1 (1)		1 (10)
	1,2-MD 300 mg/kg	12	0	1	0	7	10	8	1 (5)	1 (1)	3 (4)
[Urination]	Control (vehicle: corn oil)	12	0 ^b	0	0	0	1	0			0 (11)
(frequency/30sec)	1,2-MD 30 mg/kg	12	0	0	1	0	4	1	0 (1)		0 (11)
	1,2-MD 100 mg/kg	12	3	0	0	0	0	0	0 (1)		0 (10)
	1,2-MD 300 mg/kg	12	0	1	1	1	0	0	0 (5)	0 (1)	0 (4)
[Defecation]	Control (vehicle: corn oil)	12	0 ^b	1	0	0	0	0			0 (11)
(frequency/30sec)	1,2-MD 30 mg/kg	12	0	0	0	0	0	0	0 (1)		0 (11)
	1,2-MD 100 mg/kg	12	0	0	0	0	0	1	0 (1)		0 (10)
	1,2-MD 300 mg/kg	12	1	2	0	0	1	0	0 (5)	0 (1)	0 (4)

^a Values represent number of animals with the findings.

^b Values represent total score of each group.

Figures in parentheses indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 6-2. Detailed clinical observations of female rats, satellite group

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery ^a	
				8	15	24	30	36	42	7	14
[Fur] Soild fur	Control (vehicle: corn oil)	10	0 ^b	0	0	0	0	0	0	0	0
	1,2-MD 300 mg/kg	10	0	0	1	0	0	0	0	0	0
[Straub tail] Tail elevation	Control (vehicle: corn oil)	10	0 ^b	0	0	2	0	0	0	0	0
	1,2-MD 300 mg/kg	10	0	0	0	0	0	0	0	0	0
[Pinna reflex] Hyporeflexia	Control (vehicle: corn oil)	10	0 ^b	0	0	0	0	0	0	0	0
	1,2-MD 300 mg/kg	10	0	0	0	8	7	9	8	0	0
[Urination] (frequency/30sec)	Control (vehicle: corn oil)	10	0 ^c	1	0	0	1	0	0	0	0
	1,2-MD 300 mg/kg	10	0	1	0	1	0	1	2	1	0
[Defecation] (frequency/30sec)	Control (vehicle: corn oil)	10	0 ^c	0	0	0	0	0	0	0	0
	1,2-MD 300 mg/kg	10	0	0	0	0	0	0	0	0	0

^a The recovery test was performed in 5 animals for each of the 0 and 300 mg/kg groups.^b Values represent number of animals with the findings.^c Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 7-1. Body weights of male rats

Group	Control (vehicle: corn oil)			1,2-MD 30 mg/kg			1,2-MD 100 mg/kg			1,2-MD 300 mg/kg		
Number of males	12			12			12			12		
Days of administration												
1	392.1	±	13.8	393.4	±	15.9	389.9	±	14.5	392.1	±	16.8
3	401.0	±	15.5	401.1	±	18.1	394.0	±	16.6	386.5	±	14.1
7	415.3	±	17.3	414.1	±	19.5	407.3	±	18.5	395.6	±	13.2 *
14	439.1	±	22.7	434.3	±	22.9	430.9	±	19.1	417.4	±	17.4
21	457.9	±	26.0	453.5	±	24.9	448.5	±	17.4	426.1	±	20.1 **
28	481.8	±	32.1	477.8	±	28.8	472.4	±	19.6	442.6	±	26.2 **
35	502.2	±	35.9	490.3	±	30.0	491.6	±	19.9	465.0	±	23.3 **
42	516.5	±	40.2	504.5	±	28.8	505.4	±	23.9	484.2	±	22.9

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 7-2. Body weights of male rats at the recovery period

Group	Control (vehicle: corn oil)	1,2-MD 300 mg/kg
Number of males	5	5
Days of recovery period		
1	507.5 ± 46.5	489.6 ± 24.2
7	522.5 ± 47.1	515.3 ± 24.5
14	531.9 ± 50.1	532.7 ± 23.6

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 8-1. Body weights of female rats

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of females	12	12	12	12
Days of administration				
1	250.6 ± 11.6	249.2 ± 13.6	252.9 ± 9.4	250.2 ± 12.2
3	252.9 ± 13.8	255.5 ± 12.1	255.8 ± 10.8	248.1 ± 9.8
7	258.2 ± 15.5	262.3 ± 15.0	259.4 ± 11.0	246.2 ± 12.8
14	267.3 ± 16.0	269.7 ± 19.8	268.7 ± 10.4	256.7 ± 11.1

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 8-2. Body weights of female rats, satellite group

Group	Control (vehicle: corn oil)			1,2-MD 300 mg/kg		
Number of females	10			10		
Days of administration						
1	250.8	±	9.7	251.0	±	7.5
3	256.1	±	10.1	251.0	±	10.1
7	265.6	±	10.6	251.4	±	9.9 **
14	276.0	±	10.4	258.9	±	10.7 **
21	289.0	±	9.2	267.7	±	12.6 **
28	297.1	±	12.4	273.3	±	14.1 **
35	300.5	±	14.7	277.4	±	11.6 **
42	307.1	±	13.1	282.3	±	10.7 **

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 8-3. Body weights of female rats at the recovery period

Group	Control (vehicle: corn oil)	1,2-MD 300 mg/kg
Number of females	5	5
Days of recovery period		
1	307.6 ± 13.7	281.7 ± 9.3 **
7	316.3 ± 8.6	290.3 ± 11.1 **
14	316.9 ± 12.0	293.7 ± 15.0 *

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 9. Body weights of dams during pregnancy

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of dams	12	11	10	7
Days of pregnancy				
0	277.8 ± 17.3	279.0 ± 18.9	278.7 ± 10.1	262.0 ± 11.6
7	311.8 ± 18.6	313.1 ± 15.7	309.8 ± 7.7	293.4 ± 11.2 *
14	348.7 ± 23.6	351.6 ± 17.0	341.2 ± 10.7	317.9 ± 13.9 **
20	430.8 ± 22.2	430.3 ± 22.2	418.2 ± 15.5	383.3 ± 16.7 **

Each value shows mean ± S.D. (g).

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 10. Body weights of dams during lactation

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of dams	11	11	10	7
Days of lactation				
0	330.5 ± 32.8	323.7 ± 24.8	313.6 ± 13.5	302.9 ± 12.4
4	338.0 ± 26.0	343.0 ± 18.9	339.1 ± 11.9 (8)	307.2 ± (1)

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 11-1. Food consumption of male rats

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of males	12	12	12	12
Days of administration				
1	24.1 ± 3.2	24.9 ± 2.4	23.5 ± 2.7	21.9 ± 3.7
7	22.6 ± 2.5	24.1 ± 3.1	23.1 ± 2.7	21.5 ± 2.9
14	21.5 ± 2.5	22.7 ± 3.3	22.8 ± 1.6	22.8 ± 2.6
29	23.5 ± 2.8	23.6 ± 2.6	23.1 ± 2.8	23.0 ± 2.3
35	23.0 ± 2.4	21.7 ± 2.2	23.5 ± 1.6	24.6 ± 2.5
41	22.6 ± 2.0	22.8 ± 1.7	22.8 ± 1.6	25.6 ± 1.8 **

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 11-2. Food consumption of male rats at the recovery period

Group	Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
Number of males	5		5	
Days of recovery period				
6	26.3	± 2.5	30.8	± 2.7 *
12	29.4	± 3.9	31.8	± 4.1

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 12-1. Food consumption of female rats

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of females	12	12	12	12
Days of administration				
1	16.1 ± 2.5	18.4 ± 3.1	17.0 ± 3.0	16.8 ± 1.8
7	17.6 ± 2.3	15.4 ± 2.3	16.1 ± 2.3	13.6 ± 5.6 *
14	16.2 ± 3.8	17.7 ± 2.2	16.4 ± 2.6	18.9 ± 4.5

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 12-2. Food consumption of female rats, satellite group

Group	Control (vehicle: corn oil)	1,2-MD 300 mg/kg
Number of females	10	10
Days of administration		
1	18.7 ± 2.3	17.1 ± 3.4
7	19.0 ± 2.5	16.0 ± 3.2 *
14	17.7 ± 3.6	16.7 ± 3.4
21	15.9 ± 2.1	14.0 ± 3.1
29	16.9 ± 2.1	16.1 ± 2.4
35	18.6 ± 2.1	18.3 ± 1.9
41	18.1 ± 2.4	17.9 ± 2.8

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 12-3. Food consumption of female rats at the recovery period

Group	Control (vehicle: corn oil)	1,2-MD 300 mg/kg
Number of females	5	5
Days of recovery period		
6	18.4 ± 1.9	19.7 ± 3.4
12	18.2 ± 2.4	20.6 ± 3.4

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 13. Food consumption in dams during pregnancy

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of dams	12	11	10	7
Days of pregnancy				
0	16.4 ± 2.9	17.3 ± 2.2	18.2 ± 2.5	19.1 ± 2.7
7	23.0 ± 3.3	23.0 ± 1.9	22.7 ± 2.8	21.3 ± 1.8
14	21.8 ± 2.3	23.9 ± 3.1	21.9 ± 2.7	22.9 ± 3.2
20	17.1 ± 7.8	20.2 ± 4.9	15.9 ± 3.1	16.7 ± 8.4

Each value shows mean ± S.D. (g).

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 14. Food consumption in dams during lactation

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg	
Number of dams	11	11	10	1	
Days of lactation	3	37.6 ± 5.8	39.1 ± 5.4	29.9 ± 11.7	21.8 ±

Each value shows mean ± S.D. (g).

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 15. Functional findings of male rats

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
<u>Male at the dosing period</u>				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	80
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
<u>Male at the recovery period</u>				
Number of animals	5			5
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Preyer's reaction	100			100
Withdrawal reflex	100			100
Eyelid reflex	100			100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 16-1. Functional findings of female rats

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
<u>Female, dam</u>				
Number of animals	5	5	5	1
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 16-2. Functional findings of female rats, satellite group

Group	Control (vehicle: corn oil)	1,2-MD 300 mg/kg
<u>Female, satellite group at the dosing period</u>		
Number of animals	5	5
Righting reflex	100	100
Visual placing	100	100
Pupillary reflex	100	100
Startle reaction	100	80
Preyer's reaction	100	100
Withdrawal reflex	100	100
Eyelid reflex	100	100
<u>Female, satellite group at the recovery period</u>		
Number of animals	5	5
Righting reflex	100	100
Visual placing	100	100
Pupillary reflex	100	100
Startle reaction	100	100
Preyer's reaction	100	100
Withdrawal reflex	100	100
Eyelid reflex	100	100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 17. Assessment of grip strength of male rats

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of males	5	5	5	4
Forelimb	1.015 ± 0.064	1.156 ± 0.058	0.960 ± 0.074	0.997 ± 0.150
Hindlimb	0.664 ± 0.126	0.744 ± 0.089	0.601 ± 0.135	0.592 ± 0.147

Each value shows mean (kg) ±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 18. Assessment of grip strength of female rats

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of females	5	5	5	1
Forelimb	1.084 ± 0.084	1.097 ± 0.074	1.132 ± 0.067	1.112 ±
Hindlimb	0.696 ± 0.034	0.558 ± 0.146	0.689 ± 0.115	0.647 ±

Each value shows mean (kg) ±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

The group given 300 mg/kg of 1,2-MD was excluded from statistical analysis.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 19. Assessment of grip strength of female rats, satellite group

Group	Control (vehicle: corn oil)	1,2-MD 300 mg/kg
Number of females	5	5
Forelimb	1.057 ± 0.069	1.015 ± 0.116
Hindlimb	0.613 ± 0.113	0.512 ± 0.096

Each value shows mean (kg) ±S.D.

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 20. Motor activity of male rats

Group	Control (vehicle: corn oil)		1,2-MD 30 mg/kg		1,2-MD 100 mg/kg		1,2-MD 300 mg/kg	
Number of males	5		5		5		4	
<u>Administration period</u>								
Ambulation (counts)								
5min	1153	± 48	1179	± 67	1305	± 156	1175	± 389
10min	991	± 106	1053	± 94	1158	± 187	1206	± 300
15min	807	± 121	919	± 185	909	± 263	1170	± 406
20min	740	± 212	673	± 221	897	± 187	1254	± 460 *
Total	3691	± 334	3824	± 512	4269	± 759	4805	± 1532
Rearing (counts)								
5min	29	± 4	43	± 6	34	± 8	33	± 16
10min	23	± 7	27	± 11	30	± 7	28	± 10
15min	16	± 5	23	± 10	19	± 5	35	± 24
20min	12	± 3	12	± 9	16	± 5	40	± 18 *
Total	80	± 9	105	± 27	98	± 14	136	± 64
<u>Recovery period</u>								
Ambulation (counts)								
5min	1096	± 109					1269	± 386
10min	1002	± 139					1231	± 422
15min	896	± 110					1134	± 369
20min	725	± 171					1104	± 262 *
Total	3719	± 411					4739	± 1417
Rearing (counts)								
5min	36	± 8					34	± 4
10min	31	± 13					28	± 10
15min	22	± 5					25	± 5
20min	19	± 6					20	± 7
Total	108	± 27					108	± 14

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 21. Motor activity of female rats

Group	Control (vehicle: corn oil)			1,2-MD 30 mg/kg			1,2-MD 100 mg/kg			1,2-MD 300 mg/kg		
Number of females	5			5			5			1		
Ambulation (counts)												
5min	1078	±	73	1073	±	120	1247	±	382	1198	±	
10min	598	±	180	678	±	170	831	±	358	1161	±	
15min	389	±	216	605	±	186	641	±	564	1034	±	
20min	324	±	210	375	±	227	457	±	188	811	±	
Total	2388	±	639	2730	±	423	3176	±	1462	4204	±	
Rearing (counts)												
5min	27	±	6	31	±	10	30	±	9	29	±	
10min	15	±	9	14	±	13	11	±	6	30	±	
15min	3	±	5	13	±	9	5	±	6	22	±	
20min	2	±	3	7	±	9	3	±	1	18	±	
Total	47	±	10	66	±	39	48	±	19	99	±	

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

The group given 300 mg/kg of 1,2-MD was excluded from statistical analysis.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 22. Motor activity of female rats, satellite group

Group	Control (vehicle: corn oil)	1,2-MD 300 mg/kg
Number of females	5	5
<u>Administration period</u>		
Ambulation (counts)		
5min	1262 ± 105	1278 ± 126
10min	1111 ± 152	1329 ± 191
15min	940 ± 168	1283 ± 188 *
20min	716 ± 244	1210 ± 176 **
Total	4028 ± 550	5100 ± 607 *
Rearing (counts)		
5min	33 ± 8	36 ± 7
10min	30 ± 13	44 ± 22
15min	25 ± 8	43 ± 18
20min	17 ± 9	39 ± 16 *
Total	105 ± 28	162 ± 56
<u>Recovery period</u>		
Ambulation (counts)		
5min	1186 ± 257	1112 ± 99
10min	1041 ± 323	1084 ± 115
15min	1008 ± 262	1095 ± 175
20min	959 ± 295	1150 ± 261
Total	4194 ± 1096	4441 ± 601
Rearing (counts)		
5min	42 ± 5	30 ± 4 **
10min	29 ± 7	22 ± 9
15min	26 ± 9	28 ± 16
20min	31 ± 13	35 ± 28
Total	128 ± 30	115 ± 54

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 23-1. Urinalysis in male rats

Group	Number of males	Quality ^{a)}																									
		Color		Turbidity		pH						Protein			Glucose		Ketone			Bilirubin		Occult blood			Urobilinogen		
		Light yellow	Yellow	-	+	6.5	7.0	7.5	8.0	8.5	9.0	±	+	2+	-	-	±	+	-	-	±	2+	±	+	2+		
Control (vehicle: corn oil)	5	4	1	5	0	3	1	0	0	0	1	0	3	2	5	0	0	5	5	4	1	0	1	3	1		
1,2-MD 30 mg/kg	5	5	0	4	1	0	4	1	0	0	0	2	2	1	5	1	1	3	5	5	0	0	3	2	0		
1,2-MD 100 mg/kg	5	4	1	4	1	0	0	1	4	0	0	1	3	1	5	2	2	1	5	4	0	1	4	1	0		
1,2-MD 300 mg/kg	5	4	1	4	1	1	0	1	2	1	0	0	2	3	5	0	2	3	5	5	0	0	2	3	0		

Group	Number of males	Urinary sediments ^{a)}							Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells		White blood cells	Casts	Crystals	Epithelial cells	(mEq/L)			(mEq/24 hr)					
		-	3+	-	-	-	±	-			Na	K	Cl	Na	K	Cl
Control (vehicle: corn oil)	5	5	0	5	5	1	4	5	14.9 ±8.7	1.060 ±0.023	93.1 ±42.8	165.6 ±52.0	117.9 ±43.7	1.12 ±0.16	2.14 ±0.64	1.46 ±0.24
1,2-MD 30 mg/kg	5	5	0	5	5	2	3	5	13.7 ±4.8	1.062 ±0.017	93.5 ±41.6	129.4 ±18.1	122.3 ±39.6	1.16 ±0.26	1.71 ±0.37	1.54 ±0.18
1,2-MD 100 mg/kg	5	4	1	5	5	0	5	5	12.6 ±5.4	1.064 ±0.018	105.9 ±46.2	108.4 ±3.8	126.2 ±47.5	1.22 ±0.42	1.36 ±0.56	1.47 ±0.49
1,2-MD 300 mg/kg	5	5	0	5	5	0	5	5	13.3 ±2.1	1.064 ±0.009	95.7 ±14.6	98.1** ±6.4	106.8 ±24.3	1.26 ±0.26	1.31 ±0.27	1.41 ±0.32

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 23-2. Urinalysis in male rats of the recovery period

Group	Number of males	Quality ^{a)}															
		Color	Turbidity	pH			Protein			Glucose		Ketone		Bilirubin	Occult blood	Urobilinogen	
		Light yellow	-	7.0	7.5	8.0	±	+	2+	-	-	±	+	-	-	±	+
Control (vehicle: corn oil)	5	5	5	2	1	2	1	4	0	5	1	2	2	5	5	3	2
1,2-MD 300 mg/kg	5	5	5	2	2	1	0	3	2	5	0	2	3	5	5	1	4

Group	Number of males	Urinary sediments ^{a)}						Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells			(mEq/L)			(mEq/24 hr)		
		-	-	-	±	+	-			Na	K	Cl	Na	K	Cl
Control (vehicle: corn oil)	5	5	5	5	5	0	5	18.4	1.058	99.7	170.1	113.7	1.79	3.07	2.03
								±5.0	±0.009	±24.8	±15.8	±23.4	±0.43	±0.60	±0.41
1,2-MD 300 mg/kg	5	5	5	5	4	1	5	19.6	1.056	89.8	160.6	110.3	1.76	3.08	2.12
								±5.0	±0.012	±22.3	±23.0	±32.8	±0.68	±0.57	±0.75

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative; ±: 0.03 ≤ and < 0.06 mg/dL

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 24-1. Urinalysis in female rats, satellite group

Group	Number of females	Quality ^{a)}																			
		Color		Turbidity	pH			Protein				Glucose		Ketone		Bilirubin	Occult	blood	Urobilinogen		
		Light yellow	Yellow	-	6.5	7.0	8.5	-	±	+	2+	-	-	±	+	-	-	-	±	+	2+
Control (vehicle: corn oil)	5	4	1	5	3	1	1	1	3	0	1	5	4	0	1	5	5	4	1	0	
1,2-MD 300 mg/kg	5	3	2	5	1	4	0	1	1	1	2	5	2	1	2	5	5	2	2	1	

Group	Number of females	Urinary sediments ^{a)}						Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	(mEq/L)			(mEq/24 hr)					
		-	-	-	-	±	-			Na	K	Cl	Na	K	Cl
Control (vehicle: corn oil)	5	5	5	5	2	3	5	9.4	1.058	92.3	143.5	108.7	0.87	1.36	1.04
								±3.0	±0.010	±22.4	±20.2	±46.1	±0.36	±0.55	±0.59
1,2-MD 300 mg/kg	5	5	5	5	2	3	5	11.8	1.061	83.3	98.4**	110.2	0.92	1.16	1.19
								±3.5	±0.024	±32.7	±20.4	±55.9	±0.31	±0.44	±0.51

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, -: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 24-2. Urinalysis in female rats of the recovery period

Group	Number of females	Quality ^{a)}																				
		Color		Turbidity		pH					Protein			Glucose		Ketone		Bilirubin	Occult blood		Urobilinogen	
		Light yellow	Yellow	-	6.0	6.5	7.0	7.5	8.5	-	±	+	-	-	±	+	-	-	±	+		
Control (vehicle: corn oil)	5	5	0	5	1	2	0	2	0	1	2	2	5	3	1	1	5	5	4	1		
1,2-MD 300 mg/kg	5	4	1	5	0	1	1	2	1	1	2	2	5	5	0	0	5	5	4	1		

Group	Number of females	Urinary sediments ^{a)}						Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	(mEq/L)			(mEq/24 hr)					
		-	-	-	-	±	-	(mL/24hr)			Na	K	Cl	Na	K
Control (vehicle: corn oil)	5	5	5	5	1	4	5	9.2 ±2.9	1.067 ±0.017	133.6 ±23.4	175.9 ±30.9	154.4 ±49.8	1.20 ±0.32	1.58 ±0.40	1.38 ±0.49
1,2-MD 300 mg/kg	5	5	5	5	0	5	5	8.7 ±2.1	1.077 ±0.011	143.3 ±30.8	188.9 ±8.9	163.0 ±33.5	1.25 ±0.44	1.64 ±0.40	1.40 ±0.41

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, -: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 25-1. Hematological findings of male rats at the end of the dosing period

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of males	5	5	5	4
RBC ($\times 10^4/\mu\text{L}$)	855 $\pm$ 40	836 $\pm$ 40	815 $\pm$ 43	858 $\pm$ 33
Hemoglobin (g/dL)	15.7 $\pm$ 0.9	14.8 $\pm$ 0.5	14.8 $\pm$ 0.9	15.2 $\pm$ 0.3
Hematocrit (%)	43.9 $\pm$ 2.5	41.9 $\pm$ 1.3	42.1 $\pm$ 2.7	43.3 $\pm$ 0.9
MCV (fL)	51.3 $\pm$ 1.7	50.1 $\pm$ 1.3	51.7 $\pm$ 3.2	50.5 $\pm$ 2.3
MCH (pg)	18.3 $\pm$ 0.5	17.7 $\pm$ 0.4	18.2 $\pm$ 0.8	17.7 $\pm$ 0.6
MCHC (g/dL)	35.7 $\pm$ 0.6	35.4 $\pm$ 0.2	35.2 $\pm$ 0.8	35.2 $\pm$ 0.6
Platelet ($\times 10^4/\mu\text{L}$)	114.2 $\pm$ 13.2	106.2 $\pm$ 9.0	103.0 $\pm$ 10.3	112.6 $\pm$ 8.0
PT (sec)	16.2 $\pm$ 1.9	14.4 $\pm$ 0.9	14.2 $\pm$ 0.8	13.8 $\pm$ 1.3 *
APTT (sec)	27.0 $\pm$ 2.3	23.3 $\pm$ 1.2	24.9 $\pm$ 3.4	25.0 $\pm$ 3.1
WBC ($\times 10^2/\mu\text{L}$)	99.7 $\pm$ 23.5	96.7 $\pm$ 35.2	91.5 $\pm$ 14.7	102.9 $\pm$ 20.3
Differential leukocyte count (%)				
Neutrophil	18.5 $\pm$ 3.4	19.6 $\pm$ 12.0	22.3 $\pm$ 6.1	20.0 $\pm$ 5.7
Eosinophil	1.2 $\pm$ 0.5	1.2 $\pm$ 0.7	1.3 $\pm$ 0.4	1.3 $\pm$ 0.5
Basophil	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.1
Monocyte	4.3 $\pm$ 1.4	3.9 $\pm$ 1.0	5.0 $\pm$ 0.9	4.1 $\pm$ 0.8
Lymphocyte	76.0 $\pm$ 3.8	75.2 $\pm$ 12.4	71.4 $\pm$ 7.0	74.6 $\pm$ 6.0
Reticulocyte count (%)	3.33 $\pm$ 0.64	2.89 $\pm$ 0.20	3.55 $\pm$ 0.58	4.20 $\pm$ 0.33 *

Each value shows mean $\pm$ S.D.

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 25-2. Hematological findings of male rats at the end of the recovery period

Group	Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
Number of males	5		5	
RBC ($\times 10^4/\mu\text{L}$)	836	± 24	824	± 27
Hemoglobin (g/dL)	14.8	± 0.3	14.6	± 0.4
Hematocrit (%)	42.3	± 1.6	41.3	± 0.6
MCV (fL)	50.6	± 1.1	50.1	± 1.1
MCH (pg)	17.7	± 0.3	17.7	± 0.5
MCHC (g/dL)	34.9	± 0.7	35.4	± 0.7
Platelet ($\times 10^4/\mu\text{L}$)	110.3	± 5.5	109.8	± 4.8
PT (sec)	13.0	± 0.9	16.8	± 3.7
APTT (sec)	20.5	± 1.8	22.5	± 1.5
WBC ($\times 10^2/\mu\text{L}$)	96.0	± 18.4	101.8	± 29.0
Differential leukocyte count (%)				
Neutrophil	20.7	± 10.7	14.4	± 5.6
Eosinophil	1.6	± 0.3	1.6	± 0.4
Basophil	0.0	± 0.1	0.1	± 0.1
Monocyte	3.9	± 1.3	3.6	± 0.8
Lymphocyte	73.8	± 10.9	80.4	± 6.5
Reticulocyte count (%)	3.39	± 0.42	3.64	± 0.81

Each value shows mean $\pm$ S.D.Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 26-1. Hematological findings of female rats at the end of the dosing period

Group	Control (vehicle: corn oil)		1,2-MD 30 mg/kg		1,2-MD 100 mg/kg		1,2-MD 300 mg/kg	
Number of females	5		5		5		1	
RBC ($\times 10^4/\mu\text{L}$)	681	± 53	638	± 43	664	± 59	722	$\pm$
Hemoglobin (g/dL)	13.4	± 0.8	12.4	± 0.9	13.0	± 0.9	13.4	$\pm$
Hematocrit (%)	39.3	± 1.9	37.6	± 2.4	39.1	± 1.6	39.7	$\pm$
MCV (fL)	57.8	± 2.0	58.9	± 1.1	59.1	± 4.3	55.0	$\pm$
MCH (pg)	19.6	± 0.4	19.5	± 0.4	19.6	± 1.0	18.6	$\pm$
MCHC (g/dL)	34.0	± 0.5	33.1	± 0.2	33.1	± 1.0	33.8	$\pm$
Platelet ($\times 10^4/\mu\text{L}$)	119.4	± 19.5	113.5	± 27.4	101.0	± 10.2	132.9	$\pm$
PT (sec)	12.2	± 0.4	12.6	± 0.3	12.6	± 0.5	13.6	$\pm$
APTT (sec)	19.7	± 0.8	20.2	± 1.7	20.0	± 0.8	21.4	$\pm$
WBC ($\times 10^2/\mu\text{L}$)	108.0	± 44.1	97.9	± 35.8	69.2	± 11.3	100.0	$\pm$
Differential leukocyte count (%)								
Neutrophil	29.9	± 8.3	27.9	± 7.8	23.9	± 3.5	13.6	$\pm$
Eosinophil	1.4	± 0.3	0.6	± 0.2 *	0.9	± 0.5	1.0	$\pm$
Basophil	0.0	± 0.1	0.0	± 0.0	0.0	± 0.0	0.0	$\pm$
Monocyte	4.6	± 1.1	3.1	± 1.2	4.7	± 2.0	3.9	$\pm$
Lymphocyte	64.2	± 8.3	68.4	± 6.6	70.5	± 3.7	81.5	$\pm$
Reticulocyte count (%)	8.00	± 1.60	9.55	± 1.41	10.14	± 2.00	9.13	$\pm$

Each value shows mean $\pm$ S.D.

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 26-2. Hematological findings of female rats at the end of the dosing period, satellite group

Group	Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
Number of females	5		5	
RBC ($\times 10^4/\mu\text{L}$)	771	± 42	754	± 18
Hemoglobin (g/dL)	14.5	± 0.5	13.8	± 0.5 *
Hematocrit (%)	41.7	± 1.4	39.8	± 1.6
MCV (fL)	54.2	± 1.9	52.8	± 1.7
MCH (pg)	18.9	± 0.6	18.3	± 0.3
MCHC (g/dL)	34.8	± 0.2	34.7	± 0.8
Platelet ($\times 10^4/\mu\text{L}$)	102.6	± 18.5	103.4	± 15.8
PT (sec)	11.7	± 0.3	11.3	± 0.4
APTT (sec)	20.2	± 1.5	19.6	± 1.4
WBC ($\times 10^2/\mu\text{L}$)	51.3	± 13.6	56.9	± 26.9
Differential leukocyte count (%)				
Neutrophil	12.5	± 3.6	19.1	± 6.5
Eosinophil	2.0	± 0.7	1.8	± 0.6
Basophil	0.0	± 0.1	0.0	± 0.0
Monocyte	2.6	± 1.1	3.4	± 0.9
Lymphocyte	82.9	± 4.0	75.7	± 7.5
Reticulocyte count (%)	3.82	± 0.61	3.98	± 0.67

Each value shows mean $\pm$ S.D.

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 26-3. Hematological findings of female rats at the end of the recovery period

Group	Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
Number of females	5		5	
RBC ($\times 10^4/\mu\text{L}$)	782	± 20	777	± 29
Hemoglobin (g/dL)	14.7	± 0.3	14.2	± 0.6
Hematocrit (%)	42.4	± 0.7	40.8	± 1.7
MCV (fL)	54.2	± 1.5	52.5	± 0.9
MCH (pg)	18.8	± 0.3	18.3	± 0.2 *
MCHC (g/dL)	34.7	± 0.5	34.8	± 0.3
Platelet ($\times 10^4/\mu\text{L}$)	107.1	± 13.1	98.8	± 6.3
PT (sec)	10.8	± 0.5	11.3	± 0.5
APTT (sec)	16.5	± 1.6	18.0	± 1.5
WBC ($\times 10^2/\mu\text{L}$)	45.0	± 8.6	48.2	± 9.8
Differential leukocyte count (%)				
Neutrophil	16.3	± 7.0	18.1	± 7.9
Eosinophil	2.6	± 0.7	2.2	± 0.8
Basophil	0.0	± 0.0	0.0	± 0.0
Monocyte	4.3	± 1.0	4.0	± 1.1
Lymphocyte	76.8	± 7.2	75.7	± 6.7
Reticulocyte count (%)	2.72	± 0.61	3.12	± 0.47

Each value shows mean $\pm$ S.D.

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 27-1. Biochemical findings of male rats at the end of the dosing period

Group		Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of males		5	5	5	5
Total protein	g/dL	5.5 ± 0.3	5.5 ± 0.3	5.5 ± 0.3	5.7 ± 0.2
Albumin	g/dL	3.4 ± 0.2	3.4 ± 0.1	3.4 ± 0.1	3.5 ± 0.1
A/G		1.62 ± 0.17	1.61 ± 0.10	1.64 ± 0.15	1.62 ± 0.06
Glucose	mg/dL	140 ± 14	150 ± 15	136 ± 8	118 ± 10 *
Total cholesterol	mg/dL	55 ± 12	64 ± 7	50 ± 13	71 ± 10
Triglyceride	mg/dL	51 ± 15	56 ± 21	35 ± 27	53 ± 27
Phospholipid	mg/dL	89 ± 14	102 ± 10	81 ± 20	112 ± 17
AST	U/L	52 ± 8	54 ± 7	59 ± 6	58 ± 2
ALT	U/L	27 ± 6	28 ± 4	27 ± 3	29 ± 3
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0
LDH	U/L	183 ± 123	185 ± 126	127 ± 83	126 ± 75
Bile acid	μmol/L	13.1 ± 11.5	8.5 ± 3.9	6.6 ± 1.1	6.1 ± 2.2
BUN	mg/dL	14 ± 2	14 ± 1	14 ± 1	14 ± 2
Creatinine	mg/dL	0.5 ± 0.1	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.1
Total bilirubin	mg/dL	0.06 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.05 ± 0.01
ALP	U/L	324 ± 56	403 ± 68	358 ± 93	310 ± 31
Inorganic phosphorus	mg/dL	5.9 ± 0.1	5.8 ± 0.5	6.1 ± 0.5	7.2 ± 0.4 **
Ca	mg/dL	9.5 ± 0.4	9.5 ± 0.3	9.5 ± 0.2	9.5 ± 0.3
Na	mEq/L	144.2 ± 0.9	143.6 ± 0.7	143.3 ± 0.9	143.1 ± 0.8
K	mEq/L	3.86 ± 0.04	3.94 ± 0.16	3.91 ± 0.12	3.99 ± 0.14
Cl	mEq/L	105.9 ± 1.6	105.9 ± 1.4	105.4 ± 0.9	104.3 ± 0.9

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 27-2. Biochemical findings of male rats at the end of the recovery period

Group		Control (vehicle: corn oil)	1,2-MD 300 mg/kg
Number of males		5	5
Total protein	g/dL	5.7 ± 0.1	5.8 ± 0.3
Albumin	g/dL	3.5 ± 0.1	3.4 ± 0.2
A/G		1.58 ± 0.06	1.42 ± 0.10 *
Glucose	mg/dL	131 ± 19	139 ± 17
Total cholesterol	mg/dL	50 ± 3	43 ± 8
Triglyceride	mg/dL	30 ± 19	18 ± 7
Phospholipid	mg/dL	80 ± 10	69 ± 7
AST	U/L	63 ± 9	61 ± 4
ALT	U/L	29 ± 4	28 ± 4
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	241 ± 115	297 ± 95
Bile acid	μmol/L	9.9 ± 2.7	10.4 ± 2.2
BUN	mg/dL	15 ± 1	15 ± 1
Creatinine	mg/dL	0.6 ± 0.1	0.5 ± 0.0
Total bilirubin	mg/dL	0.05 ± 0.01	0.05 ± 0.01
ALP	U/L	293 ± 21	273 ± 30
Inorganic phosphorus	mg/dL	5.9 ± 0.6	6.5 ± 0.3
Ca	mg/dL	9.2 ± 0.2	9.2 ± 0.3
Na	mEq/L	144.5 ± 0.8	144.2 ± 0.3
K	mEq/L	3.86 ± 0.30	3.97 ± 0.11
Cl	mEq/L	107.3 ± 1.4	106.6 ± 0.7

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 28-1. Biochemical findings of female rats at the end of the dosing period

Group		Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of females		5	5	5	1
Total protein	g/dL	5.9 ± 0.2	5.8 ± 0.2	5.9 ± 0.3	5.8 ±
Albumin	g/dL	3.8 ± 0.1	3.7 ± 0.2	3.7 ± 0.2	3.6 ±
A/G		1.86 ± 0.17	1.75 ± 0.13	1.78 ± 0.21	1.64 ±
Glucose	mg/dL	127 ± 9	121 ± 13	132 ± 13	103 ±
Total cholesterol	mg/dL	48 ± 12	59 ± 13	56 ± 6	73 ±
Triglyceride	mg/dL	26 ± 4	24 ± 14	26 ± 10	20 ±
Phospholipid	mg/dL	95 ± 14	103 ± 21	96 ± 9	114 ±
AST	U/L	67 ± 7	75 ± 10	71 ± 11	93 ±
ALT	U/L	51 ± 32	42 ± 7	34 ± 4	41 ±
γ-GTP	U/L	0 ± 1	0 ± 0	0 ± 1	1 ±
LDH	U/L	99 ± 96	86 ± 24	108 ± 58	292 ±
Bile acid	μmol/L	14.9 ± 6.2	13.3 ± 4.4	15.1 ± 7.9	26.0 ±
BUN	mg/dL	14 ± 3	12 ± 4	17 ± 4	14 ±
Creatinine	mg/dL	0.5 ± 0.0	0.5 ± 0.0	0.6 ± 0.1	0.5 ±
Total bilirubin	mg/dL	0.07 ± 0.02	0.08 ± 0.01	0.07 ± 0.02	0.09 ±
ALP	U/L	180 ± 68	172 ± 51	139 ± 28	139 ±
Inorganic phosphorus	mg/dL	6.3 ± 0.6	6.0 ± 0.6	7.3 ± 1.0	7.6 ±
Ca	mg/dL	9.6 ± 0.3	9.6 ± 0.5	10.0 ± 0.3	9.5 ±
Na	mEq/L	141.6 ± 1.9	142.5 ± 1.5	142.6 ± 0.9	142.8 ±
K	mEq/L	3.79 ± 0.21	3.59 ± 0.29	3.62 ± 0.20	3.74 ±
Cl	mEq/L	107.2 ± 2.4	106.2 ± 1.6	106.1 ± 1.0	104.6 ±

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 28-2. Biochemical findings of female rats at the end of the dosing period, satellite group

Group		Control (vehicle: corn oil)	1,2-MD 300 mg/kg	
Number of females		5	5	
Total protein	g/dL	6.3 ± 0.3	6.2 ± 0.3	
Albumin	g/dL	4.3 ± 0.3	4.1 ± 0.3	
A/G		2.12 ± 0.23	2.00 ± 0.17	
Glucose	mg/dL	132 ± 17	118 ± 16	
Total cholesterol	mg/dL	56 ± 3	102 ± 8	**
Triglyceride	mg/dL	11 ± 2	16 ± 3	*
Phospholipid	mg/dL	105 ± 8	157 ± 10	**
AST	U/L	60 ± 4	82 ± 31	
ALT	U/L	21 ± 3	30 ± 8	
γ-GTP	U/L	0 ± 0	0 ± 1	
LDH	U/L	95 ± 29	122 ± 40	
Bile acid	μmol/L	12.7 ± 4.7	16.0 ± 8.3	
BUN	mg/dL	17 ± 3	16 ± 3	
Creatinine	mg/dL	0.7 ± 0.1	0.6 ± 0.1	*
Total bilirubin	mg/dL	0.08 ± 0.01	0.06 ± 0.03	
ALP	U/L	173 ± 32	128 ± 45	
Inorganic phosphorus	mg/dL	4.3 ± 0.2	5.4 ± 0.5	**
Ca	mg/dL	9.5 ± 0.3	9.3 ± 0.5	
Na	mEq/L	143.9 ± 0.9	142.3 ± 1.9	
K	mEq/L	3.59 ± 0.16	3.63 ± 0.19	
Cl	mEq/L	108.7 ± 1.7	104.9 ± 2.3	*

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 28-3. Biochemical findings of female rats at the end of the recovery period

Group		Control (vehicle: corn oil)	1,2-MD 300 mg/kg
Number of females		5	5
Total protein	g/dL	6.2 ± 0.4	6.2 ± 0.3
Albumin	g/dL	4.2 ± 0.3	4.0 ± 0.1
A/G		2.03 ± 0.14	1.79 ± 0.11 *
Glucose	mg/dL	118 ± 18	121 ± 17
Total cholesterol	mg/dL	58 ± 6	64 ± 7
Triglyceride	mg/dL	15 ± 3	12 ± 4
Phospholipid	mg/dL	109 ± 7	111 ± 11
AST	U/L	60 ± 9	70 ± 8
ALT	U/L	25 ± 6	32 ± 11
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	65 ± 27	83 ± 48
Bile acid	μmol/L	13.4 ± 7.3	12.7 ± 3.1
BUN	mg/dL	18 ± 1	21 ± 4
Creatinine	mg/dL	0.7 ± 0.1	0.7 ± 0.1
Total bilirubin	mg/dL	0.10 ± 0.01	0.08 ± 0.02
ALP	U/L	127 ± 32	149 ± 38
Inorganic phosphorus	mg/dL	4.3 ± 0.5	4.9 ± 0.4
Ca	mg/dL	9.4 ± 0.2	9.1 ± 0.2 *
Na	mEq/L	143.8 ± 0.7	143.4 ± 1.3
K	mEq/L	3.74 ± 0.18	3.59 ± 0.22
Cl	mEq/L	108.5 ± 1.0	107.5 ± 1.5

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 29-1. Organ weights of male rats at the end of the dosing period

Group		Control (vehicle: corn oil)		1,2-MD 30 mg/kg		1,2-MD 100 mg/kg		1,2-MD 300 mg/kg	
Number of males		7		12		12		7	
Body weight	(g)	498.4	± 36.9	480.9	± 29.2	481.1	± 22.8	454.8	± 20.9 *
Brain	(mg)	1997.3	± 86.4	2019.5	± 74.9	2002.5	± 74.7	1983.2	± 51.8
	(mg/g)	4.016	± 0.145	4.212	± 0.275	4.168	± 0.178	4.365	± 0.140 **
Thymus	(mg)	325.6	± 63.1	289.4	± 85.5	288.0	± 87.7	250.6	± 66.5
	(mg/g)	0.662	± 0.165	0.601	± 0.167	0.599	± 0.179	0.551	± 0.144
Heart	(mg)	1409.1	± 82.3	1390.7	± 99.2	1441.0	± 96.0	1396.7	± 92.5
	(mg/g)	2.835	± 0.186	2.894	± 0.141	2.998	± 0.201	3.071	± 0.157 *
Liver	(mg)	14103.2	± 2147.0	13117.6	± 1617.6	13627.3	± 913.7	16102.6	± 1542.5 *
	(mg/g)	28.283	± 3.655	27.215	± 2.216	28.309	± 0.819	35.355	± 2.344 **
Kidney (R)	(mg)	1617.6	± 232.0	1517.9	± 141.8	1672.8	± 172.5	1831.8	± 153.6
	(mg/g)	3.235	± 0.267	3.164	± 0.306	3.472	± 0.252	4.032	± 0.361 **
Kidney (L)	(mg)	1601.5	± 213.0	1514.1	± 150.9	1604.8	± 157.2	1793.9	± 183.1
	(mg/g)	3.204	± 0.242	3.156	± 0.331	3.332	± 0.242	3.948	± 0.421 **
Kidney	(mg)	3219.1	± 443.5	3032.1	± 284.5	3277.6	± 320.3	3625.6	± 330.0
	(mg/g)	6.440	± 0.504	6.320	± 0.620	6.804	± 0.467	7.981	± 0.768 **
Spleen	(mg)	768.0	± 42.9	833.0	± 123.7	783.7	± 138.0	809.5	± 97.7
	(mg/g)	1.551	± 0.179	1.743	± 0.323	1.623	± 0.222	1.781	± 0.216
Testis (R)	(mg)	1652.8	± 98.5	1632.1	± 93.9	1581.1	± 190.2	1577.9	± 96.7
	(mg/g)	3.336	± 0.351	3.402	± 0.228	3.289	± 0.388	3.482	± 0.351
Testis (L)	(mg)	1685.6	± 81.0	1627.8	± 79.4	1587.9	± 199.4	1603.3	± 100.6
	(mg/g)	3.398	± 0.292	3.393	± 0.209	3.304	± 0.415	3.539	± 0.380
Testis	(mg)	3338.4	± 177.0	3260.0	± 169.9	3169.1	± 385.7	3181.2	± 191.7
	(mg/g)	6.733	± 0.642	6.795	± 0.431	6.592	± 0.796	7.021	± 0.724
Epididymis (R)	(mg)	645.1	± 72.9	613.9	± 70.7	589.5	± 76.7	563.5	± 52.2
	(mg/g)	1.304	± 0.194	1.277	± 0.135	1.228	± 0.171	1.239	± 0.108
Epididymis (L)	(mg)	640.1	± 71.9	613.6	± 72.9	592.2	± 72.2	555.2	± 46.0
	(mg/g)	1.293	± 0.185	1.275	± 0.132	1.234	± 0.165	1.221	± 0.097
Epididymis	(mg)	1285.2	± 141.9	1227.5	± 137.1	1181.7	± 146.3	1118.7	± 95.3
	(mg/g)	2.596	± 0.375	2.552	± 0.253	2.463	± 0.331	2.460	± 0.198

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 29-1(continued). Organ weights of male rats at the end of the dosing period

Group		Control (vehicle: corn oil)		1,2-MD 30 mg/kg		1,2-MD 100 mg/kg		1,2-MD 300 mg/kg	
Number of males		7		12		12		7	
Body weight	(g)	498.4 ± 36.9		480.9 ± 29.2		481.1 ± 22.8		454.8 ± 20.9 *	
Prostate, ventral	(mg)	552.0 ± 158.9		647.2 ± 92.5		638.8 ± 144.4		632.6 ± 113.4	
	(mg/g)	1.104 ± 0.289		1.350 ± 0.201		1.326 ± 0.280		1.384 ± 0.197	
Seminal vesicles	(mg)	1704.5 ± 239.8		1703.5 ± 214.3		1650.0 ± 237.2		1658.8 ± 213.8	
	(mg/g)	3.438 ± 0.569		3.542 ± 0.387		3.439 ± 0.528		3.649 ± 0.456	
Thyroid gland	(mg)	22.0 ± 3.2		21.5 ± 2.6		21.4 ± 3.7		18.1 ± 1.9	
	(mg/g)	0.044 ± 0.007		0.045 ± 0.006		0.045 ± 0.008		0.040 ± 0.004	
Adrenal gland (R)	(mg)	26.3 ± 4.2		22.9 ± 2.4		22.2 ± 3.3		23.2 ± 1.8	
	(mg/g)	0.053 ± 0.008		0.048 ± 0.007		0.046 ± 0.007		0.051 ± 0.004	
Adrenal gland (L)	(mg)	27.0 ± 3.9		23.8 ± 3.8		23.4 ± 4.5		23.7 ± 3.4	
	(mg/g)	0.054 ± 0.008		0.050 ± 0.009		0.049 ± 0.010		0.052 ± 0.008	
Adrenal gland	(mg)	53.3 ± 8.1		46.7 ± 6.1		45.6 ± 7.5		46.9 ± 5.2	
	(mg/g)	0.107 ± 0.016		0.097 ± 0.015		0.095 ± 0.016		0.103 ± 0.012	

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 29-2. Organ weights of male rats at the end of the recovery period

Group		Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
Number of males		5		5	
Body weight	(g)	504.5	± 46.3	499.9	± 21.0
Brain	(mg)	2105.4	± 54.9	2056.8	± 47.1
	(mg/g)	4.193	± 0.266	4.120	± 0.196
Thymus	(mg)	302.1	± 112.2	239.3	± 81.3
	(mg/g)	0.594	± 0.197	0.474	± 0.144
Heart	(mg)	1434.4	± 99.5	1545.4	± 89.9
	(mg/g)	2.854	± 0.225	3.091	± 0.099
Liver	(mg)	12742.5	± 2270.5	13818.8	± 1450.1
	(mg/g)	25.181	± 2.868	27.591	± 1.898
Kidney (R)	(mg)	1491.4	± 134.8	1731.5	± 195.7
	(mg/g)	2.961	± 0.185	3.459	± 0.297 *
Kidney (L)	(mg)	1524.1	± 74.8	1697.9	± 197.6
	(mg/g)	3.035	± 0.233	3.392	± 0.320
Kidney	(mg)	3015.5	± 199.7	3429.4	± 385.9
	(mg/g)	5.996	± 0.380	6.852	± 0.598 *
Spleen	(mg)	781.1	± 53.3	883.3	± 140.7
	(mg/g)	1.553	± 0.099	1.767	± 0.268
Testis (R)	(mg)	1697.0	± 86.0	1563.8	± 136.1
	(mg/g)	3.379	± 0.265	3.135	± 0.335
Testis (L)	(mg)	1701.0	± 108.4	1544.5	± 99.1 *
	(mg/g)	3.390	± 0.331	3.096	± 0.279
Testis	(mg)	3398.0	± 188.7	3108.3	± 230.9
	(mg/g)	6.769	± 0.590	6.231	± 0.605
Epididymis (R)	(mg)	640.4	± 41.9	642.8	± 47.6
	(mg/g)	1.274	± 0.085	1.287	± 0.106
Epididymis (L)	(mg)	614.4	± 44.6	613.1	± 31.9
	(mg/g)	1.222	± 0.095	1.227	± 0.061
Epididymis	(mg)	1254.7	± 82.1	1256.0	± 78.2
	(mg/g)	2.496	± 0.172	2.515	± 0.167

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 29-2(continued). Organ weights of male rats at the end of the recovery period

Group		Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
Number of males		5		5	
Body weight	(g)	504.5	± 46.3	499.9	± 21.0
Prostate, ventral	(mg)	595.6	± 181.1	568.1	± 78.3
	(mg/g)	1.178	± 0.338	1.136	± 0.137
Seminal vesicles	(mg)	1517.0	± 287.6	1681.6	± 109.9
	(mg/g)	3.019	± 0.613	3.364	± 0.169
Thyroid gland	(mg)	19.5	± 5.4	19.3	± 3.6
	(mg/g)	0.038	± 0.007	0.039	± 0.008
Adrenal gland (R)	(mg)	24.8	± 2.8	25.3	± 1.7
	(mg/g)	0.050	± 0.008	0.051	± 0.002
Adrenal gland (L)	(mg)	24.9	± 3.3	26.7	± 2.9
	(mg/g)	0.050	± 0.009	0.053	± 0.005
Adrenal gland	(mg)	49.7	± 5.9	52.0	± 4.4
	(mg/g)	0.099	± 0.017	0.104	± 0.007

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 30-1. Organ weights of female rats at the end of the dosing period

Group		Control (vehicle: corn oil)		1,2-MD 30 mg/kg		1,2-MD 100 mg/kg		1,2-MD 300 mg/kg	
Number of females		11		11		8		1	
Body weight	(g)	311.6	± 23.7	315.5	± 17.8	307.2	± 14.4	288.7	±
Brain	(mg)	1916.3	± 104.5	1934.5	± 89.0	1868.4	± 98.4	1865.1	±
	(mg/g)	6.180	± 0.563	6.149	± 0.448	6.090	± 0.340	6.460	±
Thymus	(mg)	175.3	± 61.2	209.0	± 76.5	184.5	± 39.6	191.3	±
	(mg/g)	0.561	± 0.189	0.657	± 0.223	0.599	± 0.119	0.663	±
Heart	(mg)	978.8	± 75.6	982.5	± 86.9	943.9	± 55.5	900.9	±
	(mg/g)	3.149	± 0.239	3.114	± 0.205	3.074	± 0.128	3.121	±
Liver	(mg)	9813.6	± 819.3	10010.7	± 886.4	10212.9	± 683.6	12418.1	±
	(mg/g)	31.548	± 2.322	31.689	± 1.547	33.246	± 1.480	43.014	±
Kidney (R)	(mg)	974.4	± 81.0	978.1	± 106.3	916.9	± 66.5	997.3	±
	(mg/g)	3.142	± 0.351	3.103	± 0.324	2.990	± 0.237	3.454	±
Kidney (L)	(mg)	940.9	± 71.9	956.9	± 118.2	911.7	± 70.3	927.4	±
	(mg/g)	3.032	± 0.296	3.035	± 0.358	2.974	± 0.270	3.212	±
Kidney	(mg)	1915.4	± 146.6	1935.0	± 222.4	1828.6	± 135.7	1924.7	±
	(mg/g)	6.174	± 0.633	6.138	± 0.675	5.963	± 0.505	6.667	±
Spleen	(mg)	764.0	± 128.8	791.5	± 133.8	662.1	± 79.5	741.3	±
	(mg/g)	2.461	± 0.419	2.503	± 0.379	2.157	± 0.240	2.568	±
Ovary (R)	(mg)	55.4	± 4.9	51.7	± 10.6	45.6	± 6.9 *	56.9	±
	(mg/g)	0.179	± 0.022	0.164	± 0.032	0.149	± 0.024	0.197	±
Ovary (L)	(mg)	52.6	± 6.0	54.8	± 7.2	49.7	± 5.3	52.3	±
	(mg/g)	0.170	± 0.024	0.174	± 0.024	0.162	± 0.013	0.181	±
Ovary	(mg)	108.0	± 9.3	106.5	± 14.9	95.3	± 7.9	109.2	±
	(mg/g)	0.348	± 0.041	0.338	± 0.047	0.310	± 0.022	0.378	±
Uterus	(mg)	643.6	± 112.6	647.9	± 117.1	570.6	± 76.8	645.2	±
	(mg/g)	2.081	± 0.424	2.054	± 0.352	1.854	± 0.195	2.235	±
Thyroid gland	(mg)	13.9	± 3.0	16.0	± 3.3	14.4	± 3.1	16.6	±
	(mg/g)	0.045	± 0.013	0.051	± 0.014	0.047	± 0.012	0.057	±
Adrenal gland (R)	(mg)	35.9	± 5.1	35.1	± 4.2	31.3	± 3.1	34.7	±
	(mg/g)	0.115	± 0.013	0.111	± 0.010	0.102	± 0.008 *	0.120	±
Adrenal gland (L)	(mg)	38.0	± 5.5	37.0	± 4.8	33.5	± 2.7	40.7	±
	(mg/g)	0.122	± 0.015	0.117	± 0.011	0.109	± 0.011	0.141	±
Adrenal gland	(mg)	73.9	± 10.4	72.1	± 8.4	64.8	± 5.4	75.4	±
	(mg/g)	0.237	± 0.028	0.228	± 0.019	0.211	± 0.018	0.261	±

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 30-2. Organ weights of female rats at the end of the dosing period, satellite group

Group		Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
Number of females		5		5	
Body weight	(g)	288.9	± 10.3	269.2	± 10.9 *
Brain	(mg)	1925.9	± 34.4	1872.2	± 73.2
	(mg/g)	6.674	± 0.268	6.964	± 0.415
Thymus	(mg)	264.1	± 66.9	190.9	± 45.9
	(mg/g)	0.915	± 0.239	0.709	± 0.172
Heart	(mg)	882.4	± 60.2	957.1	± 73.0
	(mg/g)	3.055	± 0.172	3.552	± 0.163 **
Liver	(mg)	7617.3	± 335.2	10794.3	± 325.7 **
	(mg/g)	26.380	± 1.043	40.127	± 1.429 **
Kidney (R)	(mg)	925.1	± 53.3	1004.7	± 106.0
	(mg/g)	3.204	± 0.192	3.733	± 0.379 *
Kidney (L)	(mg)	913.6	± 21.7	986.4	± 128.6
	(mg/g)	3.165	± 0.104	3.666	± 0.474 *
Kidney	(mg)	1838.6	± 73.7	1991.1	± 232.6
	(mg/g)	6.369	± 0.285	7.399	± 0.847 *
Spleen	(mg)	575.3	± 63.8	503.6	± 46.9
	(mg/g)	1.994	± 0.243	1.869	± 0.134
Ovary (R)	(mg)	48.4	± 6.4	47.3	± 5.4
	(mg/g)	0.167	± 0.018	0.176	± 0.017
Ovary (L)	(mg)	43.4	± 4.7	45.3	± 11.1
	(mg/g)	0.150	± 0.014	0.168	± 0.039
Ovary	(mg)	91.8	± 8.7	92.6	± 16.3
	(mg/g)	0.318	± 0.020	0.343	± 0.055
Uterus	(mg)	728.0	± 279.5	538.9	± 333.2
	(mg/g)	2.523	± 0.966	1.989	± 1.205
Thyroid gland	(mg)	13.0	± 1.7	13.8	± 2.3
	(mg/g)	0.045	± 0.006	0.051	± 0.007
Adrenal gland (R)	(mg)	31.2	± 4.6	31.0	± 6.2
	(mg/g)	0.108	± 0.016	0.115	± 0.019
Adrenal gland (L)	(mg)	31.3	± 5.4	33.1	± 5.8
	(mg/g)	0.108	± 0.019	0.123	± 0.018
Adrenal gland	(mg)	62.5	± 9.7	64.2	± 12.0
	(mg/g)	0.217	± 0.034	0.237	± 0.037

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 30-3. Organ weights of female rats at the end of the recovery period

Group		Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
Number of females		5		5	
Body weight	(g)	299.5	± 11.6	274.9	± 11.0 **
Brain	(mg)	1814.0	± 55.7	1841.1	± 24.4
	(mg/g)	6.060	± 0.203	6.706	± 0.279 **
Thymus	(mg)	245.9	± 64.2	229.5	± 45.2
	(mg/g)	0.818	± 0.192	0.832	± 0.137
Heart	(mg)	895.6	± 87.3	883.9	± 53.8
	(mg/g)	2.991	± 0.282	3.216	± 0.158
Liver	(mg)	7124.5	± 573.0	7548.6	± 275.6
	(mg/g)	23.769	± 1.360	27.474	± 0.879 **
Kidney (R)	(mg)	901.0	± 92.8	949.4	± 51.6
	(mg/g)	3.013	± 0.344	3.454	± 0.155 *
Kidney (L)	(mg)	887.1	± 103.8	915.9	± 62.7
	(mg/g)	2.964	± 0.353	3.329	± 0.120
Kidney	(mg)	1788.0	± 192.3	1865.2	± 106.3
	(mg/g)	5.978	± 0.683	6.784	± 0.226 *
Spleen	(mg)	520.5	± 123.8	557.4	± 51.3
	(mg/g)	1.734	± 0.379	2.032	± 0.225
Ovary (R)	(mg)	38.7	± 12.4	44.8	± 6.2
	(mg/g)	0.129	± 0.037	0.163	± 0.018
Ovary (L)	(mg)	46.3	± 9.4	42.2	± 8.0
	(mg/g)	0.154	± 0.028	0.154	± 0.029
Ovary	(mg)	85.0	± 20.6	87.0	± 11.3
	(mg/g)	0.283	± 0.061	0.316	± 0.037
Uterus	(mg)	502.2	± 70.6	626.8	± 346.0
	(mg/g)	1.682	± 0.267	2.280	± 1.233
Thyroid gland	(mg)	15.1	± 2.5	15.0	± 1.7
	(mg/g)	0.051	± 0.010	0.055	± 0.008
Adrenal gland (R)	(mg)	30.0	± 8.2	28.8	± 2.7
	(mg/g)	0.100	± 0.025	0.105	± 0.009
Adrenal gland (L)	(mg)	30.9	± 8.7	31.1	± 2.3
	(mg/g)	0.103	± 0.026	0.113	± 0.007
Adrenal gland	(mg)	60.9	± 16.8	59.9	± 4.4
	(mg/g)	0.202	± 0.050	0.218	± 0.013

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 31-1. Macroscopic findings of male rats at the end of the dosing period

	Group	Control (vehicle: corn oil)		1,2-MD 30 mg/kg		1,2-MD 100 mg/kg		1,2-MD 300 mg/kg	
Findings	Grade	-	P	-	P	-	P	-	P
Epididymis									
Nodule, yellowish white, caudal, unilateral		6	1	12	0	12	0	7	0
Kidney									
Enlargement, bilateral		7	0	12	0	12	0	1	6
Rough surface, bilateral		7	0	12	0	12	0	6	1
Liver									
Enlargement		7	0	12	0	11	1	2	5
Testis									
Discoloration, pale colored, bilateral		7	0	12	0	11	1	7	0
Small, bilateral		7	0	12	0	10	2	7	0

Notes) - : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 31-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group Grade	Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
		-	P	-	P
All organs and tissues		5		5	

Notes) - : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 32-1. Macroscopic findings of female rats at the end of the dosing period

	Group	Control (vehicle: corn oil)		1,2-MD 30 mg/kg		1,2-MD 100 mg/kg		1,2-MD 300 mg/kg	
Findings	Grade	-	P	-	P	-	P	-	P
Liver									
Enlargement		11	0	11	0	8	0	0	1
Thymus									
Small		10	1	11	0	8	0	1	0

Notes) - : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 32-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Group Grade	Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
		-	P	-	P
All organs and tissues		5		5	

Notes) - : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 32-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group Grade	Control (vehicle: corn oil)		1,2-MD 300 mg/kg	
		-	P	-	P
All organs and tissues		5		5	

Notes) - : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 33-1. Histopathological findings of male rats at the end of the dosing period

Findings	Group Grade	Control (vehicle: corn oil)						1,2-MD 30 mg/kg						1,2-MD 100 mg/kg						1,2-MD 300 mg/kg									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain																													
Cellular infiltration, mononuclear cell, perivascular		4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		2
Spinal cord		5						2	0						12	0						12	5						2
Pituitary gland																													
Cellular infiltration, lymphocyte, focal		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	4	1	0	0	0		2
Vacuolation, cytoplasmic, basophilic cell		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	4	1	0	0	0		2
Submandibular gland		5						2	0						12	0						12	5						2
Sublingual gland		5						2	0						12	0						12	5						2
Lymph node, submandibular		5						2	0						12	0						12	5						2
Thyroid gland																													
Ectopic thymic tissue		4						1 2	5					0 7	5						0 7	5						0 2	
Ultimobranchial body		4						1 2	4					1 7	4						1 7	4						1 2	
Parathyroid gland		5						2	0						12	0						12	5						2
Thymus		5						2	0						12	0						12	5						2
Heart																													
Cellular infiltration, mononuclear cell, 																													

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 30 mg/kg							1,2-MD 100 mg/kg							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver																													
Fatty change, hepatocyte, periportal		1	2	2	0	0		2	0	3	2	0	0		7	1	2	3	0	0		6	4	3	0	0	0		
Ground glass appearance, hepatocyte, centrilobular		5	0	0	0	0		2	5	0	0	0	0		7	5	0	1	0	0		6	3	3	1	0	0		
Hypertrophy, hepatocyte, centrilobular		5	0	0	0	0		2	5	0	0	0	0		7	1	4	1	0	0		6 *,#	0	1	3	3	0		** ,##
Microgranuloma		4	1	0	0	0		2	1	2	2	0	0		7	0	3	3	0	0		6 *,#	2	5	0	0	0		
Vacuolation, cytoplasmic, hepatocyte, centrilobular		5	0	0	0	0		2	3	1	1	0	0		7	6	0	0	0	0		6	6	1	0	0	0		
Pancreas																													
Cellular infiltration, lymphocyte, interstitial		5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	3	2	0	0	0		2
Hemorrhage, focal		5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Stomach		5						2	0						12	0						12	5						2
Duodenum		5						2	0						12	0						12	5						2
Jejunum		5						2	0						12	0						12	5						2
Ileum		5						2	0						12	0						12	5						2
Cecum		5						2	0						12	0						12	5						2
Colon		5						2	0						12	0						12	5						2
Rectum		5						2	0						12	0						12	5						2
Lymph node, mesenteric		5						2	0						12	0						12	5						2
Spleen																													
Deposit, pigment, brown		0	3	2	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	0	3	2	0	0		2
Hematopoiesis, extramedullary		0	3	0	2	0		2	0	0	0	0	0		12	0	0	0	0	0		12	0	2	2	1	0		2

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Findings	Group Grade	Control (vehicle: corn oil)						1,2-MD 30 mg/kg						1,2-MD 100 mg/kg						1,2-MD 300 mg/kg										
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Kidney																														
Basophilic tubule, cortex		3	2	0	0	0		2	0	5	0	0	0		7	0	5	0	0	0		7	0	6	1	0	0		#	
Cast, hyalin		5	0	0	0	0		2	3	2	0	0	0		7	5	0	0	0	0		7	7	0	0	0	0			
Cellular infiltration, lymphocyte, interstitial		2	3	0	0	0		2	2	3	0	0	0		7	2	3	0	0	0		7	4	3	0	0	0			
Hyaline droplet, proximal tubule		5	0	0	0	0		2	4	1	0	0	0		7	0	2	3	0	0		7	**,##	0	0	3	4	0		**,##
Mineralization, medulla		4	1	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	5	2	0	0	0			
Urinary bladder																														
		5						2	0						12	0						12	5						2	
Adrenal gland																														
Hypertrophy, zona glomerulosa		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	3	2	0	0	0		2	
Increase, lipid content, zona fasciculata		3	2	0	0	0		2	2	3	0	0	0		7	2	3	0	0	0		7	1	2	2	0	0		2	
Testis																														
Atrophy, seminiferous tubule, bilateral		5	0	0	0	0		2	0	0	0	0	0		12	0	0	2	0	0		10	#	5	0	0	0	0		2
Epididymis																														
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		2	
Granuloma, spermatic, caudal, unilateral		4						1	0					0	12	0					0	12	5					0	2	
Prostate																														
Cellular infiltration, lymphocyte, interstitial		2	1	1	1	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2	
Seminal vesicle																														
		5						2	0						12	0						12	5						2	
Coagulating gland																														
		5						2	0						12	0						12	5						2	
Eyeball																														
		5						2	0						12	0						12	5						2	
Harderian gland																														
Cellular infiltration, lymphocyte, interstitial		5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2	
Sciatic nerve																														
		5						2	0						12	0						12	5						2	
Skeletal muscle																														
		5						2	0						12	0						12	5						2	
Femur																														
		5						2	0						12	0						12	5						2	
Marrow, femur																														
		5						2	0						12	0						12	5						2	

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 33-2. Histopathological findings of male rats at the end of the recovery period

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		0						5	0						5
Spinal cord		0						5	0						5
Pituitary gland		5							5						
Submandibular gland		0						5	0						5
Sublingual gland		0						5	0						5
Lymph node, submandibular		0						5	0						5
Thyroid gland															
Ultimobranchial body		4						1	3					2	
Parathyroid gland		0						5	0						5
Thymus		0						5	0						5
Heart		0						5	0						5
Trachea		0						5	0						5
Lung		0						5	0						5
Bronchus		0						5	0						5

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Numerals represent the number of animals.

Not significantly different from control.

Table 33-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Fatty change, hepatocyte, periportal		0	5	0	0	0			0	5	0	0	0		
Hypertrophy, hepatocyte, centrilobular		5	0	0	0	0			4	1	0	0	0		
Microgranuloma		4	1	0	0	0			4	1	0	0	0		
Vacuolation, cytoplasmic, hepatocyte, centrilobular		4	1	0	0	0			4	0	1	0	0		
Pancreas		0						5	0						5
Stomach		0						5	0						5
Duodenum		0						5	0						5
Jejunum		0						5	0						5
Ileum		0						5	0						5
Cecum		0						5	0						5
Colon		0						5	0						5
Rectum		0						5	0						5
Lymph node, mesenteric		0						5	0						5
Spleen		0						5	0						5

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 33-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group Grade	Control (vehicle: corn oil)						1,2-MD 300 mg/kg							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney															
Basophilic tubule, cortex		1	4	0	0	0			1	3	1	0	0		
Cast, hyalin		3	2	0	0	0			3	2	0	0	0		
Cellular infiltration, lymphocyte, interstitial		3	2	0	0	0			3	2	0	0	0		
Mineralization, cortex/medulla		4	1	0	0	0			4	1	0	0	0		
Urinary bladder		0						5	0						5
Adrenal gland															
Increase, lipid content, zona fasciculata		3	2	0	0	0			3	2	0	0	0		
Testis		0						5	0						5
Epididymis		0						5	0						5
Prostate		0						5	0						5
Seminal vesicle		0						5	0						5
Coagulating gland		0						5	0						5
Eyeball		0						5	0						5
Harderian gland		0						5	0						5
Sciatic nerve		0						5	0						5
Skeletal muscle		0						5	0						5
Femur		0						5	0						5
Marrow, femur		0						5	0						5

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 34-1. Histopathological findings of female rats at the end of the dosing period

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 30 mg/kg							1,2-MD 100 mg/kg							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5						6	0					11		0						8		1					
Spinal cord		5						6	0					11		0						8		1					
Pituitary gland																													
Remnant, Rathoke's pouch		5						0 6	4					1 6		5						0 3		1					0
Submandibular gland		5						6	0					11		0						8		1					
Sublingual gland		5						6	0					11		0						8		1					
Lymph node, submandibular		5						6	0					11		0						8		1					
Thyroid gland																													
Ultimobranchial body		3						2 6	3					2 6		4						1 3		0					1
Parathyroid gland		5						6	0					11		0						8		1					
Thymus																													
Atrophy		0	2	2	2	0		5	0	0	0	0	0	11		0	0	0	0	0	0	8		1	0	0	0	0	0
Heart		5						6	0					11		0						8		1					
Trachea		5						6	0					11		0						8		1					
Lung																													
Accumulation, foam cell, alveolus		4	1	0	0	0		6	0	0	0	0	0	11		0	0	0	0	0	0	8		1	0	0	0	0	0
Mineralization, arterial wall		4	1	0	0	0		6	0	0	0	0	0	11		0	0	0	0	0	0	8		1	0	0	0	0	0
Bronchus		5						6	0					11		0						8		1					

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

*P<0.05, **P<0.01: Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01: Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 34-1(continued). Histopathological findings of female rats at the end of the dosing period

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 30 mg/kg							1,2-MD 100 mg/kg							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver																													
Erythrophagocytosis, Kupffer cell		5	0	0	0	0		6	5	0	0	0	0		6	4	1	0	0	0		3	1	0	0	0		0	
Fatty change, hepatocyte, periportal		3	2	0	0	0		6	2	3	0	0	0		6	2	3	0	0	0		3	1	0	0	0		0	
Ground glass appearance, hepatocyte, centrilobular		5	0	0	0	0		6	5	0	0	0	0		6	3	2	0	0	0		3	0	1	0	0		0	
Hematopoiesis, extramedullary		3	2	0	0	0		6	5	0	0	0	0		6	5	0	0	0	0		3	1	0	0	0		0	
Hypertrophy, hepatocyte, centrilobular		5	0	0	0	0		6	5	0	0	0	0		6	1	1	3	0	0		3 #	0	0	1	0		0	
Microgranuloma		2	3	0	0	0		6	2	3	0	0	0		6	2	3	0	0	0		3	0	1	0	0		0	
Proliferation, Kupffer cell		5	0	0	0	0		6	2	3	0	0	0		6	4	1	0	0	0		3	1	0	0	0		0	
Pancreas																													
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0		6	0	0	0	0	0		11	0	0	0	0	0		8	1	0	0	0		0	
Stomach		5						6	0						11	0						8	1						
Duodenum		5						6	0						11	0						8	1						
Jejunum		5						6	0						11	0						8	1						
Ileum		5						6	0						11	0						8	1						
Cecum		5						6	0						11	0						8	1						
Colon		5						6	0						11	0						8	1						
Rectum		5						6	0						11	0						8	1						
Lymph node, mesenteric		5						6	0						11	0						8	1						
Spleen																													
Deposit, pigment, brown		0	3	2	0	0		5	0	0	0	0	0		11	0	0	0	0	0		8	0	0	1	0		0	
Hematopoiesis, extramedullary		0	0	0	5	0		5	0	0	0	0	0		11	0	0	0	0	0		8	0	0	1	0		0	

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

*P<0.05, **P<0.01: Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01: Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 34-1(continued). Histopathological findings of female rats at the end of the dosing period

Findings	Group Grade	Control (vehicle: corn oil)						1,2-MD 30 mg/kg						1,2-MD 100 mg/kg						1,2-MD 300 mg/kg									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney																													
Basophilic tubule, cortex		3	2	0	0	0		6	0	0	0	0	0		11	0	0	0	0	0		8	1	0	0	0	0		
Cast, hyalin		4	1	0	0	0		6	0	0	0	0	0		11	0	0	0	0	0		8	1	0	0	0	0		
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0		6	0	0	0	0	0		11	0	0	0	0	0		8	0	1	0	0	0		
Urinary bladder																													
		5						6	0						11	0						8	1						
Adrenal gland																													
Dilatation, sinus, focal		5	0	0	0	0		6	4	1	0	0	0		6	5	0	0	0	0		3	1	0	0	0	0		
Hypertrophy, zona glomerulosa		1	3	1	0	0		6	5	0	0	0	0		6	5	0	0	0	0		3	0	1	0	0	0		
Increase, lipid content, zona fasciculata		5	0	0	0	0		6	5	0	0	0	0		6	5	0	0	0	0		3	0	1	0	0	0		
Ovary																													
Increase, lipid content, lutein cell		5	0	0	0	0		6	5	0	0	0	0		6	4	1	0	0	0		3	0	1	0	0	0		
Uterus																													
		5						6	5						6	5						3	1						
Vagina																													
Mucification, epithelium		5	0	0	0	0		6	5	0	0	0	0		6	4	1	0	0	0		3	1	0	0	0	0		
Eyeball																													
		5						6	0						11	0						8	1						
Harderian gland																													
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0		6	0	0	0	0	0		11	0	0	0	0	0		8	1	0	0	0	0		
Sciatic nerve																													
		5						6	0						11	0						8	1						
Skeletal muscle																													
Degeneration, muscle fiber, myogenic		4	1	0	0	0		6	0	0	0	0	0		11	0	0	0	0	0		8	1	0	0	0	0		
Femur																													
		5						6	0						11	0						8	1						
Marrow, femur																													
Increase, hematopoiesis		0	1	4	0	0		6	0	0	0	0	0		11	0	0	0	0	0		8	0	1	0	0	0		

(Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 34-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5							5						
Spinal cord		5							5						
Pituitary gland		5							5						
Submandibular gland		5							5						
Sublingual gland		5							5						
Lymph node, submandibular		5							5						
Thyroid gland															
Cellular infiltration, lymphocyte, interstitial		5	0	0	0	0			4	0	1	0	0		
Ultimobranchial body		4					1		5					0	
Parathyroid gland															
Vacuolation, cytoplasmic		2	1	0	0	0		2	4	1	0	0	0		
Thymus															
Atrophy		2	1	2	0	0			1	3	1	0	0		
Heart		5							5						
Trachea		5							5						
Lung															
Accumulation, foam cell, alveolus		5	0	0	0	0			4	1	0	0	0		
Bronchus		5							5						

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

*P<0.05, **P<0.01: Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01: Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Fatty change, hepatocyte, periportal		0	5	0	0	0			0	3	2	0	0		
Ground glass appearance, hepatocyte, centrilobular		5	0	0	0	0			0	4	1	0	0	**	##
Hypertrophy, hepatocyte, centrilobular		5	0	0	0	0			0	0	1	4	0	**	##
Microgranuloma		2	3	0	0	0			0	5	0	0	0		
Pancreas															
		5							5						
Stomach															
		5							5						
Duodenum															
		5							5						
Jejunum															
		5							5						
Ileum															
		5							5						
Cecum															
		5							5						
Colon															
		5							5						
Rectum															
		5							5						
Lymph node, mesenteric															
		5							5						
Spleen															
Deposit, pigment, brown		0	0	2	3	0			0	0	2	3	0		
Hematopoiesis, extramedullary		0	3	1	1	0			0	1	4	0	0		

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

##P<0.05, ###P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Grade	Control (vehicle: corn oil)						1,2-MD 300 mg/kg									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE		
Kidney																	
Basophilic tubule, cortex		3	2	0	0	0			2	2	1	0	0				
Cast, hyalin		4	1	0	0	0			3	2	0	0	0				
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0			3	2	0	0	0				
Cyst, cortex		5					0		4					1			
Mineralization, cortex		5	0	0	0	0			3	2	0	0	0				
Urinary bladder																	
		5							5								
Adrenal gland																	
Hypertrophy, zona glomerulosa		4	1	0	0	0			3	2	0	0	0				
Increase, lipid content, zona fasciculata		4	1	0	0	0			3	2	0	0	0				
Ovary																	
Cyst, follicular		4	1	0	0	0			4	1	0	0	0				
Cyst, luteinized		5	0	0	0	0			4	0	1	0	0				
Increase, atretic follicle		4	1	0	0	0			3	1	1	0	0				
Uterus																	
Dilatation, cystic, uterin gland		5					0		4					1			
Dilatation, lumen		3	0	2	0	0			4	0	1	0	0				
Vagina																	
Cellular infiltration, lymphocyte, lamina propria		5	0	0	0	0			4	1	0	0	0				
Eyeball																	
		5							5								
Harderian gland																	
Cellular infiltration, lymphocyte, interstitial		5	0	0	0	0			3	2	0	0	0				
Sciatic nerve																	
		5							5								
Skeletal muscle																	
		5							5								
Femur																	
		5							5								
Marrow, femur																	
Increase, hematopoiesis		1	1	3	0	0			0	3	2	0	0				

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

*P<0.05, **P<0.01: Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01: Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 34-3. Histopathological findings of female rats at the end of the recovery period

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		0						5	0						5
Spinal cord		0						5	0						5
Pituitary gland		5							5						
Submandibular gland		0						5	0						5
Sublingual gland		0						5	0						5
Lymph node, submandibular		0						5	0						5
Thyroid gland															
Ectopic thymic tissue		4						1	5					0	
Ultimobranchial body		5						0	3					2	
Parathyroid gland		0						5	0						5
Thymus		0						5	0						5
Heart		0						5	0						5
Trachea		0						5	0						5
Lung		0						5	0						5
Bronchus		0						5	0						5

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 34-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Fatty change, hepatocyte, periportal		0	5	0	0	0			0	5	0	0	0		
Microgranuloma		0	5	0	0	0			0	5	0	0	0		
Necrosis, focal		5	0	0	0	0			4	1	0	0	0		
Pancreas		0						5	0						5
Stomach		0						5	0						5
Duodenum		0						5	0						5
Jejunum		0						5	0						5
Ileum		0						5	0						5
Cecum		0						5	0						5
Colon		0						5	0						5
Rectum		0						5	0						5
Lymph node, mesenteric		0						5	0						5
Spleen		0						5	0						5

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 34-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group Grade	Control (vehicle: corn oil)							1,2-MD 300 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney		0						5	0						5
Urinary bladder		0						5	0						5
Adrenal gland		5							5						
Ovary		5							5						
Uterus															
Dilatation, cystic, uterin gland		5					0		4					1	
Dilatation, lumen		5	0	0	0	0			4	0	1	0	0		
Vagina		5							5						
Eyeball		0						5	0						5
Harderian gland		0						5	0						5
Sciatic nerve		0						5	0						5
Skeletal muscle		0						5	0						5
Femur		0						5	0						5
Marrow, femur		0						5	0						5

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 35. Results of observations about estrous cycle

Dose	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of animals examined	12	12	12	12
<u>Pre-treatment period</u>				
Number of animals showing type of cycle				
4-day cycle	10	11	8	10
4-5-day cycle	1	1	2	1
5-day cycle	1	0	2	1
Mean length of estrous cycle in days; Mean±S.D. (N)	4.1 ± 0.3 (12)	4.0 ± 0.1 (12)	4.3 ± 0.4 (12)	4.1 ± 0.3 (12)
<u>Treatment period</u>				
Number of animals showing each type of cycle				
4-day cycle	11	9	9	1
4-5-day cycle	0	2	2	5
5-day cycle	1	1	1	3
Irregular cycle	0	0	0	3
Mean length of estrous cycle in days; Mean±S.D. (N)	4.1 ± 0.3 (12)	4.2 ± 0.3 (12)	4.2 ± 0.3 (12)	5.0 ± 1.3 ** (12)
Frequency of animals that show abnormal estrus cycles after the treatment	0 / 12	0 / 12	0 / 12	3 / 12
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.2 ± 0.4 (11)

Significantly different from the control group (*: p<0.05, **: p<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 36. Results of observations about reproductive performance

Dose	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of mated pairs [A]	12	12	12	12
Number of copulated pairs [B]	12	12	12	11
Copulation index $[(B/A) \times 100, \%$]	100.0	100.0	100.0	91.7
Number of fertile males [C]	12	11	10	7
Fertility index $[(C/B) \times 100, \%$]	100.0	91.7	83.3	63.6 *
Pairing days until copulation ; Mean $\pm$ S.D.(N)	2.8 $\pm$ 0.9 (12)	2.0 $\pm$ 0.7 (12)	2.8 $\pm$ 1.3 (12)	3.7 $\pm$ 1.6 (11)

Significantly different from the control group (*: $p < 0.05$, **: $p < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 37. Observation of offspring (F₁)

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of dams	11	11	10	7
Gestation length (days)				
Mean ± S.D. per dam	21.9 ± 0.3	22.2 ± 0.4	22.1 ± 0.3	22.6 ± 0.5 **
Number of corpora lutea				
Total	177	177	161	107
Mean ± S.D. per dam	16.1 ± 1.9	16.1 ± 1.7	16.1 ± 1.4	15.3 ± 2.1
Number of implantation scars				
Total	173	171	154	105
Mean ± S.D. per dam	15.7 ± 1.8	15.5 ± 1.1	15.4 ± 1.3	15.0 ± 2.0
Implantation index (%) ^{a)}	97.8 ± 3.1	96.9 ± 4.4	95.9 ± 7.0	98.2 ± 3.1
Delivery index (dams,%) ^{b)}	100.0	100.0	100.0	100.0
Number of offspring at birth				
Total	157	155	150	71
Mean ± S.D. per dam	14.3 ± 2.0	14.1 ± 1.4	15.0 ± 1.5	10.1 ± 5.0
Number of live offspring at birth				
Male	80	62	71	26
Female	77	92	66	30
Total	157	154	137	56
Mean ± S.D. per dam	14.3 ± 2.0	14.0 ± 1.6	13.7 ± 2.5	8.0 ± 4.8 **
Sex ratio ^{c)}				
Mean ± S.D. per dam	0.51 ± 0.10	0.40 ± 0.09	0.51 ± 0.14	0.53 ± 0.23
Number of dead offspring				
Total	0	1	13	15
Mean ± S.D. per dam	0.0 ± 0.0	0.1 ± 0.3	1.3 ± 2.0	2.1 ± 3.2 **
Delivery index (offspring) ^{d)}				
Mean% ± S.D. per dam	90.7 ± 6.4	90.9 ± 9.4	97.4 ± 4.8	68.8 ± 33.2
Birth index ^{e)}				
Mean% ± S.D. per dam	90.7 ± 6.4	90.3 ± 10.3	88.7 ± 11.8	55.2 ± 34.0 *
Live birth index ^{f)}				
Mean% ± S.D. per dam	100.0 ± 0.0	99.2 ± 2.5	91.4 ± 12.9	76.0 ± 23.7 **
Number of offspring on day 4				
Male	80	59	40	5
Female	75	90	50	4
Sex ratio ^{g)}				
Mean ± S.D. per dam	0.52 ± 0.10	0.40 ± 0.10 *	0.44 ± 0.12 (8)	0.56 ± (1)
Viability index ^{h)}				
Mean% ± S.D. per dam	98.6 ± 4.6	96.4 ± 6.6	70.0 ± 37.7 *	9.2 ± 24.3 **
Number of external abnormalities ^{b)}	0	1	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.8 ± 2.7	0.0 ± 0.0	0.0 ± 0.0

Significantly different from the control group (*: P<0.05, **: P<0.01).

a): (Number of implantation scars/Number of corpora lutea)×100.

b): (Number of dams with live offspring/number of pregnant dams)×100.

c): Number of male offspring/(number of male offspring + number of female offspring).

d): (Number of offspring at birth/Number of implantation scars)×100.

e): (Number of live offspring at birth/number of implantation scars)×100.

f): (Number of live offspring at birth/number of offspring at birth)×100.

g): (Number of live offspring 4 days after birth/number of live offspring at birth)×100.

h): Number of external abnormalities in live offspring at birth.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 38. Body weights of offspring (F₁) before weaning

Group		Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Number of dams		11	11	10	7
Male					
Days after birth					
	0	6.7 ± 0.4	6.4 ± 0.6	5.4 ± 0.3 **	4.7 ± 0.4 **
	4	10.9 ± 0.9	10.5 ± 1.6	9.6 ± 0.9 (8)	7.7 ± (1)
Number of dams		11	11	10	6
Female					
Days after birth					
	0	6.3 ± 0.3	6.0 ± 0.6	5.4 ± 0.5 **	4.4 ± 0.5 ** (6)
	4	10.3 ± 0.7	9.9 ± 1.4	9.4 ± 1.0 (8)	6.2 ± (1)

Each value shows mean ± S.D. per dam. (g).

Figures in parentheses indicate number of dams.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 39. General conditions in offspring (F₁) before weaning

Group	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
Control (vehicle: corn oil)	Number of offspring	157	157	157	157	155
	General appearance, No abnormality	157	157	157	155	155
	Abnormal findings of offspring, Lack of nursing Skin, Cyanosis					
	Abnormal findings of offspring, Short tail					
	General appearance, Death				2	
1,2-MD 30 mg/kg	Number of offspring	154	154	151	150	150
	General appearance, No abnormality	153	151	150	150	149
	Abnormal findings of offspring, Lack of nursing Skin, Cyanosis					
	Abnormal findings of offspring, Short tail	1				
	General appearance, Death		3	1		1
1,2-MD 100 mg/kg	Number of offspring	137	137	122	107	98
	General appearance, No abnormality	137	122	107	98	90
	Abnormal findings of offspring, Lack of nursing Skin, Cyanosis					
	Abnormal findings of offspring, Short tail					
	General appearance, Death		15	15	9	8
1,2-MD 300 mg/kg	Number of offspring	56	56	9	9	9
	General appearance, No abnormality	14	9	9	9	9
	Abnormal findings of offspring, Lack of nursing Skin, Cyanosis	42				
	Abnormal findings of offspring, Short tail	4				
	General appearance, Death		47			

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Table 40. Morphological observations of offspring (F₁)

Group	Control (vehicle: corn oil)	1,2-MD 30 mg/kg	1,2-MD 100 mg/kg	1,2-MD 300 mg/kg
Dead pups				
Number of dead pups ^{a)}	2	6	60	61
Number of missing pups	2	2	24	14
Number of dead pups examined	0	4 (2)	36 (16)	50 (37)
Number of dead pups with external changes	0	0	0	0
Number of dead pups with visceral changes	0	0	0	0
Live pups				
Number of live pups examined (postnatal day 0)	157	154	137	56
Number of live pups with external changes	0	1	0	0
Types and number				
Short tail	0	1	0	0

Number of live pups examined (postnatal day 4)	155	149	90	9
Number of live pups with external changes	0	0	0	0
Number of live pups with visceral changes	0	0	0	0

Significantly different from the control group (*: p<0.05, **: p<0.01)

^{a)} including missing pups

^{b)} parenthesis indicates number of dead pups with rotten internal organ

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 1-1-1. General conditions of male rats

[illegible]

Control (vehicle: corn oil)																																				
Male No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pre: Before administration, Post: after administration.																																				
-: General appearance, No abnormality.																																				
a: Fur, Hair, Coat, Piloerection.																																				

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 1-1-2. General conditions of male rats

[illegible]

Male No.		Days of administration																																					
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43			
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
M02013		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02021		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02022		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02023		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02024		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
-		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
a		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Fur, Hair, Coat, Piloerection.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 1-1-3. General conditions of male rats

[illegible]

1,2-MD 100 mg/kg																																					
Male No.		Days of administration																																			
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
	M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	M03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
-		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
a		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Fur, Hair, Coat, Piloerection.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 1-1-4. General conditions of male rats

[illegible]

1,2-MD 300 mg/kg																																						
Male No.		Days of administration																																				
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43		
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04046	a	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
-	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
a	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Pre: Before administration, Post: after administration.																																						
-: General appearance, No abnormality.																																						
a: Fur, Hair, Coat, Piloerection.																																						

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 1-2-1. General conditions of male rats at the recovery period

Control (vehicle: corn oil)															
Male No.	Days of recovery period														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 1-2-2. General conditions of male rats at the recovery period

1,2-MD 300 mg/kg

Male No.	Days of recovery period														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 2-1-1. General conditions of female rats

[illegible]

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 2-1-2. General conditions of female rats

[illegible]

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 2-1-3. General conditions of female rats

1,2-MD 100 mg/kg Female No.		Days of administration																																																			
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25			
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post				
F03025		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03026		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03027		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03028		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03029		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03030		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03031		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03032		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03033		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03034		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03035		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03036		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	8	8	3	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	8	8	3	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
a		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
b		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Pre: Before administration, Post: after administration.																																																					
-: General appearance, No abnormality.																																																					
a: Excretion, Decrease in amount of feces.																																																					
b: Posture, Body position, Prone position.																																																					
(Continued)																																																					

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 2-1-4. General conditions of female rats

[illegible]

(Continued)

1,2-MD 300 mg/kg		Days of administration																																																	
Female No.																																																			
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43		44		45		46		47		48		49		50	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F04046																																																			
Number of females		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pre: Before administration, Post: after administration.																																																			
		(Continued)																																																	

(Continued)

1,2-MD 300 mg/kg						
Female No.	Days of administration					
	51		52		53	
	Pre	Post	Pre	Post	Pre	
F04046	-	-	-	-	-	
Number of females	1	1	1	1	1	
-	1	1	1	1	1	

Pre: Before administration, Post: after administration.
-: General appearance. No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 2-2-1. General conditions of female rats, satellite group

Control (vehicle: corn oil)																																																					
Female No.	Days of administration																																																				
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25				
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post					
F05049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F05050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F05051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F05052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F05053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Fur, Hair, Coat, Soiled fur.

b: Anorectal region, Soiled perineal region.

(Continued)

(Continued)

Female No.		Days of administration																																			
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F05049		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05050		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05051		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05052		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05053		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05054		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05055		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05056		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05057		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05058		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
-		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 2-2-2. General conditions of female rats, satellite group

[illegible]

1,2-MD 300 mg/kg	
Female No.	

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 2-3-1. General conditions of female rats at the recovery period

Control (vehicle: corn oil)															
Female No.	Days of recovery period														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 2-3-2. General conditions of female rats at the recovery period

1,2-MD 300 mg/kg															
Female No.	Days of recovery period														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F06064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 3-1. General conditions in dams during pregnancy

Control (vehicle: corn oil)

Female No.	Days of pregnancy																											
	0		1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 3-1(continued). General conditions in dams during pregnancy

Control (vehicle: corn oil)

Female No.	Days of pregnancy																									
	14		15		16		17		18		19		20		21		22		23		24		25		26	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a									
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	3	0	0	0	0	0	0	0	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	0	0	0	0	0	0	0	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 3-2. General conditions in dams during pregnancy

1,2-MD 30 mg/kg

Female No.	Days of pregnancy																											
	0		1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 3-2(continued). General conditions in dams during pregnancy

1,2-MD 30 mg/kg

Female No.	Days of pregnancy																								
	14		15		16		17		18		19		20		21		22		23		24		25		26
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	1	1	1	1	1	1	1
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	1	1	1	1	1	1	1
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 3-3. General conditions in dams during pregnancy

1,2-MD 100 mg/kg

Female No.	Days of pregnancy																											
	0		1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 3-3(continued). General conditions in dams during pregnancy

1,2-MD 100 mg/kg

Female No.	Days of pregnancy																									
	14		15		16		17		18		19		20		21		22		23		24		25		26	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	2	2	2	2	2	2	2	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	2	2	2	2	2	2	2	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 3-4. General conditions in dams during pregnancy

1,2-MD 300 mg/kg

Female No.	Days of pregnancy																											
	0		1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 3-4(continued). General conditions in dams during pregnancy

1,2-MD 300 mg/kg

Female No.	Days of pregnancy																									
	14		15		16		17		18		19		20		21		22		23		24		25		26	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4	4	4	4	4	4	4
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4	4	4	4	4	4	4
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 4-1. General conditions in dams during lactation

Control (vehicle: corn oil)

Female No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F01001	-	-	-	-	-	-	-	-	-	-	-
F01002	#	#	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-
F01005	#	#	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-	-
F01008	#	#	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-
F01010	#	#	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-
Number of females	7	7	11	11	11	11	11	11	11	11	11
-	7	7	11	11	11	11	11	11	11	11	11
a	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Anorectal region, Soiled perineal region.

b: Anorectal region, Vaginal hemorrhage.

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 4-2. General conditions in dams during lactation

1,2-MD 30 mg/kg

Female No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F02013	-	-	-	-	-	-	-	-	-	-	-
F02014	-	-	-	-	-	-	-	-	-	-	-
F02015	-	-	-	-	-	-	-	-	-	-	-
F02016	#	#	-	-	-	-	-	-	-	-	-
F02017	#	#	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-
Number of females	9	9	11	11	11	11	11	11	11	11	11
-	9	9	11	11	11	11	11	11	11	11	11
a	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Anorectal region, Soiled perineal region.

b: Anorectal region, Vaginal hemorrhage.

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 4-3. General conditions in dams during lactation

1,2-MD 100 mg/kg

Female No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F03025	-	-	-	-	-	-	-	-	-	-	-
F03026	-	-	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-
F03028	#	#	-	-	a,b	a,b	-	-	-	Total litter loss	
F03029	-	-	-	-	-	-	-	-	-	-	-
F03030	#	#	-	-	-	-	-	-	-	-	-
F03031	#	#	-	-	-	-	-	-	-	Total litter loss	
F03033	-	-	-	-	-	-	-	-	-	-	-
F03034	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-
Number of females	7	7	10	10	10	10	10	10	10	8	8
-	7	7	10	10	9	9	10	10	10	8	8
a	0	0	0	0	1	1	0	0	0	0	0
b	0	0	0	0	1	1	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Anorectal region, Soiled perineal region.

b: Anorectal region, Vaginal hemorrhage.

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 4-4. General conditions in dams during lactation

1,2-MD 300 mg/kg

Female No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F04039	-	-	-	-	Total litter loss						
F04040	-	-	-	-	Total litter loss						
F04041	#	#	-	-	Total litter loss						
F04042	#	#	-	-	Total litter loss						
F04043	#	#	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	Total litter loss						
F04048	-	-	-	-	Total litter loss						
Number of females	4	4	7	2	1	1	1	1	1	1	1
-	4	4	7	2	1	1	1	1	1	1	1
a	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Anorectal region, Soiled perineal region.

b: Anorectal region, Vaginal hemorrhage.

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 5-1. Detailed clinical observations of male rats

Control (vehicle: corn oil)

Male No.	Open-field observations ^{c)}																				Piloerection										Abnormal gait										Pinna reflex									
	Straub tail																																																	
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14														
M01001	2	2	2	2	2	2	2			2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	2	2	2																
M01002	2	2	2	2	2	2	2			2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	2	2	2																
M01003	2	2	2	2	2	2	2			2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	2	2	2																
M01004	2	2	2	2	2	2	2			2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	2	2	2																
M01005	2	2	2	2	2	2	2			2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	2	2	2																
M01006	2	2	2	2	2	2	2			2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	2	2	2																
M01007	2	2	2	2	2	2	2			2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	2	2	2																
M01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2	2													
M01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2	2													
M01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2	2													
M01011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2	2													
M01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2	2													
Total	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0													
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)													

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Straub tail [2, not observed; 3, tail elevation]

Piloerection [2, not observed; 3, slight]

Abnormal gait [0, not observed; 1, reluctance to walk]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 5-1(continued). Detailed clinical observations of male rats

Corn oil (control)																		
Male No.	Open-field observations ^{c)}																	
	Urination									Defecation								
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M01001	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01002	0	0	0	0	0	0	0			0	2	0	0	0	0	0		
M01003	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01004	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01005	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01006	0	0	0	1	0	0	0			0	0	0	0	0	0	0		
M01007	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01008	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01009	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01010	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0
M01011	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01012	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	2	0	0	0	0	0	0	2	1	1	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 5-2. Detailed clinical observations of male rats

1,2-MD 30 mg/kg

Male No.	Open-field observations ^{c)}																											
	Straub tail							Piloerection							Abnormal gait							Pinna reflex						
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02014	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02015	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02016	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02017	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02018	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02019	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02020	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02021	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02022	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02023	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M02024	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

^a pre-treatment; ^b day 8 of treatment

Straub tail [2, not observed; 3, tail elevation]

Piloerection [2, not observed; 3, slight]

Abnormal gait [0, not observed; 1, reluctance to walk]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 5-2(continued). Detailed clinical observations of male rats

1,2-MD (30 mg/kg)

Male No.	Open-field observations ^{c)}													
	Urination							Defecation						
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M02013	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M02014	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M02015	0	0	0	0	0	1	1	0	0	0	0	0	0	0
M02016	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M02017	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M02018	1	0	1	1	2	1	1	1	0	1	1	0	0	0
M02019	0	1	0	1	0	1	1	0	0	0	0	0	0	0
M02020	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02023	0	0	0	1	0	0	1	0	0	0	0	0	0	0
M02024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	1	1	1	7	2	3	4	1	0	1	1	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

^a pre-treatment; ^b day 8 of treatment

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 5-3. Detailed clinical observations of male rats

1,2-MD 100 mg/kg

Male No.	Open-field observations ^{c)}																											
	Straub tail							Piloerection							Abnormal gait							Pinna reflex						
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M03025	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03026	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03027	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03028	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03029	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03030	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03031	2	2	2	3	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03032	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03033	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03034	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03035	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
M03036	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	2	2	2	2	2	2	2
Total score	3:0	3:0	3:0	3:1	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

^a pre-treatment; ^b day 8 of treatment

Straub tail [2, not observed; 3, tail elevation]

Piloerection [2, not observed; 3, slight]

Abnormal gait [0, not observed; 1, reluctance to walk]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 5-3(continued). Detailed clinical observations of male rats

1,2-MD (100 mg/kg)													
Male No.	Open-field observations ^{c)}												
	Urination							Defecation					
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36 T42
M03025	0	0	1	1	1	1	0	0	0	1	1	0	0 0
M03026	0	0	0	0	0	0	0	0	0	0	0	0	0 0
M03027	0	0	0	0	0	0	0	0	0	0	0	0	0 0
M03028	0	0	0	0	0	1	0	0	0	0	0	0	0 0
M03029	1	0	0	0	0	0	0	0	0	0	0	0	0 0
M03030	0	0	0	0	0	0	0	0	0	0	0	0	0 0
M03031	0	0	0	0	0	0	0	0	0	0	0	0	0 0
M03032	0	0	0	0	0	0	0	0	0	0	0	0	0 0
M03033	0	0	0	0	0	0	0	0	0	0	0	0	0 0
M03034	0	0	0	0	0	0	0	0	0	0	0	0	0 0
M03035	0	0	0	0	0	0	0	0	0	0	0	0	0 0
M03036	0	0	0	1	0	1	1	0	0	0	0	0	0 0
Total score	1	0	1	2	1	3	1	0	0	1	1	0	0 0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

^a pre-treatment; ^b day 8 of treatment

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 5-4. Detailed clinical observations of male rats

1,2-MD 300 mg/kg

Male No.	Open-field observations ^{c)}																																							
	Straub tail										Piloerection										Abnormal gait										Pinna reflex									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14				
M04037	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	2	1	1						
M04038	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	1	1	1						
M04039	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			0	0	0	1	0	0	0			2	2	2	2	1	1	1						
M04040	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	1	1	2						
M04041	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			0	0 ^c	0	0	0	0	0			2	2	2	1	1	2	2						
M04042	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	2	2	2	2						
M04043	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			2	2	2	1	1	1	1						
M04044	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	1	1	1	1	2	2				
M04045	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2				
M04046	2	2	2	2	2	2	2	2	2	2	2	2	3	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	2	1	1	1	2	2				
M04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	1	2	2	1	2	2				
M04048	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	2	2	2	1	1	1	1	2	2				
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:1	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:1	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:5	1:8	1:8	1:8	1:0	1:0			
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)				

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Straub tail [2, not observed; 3, tail elevation]

Piloerection [2, not observed; 3, slight]

Abnormal gait [0, not observed; 1, reluctance to walk]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 5-4(continued). Detailed clinical observations of male rats

1,2-MD (300 mg/kg)

Male No.	Open-field observations ^{c)}																		
	Urination										Defecation								
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	
M04037	0	0	0	0	0	0	0			0	0	0	0	0	0	0			
M04038	1	0	0	0	0	0	1			0	0	0	0	0	0	0			
M04039	0	0	0	2	0	0	0			0	0	0	0	0	0	0			
M04040	0	0	0	0	0	0	0			0	0	0	0	0	0	0			
M04041	1	0	0	0	0	0	0			0	0	0	0	0	0	0			
M04042	0	0	0	1	0	0	1			0	0	0	0	0	0	0			
M04043	0	0	0	0	0	0	2			0	0	0	0	0	0	0			
M04044	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
M04045	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	
M04046	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
M04047	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
M04048	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Total score	2	0	0	3	0	0	4	0	1	0	0	0	0	0	0	0	0	0	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-1-1. Detailed clinical observations of female rats

Control (vehicle: corn oil)																																						
Female No.	Cage-side observations ^{a)}												Removing from cage / Observations made while handling ^{b)}												Open-field observations ^{c)}													
	Posture in home-cage							Locomotor in home-cage							Fur							Pinna reflex																
	Pre ^a	T8 ^b	T15	T24	T30	T36	L ^c	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L			
F01001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F01011	2	2	2	2	2	2	2	Died on day 22 of pregnancy	2	2	2	2	2	2	2	Died on day 22 of pregnancy	2	2	2	2	2	2	2	Died on day 22 of pregnancy	2	2	2	2	2	2	2	Died on day 22 of pregnancy	2	2	2	2	2	Died on day 22 of pregnancy
F01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0		
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)		

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Posture in home-cage [2, sitting or standing; 1, prone position or crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity]

Fur [2, normal; 1, soiled fur]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-1-1(continued). Detailed clinical observations of female rats

Control (vehicle: corn oil)																
Female No.	Open-field observations ^{a)}									Defecation						
	Urination															
	Pre ^a	T8 ^b	T15	T24	T30	T36	L ^c	Pre		T8	T15	T24	T30	T36	L	
F01001	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01002	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01003	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01004	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01005	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01006	0	0	0	0	0	0	0		0	1	0	0	0	0	0	
F01007	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01008	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01009	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01010	0	0	0	0	1	0	0		0	0	0	0	0	0	0	
F01011	0	0	0	0	0	0	Died on day 22 of pregnancy		0	0	0	0	0	0	Died on day 22 of pregnancy	
F01012	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
Total score	0	0	0	0	1	0	0		0	1	0	0	0	0	0	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)		(12)	(12)	(12)	(12)	(12)	(12)	(12)	

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-1-2. Detailed clinical observations of female rats

1,2-MD 30 mg/kg																																	
Female No.	Cage-side observations ^{a)}								Locomotor in home-cage								Removing from cage / Observations made while handling ^{b)}								Open-field observations ^{c)}								
	Posture in home-cage																Fur								Pinna reflex								
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	L ^c	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	
F02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02014	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02015	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02016	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02017	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02018	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02019	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02020	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02021	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02022	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02023	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F02024	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0		
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(11)	

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Posture in home-cage [2, sitting or standing; 1, prone position or crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity]

Fur [2, normal; 1, soiled fur]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-1-2(continued). Detailed clinical observations of female rats

1,2-MD 30 mg/kg

Female No.	Open-field observations ^{c)}																										
	Urination								Defecation																		
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	L ^c	Pre	T8	T15	T24	T30	T36	T42	L											
F02013	0	0	1	0	0	0		0	0	0	0	0	0	0		0											
F02014	0	0	0	0	1	0		0	0	0	0	0	0	0		0											
F02015	0	0	0	0	0	0		0	0	0	0	0	0	0		0											
F02016	0	0	0	0	0	0		0	0	0	0	0	0	0		0											
F02017	0	0	0	0	1	0		0	0	0	0	0	0	0		0											
F02018	0	0	0	0	0	0		0	0	0	0	0	0	0		0											
F02019	0	0	0	0	0	0	0	Non pregnant	0	0	0	0	0	0	0	0	Non pregnant										
F02020	0	0	0	0	0	0	0		0	0	0	0	0	0	0			0									
F02021	0	0	0	0	0	0	0		0	0	0	0	0	0	0			0									
F02022	0	0	0	0	0	0	0		0	0	0	0	0	0	0			0									
F02023	0	0	0	0	2	1	0		0	0	0	0	0	0	0			0									
F02024	0	0	0	0	0	0		0	0	0	0	0	0	0		0											
Total score	0	0	1	0	4	1	0	0	0	0	0	0	0	0	0	0											
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(11)											

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-1-3. Detailed clinical observations of female rats

1,2-MD 100 mg/kg

Female No.	Cage-side observations ^{a)}								Locomotor in home-cage								Removing from cage / Observations made while handling ^{b)}								Open-field observations ^{c)}									
	Posture in home-cage																Fur								Pinna reflex									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	L ^c	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L		
F03025	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F03026	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F03027	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2			
F03028	2	2	2	2	2	2	2	2	Total litter loss.	2	2	2	2	2	2	2	Total litter loss.	2	2	2	2	2	2	2	1	Total litter loss.	2	2	2	2	2	2	1	Total litter loss.
F03029	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F03030	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F03031	2	2	2	2	2	2	2	2	Total litter loss.	2	2	2	2	2	2	2	Total litter loss.	2	2	2	2	2	2	2	2	Total litter loss.	2	2	2	2	2	2	2	Total litter loss.
F03032	2	2	2	2	2	2	2	2	Non pregnant	2	2	2	2	2	2	2	Non pregnant	2	2	2	2	2	2	2	Non pregnant	2	2	2	2	2	2	2	Non pregnant	
F03033	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2			
F03034	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F03035	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F03036	2	2	2	2	2	2	2	2	Non pregnant	2	2	2	2	2	2	2	Non pregnant	2	2	2	2	2	2	2	Non pregnant	2	2	2	2	2	2	1	Non pregnant	
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0		1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:1	1:0	1:0	1:0	1:1	1:1	1:1	1:1	1:1			
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(10)		(12)	(12)	(12)	(12)	(12)	(12)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(10)	

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Posture in home-cage [2, sitting or standing; 1, prone position or crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity]

Fur [2, normal; 1, soiled fur]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-1-3(continued). Detailed clinical observations of female rats

1,2-MD 100 mg/kg

Female No.	Open-field observations ^{c)}																	
	Urination								Defecation									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	L ^c	Pre	T8	T15	T24	T30	T36	T42	L		
F03025	0	0	0	0	0	0		0	0	0	0	0	0	0		0		
F03026	0	0	0	0	0	0		0	0	0	0	0	0	0		0		
F03027	0	0	0	0	0	0		0	0	0	0	0	0	0		0		
F03028	0	0	0	0	0	0		0	Total litter loss.	0	0	0	0	0	1	0	Total litter loss.	
F03029	0	0	0	0	0	0		0	0	0	0	0	0	0	0		0	
F03030	0	0	0	0	0	0		0	0	0	0	0	0	0	0		0	
F03031	1	0	0	0	0	0		0	Total litter loss.	0	0	0	0	0	0		0	Total litter loss.
F03032	1	0	0	0	0	0			Non pregnant	0	0	0	0	0	0			Non pregnant
F03033	1	0	0	0	0	0		0	0	0	0	0	0	0	0		0	
F03034	0	0	0	0	0	0		0	0	0	0	0	0	0	0		0	
F03035	0	0	0	0	0	0		0	0	0	0	0	0	0	0		0	
F03036	0	0	0	0	0	0	0		Non pregnant	0	0	0	0	0	0	0		Non pregnant
Total score	3	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0		
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(10)		

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-1-4. Detailed clinical observations of female rats

1,2-MD 300 mg/kg

Female No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}																
	Posture in home-cage								Locomotor in home-cage								Fur								Pinna reflex												
	Pre	^a T8	^b T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	
F04037	2	2	2	2	2	2	2		Non pregnant	2	2	2	2	2	2	2		Non pregnant	2	2	2	2	2	2	2		Non pregnant	2	2	2	1	1	1	1		Non pregnant	
F04038	2	2	2	2	2	2	2		Non pregnant	2	2	2	2	2	2	2		Non pregnant	2	2	2	2	2	2	2		Non pregnant	2	2	2	2	1	1	2		Non pregnant	
F04039	2	2	2	2	2	2		2	Total litter loss.	2	2	2	2	2	2		2	Total litter loss.	2	2	2	2	2	2		2	Total litter loss.	2	2	2	1	1	1		1	Total litter loss.	
F04040	2	2	2	2	2	2		2	Total litter loss.	2	2	2	2	2	2		2	Total litter loss.	2	2	2	2	2	2		2	Total litter loss.	2	2	2	1	1	1		1	Total litter loss.	
F04041	2	2	2	2	2	2			Total litter loss.	2	2	2	2	2	2			Total litter loss.	2	2	2	2	2	2			Total litter loss.	2	2	2	2	1	1			Total litter loss.	
F04042	2	2	2	2	2	2			Total litter loss.	2	2	2	2	2	2			Total litter loss.	2	2	2	2	2	2			Total litter loss.	2	2	2	1	1	1			Total litter loss.	
F04043	2	2	2	2	2	2		2		2	2	2	2	2	2		2		2	2	2	2	2	2		2		2	2	2	1	2		1			
F04044	2	2	2	2	2	2		2	Total litter loss.	2	2	2	2	2	2		2	Total litter loss.	2	2	2	2	2	2		2	Total litter loss.	2	2	2	1	1	2		2	Total litter loss.	
F04045	2	1	2	2	2	2	2		Non pregnant	2	1	2	2	2	2	2		Non pregnant	2	2	2	2	2	2	2		Non pregnant	2	1	2	1	1	1	2		Non pregnant	
F04046	2	2	2	2	2	2	2	2	Non copulation	2	2	2	2	2	2	2	2	Non copulation	2	2	2	2	2	2	2	2	Non copulation	2	2	2	2	1	2	2	1	Non copulation	
F04047	2	2	2	2	2	2	2		Non pregnant	2	2	2	2	2	2	2		Non pregnant	2	2	2	2	2	2	2		Non pregnant	2	2	2	1	2	2	2		Non pregnant	
F04048	2	2	2	2	2	2	2		Total litter loss.	2	2	2	2	2	2			Total litter loss.	2	2	2	2	2	2			Total litter loss.	2	2	2	2	2	1			Total litter loss.	
Total score	1:0	1:1	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:1	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:1	1:7	1:10	1:8	1:1	1:1	1:3	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(1)	(4)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(1)	(4)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(1)	(4)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(1)	(4)

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Posture in home-cage [2, sitting or standing; 1, prone position or crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity]

Fur [2, normal; 1, soiled fur]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-1-4(continued). Detailed clinical observations of female rats

1,2-MD 300 mg/kg

Female No.	Open-field observations ^{a)}																		
	Urination									Defecation									
	Pre	a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c	Pre	T8	T15	T24	T30	T36	T42	T49	L
F04037	0	0	0	0	0	0	0			Non pregnant	0	0	0	0	0	0			Non pregnant
F04038	0	0	0	0	0	0	0			Non pregnant	0	0	0	0	0	0			Non pregnant
F04039	0	1	0	0	0	0			0	Total litter loss.	0	2	0	0	1	0			0 Total litter loss.
F04040	0	0	0	1	0	0			0	Total litter loss.	0	0	0	0	0	0			0 Total litter loss.
F04041	0	0	0	0	0	0				Total litter loss.	0	0	0	0	0	0			Total litter loss.
F04042	0	0	0	0	0	0				Total litter loss.	0	0	0	0	0	0			Total litter loss.
F04043	0	0	0	0	0	0			0		0	0	0	0	0	0			0
F04044	0	0	0	0	0	0			0	Total litter loss.	0	0	0	0	0	0			0 Total litter loss.
F04045	0	0	0	0	0	0	0			Non pregnant	0	0	0	0	0	0	0		Non pregnant
F04046	0	0	0	0	0	0	0	0	0	Non copulation	0	0	0	0	0	0	0	0	Non copulation
F04047	0	0	1	0	0	0	0	0		Non pregnant	0	0	0	0	0	0	0		Non pregnant
F04048	0	0	0	0	0	0				Total litter loss.	1	0	0	0	0	0			Total litter loss.
Total score	0	1	1	1	0	0	0	0	0		1	2	0	0	1	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(1)	(4)		(12)	(12)	(12)	(12)	(12)	(12)	(5)	(1)	(4)

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-2-1. Detailed clinical observations of female rats, satellite group

Control (vehicle: corn oil)

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}																			
	Fur										Straub tail										Pinna reflex									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14			
F05049	2	2	2	2	2	2	2			2	2	2	3	2	2	2			2	2	2	2	2	2	2					
F05050	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
F05051	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
F05052	2	2	2	2	2	2	2			2	2	2	3	2	2	2			2	2	2	2	2	2	2					
F05053	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
F05054	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F05055	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F05056	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F05057	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F05058	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:2	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0			
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)			

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Fur [2, normal; 1, soiled fur]

Straub tail [2, not observed; 3, tail elevation]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-2-1(continued). Detailed clinical observations of female rats, satellite group

Control (vehicle: corn oil)

Female No.	Open-field observations ^{c)}																	
	Urination									Defecation								
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F05049	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05050	0	1	0	0	1	0	0			0	0	0	0	0	0	0		
F05051	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05052	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05053	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05054	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05055	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05056	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05057	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05058	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomotor activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-2-2. Detailed clinical observations of female rats, satellite group

1,2-MD 300 mg/kg

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}																			
	Fur										Straub tail										Pinna reflex									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14			
F06059	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	1	1	1	1					
F06060	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	1	1	1	1					
F06061	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	1	2	1	1					
F06062	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	1	1	1					
F06063	2	2	1	2	2	2	2			2	2	2	2	2	2	2			2	2	2	1	2	1	1					
F06064	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F06065	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	2			
F06066	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2			
F06067	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2			
F06068	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2			
Total score	1:0	1:0	1:1	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:8	1:7	1:9	1:8	1:0	1:0			
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)			

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Fur [2, normal; 1, soiled fur]

Straub tail [2, not observed; 3, tail elevation]

Pinna reflex [2, normal; 1, hyporeflexia]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 6-2-2(continued). Detailed clinical observations of female rats, satellite group

1,2-MD 300 mg/kg

Female No.	Open-field observations ^{c)}																			
	Urination										Defecation									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14		Pre	T8	T15	T24	T30	T36	T42	R7	R14	
F06059	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
F06060	0	1	0	0	0	0	0				0	0	0	0	0	0	0			
F06061	0	0	0	1	0	1	1				0	0	0	0	0	0	0			
F06062	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
F06063	0	0	0	0	0	0	1				0	0	0	0	0	0	0			
F06064	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
F06065	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
F06066	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
F06067	0	0	0	0	0	0	0	1	0		0	0	0	0	0	0	0	0	0	
F06068	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
Total score	0	1	0	1	0	1	2	1	0		0	0	0	0	0	0	0	0	0	
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)		(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomotor activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 7-1-1. Body weights of male rats

Control (vehicle: corn oil)								
Male No.	Days of administration							
	1	3	7	14	21	28	35	42
M01001	375.2	386.1	399.9	417.6	428.7	445.8	459.3	463.3
M01002	405.3	412.9	428.8	458.3	479.0	506.3	534.1	542.7
M01003	394.3	401.0	412.0	436.4	455.4	475.8	504.2	515.9
M01004	386.1	397.9	416.1	445.5	466.5	494.8	522.8	533.3
M01005	392.7	398.5	415.3	427.9	454.7	473.5	490.4	503.8
M01006	401.3	408.9	417.1	441.4	449.4	487.6	500.3	522.4
M01007	406.1	422.0	443.7	475.6	503.1	534.9	561.1	583.0
M01008	372.3	380.3	392.7	414.7	430.3	447.8	464.3	484.9
M01009	371.6	374.5	385.2	402.0	425.8	440.9	455.6	460.3
M01010	407.7	414.1	423.8	453.2	474.5	495.2	519.6	533.2
M01011	407.1	421.2	438.3	470.1	493.3	529.4	548.1	576.1
M01012	386.0	395.0	410.5	426.0	433.5	449.4	466.7	479.2
Number of males	12	12	12	12	12	12	12	12
Mean	392.1	401.0	415.3	439.1	457.9	481.8	502.2	516.5
S.D.	13.8	15.5	17.3	22.7	26.0	32.1	35.9	40.2

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 7-1-2. Body weights of male rats

1,2-MD 30 mg/kg

Male No.	Days of administration							
	1	3	7	14	21	28	35	42
M02013	393.5	397.3	417.6	437.9	472.9	506.3	523.6	538.5
M02014	398.0	407.6	423.6	437.5	462.2	490.1	498.8	517.8
M02015	414.1	423.7	444.0	467.8	490.7	513.7	531.7	543.8
M02016	405.7	411.5	420.9	445.2	462.9	493.1	508.8	524.3
M02017	422.9	427.9	433.9	469.0	485.9	516.4	529.2	539.8
M02018	395.2	412.8	426.3	444.2	463.0	483.5	492.6	504.7
M02019	369.7	373.2	375.5	387.6	407.8	426.9	437.6	455.9
M02020	380.4	384.5	401.2	424.4	445.2	469.4	486.8	495.5
M02021	386.6	396.3	406.2	423.7	430.8	448.5	457.7	474.8
M02022	370.6	372.0	386.8	408.4	421.5	438.9	457.7	472.5
M02023	395.3	411.4	424.7	440.6	454.0	477.2	480.3	494.7
M02024	388.7	394.9	408.1	425.1	445.4	469.3	478.3	491.5
Number of males	12	12	12	12	12	12	12	12
Mean	393.4	401.1	414.1	434.3	453.5	477.8	490.3	504.5
S.D.	15.9	18.1	19.5	22.9	24.9	28.8	30.0	28.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	AN	DU	DU	DU	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 7-1-3. Body weights of male rats

1,2-MD 100 mg/kg								
Male No.	Days of administration							
	1	3	7	14	21	28	35	42
M03025	384.1	382.5	390.9	413.4	437.6	463.8	482.8	499.7
M03026	392.5	394.1	405.7	435.4	451.7	475.1	487.6	493.2
M03027	361.1	367.3	376.7	400.5	420.2	448.5	471.1	469.9
M03028	390.2	393.2	415.5	442.7	455.9	482.2	507.3	521.9
M03029	408.6	413.3	427.3	444.7	463.6	491.2	507.0	499.3
M03030	378.9	376.3	391.7	417.3	436.8	455.3	478.4	500.3
M03031	368.0	368.7	379.0	398.1	419.6	435.5	455.0	468.8
M03032	404.8	413.3	431.7	453.7	467.5	496.3	511.1	527.6
M03033	394.9	402.7	416.5	438.3	444.3	470.8	484.1	499.4
M03034	402.2	409.4	422.2	447.4	465.2	484.1	502.5	533.9
M03035	396.4	404.4	417.9	448.7	470.4	499.5	526.9	548.1
M03036	397.2	402.4	412.0	430.5	449.2	466.9	485.3	503.2
Number of males	12	12	12	12	12	12	12	12
Mean	389.9	394.0	407.3	430.9	448.5	472.4	491.6	505.4
S.D.	14.5	16.6	18.5	19.1	17.4	19.6	19.9	23.9
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	AN	DU	DU	DU	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 7-1-4. Body weights of male rats

1,2-MD 300 mg/kg

Male No.	Days of administration							
	1	3	7	14	21	28	35	42
M04037	376.7	373.8	373.8	388.8	400.4	408.0	426.8	442.0
M04038	408.8	401.1	411.8	423.5	426.1	440.7	444.4	477.5
M04039	414.1	411.3	413.2	441.2	455.0	472.3	494.1	505.7
M04040	380.5	375.0	387.4	409.7	411.0	441.2	469.7	483.2
M04041	389.8	381.3	388.7	408.7	423.1	436.1	463.7	487.4
M04042	402.7	385.9	400.7	433.8	448.1	473.8	485.6	500.6
M04043	366.1	368.1	381.6	400.6	421.2	439.8	465.4	475.4
M04044	400.5	396.1	403.4	424.1	451.0	471.0	500.2	521.5
M04045	385.5	379.3	393.2	398.6	400.2	415.3	432.4	449.8
M04046	404.9	391.7	401.0	433.1	407.4	397.9	456.7	480.4
M04047	367.0	370.7	381.4	407.9	420.5	442.4	457.7	480.3
M04048	408.7	403.6	410.8	439.1	449.5	472.5	483.6	506.9
Number of males	12	12	12	12	12	12	12	12
Mean	392.1	386.5	395.6	417.4	426.1	442.6	465.0	484.2
S.D.	16.8	14.1	13.2	17.4	20.1	26.2	23.3	22.9
Significance	NS	NS	*	NS	**	**	**	NS
Statistical method	AN	AN	DU	AN	DU	DU	DU	AN

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 7-2-1. Body weights of male rats at the recovery period

Control (vehicle: corn oil)			
Male No.	Days of recovery period		
	1	7	14
M01008	487.6	497.6	501.0
M01009	463.7	470.0	483.7
M01010	530.4	546.6	556.5
M01011	577.9	591.0	607.4
M01012	478.0	507.3	510.7
Number of males	5	5	5
Mean	507.5	522.5	531.9
S.D.	46.5	47.1	50.1

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 7-2-2. Body weights of male rats at the recovery period

1,2-MD 300 mg/kg

Male No.	Days of recovery period		
	1	7	14
M04044	521.9	540.6	561.4
M04045	458.5	478.5	501.3
M04046	481.7	513.3	527.5
M04047	481.7	509.6	523.0
M04048	504.2	534.4	550.1
Number of males	5	5	5
Mean	489.6	515.3	532.7
S.D.	24.2	24.5	23.6
Significance	NS	NS	NS
Statistical method	TT	TT	TT

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 8-1-1. Body weights of female rats

Control (vehicle: corn oil)									
Female No.	Days of administration								
	1	3	7	14	21	28	35	42	49
F01001	252.7	247.4	245.1	264.4					
F01002	232.6	238.6	238.5	244.1					
F01003	248.6	249.1	256.1	261.6					
F01004	255.2	247.7	250.8	266.1					
F01005	270.2	272.8	280.2	285.0					
F01006	245.4	247.9	259.8	258.4					
F01007	242.4	252.0	258.7	264.9					
F01008	250.8	255.1	260.6	264.7					
F01009	232.8	224.8	230.3	242.7					
F01010	253.2	261.3	266.7	278.7					
F01011	267.9	273.2	280.8	298.2					
F01012	255.5	264.3	270.9	278.8					
Number of females	12	12	12	12					
Mean	250.6	252.9	258.2	267.3					
S.D.	11.6	13.8	15.5	16.0					

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 8-1-2. Body weights of female rats

1,2-MD 30 mg/kg

Female No.	Days of administration								
	1	3	7	14	21	28	35	42	49
F02013	263.2	264.9	271.7	283.7					
F02014	265.2	269.1	279.6	289.7					
F02015	238.5	240.0	239.2	234.7					
F02016	245.6	254.2	257.4	270.3					
F02017	231.1	241.2	250.3	260.7					
F02018	262.0	273.2	283.7	294.7					
F02019	259.7	265.2	267.3	270.9					
F02020	239.3	246.5	252.1	258.9					
F02021	265.0	264.2	278.5	286.8					
F02022	227.8	238.0	239.8	235.4					
F02023	250.8	258.4	268.0	283.6					
F02024	242.4	250.6	259.5	267.5					
Number of females	12	12	12	12					
Mean	249.2	255.5	262.3	269.7					
S.D.	13.6	12.1	15.0	19.8					
Significance	NS	NS	NS	NS	---	---	---	---	---
Statistical method	AN	AN	DU	AN	NA	NA	NA	NA	NA

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 8-1-3. Body weights of female rats

1,2-MD 100 mg/kg

Female No.	Days of administration								
	1	3	7	14	21	28	35	42	49
F03025	255.7	251.6	251.4	268.8					
F03026	252.3	259.8	264.0	266.3					
F03027	261.3	271.4	271.3	281.4					
F03028	240.3	235.5	240.1	257.3					
F03029	260.8	260.5	267.9	285.2					
F03030	248.3	251.2	256.6	263.4					
F03031	267.0	273.0	276.2	283.7					
F03032	254.7	258.3	262.2	271.4					
F03033	242.8	251.1	254.0	264.7					
F03034	235.7	240.9	242.3	250.7					
F03035	259.5	258.0	263.4	263.9					
F03036	256.4	258.2	263.1	267.6					
Number of females	12	12	12	12					
Mean	252.9	255.8	259.4	268.7					
S.D.	9.4	10.8	11.0	10.4					
Significance	NS	NS	NS	NS	---	---	---	---	---
Statistical method	AN	AN	DU	AN	NA	NA	NA	NA	NA

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 8-1-4. Body weights of female rats

1,2-MD 300 mg/kg

Female No.	Days of administration								
	1	3	7	14	21	28	35	42	49
F04037	257.8	246.7	251.6	255.3					
F04038	261.3	250.7	252.7	254.3					
F04039	238.0	237.9	239.5	243.5					
F04040	235.6	237.5	236.6	239.9					
F04041	237.3	245.6	246.5	256.0					
F04042	258.8	259.5	249.5	269.2					
F04043	251.3	251.2	262.0	262.8					
F04044	234.7	238.0	237.1	245.6	252.4				
F04045	264.3	257.5	222.3	258.1					
F04046	249.7	249.7	246.4	260.4	263.8	285.6	276.7	297.1	293.4
F04047	244.4	236.4	238.8	255.3					
F04048	269.6	266.7	271.4	280.1					
Number of females	12	12	12	12					
Mean	250.2	248.1	246.2	256.7					
S.D.	12.2	9.8	12.8	11.1					
Significance	NS	NS	NS	NS	---	---	---	---	---
Statistical method	AN	AN	DU	AN	NA	NA	NA	NA	NA

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 8-2-1. Body weights of female rats, satellite group

Control (vehicle: corn oil)								
Female No.	Days of administration							
	1	3	7	14	21	28	35	42
F05049	259.2	257.4	262.5	266.1	281.9	292.1	296.1	305.7
F05050	250.8	260.1	268.9	289.3	297.7	307.8	311.5	327.0
F05051	267.6	265.2	272.2	289.1	298.0	300.5	302.9	308.7
F05052	251.7	264.1	271.7	276.6	293.5	290.9	287.0	298.1
F05053	244.3	248.0	254.3	269.1	277.1	279.7	285.0	290.9
F05054	242.2	256.5	260.4	265.1	285.7	295.5	291.2	294.8
F05055	246.1	250.9	261.3	272.5	286.0	313.6	324.5	324.4
F05056	262.2	265.5	282.7	285.9	304.7	307.1	310.4	314.1
F05057	236.2	232.7	247.0	262.2	277.6	276.6	281.0	291.9
F05058	248.0	260.8	275.1	283.6	287.5	307.2	315.5	314.9
Number of females	10	10	10	10	10	10	10	10
Mean	250.8	256.1	265.6	276.0	289.0	297.1	300.5	307.1
S.D.	9.7	10.1	10.6	10.4	9.2	12.4	14.7	13.1

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 8-2-2. Body weights of female rats, satellite group

1,2-MD 300 mg/kg

Female No.	Days of administration							
	1	3	7	14	21	28	35	42
F06059	262.9	265.0	251.7	266.7	275.8	280.4	285.6	286.9
F06060	262.2	269.9	270.6	276.1	291.0	300.6	287.3	299.4
F06061	250.4	250.7	255.1	256.1	264.5	273.1	276.7	276.4
F06062	253.0	245.8	243.2	258.0	269.0	278.6	282.3	292.3
F06063	243.9	242.8	242.3	247.9	257.0	261.3	259.3	271.7
F06064	250.2	259.3	264.6	273.1	280.4	281.5	289.5	285.8
F06065	255.3	244.8	244.4	248.8	255.8	256.5	267.6	264.4
F06066	248.0	247.4	251.5	259.8	266.3	273.0	282.5	281.0
F06067	241.9	240.4	240.5	243.6	248.1	251.9	257.9	274.6
F06068	242.1	244.3	249.8	258.7	269.4	276.0	284.8	290.7
Number of females	10	10	10	10	10	10	10	10
Mean	251.0	251.0	251.4	258.9	267.7	273.3	277.4	282.3
S.D.	7.5	10.1	9.9	10.7	12.6	14.1	11.6	10.7
Significance	NS	NS	**	**	**	**	**	**
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 8-3-1. Body weights of female rats at the recovery period

Control (vehicle: corn oil)

Female No.	Days of recovery period		
	1	7	14
F05054	294.8	307.8	304.4
F05055	319.6	328.0	315.7
F05056	314.9	321.1	332.0
F05057	290.7	308.2	306.5
F05058	317.8	316.6	326.1
Number of females	5	5	5
Mean	307.6	316.3	316.9
S.D.	13.7	8.6	12.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 8-3-2. Body weights of female rats at the recovery period

1,2-MD 300 mg/kg

Female No.	Days of recovery period		
	1	7	14
F06064	291.6	303.3	308.8
F06065	268.5	283.6	281.4
F06066	282.6	285.1	280.5
F06067	277.1	278.5	286.8
F06068	288.8	301.0	310.9
Number of females	5	5	5
Mean	281.7	290.3	293.7
S.D.	9.3	11.1	15.0
Significance	**	**	*
Statistical method	TT	TT	TT

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 9-1. Body weights of dams during pregnancy

Control (vehicle: corn oil)					
Dam No.	Days of pregnancy				
	0	7	14	20	26
F01001	275.6	305.2	336.6	412.6	
F01002	247.8	274.8	304.8	390.1	
F01003	282.8	328.7	371.5	443.4	
F01004	274.6	309.4	340.6	423.7	
F01005	300.9	347.8	390.8	481.6	
F01006	260.0	304.0	333.2	427.7	
F01007	285.4	305.6	339.8	425.2	
F01008	278.1	310.2	348.8	435.3	
F01009	252.1	292.5	329.8	423.4	
F01010	284.9	325.1	376.9	452.0	
F01011	302.4	324.1	364.1	431.1	
F01012	288.5	314.1	348.0	422.9	
Number of dams	12	12	12	12	
Mean	277.8	311.8	348.7	430.8	
S.D.	17.3	18.6	23.6	22.2	

>: Excluded from analysis (not pregnant)

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 9-2. Body weights of dams during pregnancy

1,2-MD 30 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F02013	281.2	323.1	362.0	448.6	
F02014	306.3	330.6	373.3	453.4	
F02015	250.1	285.1	318.0	379.7	
F02016	272.7	308.1	346.1	433.4	
F02017	273.4	305.8	343.4	408.5	
F02018	309.9	324.9	356.2	433.4	
F02019	> 284.4	> 312.7	> 336.1	> 314.3	> 316.2
F02020	269.8	304.2	339.6	417.8	
F02021	293.8	330.1	368.1	442.8	
F02022	254.8	289.8	333.4	421.5	
F02023	283.4	324.0	367.8	441.5	
F02024	273.2	318.1	359.5	452.9	
Number of dams	11	11	11	11	
Mean	279.0	313.1	351.6	430.3	
S.D.	18.9	15.7	17.0	22.2	
Significance	NS	NS	NS	NS	---
Statistical method	AN	DU	DU	DU	NA

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 9-3. Body weights of dams during pregnancy

1,2-MD 100 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F03025	279.8	308.0	332.2	406.7	
F03026	276.9	316.9	347.6	430.5	
F03027	290.5	319.2	349.7	423.0	
F03028	275.1	308.4	343.5	425.8	
F03029	288.6	312.9	351.1	426.8	
F03030	275.0	298.3	322.9	387.6	
F03031	292.7	317.9	356.0	442.5	
F03032	> 272.3 >	319.0 >	334.6 >	296.0 >	300.9
F03033	262.7	304.1	338.1	416.8	
F03034	264.5	298.5	328.6	404.1	
F03035	280.7	314.1	342.6	417.9	
F03036	> 275.9 >	290.6 >	295.6 >	302.8 >	302.4
Number of dams	10	10	10	10	
Mean	278.7	309.8	341.2	418.2	
S.D.	10.1	7.7	10.7	15.5	
Significance	NS	NS	NS	NS	---
Statistical method	AN	DU	DU	DU	NA

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 9-4. Body weights of dams during pregnancy

1,2-MD 300 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F04037	> 264.3	> 276.8	> 276.5	> 279.7	> 285.2
F04038	> 258.9	> 266.6	> 272.3	> 266.5	> 276.8
F04039	248.6	281.8	305.7	357.8	
F04040	250.0	283.9	309.3	374.3	
F04041	253.2	283.9	304.7	373.5	
F04042	271.2	301.4	320.0	378.4	
F04043	272.7	307.0	344.3	401.2	
F04044	261.9	289.6	316.1	401.0	
F04045	> 274.6	> 307.5	> 330.9	> 320.6	> 313.8
F04047	> 272.2	> 296.2	> 290.3	> 283.6	> 283.5
F04048	276.5	306.5	325.0	397.0	
Number of dams	7	7	7	7	
Mean	262.0	293.4	317.9	383.3	
S.D.	11.6	11.2	13.9	16.7	
Significance	NS	*	**	**	---
Statistical method	AN	DU	DU	DU	NA

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 10-1. Body weights of dams during lactation

Control (vehicle: corn oil)		
Dam No.	Days of lactation	
	0	4
F01001	303.0	325.0
F01002	302.3	287.7
F01003	358.9	370.6
F01004	329.9	350.3
F01005	396.0	376.5
F01006	290.3	328.1
F01007	323.0	320.8
F01008	329.2	338.0
F01009	299.4	314.7
F01010	368.2	352.5
F01012	335.1	353.6
Number of dams	11	11
Mean	330.5	338.0
S.D.	32.8	26.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 10-2. Body weights of dams during lactation

1,2-MD 30 mg/kg		
Dam No.	Days of lactation	
	0	4
F02013	351.7	350.9
F02014	341.3	365.4
F02015	269.9	294.0
F02016	327.7	343.5
F02017	343.3	352.5
F02018	328.9	353.6
F02020	296.8	326.9
F02021	322.2	348.9
F02022	300.5	338.1
F02023	339.9	351.2
F02024	338.5	347.9
Number of dams	11	11
Mean	323.7	343.0
S.D.	24.8	18.9
Significance	NS	NS
Statistical method	KW	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

AN: Analysis by variance (one-way layout).

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 10-3. Body weights of dams during lactation

1,2-MD 100 mg/kg

Dam No.	Days of lactation	
	0	4
F03025	305.8	322.8
F03026	332.6	346.6
F03027	313.9	341.5
F03028	299.1	Total litter loss
F03029	321.6	344.8
F03030	286.6	320.2
F03031	315.1	Total litter loss
F03033	320.2	340.0
F03034	314.2	341.1
F03035	327.0	355.6
Number of dams	10	8
Mean	313.6	339.1
S.D.	13.5	11.9
Significance	NS	NS
Statistical method	KW	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

AN: Analysis by variance (one-way layout).

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 10-4. Body weights of dams during lactation

1,2-MD 300 mg/kg

Dam No.	Days of lactation	
	0	4
F04039	289.9	Total litter loss
F04040	283.4	Total litter loss
F04041	314.8	Total litter loss
F04042	313.2	Total litter loss
F04043	314.0	307.2
F04044	301.6	Total litter loss
F04048	303.4	Total litter loss
Number of dams	7	1
Mean	302.9	307.2
S.D.	12.4	
Significance	NS	---
Statistical method	KW	NA

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 11-1-1. Food consumption of male rats

Control (vehicle: corn oil)

Male No.	Days of administration					
	1	7	14	29	35	41
M01001	21.0	19.2	17.0	18.8	18.0	18.3
M01002	26.5	23.9	22.3	26.4	23.8	25.4
M01003	27.6	23.7	21.4	21.4	22.5	23.6
M01004	23.0	25.0	23.9	24.3	23.2	21.8
M01005	21.0	21.3	21.7	22.7	23.3	22.0
M01006	22.5	20.1	18.4	23.0	24.3	22.5
M01007	27.6	24.0	23.0	27.6	23.6	24.3
M01008	20.7	20.6	21.4	22.0	22.9	23.2
M01009	20.0	20.3	19.3	20.8	19.9	20.1
M01010	23.7	26.6	21.1	27.3	26.3	21.8
M01011	29.3	25.7	26.5	26.3	26.5	25.3
M01012	26.4	20.6	22.0	21.5	22.2	22.4
Number of males	12	12	12	12	12	12
Mean	24.1	22.6	21.5	23.5	23.0	22.6
S.D.	3.2	2.5	2.5	2.8	2.4	2.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 11-1-2. Food consumption of male rats

1,2-MD 30 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02013	21.6	21.4	23.8	26.1	21.9	23.0
M02014	28.2	30.3	24.8	25.9	19.5	22.8
M02015	27.6	28.5	24.4	23.5	24.6	24.3
M02016	27.2	24.0	27.7	27.8	25.9	25.1
M02017	24.2	25.2	26.5	26.9	23.1	24.4
M02018	24.7	26.5	24.1	21.8	21.5	21.5
M02019	19.9	19.1	16.2	20.1	18.9	21.1
M02020	24.0	23.6	22.2	23.8	21.1	21.0
M02021	26.0	23.1	19.3	21.6	22.0	23.5
M02022	23.9	21.7	23.4	21.9	23.1	23.7
M02023	26.6	23.5	20.0	23.4	19.1	19.6
M02024	24.6	22.7	20.0	20.3	19.9	23.6
Number of males	12	12	12	12	12	12
Mean	24.9	24.1	22.7	23.6	21.7	22.8
S.D.	2.4	3.1	3.3	2.6	2.2	1.7
Significance	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	DU	DU

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 11-1-3. Food consumption of male rats

1,2-MD 100 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03025	18.8	18.0	21.2	23.3	24.3	22.5
M03026	23.3	23.9	22.6	23.7	25.0	21.3
M03027	22.5	21.8	25.0	23.9	22.8	22.0
M03028	20.1	24.1	23.3	27.5	25.1	22.9
M03029	22.5	24.5	23.7	20.5	22.4	22.1
M03030	25.0	23.8	25.0	24.6	22.3	24.7
M03031	21.7	18.6	20.2	19.0	22.0	21.6
M03032	25.3	24.8	23.9	20.6	23.8	24.7
M03033	23.3	21.6	20.6	20.2	22.9	20.5
M03034	27.8	24.4	23.5	23.2	23.9	23.4
M03035	26.8	27.4	23.2	28.2	26.8	25.9
M03036	25.4	24.3	21.4	23.0	21.1	22.2
Number of males	12	12	12	12	12	12
Mean	23.5	23.1	22.8	23.1	23.5	22.8
S.D.	2.7	2.7	1.6	2.8	1.6	1.6
Significance	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	DU	DU

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 11-1-4. Food consumption of male rats

1,2-MD 300 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04037	21.4	14.0	18.2	20.4	20.9	24.2
M04038	27.7	21.0	20.2	20.5	20.9	28.1
M04039	22.3	22.2	21.2	26.3	27.6	25.2
M04040	17.9	21.4	24.8	25.4	23.5	25.3
M04041	17.9	21.3	22.4	21.3	25.3	25.4
M04042	16.7	23.8	22.3	22.3	23.9	24.7
M04043	21.6	23.8	23.6	23.8	25.8	26.7
M04044	24.5	18.3	27.4	24.3	26.5	25.8
M04045	21.3	22.8	21.0	20.1	23.2	22.9
M04046	18.9	21.9	22.4	25.2	29.4	27.2
M04047	26.1	23.8	23.1	21.4	23.1	23.2
M04048	26.5	24.0	26.7	25.3	25.0	28.5
Number of males	12	12	12	12	12	12
Mean	21.9	21.5	22.8	23.0	24.6	25.6
S.D.	3.7	2.9	2.6	2.3	2.5	1.8
Significance	NS	NS	NS	NS	NS	**
Statistical method	AN	AN	AN	AN	DU	DU

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 11-2-1. Food consumption of male rats at the recovery period

Control (vehicle: corn oil)		
Male No.	Days of recovery period	
	6	12
M01008	25.1	28.6
M01009	22.9	23.8
M01010	27.0	28.3
M01011	26.8	32.8
M01012	29.8	33.4
Number of males	5	5
Mean	26.3	29.4
S.D.	2.5	3.9

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 11-2-2. Food consumption of male rats at the recovery period

1,2-MD 300 mg/kg

Male No.	Days of recovery period	
	6	12
M04044	33.9	36.8
M04045	27.1	30.8
M04046	32.1	30.4
M04047	28.9	26.2
M04048	31.9	34.8
Number of males	5	5
Mean	30.8	31.8
S.D.	2.7	4.1
Significance	*	NS
Statistical method	TT	TT

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 12-1-1. Food consumption of female rats

Control (vehicle: corn oil)

Female No.	Days of administration						
	1	7	14	29	35	41	48
F01001	18.8	16.8	8.4				
F01002	15.2	17.0	18.6				
F01003	15.1	18.8	17.4				
F01004	18.4	17.3	9.7				
F01005	15.5	20.3	17.7				
F01006	13.9	17.2	15.9				
F01007	15.8	19.5	18.0				
F01008	14.0	19.1	17.7				
F01009	16.3	15.7	13.3				
F01010	18.8	11.6	19.7				
F01011	11.3	19.5	19.3				
F01012	20.1	18.2	19.1				
Number of females	12	12	12				
Mean	16.1	17.6	16.2				
S.D.	2.5	2.3	3.8				

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 12-1-2. Food consumption of female rats

1,2-MD 30 mg/kg

Female No.	Days of administration						
	1	7	14	29	35	41	48
F02013	17.3	11.8	17.3				
F02014	18.8	19.3	19.7				
F02015	10.3	14.2	13.8				
F02016	16.0	15.9	16.5				
F02017	17.6	17.5	19.6				
F02018	21.1	18.8	20.9				
F02019	18.5	15.2	15.8				
F02020	19.3	12.1	16.1				
F02021	22.3	15.0	20.2				
F02022	18.1	15.1	15.7				
F02023	21.2	14.7	19.2				
F02024	19.8	14.9	17.4				
Number of females	12	12	12				
Mean	18.4	15.4	17.7				
S.D.	3.1	2.3	2.2				
Significance	NS	NS	NS	---	---	---	---
Statistical method	AN	DT	AN	NA	NA	NA	NA

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 12-1-3. Food consumption of female rats

1,2-MD 100 mg/kg

Female No.	Days of administration						
	1	7	14	29	35	41	48
F03025	16.9	17.8	11.3				
F03026	15.3	18.3	18.0				
F03027	20.7	16.7	18.9				
F03028	14.6	14.8	14.9				
F03029	19.8	16.5	19.9				
F03030	12.2	15.9	16.7				
F03031	19.2	19.4	17.6				
F03032	17.7	12.8	17.4				
F03033	20.5	12.9	17.8				
F03034	19.6	12.9	17.5				
F03035	13.4	18.2	15.1				
F03036	14.2	16.7	12.2				
Number of females	12	12	12				
Mean	17.0	16.1	16.4				
S.D.	3.0	2.3	2.6				
Significance	NS	NS	NS	---	---	---	---
Statistical method	AN	DT	AN	NA	NA	NA	NA

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 12-1-4. Food consumption of female rats

1,2-MD 300 mg/kg

Female No.	Days of administration						
	1	7	14	29	35	41	48
F04037	15.4	12.0	18.1				
F04038	17.3	13.5	14.2				
F04039	17.1	16.7	17.8				
F04040	13.0	11.2	15.8				
F04041	16.4	17.4	15.8				
F04042	18.3	7.0	21.1				
F04043	16.9	16.6	18.5				
F04044	15.7	15.1	16.4				
F04045	17.8	0.0 #	31.4				
F04046	15.0	18.3	16.2	19.4	16.0	21.9	16.4
F04047	19.6	15.7	20.6				
F04048	18.6	20.0	20.6				
Number of females	12	12	12				
Mean	16.8	13.6	18.9				
S.D.	1.8	5.6	4.5				
Significance	NS	*	NS	---	---	---	---
Statistical method	AN	DT	AN	NA	NA	NA	NA

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

NA: Not analyzed.

#, Expressed as "0.0" because the food consumption indicated a negative value.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 12-2-1. Food consumption of female rats, satellite group

Control (vehicle: corn oil)

Female No.	Days of administration						
	1	7	14	21	29	35	41
F05049	15.4	17.2	19.0	11.2	11.5	21.5	20.4
F05050	18.0	16.7	19.9	16.5	16.8	18.3	19.5
F05051	16.9	17.4	13.7	15.4	17.1	16.3	15.4
F05052	20.0	18.8	13.2	17.2	18.9	19.9	17.7
F05053	20.3	15.5	18.5	18.0	16.7	15.2	19.1
F05054	17.8	19.6	16.2	15.6	16.4	17.9	12.7
F05055	15.8	24.1	20.9	13.7	17.8	18.0	20.3
F05056	22.4	21.7	22.1	17.9	19.3	22.0	17.4
F05057	21.2	19.3	12.1	16.3	16.5	18.1	19.2
F05058	19.5	19.8	21.3	16.7	17.5	19.2	19.2
Number of females	10	10	10	10	10	10	10
Mean	18.7	19.0	17.7	15.9	16.9	18.6	18.1
S.D.	2.3	2.5	3.6	2.1	2.1	2.1	2.4

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 12-2-2. Food consumption of female rats, satellite group

1,2-MD 300 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06059	14.3	9.2	18.5	18.1	17.1	20.3	16.7
F06060	19.8	20.2	20.6	9.6	14.8	15.8	18.5
F06061	16.0	16.9	20.4	9.1	10.7	20.9	16.7
F06062	14.9	13.0	17.9	14.1	15.9	15.9	20.7
F06063	12.5	16.5	13.0	13.7	15.7	16.6	14.7
F06064	20.6	19.3	14.3	16.5	19.5	17.6	13.5
F06065	14.1	16.3	17.4	13.9	15.1	16.9	16.5
F06066	19.5	15.2	16.6	14.5	17.8	18.8	18.7
F06067	16.0	15.0	9.9	12.4	16.1	19.5	21.9
F06068	23.1	18.0	18.1	18.4	18.2	20.3	21.2
Number of females	10	10	10	10	10	10	10
Mean	17.1	16.0	16.7	14.0	16.1	18.3	17.9
S.D.	3.4	3.2	3.4	3.1	2.4	1.9	2.8
Significance	NS	*	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 12-3-1. Food consumption of female rats at the recovery period

Control (vehicle: corn oil)		
Female No.	Days of recovery period	
	6	12
F05054	19.6	18.5
F05055	19.0	20.1
F05056	18.4	15.8
F05057	19.9	15.7
F05058	15.1	20.8
Number of females	5	5
Mean	18.4	18.2
S.D.	1.9	2.4

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 12-3-2. Food consumption of female rats at the recovery period

1,2-MD 300 mg/kg

Female No.	Days of recovery period	
	6	12
F06064	23.7	21.7
F06065	21.3	15.5
F06066	16.7	19.1
F06067	15.7	21.9
F06068	21.1	24.6
Number of females	5	5
Mean	19.7	20.6
S.D.	3.4	3.4
Significance	NS	NS
Statistical method	TT	TT

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 13-1. Food consumption in dams during pregnancy

Control (vehicle: corn oil)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	16.2	25.0	23.0	10.7
F01002	11.3	20.2	20.3	18.9
F01003	18.5	24.4	22.3	26.9
F01004	14.8	21.2	21.2	20.6
F01005	20.9	28.1	25.9	19.3
F01006	18.1	19.8	17.1	17.1
F01007	15.8	19.8	20.9	4.4
F01008	15.7	22.7	24.5	24.0
F01009	14.0	20.8	20.4	17.4
F01010	21.0	30.1	23.8	22.3
F01011	13.7	22.8	20.9	1.5
F01012	16.3	21.3	21.0	22.0
Number of dams	12	12	12	12
Mean	16.4	23.0	21.8	17.1
S.D.	2.9	3.3	2.3	7.8

>: Excluded from analysis (not pregnant)

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 13-2. Food consumption in dams during pregnancy

1,2-MD 30 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	20.8	22.7	25.1	24.1
F02014	15.4	20.8	21.8	24.5
F02015	17.3	24.7	17.1	20.0
F02016	14.3	22.8	23.9	18.7
F02017	17.6	25.0	25.7	24.4
F02018	17.4	23.0	25.5	25.0
F02019	> 17.4	> 20.8	> 18.1	> 15.3
F02020	17.2	20.8	21.7	8.2
F02021	18.1	25.8	21.5	19.4
F02022	14.8	20.1	26.0	15.9
F02023	21.3	23.2	25.7	20.5
F02024	15.7	24.3	28.6	21.3
Number of dams	11	11	11	11
Mean	17.3	23.0	23.9	20.2
S.D.	2.2	1.9	3.1	4.9
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 13-3. Food consumption in dams during pregnancy

1,2-MD 100 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03025	17.0	23.3	18.1	17.7
F03026	22.7	23.7	23.6	18.8
F03027	16.7	22.9	23.0	15.5
F03028	19.1	22.4	21.7	10.9
F03029	17.4	24.1	27.1	18.1
F03030	14.4	28.1	18.3	11.3
F03031	17.2	21.5	20.0	13.9
F03032	> 18.0	> 25.6	> 17.9	> 9.0
F03033	21.8	19.6	23.3	20.2
F03034	17.3	23.9	23.2	15.3
F03035	18.2	17.9	20.9	17.5
F03036	> 16.2	> 14.0	> 16.7	> 10.6
Number of dams	10	10	10	10
Mean	18.2	22.7	21.9	15.9
S.D.	2.5	2.8	2.7	3.1
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 13-4. Food consumption in dams during pregnancy

1,2-MD 300 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	> 19.8	> 16.7	> 19.8	> 19.4
F04038	> 18.1	> 10.9	> 14.9	> 17.4
F04039	18.4	24.4	20.9	16.9
F04040	22.5	21.9	21.7	24.0
F04041	21.7	19.6	23.0	22.5
F04042	19.1	22.3	18.1	20.3
F04043	18.5	20.6	28.3	6.1
F04044	14.1	19.3	24.9	23.1
F04045	> 21.9	> 23.6	> 19.3	> 14.7
F04047	> 21.0	> 24.7	> 19.7	> 16.7
F04048	19.4	20.9	23.3	3.7
Number of dams	7	7	7	7
Mean	19.1	21.3	22.9	16.7
S.D.	2.7	1.8	3.2	8.4
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 14-1. Food consumption in dams during lactation

Control (vehicle: corn oil)

Dam No.	Days of lactation
	3
F01001	31.4
F01002	29.1
F01003	37.3
F01004	45.0
F01005	37.3
F01006	46.7
F01007	30.7
F01008	38.8
F01009	39.3
F01010	34.6
F01012	42.9
Number of dams	11
Mean	37.6
S.D.	5.8

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 14-2. Food consumption in dams during lactation

1,2-MD 30 mg/kg	
Dam No.	Days of lactation
	3
F02013	35.5
F02014	41.4
F02015	28.5
F02016	39.6
F02017	34.8
F02018	41.4
F02020	48.7
F02021	35.6
F02022	44.5
F02023	38.8
F02024	40.9
Number of dams	11
Mean	39.1
S.D.	5.4
Significance	NS
Statistical method	KW

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$)

NS: Not significantly different from the control group.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 14-3. Food consumption in dams during lactation

1,2-MD 100 mg/kg

Dam No.	Days of lactation
	3
F03025	32.1
F03026	36.5
F03027	34.5
F03028	4.6
F03029	39.9
F03030	38.1
F03031	12.4
F03033	34.2
F03034	30.9
F03035	35.8
Number of dams	10
Mean	29.9
S.D.	11.7
Significance	NS
Statistical method	KW

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$)

NS: Not significantly different from the control group.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 14-4. Food consumption in dams during lactation

1,2-MD 300 mg/kg

Dam No.	Days of lactation
	3
F04043	21.8
Number of dams	1
Mean	21.8
S.D.	
Significance	---
Statistical method	NA

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$)

NS: Not significantly different from the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 15-1. Functional findings of male rats

Control (vehicle: corn oil)

Male at the dosing period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M01001	2	2	2	2	+	+	+
M01002	2	2	2	2	+	+	+
M01003	2	2	2	2	+	+	+
M01004	2	2	2	2	+	+	+
M01005	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 15-2. Functional findings of male rats

1,2-MD 30 mg/kg

Male at the dosing period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M02013	2	2	2	2	+	+	+
M02014	2	2	2	2	+	+	+
M02015	2	2	2	2	+	+	+
M02016	2	2	2	2	+	+	+
M02017	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 15-3. Functional findings of male rats

1,2-MD 100 mg/kg

Male at the dosing period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M03025	2	2	2	2	+	+	+
M03026	2	2	2	2	+	+	+
M03027	2	2	2	2	+	+	+
M03028	2	2	2	2	+	+	+
M03029	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 15-4. Functional findings of male rats

1,2-MD 300 mg/kg

Male at the dosing period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M04037	2	2	2	2	+	+	+
M04038	2	2	2	2	+	+	+
M04039	2	2	2	2	+	+	+
M04040	2	2	2	1	+	+	+
M04041	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 4	+: 5	+: 5	+: 5

2 or +, normal

1, decrease of reflex/reaction

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 15-5. Functional findings of male rats

Control (vehicle: corn oil)

Male at the recovery period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M01008	2	2	2	2	+	+	+
M01009	2	2	2	2	+	+	+
M01010	2	2	2	2	+	+	+
M01011	2	2	2	2	+	+	+
M01012	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 15-6. Functional findings of male rats

1,2-MD 300 mg/kg

Male at the recovery period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M04044	2	2	2	2	+	+	+
M04045	2	2	2	2	+	+	+
M04046	2	2	2	2	+	+	+
M04047	2	2	2	2	+	+	+
M04048	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 16-1-1. Functional findings of female rats

Control (vehicle: corn oil)

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F01002	2	2	2	2	+	+	+
F01003	2	2	2	2	+	+	+
F01005	2	2	2	2	+	+	+
F01010	2	2	2	2	+	+	+
F01012	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 16-1-2. Functional findings of female rats

1,2-MD 30 mg/kg

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F02013	2	2	2	2	+	+	+
F02014	2	2	2	2	+	+	+
F02015	2	2	2	2	+	+	+
F02016	2	2	2	2	+	+	+
F02021	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 16-1-3. Functional findings of female rats

1,2-MD 100 mg/kg

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F03026	2	2	2	2	+	+	+
F03027	2	2	2	2	+	+	+
F03029	2	2	2	2	+	+	+
F03030	2	2	2	2	+	+	+
F03033	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 16-1-4. Functional findings of female rats

1,2-MD 300 mg/kg

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F04043	2	2	2	2	+	+	+
Total	2: 1	2: 1	2: 1	2: 1	2: 1	2: 1	2: 1

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 16-2-1. Functional findings of female rats, satellite group

Control (vehicle: corn oil)

Female, satellite group at the dosing period

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F05049	2	2	2	2	+	+	+
F05050	2	2	2	2	+	+	+
F05051	2	2	2	2	+	+	+
F05052	2	2	2	2	+	+	+
F05053	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 16-2-2. Functional findings of female rats, satellite group

1,2-MD 300 mg/kg

Female, satellite group at the dosing period

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F06059	2	2	2	2	+	+	+
F06060	2	2	2	2	+	+	+
F06061	2	2	2	2	+	+	+
F06062	2	2	2	2	+	+	+
F06063	2	2	2	1	+	+	+
Total	2: 5	2: 5	2: 5	2: 4	+: 5	+: 5	+: 5

2 or +, normal

1, decrease of reflex/reaction

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 16-2-3. Functional findings of female rats, satellite group

Control (vehicle: corn oil)

Female, satellite group at the recovery period

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F05054	2	2	2	2	+	+	+
F05055	2	2	2	2	+	+	+
F05056	2	2	2	2	+	+	+
F05057	2	2	2	2	+	+	+
F05058	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 16-2-4. Functional findings of female rats, satellite group

1,2-MD 300 mg/kg

Female, satellite group at the recovery period

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F06064	2	2	2	2	+	+	+
F06065	2	2	2	2	+	+	+
F06066	2	2	2	2	+	+	+
F06067	2	2	2	2	+	+	+
F06068	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 17. Assessment of grip strength of male rats

Control (vehicle: corn oil)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M01001	0.952	0.681
M01002	1.076	0.818
M01003	0.998	0.727
M01004	1.089	0.609
M01005	0.962	0.483
Number of males	5	5
Mean	1.015	0.664
S.D.	0.064	0.126

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

1,2-MD 30 mg/kg

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M02013	1.074	0.682
M02014	1.174	0.858
M02015	1.206	0.645
M02016	1.119	0.725
M02017	1.206	0.810
Number of males	5	5
Mean	1.156	0.744
S.D.	0.058	0.089

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

1,2-MD 100 mg/kg

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M03025	1.067	0.766
M03026	0.966	0.698
M03027	0.858	0.473
M03028	0.962	0.462
M03029	0.948	0.608
Number of males	5	5
Mean	0.960	0.601
S.D.	0.074	0.135

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

1,2-MD 300 mg/kg

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M04037	0.750	0.446
M04038	1.080	0.627
M04039	1.033	0.786
M04040	0.983	0.442
M04041	1.140	0.657
Number of males	5	5
Mean	0.997	0.592
S.D.	0.150	0.147

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 18. Assessment of grip strength of female rats

Control (vehicle: corn oil)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F01002	1.086	0.700
F01003	0.953	0.638
F01005	1.135	0.699
F01010	1.072	0.716
F01012	1.175	0.725
Number of females	5	5
Mean	1.084	0.696
S.D.	0.084	0.034

Significantly different from the control group (*: P<0.05, **: P<0.01).

1,2-MD 100 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F03026	1.206	0.652
F03027	1.096	0.519
F03029	1.173	0.686
F03030	1.150	0.796
F03033	1.036	0.793
Number of females	5	5
Mean	1.132	0.689
S.D.	0.067	0.115

Significantly different from the control group (*: P<0.05, **: P<0.01).

1,2-MD 30 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F02013	1.074	0.661
F02014	1.027	0.436
F02015	1.070	0.489
F02016	1.092	0.442
F02021	1.222	0.761
Number of females	5	5
Mean	1.097	0.558
S.D.	0.074	0.146

Significantly different from the control group (*: P<0.05, **: P<0.01).

1,2-MD 300 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F04043	1.112	0.647
Number of females	1	1
Mean	1.112	0.647
S.D.		

The group given 300 mg/kg of 1,2-MD was excluded from statistical analysis.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 19. Assessment of grip strength of female rats, satellite group

Corn oil (vehicle)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F05049	1.100	0.639
F05050	1.082	0.596
F05051	0.946	0.791
F05052	1.118	0.544
F05053	1.038	0.495
Number of females	5	5
Mean	1.057	0.613
S.D.	0.069	0.113

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

1,2-MD (300 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F06059	0.881	0.428
F06060	0.991	0.468
F06061	1.040	0.439
F06062	0.968	0.581
F06063	1.194	0.646
Number of females	5	5
Mean	1.015	0.512
S.D.	0.116	0.096

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 20-1. Motor activity of male rats

Control (vehicle: corn oil)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1153	1030	605	507	3295	33	30	10	12	85
M01002	1127	932	930	846	3835	25	16	19	15	75
M01003	1088	1086	827	760	3761	32	31	16	10	89
M01004	1212	836	824	560	3432	28	17	13	8	66
M01005	1185	1072	850	1026	4133	26	21	22	16	85
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1153	991	807	740	3691	29	23	16	12	80
S.D.	48	106	121	212	334	4	7	5	3	9

Male No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01008	975	863	970	805	3613	32	27	24	21	104
M01009	1255	1225	1055	831	4366	47	55	27	26	155
M01010	1015	971	820	422	3228	39	23	23	13	98
M01011	1113	921	820	797	3651	35	25	15	11	86
M01012	1122	1028	816	771	3737	27	26	20	22	95
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1096	1002	896	725	3719	36	31	22	19	108
S.D.	109	139	110	171	411	8	13	5	6	27

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 20-2. Motor activity of male rats

1,2-MD 30 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02013	1109	1083	1029	668	3889	49	32	35	6	122
M02014	1111	944	610	428	3093	34	24	11	10	79
M02015	1263	1173	987	895	4318	47	25	18	19	109
M02016	1202	1093	1075	895	4265	42	43	30	24	139
M02017	1212	970	893	481	3556	44	12	20	2	78
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1179	1053	919	673	3824	43	27	23	12	105
S.D.	67	94	185	221	512	6	11	10	9	27

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 20-3. Motor activity of male rats

1,2-MD 100 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03025	1170	1032	675	749	3626	24	25	19	13	81
M03026	1270	1146	1000	841	4257	41	40	19	14	114
M03027	1326	1073	678	905	3982	43	29	12	17	101
M03028	1198	1055	885	777	3915	32	31	22	24	109
M03029	1561	1483	1309	1213	5566	28	23	24	11	86
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1305	1158	909	897	4269	34	30	19	16	98
S.D.	156	187	263	187	759	8	7	5	5	14

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 20-4. Motor activity of male rats

1,2-MD 300 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04037	828	1055	866	948	3697	14	14	11	22	61
M04038	1225	1264	1258	1484	5231	34	28	35	38	135
M04039	1613	1472	1413	1606	6104	52	35	29	49	165
M04040	730	768	655	597	2750	21	21	26	25	93
M04041	1479	1471	1656	1636	6242	46	40	76	65	227
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1175	1206	1170	1254 *	4805	33	28	35	40 *	136
S.D.	389	300	406	460	1532	16	10	24	18	64

Male No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04044	962	757	810	852	3381	40	14	23	24	101
M04045	1056	1117	1135	1102	4410	31	30	20	24	105
M04046	1278	1280	982	1076	4616	37	35	34	24	130
M04047	1123	1097	981	954	4155	34	23	26	9	92
M04048	1928	1904	1761	1538	7131	30	39	23	18	110
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1269	1231	1134	1104 *	4739	34	28	25	20	108
S.D.	386	422	369	262	1417	4	10	5	7	14

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 21-1. Motor activity of female rats

Control (vehicle: corn oil)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01002	1144	703	715	598	3160	32	5	12	6	55
F01003	1032	502	236	166	1936	17	16	0	1	34
F01005	989	409	178	222	1798	28	29	0	1	58
F01010	1064	518	335	135	2052	28	13	1	0	42
F01012	1159	856	483	498	2996	30	14	2	0	46
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1078	598	389	324	2388	27	15	3	2	47
S.D.	73	180	216	210	639	6	9	5	3	10

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 21-2. Motor activity of female rats

1,2-MD 30 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02013	1065	897	858	605	3425	46	37	28	22	133
F02014	1037	652	354	432	2475	20	11	6	7	44
F02015	1021	661	604	46	2332	31	8	12	0	51
F02016	964	750	528	537	2779	23	7	4	5	39
F02021	1276	431	680	253	2640	36	9	15	1	61
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1073	678	605	375	2730	31	14	13	7	66
S.D.	120	170	186	227	423	10	13	9	9	39

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 21-3. Motor activity of female rats

1,2-MD 100 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03026	1189	881	416	355	2841	33	18	4	3	58
F03027	1179	681	454	356	2670	36	9	3	4	52
F03029	985	561	543	411	2500	21	4	1	3	29
F03030	977	600	171	372	2120	20	7	0	2	29
F03033	1906	1433	1619	790	5748	39	16	16	2	73
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1247	831	641	457	3176	30	11	5	3	48
S.D.	382	358	564	188	1462	9	6	6	1	19

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 21-4. Motor activity of female rats

1,2-MD 300 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04043	1198	1161	1034	811	4204	29	30	22	18	99
Number of females	1	1	1	1	1	1	1	1	1	1
Mean	1198	1161	1034	811	4204	29	30	22	18	99
S.D.										

The group given 300 mg/kg of 1,2-MD was excluded from statistical analysis.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 22-1. Motor activity of female rats, satellite group

Control (vehicle: corn oil)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05049	1275	1151	1047	811	4284	32	22	23	24	101
F05050	1188	1060	1103	814	4165	24	20	32	23	99
F05051	1198	892	773	280	3143	30	22	21	2	75
F05052	1207	1141	743	850	3941	34	35	14	18	101
F05053	1440	1309	1034	825	4608	47	51	34	19	151
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1262	1111	940	716	4028	33	30	25	17	105
S.D.	105	152	168	244	550	8	13	8	9	28

Female No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05054	786	595	649	674	2704	37	25	24	34	120
F05055	1368	993	957	851	4169	45	27	25	25	122
F05056	1435	1477	1364	1438	5714	45	42	42	52	181
F05057	1106	960	948	809	3823	47	29	17	16	109
F05058	1233	1179	1123	1024	4559	35	24	23	28	110
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1186	1041	1008	959	4194	42	29	26	31	128
S.D.	257	323	262	295	1096	5	7	9	13	30

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 22-2. Motor activity of female rats, satellite group

1,2-MD 300 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06059	1069	1052	1089	1121	4331	25	16	22	36	99
F06060	1379	1508	1571	1486	5944	38	72	72	68	250
F06061	1251	1236	1231	1042	4760	33	34	46	27	140
F06062	1348	1496	1168	1125	5137	42	58	37	30	167
F06063	1342	1355	1355	1275	5327	40	39	37	36	152
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1278	1329	1283 *	1210 **	5100 *	36	44	43	39 *	162
S.D.	126	191	188	176	607	7	22	18	16	56

Female No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06064	988	940	881	782	3591	26	11	15	7	59
F06065	1184	1157	1180	1196	4717	29	20	40	38	127
F06066	1056	1044	940	1276	4316	30	24	18	50	122
F06067	1235	1237	1288	1471	5231	36	36	51	73	196
F06068	1096	1041	1186	1025	4348	27	21	16	9	73
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1112	1084	1095	1150	4441	30 **	22	28	35	115
S.D.	99	115	175	261	601	4	9	16	28	54

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 23-1-1. Urinalysis in male rats

Control (vehicle: corn oil)

Male No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	Light yellow	-	7.0	+	-	+	-	±	+	-	-	-	±	-
M01002	Light yellow	-	9.0	+	-	+	-	-	±	-	-	-	±	-
M01003	Yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-
M01004	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	-	-
M01005	Light yellow	-	6.5	2+	-	+	-	-	2+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M01001	9.4	1.070	131.4	189.7 §	154.8	1.24	1.78	1.46
M01002	10.7	1.070	84.8	174.0 §	137.5	0.91	1.86	1.47
M01003	7.1	1.088	143.2	235.6	154.9	1.02	1.67	1.10
M01004	28.4	1.034	46.6	113.6	62.4	1.32	3.23	1.77
M01005	18.7	1.040	59.5	115.1 §	79.9	1.11	2.15	1.49
Number of males	5	5	5	5	5	5	5	5
Mean	14.9	1.060	93.1	165.6	117.9	1.12	2.14	1.46
±S.D.	8.7	0.023	42.8	52.0	43.7	0.16	0.64	0.24

Turbidity, -: negative

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 23-1-2. Urinalysis in male rats

1,2-MD 30 mg/kg

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02013	Light yellow	-	7.5	+	-	+	-	-	+	-	-	-	±	-
M02014	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	-	-
M02015	Light yellow	-	7.0	2+	-	+	-	-	±	-	-	-	±	-
M02016	Light yellow	-	7.0	±	-	±	-	-	±	-	-	-	-	-
M02017	Light yellow	+	7.0	+	-	+	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M02013	11.0	1.073	68.2	136.1	118.9	0.75	1.50	1.31
M02014	20.4	1.041	57.4	105.8	78.7	1.17	2.16	1.61
M02015	9.3	1.075	145.4	154.9	159.6	1.35	1.44	1.48
M02016	17.1	1.047	64.7	121.9 §	88.9	1.11	2.08	1.52
M02017	10.8	1.075	131.6	128.5 §	165.4	1.42	1.39	1.79
Number of males	5	5	5	5	5	5	5	5
Mean	13.7	1.062	93.5	129.4	122.3	1.16	1.71	1.54
±S.D.	4.8	0.017	41.6	18.1	39.6	0.26	0.37	0.18

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 23-1-3. Urinalysis in male rats

1,2-MD 100 mg/kg

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03025	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	±	-
M03026	Light yellow	-	8.0	+	-	-	-	-	±	-	-	-	±	-
M03027	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
M03028	Yellow	+	7.5	2+	-	+	-	2+	+	3+	-	-	±	-
M03029	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M03025	18.1	1.044	86.4	110.1 §	112.2	1.56	1.99	2.03
M03026	18.8	1.045	65.9	102.5	76.6	1.24	1.93	1.44
M03027	9.0	1.078	184.5	111.9	203.9	1.66	1.01	1.84
M03028	9.8	1.072	106.3	106.8	130.2	1.04	1.05	1.28
M03029	7.2	1.080	86.6	110.8 §	108.1	0.62	0.80	0.78
Number of males	5	5	5	5	5	5	5	5
Mean	12.6	1.064	105.9	108.4	126.2	1.22	1.36	1.47
±S.D.	5.4	0.018	46.2	3.8	47.5	0.42	0.56	0.49

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 23-1-4. Urinalysis in male rats

1,2-MD 300 mg/kg

Male No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04037	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
M04038	Yellow	+	7.5	2+	-	+	-	-	+	-	-	-	±	-
M04039	Light yellow	-	8.0	2+	-	+	-	-	+	-	-	-	±	-
M04040	Light yellow	-	8.5	+	-	±	-	-	±	-	-	-	±	-
M04041	Light yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M04037	13.3	1.053	73.2	97.1 §	78.6	0.97	1.29	1.05
M04038	10.3	1.075	112.1	95.4 §	134.6	1.15	0.98	1.39
M04039	12.8	1.071	91.4	89.3	88.5	1.17	1.14	1.13
M04040	16.2	1.058	101.7	103.4	104.6	1.65	1.68	1.69
M04041	13.8	1.064	100.3	105.3 §	127.9	1.38	1.45	1.77
Number of males	5	5	5	5	5	5	5	5
Mean	13.3	1.064	95.7	98.1**	106.8	1.26	1.31	1.41
±S.D.	2.1	0.009	14.6	6.4	24.3	0.26	0.27	0.32

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 23-2-1. Urinalysis in male rats of the recovery period

Control (vehicle: corn oil)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01008	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
M01009	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
M01010	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
M01011	Light yellow	-	7.5	+	-	±	-	-	+	-	-	-	±	-
M01012	Light yellow	-	8.0	+	-	+	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M01008	25.7	1.042	75.3 §	146.9 §	78.9	1.94	3.78	2.03
M01009	12.3	1.065	88.3	181.1 §	109.0	1.09	2.23	1.34
M01010	17.1	1.058	112.3	164.3	124.3	1.92	2.81	2.13
M01011	20.2	1.059	85.8	170.8	113.3	1.73	3.45	2.29
M01012	16.5	1.065	136.8	187.6 §	142.9	2.26	3.10	2.36
Number of males	5	5	5	5	5	5	5	5
Mean	18.4	1.058	99.7	170.1	113.7	1.79	3.07	2.03
±S.D.	5.0	0.009	24.8	15.8	23.4	0.43	0.60	0.41

Turbidity, -: negative

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative; ±: 0.03 ≤ and < 0.06 mg/dL

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 23-2-2. Urinalysis in male rats of the recovery period

1,2-MD 300 mg/kg

Male No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04044	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M04045	Light yellow	-	8.0	+	-	+	-	-	+	-	-	-	±	-
M04046	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
M04047	Light yellow	-	7.5	2+	-	+	-	-	+	-	-	-	+	-
M04048	Light yellow	-	7.0	2+	-	±	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M04044	26.2	1.049	112.0	147.6	129.8	2.93	3.87	3.40
M04045	15.5	1.065	78.8	155.0	109.7	1.22	2.40	1.70
M04046	14.1	1.071	115.7	193.2 §	153.6	1.63	2.72	2.17
M04047	19.4	1.050	68.5	173.0 §	87.3	1.33	3.36	1.69
M04048	22.8	1.043	74.0	134.1	71.2	1.69	3.06	1.62
Number of males	5	5	5	5	5	5	5	5
Mean	19.6	1.056	89.8	160.6	110.3	1.76	3.08	2.12
±S.D.	5.0	0.012	22.3	23.0	32.8	0.68	0.57	0.75

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative; ±: 0.03 ≤ and < 0.06 mg/dL

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 24-1-1. Urinalysis in female rats, satellite group

Control (vehicle: corn oil)

Female No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05049	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	-	-
F05050	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F05051	Light yellow	-	8.5	±	-	-	-	-	±	-	-	-	±	-
F05052	Light yellow	-	6.5	±	-	-	-	-	±	-	-	-	-	-
F05053	Yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05049	10.3	1.048	84.8	123.6	77.6	0.87	1.27	0.80
F05050	14.2	1.058	98.3	160.5 §	134.7	1.40	2.28	1.91
F05051	7.3	1.07	115.5	158.5	160.8	0.84	1.16	1.17
F05052	8.4	1.065	105.3	155.5 §	124.3	0.88	1.31	1.04
F05053	6.6	1.048	57.5	119.4 §	46.2	0.38	0.79	0.30
Number of females	5	5	5	5	5	5	5	5
Mean	9.4	1.058	92.3	143.5	108.7	0.87	1.36	1.04
±S.D.	3.0	0.010	22.4	20.2	46.1	0.36	0.55	0.59

Turbidity, -: negative

Protein, -: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 24-1-2. Urinalysis in female rats, satellite group

1,2-MD 300 mg/kg

Female No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06059	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	-	-
F06060	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-
F06061	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	-	-
F06062	Yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-
F06063	Yellow	-	7.0	2+	-	+	-	-	2+	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06059	16.5	1.052	78.5	113.9	101.6	1.30	1.88	1.68
F06060	10.1	1.063	82.3	109.3	110.2	0.83	1.10	1.11
F06061	14.1	1.028	32.9	65.5 §	24.8	0.46	0.92	0.35
F06062	7.7	1.094	119.7	91.8 §	176.0	0.92	0.71	1.36
F06063	10.5	1.066	102.9	111.5 §	138.3	1.08	1.17	1.45
Number of females	5	5	5	5	5	5	5	5
Mean	11.8	1.061	83.3	98.4**	110.2	0.92	1.16	1.19
±S.D.	3.5	0.024	32.7	20.4	55.9	0.31	0.44	0.51

Turbidity, -: negative

Protein, -: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 24-2-1. Urinalysis in female rats of the recovery period

Control (vehicle: corn oil)

Female No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells ^{a)}	White blood cells ^{a)}	Casts ^{a)}	Crystals ^{b)}	Epithelial cells ^{b)}
F05054	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	-
F05055	Light yellow	-	6.0	-	-	-	-	-	±	-	-	-	-	-
F05056	Light yellow	-	6.5	±	-	±	-	-	±	-	-	-	±	-
F05057	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	±	-
F05058	Light yellow	-	7.5	+	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05054	13.8	1.052	117.5	163.3	139.5	1.62	2.25	1.93
F05055	9.1	1.051	100.3	138.0 §	74.9	0.91	1.26	0.68
F05056	8.1	1.066	147.2	188.4 §	170.8	1.19	1.53	1.38
F05057	5.9	1.092	150.7	220.9 §	198.7	0.89	1.30	1.17
F05058	9.3	1.076	152.1	168.7	188.2	1.41	1.57	1.75
Number of females	5	5	5	5	5	5	5	5
Mean	9.2	1.067	133.6	175.9	154.4	1.20	1.58	1.38
±S.D.	2.9	0.017	23.4	30.9	49.8	0.32	0.40	0.49

Turbidity, -: negative

Protein, -: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 24-2-2. Urinalysis in female rats of the recovery period

1,2-MD 300 mg/kg

Female No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells ^{a)}	White blood cells ^{a)}	Casts ^{a)}	Crystals ^{b)}	Epithelial cells ^{b)}
F06064	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	±	-
F06065	Light yellow	-	6.5	+	-	-	-	-	+	-	-	-	±	-
F06066	Yellow	-	8.5	+	-	-	-	-	±	-	-	-	±	-
F06067	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	-
F06068	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06064	10.2	1.065	94.3	176.7 §	105.8	0.96	1.80	1.08
F06065	5.4	1.092	136.2	189.6 §	164.0	0.74	1.02	0.89
F06066	8.9	1.070	168.7	201.7 §	177.8	1.50	1.80	1.58
F06067	8.1	1.084	147.8	187.5	192.3	1.20	1.52	1.56
F06068	10.9	1.074	169.3	189.1 §	175.0	1.85	2.06	1.91
Number of females	5	5	5	5	5	5	5	5
Mean	8.7	1.077	143.3	188.9	163.0	1.25	1.64	1.40
±S.D.	2.1	0.011	30.8	8.9	33.5	0.44	0.40	0.41

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, -: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 25-1-1. Hematological findings of male rats at the end of the dosing period

Control (vehicle: corn oil)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M01001	896	17.0	47.0	52.5	19.0	36.2	131.9	18.4	30.3 §
M01002	795	14.5	40.3	50.7	18.2	36.0	108.8	17.0	24.5
M01003	847	15.6	43.4	51.2	18.4	35.9	96.6	16.1	26.4 §
M01004	851	15.7	45.3	53.2	18.4	34.7	112.8	16.3	28.3 §
M01005	888	15.5	43.3	48.8	17.5	35.8	121.1	13.2	25.4
Number of males	5	5	5	5	5	5	5	5	5
Mean	855	15.7	43.9	51.3	18.3	35.7	114.2	16.2	27.0
S.D.	40	0.9	2.5	1.7	0.5	0.6	13.2	1.9	2.3

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M01001	134.5	18.1	0.6	0.0	3.3	78.0	3.06
M01002	74.3	18.2	1.6	0.0	3.9	76.3	3.25
M01003	95.5	24.0	0.7	0.0	4.6	70.7	2.47
M01004	109.8	17.5	1.4	0.0	6.6	74.5	4.12
M01005	84.4	14.6	1.7	0.0	3.0	80.7	3.76
Number of males	5	5	5	5	5	5	5
Mean	99.7	18.5	1.2	0.0	4.3	76.0	3.33
S.D.	23.5	3.4	0.5	0.0	1.4	3.8	0.64

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 25-1-2. Hematological findings of male rats at the end of the dosing period

1,2-MD 30 mg/kg

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M02013	861	15.2	42.7	49.6	17.7	35.6	113.8	13.5	24.2 §
M02014	823	14.5	41.0	49.8	17.6	35.4	100.1	13.5	21.5
M02015	784	14.4	41.1	52.4	18.4	35.0	93.6	14.9	24.0
M02016	890	15.6	43.8	49.2	17.5	35.6	113.5	15.4	24.3
M02017	824	14.4	40.7	49.4	17.5	35.4	110.0	14.9	22.6
Number of males	5	5	5	5	5	5	5	5	5
Mean	836	14.8	41.9	50.1	17.7	35.4	106.2	14.4	23.3
S.D.	40	0.5	1.3	1.3	0.4	0.2	9.0	0.9	1.2

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M02013	158.4	10.8	0.6	0.0	3.4	85.2	3.19
M02014	77.8	10.4	0.6	0.0	3.1	85.9	2.73
M02015	74.2	15.2	1.1	0.0	5.3	78.4	3.01
M02016	80.1	22.6	2.1	0.0	4.5	70.8	2.76
M02017	93.1	39.2	1.8	0.0	3.1	55.9	2.77
Number of males	5	5	5	5	5	5	5
Mean	96.7	19.6	1.2	0.0	3.9	75.2	2.89
S.D.	35.2	12.0	0.7	0.0	1.0	12.4	0.20

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.

The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 25-1-3. Hematological findings of male rats at the end of the dosing period

1,2-MD 100 mg/kg

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M03025	823	14.7	41.9	50.9	17.9	35.1	118.1	13.1	21.4 §
M03026	777	13.6	38.3	49.3	17.5	35.5	95.0	13.8	24.3 §
M03027	786	14.4	41.5	52.8	18.3	34.7	91.8	14.9	30.5
M03028	804	15.6	45.6	56.7	19.4	34.2	104.0	14.2	23.8 §
M03029	885	15.7	43.3	48.9	17.7	36.3	106.0	14.9	24.5 §
Number of males	5	5	5	5	5	5	5	5	5
Mean	815	14.8	42.1	51.7	18.2	35.2	103.0	14.2	24.9
S.D.	43	0.9	2.7	3.2	0.8	0.8	10.3	0.8	3.4

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M03025	82.6	14.4	1.1	0.0	3.9	80.6	3.32
M03026	116.1	22.1	0.7	0.1	5.2	71.9	3.05
M03027	93.0	19.6	1.3	0.0	4.4	74.7	3.82
M03028	86.6	24.7	1.7	0.0	6.4	67.2	4.43
M03029	79.3	30.9	1.8	0.0	4.9	62.4	3.13
Number of males	5	5	5	5	5	5	5
Mean	91.5	22.3	1.3	0.0	5.0	71.4	3.55
S.D.	14.7	6.1	0.4	0.0	0.9	7.0	0.58

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 25-1-4. Hematological findings of male rats at the end of the dosing period

1,2-MD 300 mg/kg

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M04037	896	15.3	42.8	47.8	17.1	35.7	115.0	14.7	23.1
M04038	866	14.9	42.5	49.1	17.2	35.1	111.6	13.0	23.3 §
M04039	882	15.6	44.6	50.6	17.7	35.0	124.0	12.3	21.9
M04040	818	15.0	43.9	53.7	18.3	34.2	110.5	15.6	27.8
M04041	830	15.3	42.7	51.4	18.4	35.8	101.8	13.6	28.8
Number of males	5	5	5	5	5	5	5	5	5
Mean	858	15.2	43.3	50.5	17.7	35.2	112.6	13.8 *	25.0
S.D.	33	0.3	0.9	2.3	0.6	0.6	8.0	1.3	3.1

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M04037	130.4	23.3	1.0	0.1	4.1	71.5	4.30
M04038	75.3	26.8	1.1	0.0	5.3	66.8	4.48
M04039	112.1	11.7	2.2	0.1	3.1	82.9	3.72
M04040	99.1	18.9	1.0	0.0	3.9	76.2	4.01
M04041	97.7	19.3	1.4	0.0	3.9	75.4	4.50
Number of males	5	5	5	5	5	5	5
Mean	102.9	20.0	1.3	0.0	4.1	74.6	4.20 *
S.D.	20.3	5.7	0.5	0.1	0.8	6.0	0.33

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

§. The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 25-2-1. Hematological findings of male rats at the end of the recovery period

Control (vehicle: corn oil)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M01008	854	14.7	41.8	48.9	17.2	35.2	110.1	12.4	17.7
M01009	796	14.3	40.0	50.3	18.0	35.8	104.3	12.4	20.8
M01010	835	14.7	42.1	50.4	17.6	34.9	117.7	12.4	22.7
M01011	839	15.1	43.2	51.5	18.0	35.0	105.9	14.0	20.4
M01012	857	15.0	44.4	51.8	17.5	33.8	113.5	14.0	21.1
Number of males	5	5	5	5	5	5	5	5	5
Mean	836	14.8	42.3	50.6	17.7	34.9	110.3	13.0	20.5
S.D.	24	0.3	1.6	1.1	0.3	0.7	5.5	0.9	1.8

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M01008	81.1	13.9	1.8	0.0	4.8	79.5	2.94
M01009	87.6	36.6	1.1	0.1	5.1	57.1	3.72
M01010	117.9	11.1	1.5	0.1	2.3	85.0	2.94
M01011	113.7	26.6	1.5	0.0	2.8	69.1	3.71
M01012	79.5	15.4	2.0	0.0	4.5	78.1	3.66
Number of males	5	5	5	5	5	5	5
Mean	96.0	20.7	1.6	0.0	3.9	73.8	3.39
S.D.	18.4	10.7	0.3	0.1	1.3	10.9	0.42

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 25-2-2. Hematological findings of male rats at the end of the recovery period

1,2-MD 300 mg/kg

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M04044	813	15.1	41.4	50.9	18.6	36.5	104.8	21.7	23.3
M04045	861	14.9	41.7	48.4	17.3	35.7	113.5	19.5	22.8
M04046	803	14.3	41.2	51.3	17.8	34.7	114.3	13.2	20.2
M04047	800	14.0	40.2	50.3	17.5	34.8	104.3	15.7	24.1
M04048	842	14.7	41.8	49.6	17.5	35.2	111.9	14.0	22.2
Number of males	5	5	5	5	5	5	5	5	5
Mean	824	14.6	41.3	50.1	17.7	35.4	109.8	16.8	22.5
S.D.	27	0.4	0.6	1.1	0.5	0.7	4.8	3.7	1.5

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M04044	144.9	11.9	1.4	0.1	4.3	82.3	3.76
M04045	81.6	24.4	2.2	0.1	4.5	68.8	4.11
M04046	108.6	11.8	1.7	0.1	3.3	83.1	2.23
M04047	104.7	12.4	1.2	0.0	2.4	84.0	4.15
M04048	69.4	11.3	1.6	0.0	3.5	83.6	3.97
Number of males	5	5	5	5	5	5	5
Mean	101.8	14.4	1.6	0.1	3.6	80.4	3.64
S.D.	29.0	5.6	0.4	0.1	0.8	6.5	0.81

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 26-1-1. Hematological findings of female rats at the end of the dosing period

Control (vehicle: corn oil)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F01002	696	13.5	39.8	57.2	19.4	33.9	109.5	12.3	19.4
F01003	642	13.0	38.3	59.7	20.2	33.9	99.2	12.7	20.7
F01005	609	12.2	36.6	60.1	20.0	33.3	128.2	11.5	18.7
F01010	727	14.1	40.6	55.8	19.4	34.7	148.9	12.0	20.2
F01012	730	14.0	41.2	56.4	19.2	34.0	111.3	12.3	19.4
Number of females	5	5	5	5	5	5	5	5	5
Mean	681	13.4	39.3	57.8	19.6	34.0	119.4	12.2	19.7
S.D.	53	0.8	1.9	2.0	0.4	0.5	19.5	0.4	0.8

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F01002	54.9	22.3	0.9	0.0	5.6	71.2	9.11
F01003	138.8	22.1	1.4	0.1	5.0	71.4	7.29
F01005	68.6	38.0	1.2	0.0	4.2	56.6	9.16
F01010	155.6	27.7	1.7	0.1	2.8	67.7	5.50
F01012	122.3	39.2	1.6	0.0	5.2	54.0	8.93
Number of females	5	5	5	5	5	5	5
Mean	108.0	29.9	1.4	0.0	4.6	64.2	8.00
S.D.	44.1	8.3	0.3	0.1	1.1	8.3	1.60

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 26-1-2. Hematological findings of female rats at the end of the dosing period

1,2-MD 30 mg/kg

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F02013	696	13.8	41.3	59.3	19.8	33.4	147.4	12.6	23.0
F02014	643	12.5	37.5	58.3	19.4	33.3	116.6	12.7	19.5
F02015	630	12.0	36.5	57.9	19.0	32.9	93.8	12.5	19.5
F02016	648	12.4	37.7	58.2	19.1	32.9	130.5	12.1	18.5
F02021	575	11.5	34.9	60.7	20.0	33.0	79.4	12.9	20.7
Number of females	5	5	5	5	5	5	5	5	5
Mean	638	12.4	37.6	58.9	19.5	33.1	113.5	12.6	20.2
S.D.	43	0.9	2.4	1.1	0.4	0.2	27.4	0.3	1.7

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F02013	59.8	17.6	0.8	0.0	5.2	76.4	7.43
F02014	151.2	26.7	0.8	0.0	2.8	69.7	10.61
F02015	97.3	26.2	0.8	0.0	2.7	70.3	9.18
F02016	109.5	39.2	0.4	0.0	2.2	58.2	9.53
F02021	71.6	29.7	0.3	0.0	2.7	67.3	11.02
Number of females	5	5	5	5	5	5	5
Mean	97.9	27.9	0.6 *	0.0	3.1	68.4	9.55
S.D.	35.8	7.8	0.2	0.0	1.2	6.6	1.41

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 26-1-3. Hematological findings of female rats at the end of the dosing period

1,2-MD 100 mg/kg

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F03026	626	12.1	37.4	59.7	19.3	32.4	96.4	12.1	19.5
F03027	700	13.2	39.0	55.7	18.9	33.8	100.8	12.1	19.6
F03029	752	14.2	41.0	54.5	18.9	34.6	102.9	12.4	19.1
F03030	624	12.1	37.6	60.3	19.4	32.2	116.4	13.2	21.1
F03033	619	13.2	40.4	65.3	21.3	32.7	88.7	13.1	20.5
Number of females	5	5	5	5	5	5	5	5	5
Mean	664	13.0	39.1	59.1	19.6	33.1	101.0	12.6	20.0
S.D.	59	0.9	1.6	4.3	1.0	1.0	10.2	0.5	0.8

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F03026	56.6	21.0	1.1	0.0	5.1	72.8	8.97
F03027	71.2	29.9	0.6	0.0	3.9	65.6	9.37
F03029	72.7	22.9	1.7	0.0	8.0	67.4	8.45
F03030	85.3	23.5	0.4	0.0	3.3	72.8	13.46
F03033	60.2	22.2	0.7	0.0	3.3	73.8	10.44
Number of females	5	5	5	5	5	5	5
Mean	69.2	23.9	0.9	0.0	4.7	70.5	10.14
S.D.	11.3	3.5	0.5	0.0	2.0	3.7	2.00

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 26-1-4. Hematological findings of female rats at the end of the dosing period

1,2-MD 300 mg/kg

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F04043	722	13.4	39.7	55.0	18.6	33.8	132.9	13.6	21.4

Number of females	1	1	1	1	1	1	1	1	1
Mean	722	13.4	39.7	55.0	18.6	33.8	132.9	13.6	21.4
S.D.									

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F04043	100.0	13.6	1.0	0.0	3.9	81.5	9.13

Number of females	1	1	1	1	1	1	1
Mean	100.0	13.6	1.0	0.0	3.9	81.5	9.13
S.D.							

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 26-2-1. Hematological findings of female rats at the end of the dosing period, satellite group

Control (vehicle: corn oil)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F05049	784	14.5	41.4	52.8	18.5	35.0	80.5	12.2	21.0
F05050	818	15.3	43.7	53.4	18.7	35.0	98.3	11.4	17.9
F05051	707	13.9	39.9	56.4	19.7	34.8	91.9	11.7	19.7
F05052	791	14.4	41.4	52.3	18.2	34.8	116.3	11.4	22.0
F05053	753	14.5	42.1	55.9	19.3	34.4	126.2	11.8	20.2
Number of females	5	5	5	5	5	5	5	5	5
Mean	771	14.5	41.7	54.2	18.9	34.8	102.6	11.7	20.2
S.D.	42	0.5	1.4	1.9	0.6	0.2	18.5	0.3	1.5

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F05049	41.7	14.1	2.2	0.2	2.9	80.6	4.75
F05050	69.9	13.6	1.4	0.0	1.7	83.3	3.41
F05051	54.6	6.4	1.3	0.0	2.6	89.7	3.29
F05052	34.7	12.7	2.0	0.0	4.3	81.0	3.53
F05053	55.8	15.8	2.9	0.0	1.4	79.9	4.13
Number of females	5	5	5	5	5	5	5
Mean	51.3	12.5	2.0	0.0	2.6	82.9	3.82
S.D.	13.6	3.6	0.7	0.1	1.1	4.0	0.61

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 26-2-2. Hematological findings of female rats at the end of the dosing period, satellite group

1,2-MD 300 mg/kg

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F06059	745	13.5	37.6	50.5	18.1	35.9	91.3	11.9	18.1
F06060	783	14.6	42.0	53.6	18.6	34.8	89.6	10.9	18.4
F06061	739	13.7	39.9	54.0	18.5	34.3	128.9	11.3	19.6
F06062	761	13.6	39.2	51.5	17.9	34.7	105.2	11.1	20.4
F06063	742	13.6	40.3	54.3	18.3	33.7	101.8	11.2	21.6
Number of females	5	5	5	5	5	5	5	5	5
Mean	754	13.8 *	39.8	52.8	18.3	34.7	103.4	11.3	19.6
S.D.	18	0.5	1.6	1.7	0.3	0.8	15.8	0.4	1.4

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F06059	102.8	22.9	1.8	0.1	4.4	70.8	2.84
F06060	53.6	15.2	0.9	0.0	3.5	80.4	4.56
F06061	51.8	13.0	1.5	0.0	2.1	83.4	4.38
F06062	43.3	28.7	2.3	0.0	3.9	65.1	4.00
F06063	33.2	15.7	2.4	0.0	3.0	78.9	4.14
Number of females	5	5	5	5	5	5	5
Mean	56.9	19.1	1.8	0.0	3.4	75.7	3.98
S.D.	26.9	6.5	0.6	0.0	0.9	7.5	0.67

Significantly different from the control group (*: $P<0.05$, **: $P<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 26-3-1. Hematological findings of female rats at the end of the recovery period

Control (vehicle: corn oil)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F05054	800	14.9	43.0	53.8	18.6	34.7	130.0	10.8	16.9
F05055	796	15.0	42.5	53.4	18.8	35.3	98.6	10.2	14.1
F05056	786	14.8	42.8	54.5	18.8	34.6	98.6	11.5	18.4
F05057	749	14.4	42.5	56.7	19.2	33.9	102.6	11.0	17.2
F05058	780	14.4	41.1	52.7	18.5	35.0	105.6	10.4	16.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	782	14.7	42.4	54.2	18.8	34.7	107.1	10.8	16.5
S.D.	20	0.3	0.7	1.5	0.3	0.5	13.1	0.5	1.6

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F05054	50.8	15.0	2.0	0.0	4.9	78.1	2.55
F05055	44.9	10.9	2.9	0.0	5.6	80.6	1.82
F05056	50.1	11.8	1.6	0.0	3.2	83.4	3.32
F05057	49.2	28.4	3.3	0.0	3.7	64.6	2.69
F05058	30.2	15.2	3.0	0.0	4.3	77.5	3.24
Number of females	5	5	5	5	5	5	5
Mean	45.0	16.3	2.6	0.0	4.3	76.8	2.72
S.D.	8.6	7.0	0.7	0.0	1.0	7.2	0.61

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 26-3-2. Hematological findings of female rats at the end of the recovery period

1,2-MD 300 mg/kg

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F06064	815	15.0	43.3	53.1	18.4	34.6	92.8	11.5	17.7
F06065	769	14.1	40.0	52.0	18.3	35.3	99.9	11.1	17.0
F06066	767	13.7	39.3	51.2	17.9	34.9	107.9	10.6	17.4
F06067	793	14.6	41.9	52.8	18.4	34.8	100.6	11.1	17.2
F06068	739	13.7	39.6	53.6	18.5	34.6	92.9	12.0	20.6
Number of females	5	5	5	5	5	5	5	5	5
Mean	777	14.2	40.8	52.5	18.3 *	34.8	98.8	11.3	18.0
S.D.	29	0.6	1.7	0.9	0.2	0.3	6.3	0.5	1.5

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F06064	42.9	14.5	1.6	0.0	4.9	79.0	3.67
F06065	62.4	15.7	2.4	0.0	4.5	77.4	3.06
F06066	38.4	14.8	2.6	0.0	2.9	79.7	2.46
F06067	43.1	13.2	3.2	0.0	4.9	78.7	3.46
F06068	54.2	32.1	1.3	0.0	2.8	63.8	2.96
Number of females	5	5	5	5	5	5	5
Mean	48.2	18.1	2.2	0.0	4.0	75.7	3.12
S.D.	9.8	7.9	0.8	0.0	1.1	6.7	0.47

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 27-1-1. Biochemical findings of male rats at the end of the dosing period

Control (vehicle: corn oil)																
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01001	5.5	3.5	1.75	140	51	39	83	60	35	0	136	33.4	13	0.5	0.08	263
M01002	5.3	3.2	1.52	138	40	42	72	57	28	0	365	4.9	14	0.5	0.04	275
M01003	5.4	3.2	1.45	136	51	66	85	55	27	0	238	9.6	11	0.4	0.05	400
M01004	6.1	3.7	1.54	162	72	67	109	45	26	0	136	9.4	14	0.5	0.06	348
M01005	5.4	3.5	1.84	123	60	39	96	43	19	0	42	8.1	16	0.4	0.06	336
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.4	1.62	140	55	51	89	52	27	0	183	13.1	14	0.5	0.06	324
S.D.	0.3	0.2	0.17	14	12	15	14	8	6	0	123	11.5	2	0.1	0.01	56

(Continued)

Control (vehicle: corn oil)

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01001	6.0	9.5	143.7	3.80	105.3
M01002	6.1	9.0	144.9	3.90	107.7
M01003	5.8	9.6	145.2	3.85	107.5
M01004	5.8	10.0	144.3	3.89	103.9
M01005	5.8	9.5	143.0	3.86	105.2
Number of males	5	5	5	5	5
Mean	5.9	9.5	144.2	3.86	105.9
S.D.	0.1	0.4	0.9	0.04	1.6

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 27-1-2. Biochemical findings of male rats at the end of the dosing period

1,2-MD 30 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M02013	5.8	3.5	1.52	170	72	46	110	46	27	0	86	4.8	13	0.5	0.05	388
M02014	5.2	3.2	1.60	150	67	91	107	55	33	0	270	6.6	14	0.5	0.06	393
M02015	5.8	3.5	1.52	159	54	45	86	49	22	0	81	15.1	13	0.5	0.05	311
M02016	5.5	3.5	1.75	131	64	58	106	61	26	0	363	8.2	14	0.5	0.06	498
M02017	5.3	3.3	1.65	142	61	39	99	61	30	0	126	7.8	15	0.5	0.06	427
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.4	1.61	150	64	56	102	54	28	0	185	8.5	14	0.5	0.06	403
S.D.	0.3	0.1	0.10	15	7	21	10	7	4	0	126	3.9	1	0.0	0.01	68
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	DU	AN	AN	AN	AN	KW	AN	AN	AN	AN

(Continued)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

1,2-MD 30 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M02013	6.3	9.5	142.6	4.20	103.7
M02014	5.0	9.1	143.7	3.79	107.1
M02015	5.6	9.9	144.4	3.85	106.8
M02016	5.9	9.5	144.1	3.94	106.7
M02017	6.2	9.5	143.2	3.94	105.2
Number of males	5	5	5	5	5
Mean	5.8	9.5	143.6	3.94	105.9
S.D.	0.5	0.3	0.7	0.16	1.4
Significance	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 27-1-3. Biochemical findings of male rats at the end of the dosing period

1,2-MD 100 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M03025	5.8	3.5	1.52	146	56	36	86	51	26	0	68	5.4	14	0.6	0.05	510
M03026	5.2	3.2	1.60	127	39	18	64	65	26	0	63	5.8	14	0.5	0.05	316
M03027	5.3	3.3	1.65	142	38	8	65	55	24	0	246	7.3	16	0.5	0.05	365
M03028	5.2	3.4	1.89	130	47	37	75	66	31	0	76	8.0	14	0.5	0.07	336
M03029	5.8	3.5	1.52	134	68	78	113	58	28	0	184	6.5	12	0.5	0.04	264
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.4	1.64	136	50	35	81	59	27	0	127	6.6	14	0.5	0.05	358
S.D.	0.3	0.1	0.15	8	13	27	20	6	3	0	83	1.1	1	0.0	0.01	93
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	DU	AN	AN	AN	AN	KW	AN	AN	AN	AN

(Continued)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

1,2-MD 100 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M03025	6.1	9.8	143.1	4.05	104.4
M03026	6.0	9.4	141.8	3.85	105.3
M03027	5.4	9.2	143.8	3.74	106.8
M03028	6.6	9.6	143.9	4.01	105.6
M03029	6.4	9.7	143.9	3.91	105
Number of males	5	5	5	5	5
Mean	6.1	9.5	143.3	3.91	105.4
S.D.	0.5	0.2	0.9	0.12	0.9
Significance	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 27-1-4. Biochemical findings of male rats at the end of the dosing period

1,2-MD 300 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04037	5.4	3.4	1.70	133	58	46	94	56	24	0	90	6.0	17	0.5	0.05	331
M04038	6.0	3.7	1.61	121	80	94	132	56	28	0	75	5.0	12	0.4	0.04	283
M04039	5.8	3.6	1.64	117	79	63	125	59	30	0	185	5.1	16	0.5	0.05	333
M04040	5.5	3.4	1.62	109	61	22	94	56	33	0	55	9.9	13	0.4	0.04	269
M04041	5.8	3.5	1.52	110	76	39	114	61	29	0	225	4.3	12	0.5	0.07	334
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.5	1.62	118	71	53	112	58	29	0	126	6.1	14	0.5	0.05	310
S.D.	0.2	0.1	0.06	10	10	27	17	2	3	0	75	2.2	2	0.1	0.01	31
Significance	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	DU	AN	AN	AN	AN	KW	AN	AN	AN	AN

(Continued)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

1,2-MD 300 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04037	7.0	9.1	142.5	4.08	105.1
M04038	6.5	9.7	142.7	3.91	103.7
M04039	7.5	9.8	143.7	4.20	104.7
M04040	7.4	9.6	142.4	3.91	103.1
M04041	7.4	9.5	144.2	3.87	105.1
Number of males	5	5	5	5	5
Mean	7.2	9.5	143.1	3.99	104.3
S.D.	0.4	0.3	0.8	0.14	0.9
Significance	**	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 27-2-1. Biochemical findings of male rats at the end of the recovery period

Control (vehicle: corn oil)																
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01008	5.6	3.4	1.55	123	49	30	79	72	29	0	163	9.4	17	0.6	0.05	296
M01009	5.8	3.5	1.52	118	49	12	71	73	36	0	379	12.5	14	0.6	0.06	303
M01010	5.6	3.4	1.55	120	47	26	75	54	26	0	93	10.9	15	0.6	0.06	270
M01011	5.9	3.7	1.68	165	55	62	96	62	31	0	318	5.4	14	0.5	0.04	274
M01012	5.7	3.5	1.59	128	51	22	81	55	25	0	251	11.1	14	0.5	0.03	321
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.5	1.58	131	50	30	80	63	29	0	241	9.9	15	0.6	0.05	293
S.D.	0.1	0.1	0.06	19	3	19	10	9	4	0	115	2.7	1	0.1	0.01	21

(Continued)

Control (vehicle: corn oil)					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01008	6.6	9.1	143.4	4.24	106.2
M01009	6.0	9.3	144.4	4.12	107.3
M01010	6.3	9.4	144.6	3.70	106.4
M01011	5.4	9.4	144.4	3.59	107.1
M01012	5.3	9.0	145.7	3.66	109.7
Number of males	5	5	5	5	5
Mean	5.9	9.2	144.5	3.86	107.3
S.D.	0.6	0.2	0.8	0.30	1.4

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 27-2-2. Biochemical findings of male rats at the end of the recovery period

1,2-MD 300 mg/kg																
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04044	5.9	3.3	1.27	161	35	23	63	66	33	0	336	9.7	15	0.5	0.06	253
M04045	5.8	3.4	1.42	128	50	11	76	62	26	0	263	8.6	17	0.5	0.06	233
M04046	5.3	3.1	1.41	121	42	28	68	60	29	0	152	10.7	15	0.5	0.03	309
M04047	5.7	3.4	1.48	153	35	17	62	55	23	0	330	14.1	15	0.6	0.04	280
M04048	6.1	3.7	1.54	134	51	13	76	60	27	0	402	9.0	15	0.5	0.05	291
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.4	1.42	139	43	18	69	61	28	0	297	10.4	15	0.5	0.05	273
S.D.	0.3	0.2	0.10	17	8	7	7	4	4	0	95	2.2	1	0.0	0.01	30
Significance	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

(Continued)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

1,2-MD 300 mg/kg					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04044	6.7	9.1	143.9	4.09	105.6
M04045	6.7	9.2	144.6	4.01	106.5
M04046	6.1	9.2	144.0	3.99	107.6
M04047	6.5	9.0	144.4	3.97	106.5
M04048	6.3	9.7	144.2	3.80	106.8
Number of males	5	5	5	5	5
Mean	6.5	9.2	144.2	3.97	106.6
S.D.	0.3	0.3	0.3	0.11	0.7
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 28-1-1. Biochemical findings of female rats at the end of the dosing period

Control (vehicle: corn oil)																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F01002	6.1	4.0	1.90	131	35	24	75	70	35	1	57	8.1	17	0.5	0.06	142
F01003	6.1	3.9	1.77	112	42	24	92	62	109	0	44	23.4	15	0.5	0.10	160
F01005	5.8	3.9	2.05	129	48	22	97	76	40	0	74	9.7	11	0.5	0.05	299
F01010	6.0	3.7	1.61	127	66	31	113	69	38	1	270	16.0	11	0.6	0.08	164
F01012	5.6	3.7	1.95	136	49	29	99	58	35	0	50	17.2	14	0.5	0.08	133
Number of Females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	3.8	1.86	127	48	26	95	67	51	0	99	14.9	14	0.5	0.07	180
S.D.	0.2	0.1	0.17	9	12	4	14	7	32	1	96	6.2	3	0.0	0.02	68

(Continued)

Control (vehicle: corn oil)					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F01002	6.8	10.0	142.7	3.82	107.5
F01003	6.7	9.6	139.6	4.08	106.2
F01005	5.4	9.3	144.0	3.48	110.6
F01010	6.2	9.8	141.9	3.76	107.7
F01012	6.2	9.5	139.8	3.81	103.9
Number of males	5	5	5	5	5
Mean	6.3	9.6	141.6	3.79	107.2
S.D.	0.6	0.3	1.9	0.21	2.4

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 28-1-2. Biochemical findings of female rats at the end of the dosing period

1,2-MD 30 mg/kg																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F02013	6.0	3.8	1.73	116	49	16	85	73	38	0	73	17.5	16	0.5	0.09	110
F02014	5.6	3.4	1.55	144	62	17	102	84	45	0	86	12.1	15	0.5	0.06	239
F02015	5.8	3.8	1.90	115	49	19	92	87	53	0	126	18.3	11	0.5	0.10	199
F02016	5.6	3.6	1.80	110	81	49	138	64	37	0	78	9.0	10	0.5	0.08	138
F02021	5.8	3.7	1.76	120	53	18	96	67	35	1	66	9.4	7	0.5	0.08	176
Number of Females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.7	1.75	121	59	24	103	75	42	0	86	13.3	12	0.5	0.08	172
S.D.	0.2	0.2	0.13	13	13	14	21	10	7	0	24	4.4	4	0.0	0.01	51
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	AN	AN	AN	AN	AN

(Continued)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DU: Analysis by Dunnett's test.

1,2-MD 30 mg/kg					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F02013	6.9	10.5	144.3	3.83	104.2
F02014	5.7	9.1	140.8	3.56	105.1
F02015	5.4	9.5	141.1	3.94	108.1
F02016	6.0	9.6	143.1	3.34	106.4
F02021	5.8	9.5	143.2	3.27	107.3
Number of males	5	5	5	5	5
Mean	6.0	9.6	142.5	3.59	106.2
S.D.	0.6	0.5	1.5	0.29	1.6
Significance	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 28-1-3. Biochemical findings of female rats at the end of the dosing period

1,2-MD 100 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F03026	5.9	3.7	1.68	122	54	19	95	69	33	0	59	5.7	16	0.5	0.04	114
F03027	5.5	3.7	2.06	118	61	21	102	68	39	1	65	13.8	14	0.5	0.08	139
F03029	5.9	3.9	1.95	144	46	24	83	91	37	1	91	26.4	24	0.6	0.08	148
F03030	6.3	3.9	1.63	129	57	44	95	61	32	0	127	18.7	15	0.6	0.06	112
F03033	5.7	3.5	1.59	146	60	23	106	67	28	0	200	10.8	15	0.6	0.07	180
Number of Females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	3.7	1.78	132	56	26	96	71	34	0	108	15.1	17	0.6	0.07	139
S.D.	0.3	0.2	0.21	13	6	10	9	11	4	1	58	7.9	4	0.1	0.02	28
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	AN	AN	AN	AN	AN

(Continued)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DU: Analysis by Dunnett's test.

1,2-MD 100 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F03026	6.9	9.8	143.2	3.75	106.6
F03027	6.2	9.7	141.5	3.57	106.7
F03029	7.5	9.9	142.7	3.90	106.1
F03030	7.1	10.4	141.9	3.47	104.4
F03033	8.8	10.0	143.8	3.41	106.8
Number of males	5	5	5	5	5
Mean	7.3	10	142.6	3.62	106.1
S.D.	1.0	0.3	0.9	0.20	1.0
Significance	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 28-1-4. Biochemical findings of female rats at the end of the dosing period

1,2-MD 300 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F04043	5.8	3.6	1.64	103	73	20	114	93	41	1	292	26.0	14	0.5	0.09	139
Number of Females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mean	5.8	3.6	1.64	103	73	20	114	93	41	1	292	26.0	14	0.5	0.09	139
S.D.																
Significance	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Statistical method	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

(Continued)

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

1,2-MD 300 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F04043	7.6	9.5	142.8	3.74	104.6
Number of males	1	1	1	1	1
Mean	7.6	9.5	142.8	3.74	104.6
S.D.					
Significance	---	---	---	---	---
Statistical method	NA	NA	NA	NA	NA

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 28-2-1. Biochemical findings of female rats at the end of the dosing period, satellite group

Control (vehicle: corn oil)																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05049	6.7	4.7	2.35	108	57	11	117	62	22	0	113	12.1	21	0.7	0.09	139
F05050	6.3	4.0	1.74	121	56	9	96	63	23	0	93	20.5	20	0.7	0.09	211
F05051	6.4	4.4	2.20	144	54	8	101	63	25	0	84	9.7	14	0.7	0.09	200
F05052	5.8	4.0	2.22	144	59	13	105	55	18	0	54	8.6	14	0.8	0.07	169
F05053	6.2	4.2	2.10	144	52	13	106	55	18	0	130	12.6	16	0.6	0.07	148
Number of Females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.3	4.3	2.12	132	56	11	105	60	21	0	95	12.7	17	0.7	0.08	173
S.D.	0.3	0.3	0.23	17	3	2	8	4	3	0	29	4.7	3	0.1	0.01	32

(Continued)

Control (vehicle: corn oil)

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05049	4.4	10.0	143.0	3.75	106.4
F05050	4.4	9.5	144.3	3.43	108.4
F05051	4.3	9.4	143.8	3.74	109.5
F05052	4.5	9.5	143.4	3.41	108.3
F05053	4.0	9.3	145.2	3.61	111.0
Number of males	5	5	5	5	5
Mean	4.3	9.5	143.9	3.59	108.7
S.D.	0.2	0.3	0.9	0.16	1.7

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 28-2-2. Biochemical findings of female rats at the end of the dosing period, satellite group

1,2-MD 300 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06059	6.6	4.4	2.00	118	105	13	171	137	42	1	185	21.3	16	0.6	0.10	81
F06060	6.0	4.1	2.16	135	103	20	161	66	23	0	98	5.0	14	0.6	0.05	122
F06061	6.4	4.2	1.91	104	102	14	154	73	27	0	132	18.7	17	0.7	0.08	104
F06062	5.8	3.7	1.76	100	110	19	155	73	33	0	80	25.1	21	0.5	0.04	200
F06063	6.0	4.1	2.16	131	89	14	144	62	24	1	114	9.8	14	0.5	0.05	131
Number of Females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.2	4.1	2.00	118	102	16	157	82	30	0	122	16.0	16	0.6	0.06	128
S.D.	0.3	0.3	0.17	16	8	3	10	31	8	1	40	8.3	3	0.1	0.03	45
Significance	NS	NS	NS	NS	**	*	**	NS	NS	NS	NS	NS	NS	*	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT

(Continued)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

1,2-MD 300 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06059	5.5	9.9	139.4	3.94	102.5
F06060	5.2	9.2	142.2	3.56	106.8
F06061	5.9	9.8	143.7	3.65	103.6
F06062	5.6	8.7	141.8 §	3.46	103.7
F06063	4.7	9.0	144.3	3.53	107.8
Number of Females	5	5	5	5	5
Mean	5.4	9.3	142.3	3.63	104.9
S.D.	0.5	0.5	1.9	0.19	2.3
Significance	**	NS	NS	NS	*
Statistical method	TT	TT	TT	TT	TT

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 28-3-1. Biochemical findings of female rats at the end of the recovery period

Control (vehicle: corn oil)																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05054	6.4	4.2	1.91	113	63	12	111	69	33	0	69	25.2	20	0.7	0.09	83
F05055	6.0	4.0	2.00	121	66	13	114	61	21	0	109	9.9	17	0.7	0.10	113
F05056	6.1	4.0	1.90	96	54	15	100	62	22	0	52	14.2	19	0.7	0.11	131
F05057	5.8	4.0	2.22	114	54	20	104	63	31	0	60	5.7	17	0.6	0.09	142
F05058	6.9	4.7	2.14	146	55	14	115	46	19	0	37	12.1	19	0.8	0.09	167
Number of Females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.2	4.2	2.03	118	58	15	109	60	25	0	65	13.4	18	0.7	0.10	127
S.D.	0.4	0.3	0.14	18	6	3	7	9	6	0	27	7.3	1	0.1	0.01	32

(Continued)

Control (vehicle: corn oil)					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05054	4.5	9.6	144.8	3.66	107.8
F05055	4.5	9.5	144.1	3.51	109.9
F05056	4.9	9.3	143.0	3.71	107.6
F05057	3.7	9.1	143.3	3.85	109.2
F05058	4.1	9.5	143.7	3.99	108.1
Number of males	5	5	5	5	5
Mean	4.3	9.4	143.8	3.74	108.5
S.D.	0.5	0.2	0.7	0.18	1.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 28-3-2. Biochemical findings of female rats at the end of the recovery period

1,2-MD 300 mg/kg																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06064	5.9	3.8	1.81	133	58	16	101	66	30	0	168	17.4	17	0.6	0.10	157
F06065	6.5	4.0	1.60	136	58	6	100	62	24	0	73	13.7	21	0.8	0.06	209
F06066	6.2	4.0	1.82	106	75	11	123	67	21	0	59	12.3	21	0.7	0.08	120
F06067	6.1	4.0	1.90	133	62	14	112	81	50	0	61	9.2	18	0.6	0.07	145
F06068	6.5	4.2	1.83	99	65	15	120	74	36	0	52	11.1	26	0.7	0.09	114
Number of Females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.2	4.0	1.79	121	64	12	111	70	32	0	83	12.7	21	0.7	0.08	149
S.D.	0.3	0.1	0.11	17	7	4	11	8	11	0	48	3.1	4	0.1	0.02	38
Significance	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

(Continued)

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

1,2-MD 300 mg/kg					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06064	4.2	9.3	145.3	3.51	109.8
F06065	5.1	9.1	142.4	3.92	105.7
F06066	5.0	9.0	144.2	3.53	107.4
F06067	5.3	9.0	142.8	3.34	108.0
F06068	5.0	9.3	142.5	3.67	106.7
Number of males	5	5	5	5	5
Mean	4.9	9.1	143.4	3.59	107.5
S.D.	0.4	0.2	1.3	0.22	1.5
Significance	NS	*	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-1. Organ weights of male rats at the end of the dosing period

Control (vehicle: corn oil)																	
Male No.	Body weight (g)	Brain (mg)		Thymus (mg/g)		Heart (mg)		Liver (mg)		Kidney (R) (mg/g)		Kidney (L) (mg/g)		Kidney (mg/g)		Spleen (mg)	
M01001	437.5	1838.7	4.203	388.7	0.888	1302.6	2.977	11621.1	26.563	1360.8	3.110	1321.3	3.020	2682.1	6.131	817.0	1.867
M01002	512.8	2023.8	3.947	262.4	0.512	1389.7	2.710	13321.7	25.978	1517.5	2.959	1504.6	2.934	3022.1	5.893	811.3	1.582
M01003	491.3	2047.3	4.167	426.6	0.868	1382.7	2.814	13418.6	27.312	1508.1	3.070	1502.1	3.057	3010.2	6.127	751.7	1.530
M01004	508.8	2003.8	3.938	313.9	0.617	1520.1	2.988	18498.4	36.357	1791.9	3.522	1768.1	3.475	3560.0	6.997	776.6	1.526
M01005	485.7	1971.0	4.058	307.8	0.634	1334.6	2.748	13839.0	28.493	1460.7	3.007	1478.1	3.043	2938.8	6.051	720.3	1.483
M01006	492.1	1976.0	4.015	326.2	0.663	1509.7	3.068	13299.8	27.027	1643.2	3.339	1681.4	3.417	3324.6	6.756	791.1	1.608
M01007	560.9	2120.8	3.781	253.3	0.452	1424.6	2.540	14723.8	26.250	2041.0	3.639	1955.0	3.485	3996.0	7.124	707.8	1.262
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	498.4	1997.3	4.016	325.6	0.662	1409.1	2.835	14103.2	28.283	1617.6	3.235	1601.5	3.204	3219.1	6.440	768.0	1.551
S.D.	36.9	86.4	0.145	63.1	0.165	82.3	0.186	2147.0	3.655	232.0	0.267	213.0	0.242	443.5	0.504	42.9	0.179

Control (vehicle: corn oil)													
Male No.	Testis (R) (mg/g)		Testis (L) (mg/g)		Testis (mg/g)		Epididymis (R) (mg/g)		Epididymis (L) (mg/g)		Epididymis (mg/g)		
M01001	1601.7	3.661	1597.9	3.652	3199.6	7.313	642.7	1.469	612.4	1.400	1255.1	2.869	
M01002	1695.9	3.307	1742.6	3.398	3438.5	6.705	654.4	1.276	683.5	1.333	1337.9	2.609	
M01003	1723.4	3.508	1740.9	3.543	3464.3	7.051	580.7	1.182	599.5	1.220	1180.2	2.402	
M01004	1556.3	3.059	1612.1	3.168	3168.4	6.227	684.4	1.345	630.7	1.240	1315.1	2.585	
M01005	1705.6	3.512	1706.2	3.513	3411.8	7.025	641.2	1.320	650.0	1.338	1291.2	2.658	
M01006	1778.5	3.614	1797.4	3.653	3575.9	7.267	769.9	1.565	766.9	1.558	1536.8	3.123	
M01007	1508.4	2.689	1601.8	2.856	3110.2	5.545	542.7	0.968	537.7	0.959	1080.4	1.926	
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	
Mean	1652.8	3.336	1685.6	3.398	3338.4	6.733	645.1	1.304	640.1	1.293	1285.2	2.596	
S.D.	98.5	0.351	81.0	0.292	177.0	0.642	72.9	0.194	71.9	0.185	141.9	0.375	

Control (vehicle: corn oil)													
Male No.	Prostate, ventral (mg/g)		Seminal vesicles (mg/g)		Thyroid gland (mg/g)		Adrenal gland (R) (mg/g)		Adrenal gland (L) (mg/g)		Adrenal gland (mg/g)		
M01001	495.5	1.133	1894.3	4.330	24.6	0.056	23.7	0.054	24.6	0.056	48.3	0.110	
M01002	562.7	1.097	1960.3	3.823	21.7	0.042	24.1	0.047	24.7	0.048	48.8	0.095	
M01003	774.4	1.576	1835.6	3.736	17.3	0.035	23.3	0.047	26.5	0.054	49.8	0.101	
M01004	416.5	0.819	1325.3	2.605	25.5	0.050	28.3	0.056	29.0	0.057	57.3	0.113	
M01005	362.5	0.746	1478.7	3.044	23.2	0.048	22.0	0.045	22.1	0.046	44.1	0.091	
M01006	496.7	1.009	1593.6	3.238	18.1	0.037	33.9	0.069	34.3	0.070	68.2	0.139	
M01007	755.6	1.347	1843.6	3.287	23.6	0.042	28.6	0.051	27.8	0.050	56.4	0.101	
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	
Mean	552.0	1.104	1704.5	3.438	22.0	0.044	26.3	0.053	27.0	0.054	53.3	0.107	
S.D.	158.9	0.289	239.8	0.569	3.2	0.007	4.2	0.008	3.9	0.008	8.1	0.016	

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-2. Organ weights of male rats at the end of the dosing period

1,2-MD 30 mg/kg																	
Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidney		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	519.3	2068.5	3.983	446.4	0.860	1556.1	2.997	16114.7	31.032	1486.0	2.862	1512.7	2.913	2998.7	5.775	978.4	1.884
M02014	498.5	2110.7	4.234	203.7	0.409	1347.9	2.704	13251.4	26.583	1274.7	2.557	1203.9	2.415	2478.6	4.972	775.4	1.555
M02015	517.1	1986.6	3.842	393.7	0.761	1575.0	3.046	15303.3	29.594	1750.9	3.386	1777.9	3.438	3528.8	6.824	842.1	1.629
M02016	491.3	2053.4	4.180	311.5	0.634	1493.5	3.040	14029.1	28.555	1411.8	2.874	1426.3	2.903	2838.1	5.777	735.6	1.497
M02017	519.3	2041.0	3.930	281.8	0.543	1364.4	2.627	13754.4	26.486	1595.1	3.072	1581.9	3.046	3177.0	6.118	685.7	1.320
M02018	485.3	2098.0	4.323	208.1	0.429	1309.7	2.699	13030.1	26.850	1735.2	3.576	1666.9	3.435	3402.1	7.010	694.6	1.431
M02019	433.4	2103.7	4.854	269.4	0.622	1254.7	2.895	10001.7	23.077	1398.5	3.227	1415.9	3.267	2814.4	6.494	1112.8	2.568
M02020	467.3	1928.0	4.126	331.0	0.708	1371.3	2.935	11677.0	24.988	1458.5	3.121	1617.6	3.462	3076.1	6.583	881.9	1.887
M02021	450.9	2019.2	4.478	308.0	0.683	1338.1	2.968	13131.2	29.122	1650.6	3.661	1620.6	3.594	3271.2	7.255	746.7	1.656
M02022	448.6	1911.0	4.260	321.4	0.716	1318.4	2.939	12630.5	28.155	1435.3	3.200	1474.2	3.286	2909.5	6.486	821.9	1.832
M02023	474.0	1897.8	4.004	126.4	0.267	1368.3	2.887	11917.3	25.142	1505.4	3.176	1393.9	2.941	2899.3	6.117	903.7	1.907
M02024	465.6	2016.1	4.330	271.2	0.582	1390.4	2.986	12570.0	26.997	1513.3	3.250	1477.6	3.174	2990.9	6.424	817.3	1.755
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	480.9	2019.5	4.212	289.4	0.601	1390.7	2.894	13117.6	27.215	1517.9	3.164	1514.1	3.156	3032.1	6.320	833.0	1.743
S.D.	29.2	74.9	0.275	85.5	0.167	99.2	0.141	1617.6	2.216	141.8	0.306	150.9	0.331	284.5	0.620	123.7	0.323
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	DU	AN	AN	AN	DU	DU	DT	DU	DU	DU	DU	DU	DU	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-2(continued). Organ weights of male rats at the end of the dosing period

1,2-MD 30 mg/kg

Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymis	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	1737.2	3.345	1773.5	3.415	3510.7	6.760	588.6	1.133	657.4	1.266	1246.0	2.399
M02014	1668.3	3.347	1639.1	3.288	3307.4	6.635	593.6	1.191	616.5	1.237	1210.1	2.427
M02015	1484.0	2.870	1501.2	2.903	2985.2	5.773	650.5	1.258	647.1	1.251	1297.6	2.509
M02016	1829.8	3.724	1763.0	3.588	3592.8	7.313	743.2	1.513	642.1	1.307	1385.3	2.820
M02017	1636.8	3.152	1616.5	3.113	3253.3	6.265	602.6	1.160	632.6	1.218	1235.2	2.379
M02018	1672.2	3.446	1676.9	3.455	3349.1	6.901	655.3	1.350	651.0	1.341	1306.3	2.692
M02019	1545.3	3.566	1542.5	3.559	3087.8	7.125	451.7	1.042	415.1	0.958	866.8	2.000
M02020	1530.0	3.274	1590.3	3.403	3120.3	6.677	591.2	1.265	578.5	1.238	1169.7	2.503
M02021	1624.7	3.603	1629.7	3.614	3254.4	7.218	595.3	1.320	597.9	1.326	1193.2	2.646
M02022	1578.4	3.519	1604.4	3.576	3182.8	7.095	605.6	1.350	640.5	1.428	1246.1	2.778
M02023	1660.9	3.504	1608.0	3.392	3268.9	6.896	694.0	1.464	711.4	1.501	1405.4	2.965
M02024	1618.1	3.475	1588.7	3.412	3206.8	6.887	595.3	1.279	572.9	1.230	1168.2	2.509
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1632.1	3.402	1627.8	3.393	3260.0	6.795	613.9	1.277	613.6	1.275	1227.5	2.552
S.D.	93.9	0.228	79.4	0.209	169.9	0.431	70.7	0.135	72.9	0.132	137.1	0.253
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN	KW	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-2(continued). Organ weights of male rats at the end of the dosing period

1,2-MD 30 mg/kg												
Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	675.7	1.301	2067.9	3.982	19.5	0.038	20.7	0.040	22.5	0.043	43.2	0.083
M02014	493.9	0.991	1813.6	3.638	21.8	0.044	22.7	0.046	23.8	0.048	46.5	0.093
M02015	778.4	1.505	1955.5	3.782	25.8	0.050	25.9	0.050	31.1	0.060	57.0	0.110
M02016	571.5	1.163	1599.1	3.255	19.8	0.040	20.7	0.042	19.7	0.040	40.4	0.082
M02017	650.6	1.253	1757.1	3.384	20.2	0.039	21.5	0.041	20.6	0.040	42.1	0.081
M02018	824.0	1.698	1702.2	3.508	23.1	0.048	24.2	0.050	26.4	0.054	50.6	0.104
M02019	695.4	1.605	1781.2	4.110	23.4	0.054	23.4	0.054	22.4	0.052	45.8	0.106
M02020	605.8	1.296	1294.4	2.770	21.4	0.046	20.7	0.044	21.6	0.046	42.3	0.091
M02021	674.5	1.496	1694.4	3.758	17.6	0.039	27.4	0.061	29.1	0.065	56.5	0.125
M02022	635.5	1.417	1562.8	3.484	20.3	0.045	23.6	0.053	26.2	0.058	49.8	0.111
M02023	610.6	1.288	1795.8	3.789	19.7	0.042	19.2	0.041	18.4	0.039	37.6	0.079
M02024	550.2	1.182	1418.4	3.046	25.9	0.056	24.7	0.053	23.6	0.051	48.3	0.104
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	647.2	1.350	1703.5	3.542	21.5	0.045	22.9	0.048	23.8	0.050	46.7	0.097
S.D.	92.5	0.201	214.3	0.387	2.6	0.006	2.4	0.007	3.8	0.009	6.1	0.015
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-3. Organ weights of male rats at the end of the dosing period

1,2-MD 100 mg/kg																	
Male No.	Body weight (g)	Brain (mg)		Thymus (mg)		Heart (mg)		Liver (mg)		Kidney (R) (mg)		Kidney (L) (mg)		Kidney (mg)		Spleen (mg)	
M03025	467.1	1895.9	4.059	318.6	0.682	1387.3	2.970	13508.7	28.920	1453.5	3.112	1509.9	3.232	2963.4	6.344	652.7	1.397
M03026	467.5	2025.1	4.332	372.3	0.796	1441.0	3.082	13082.0	27.983	1571.3	3.361	1525.5	3.263	3096.8	6.624	845.7	1.809
M03027	449.0	2041.9	4.548	286.9	0.639	1534.5	3.418	12496.8	27.833	1504.6	3.351	1397.6	3.113	2902.2	6.464	701.8	1.563
M03028	496.8	2080.1	4.187	214.7	0.432	1491.0	3.001	14009.4	28.199	1741.6	3.506	1701.4	3.425	3443.0	6.930	784.9	1.580
M03029	477.9	1906.8	3.990	146.7	0.307	1283.4	2.685	13883.8	29.052	1562.5	3.270	1510.0	3.160	3072.5	6.429	739.5	1.547
M03030	475.5	2004.3	4.215	289.5	0.609	1467.9	3.087	13212.6	27.787	1859.3	3.910	1798.4	3.782	3657.7	7.692	732.1	1.540
M03031	450.3	1974.6	4.385	186.0	0.413	1331.6	2.957	12341.0	27.406	1404.5	3.119	1345.6	2.988	2750.1	6.107	603.1	1.339
M03032	502.7	1991.2	3.961	477.6	0.950	1405.3	2.796	14740.7	29.323	1686.8	3.355	1572.5	3.128	3259.3	6.484	797.0	1.585
M03033	475.1	1910.2	4.021	300.9	0.633	1532.9	3.226	13249.3	27.887	1774.1	3.734	1579.2	3.324	3353.3	7.058	765.7	1.612
M03034	514.2	2120.5	4.124	247.5	0.481	1546.1	3.007	15433.5	30.015	1862.5	3.622	1822.7	3.545	3685.2	7.167	879.1	1.710
M03035	519.4	2097.4	4.038	273.2	0.526	1556.1	2.996	14440.8	27.803	1934.4	3.724	1730.0	3.331	3664.4	7.055	1149.6	2.213
M03036	477.4	1981.9	4.151	342.2	0.717	1315.3	2.755	13128.5	27.500	1718.2	3.599	1765.2	3.698	3483.4	7.297	753.2	1.578
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	481.1	2002.5	4.168	288.0	0.599	1441.0	2.998	13627.3	28.309	1672.8	3.472	1604.8	3.332	3277.6	6.804	783.7	1.623
S.D.	22.8	74.7	0.178	87.7	0.179	96.0	0.201	913.7	0.819	172.5	0.252	157.2	0.242	320.3	0.467	138.0	0.222
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	DU	AN	AN	AN	DU	DU	DT	DU	DU	DU	DU	DU	DU	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-3(continued). Organ weights of male rats at the end of the dosing period

1,2-MD 100 mg/kg												
Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymis	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	1226.3	2.625	1260.6	2.699	2486.9	5.324	512.3	1.097	575.2	1.231	1087.5	2.328
M03026	1261.6	2.699	1221.7	2.613	2483.3	5.312	548.1	1.172	543.8	1.163	1091.9	2.336
M03027	1529.4	3.406	1617.5	3.602	3146.9	7.009	555.5	1.237	586.6	1.306	1142.1	2.544
M03028	1542.3	3.104	1554.6	3.129	3096.9	6.234	577.6	1.163	561.1	1.129	1138.7	2.292
M03029	1816.3	3.801	1782.7	3.730	3599.0	7.531	665.1	1.392	671.5	1.405	1336.6	2.797
M03030	1754.4	3.690	1730.9	3.640	3485.3	7.330	618.0	1.300	584.7	1.230	1202.7	2.529
M03031	1661.6	3.690	1658.6	3.683	3320.2	7.373	608.7	1.352	603.1	1.339	1211.8	2.691
M03032	1490.9	2.966	1376.1	2.737	2867.0	5.703	419.1	0.834	409.1	0.814	828.2	1.648
M03033	1525.1	3.210	1582.1	3.330	3107.2	6.540	659.0	1.387	652.4	1.373	1311.4	2.760
M03034	1677.2	3.262	1746.0	3.396	3423.2	6.657	567.4	1.103	607.8	1.182	1175.2	2.285
M03035	1753.2	3.375	1757.1	3.383	3510.3	6.758	648.3	1.248	626.0	1.205	1274.3	2.453
M03036	1735.3	3.635	1767.2	3.702	3502.5	7.337	694.5	1.455	685.3	1.435	1379.8	2.890
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1581.1	3.289	1587.9	3.304	3169.1	6.592	589.5	1.228	592.2	1.234	1181.7	2.463
S.D.	190.2	0.388	199.4	0.415	385.7	0.796	76.7	0.171	72.2	0.165	146.3	0.331
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN	KW	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-3(continued). Organ weights of male rats at the end of the dosing period

1,2-MD 100 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	677.2	1.450	1624.5	3.478	18.9	0.040	18.7	0.040	19.5	0.042	38.2	0.082
M03026	425.0	0.909	1699.6	3.636	24.3	0.052	27.2	0.058	26.5	0.057	53.7	0.115
M03027	677.7	1.509	1634.2	3.640	22.7	0.051	20.6	0.046	19.6	0.044	40.2	0.090
M03028	524.1	1.055	1277.7	2.572	21.9	0.044	18.0	0.036	19.1	0.038	37.1	0.075
M03029	523.5	1.095	1569.1	3.283	21.1	0.044	24.1	0.050	22.8	0.048	46.9	0.098
M03030	431.4	0.907	2149.6	4.521	24.8	0.052	27.6	0.058	34.1	0.072	61.7	0.130
M03031	637.8	1.416	1419.6	3.153	14.6	0.032	21.9	0.049	23.3	0.052	45.2	0.100
M03032	680.1	1.353	1488.0	2.960	17.0	0.034	19.3	0.038	22.3	0.044	41.6	0.083
M03033	602.8	1.269	1811.2	3.812	28.4	0.060	20.6	0.043	20.9	0.044	41.5	0.087
M03034	825.4	1.605	1444.6	2.809	22.5	0.044	20.1	0.039	19.1	0.037	39.2	0.076
M03035	827.4	1.593	1836.9	3.537	21.4	0.041	26.0	0.050	25.1	0.048	51.1	0.098
M03036	833.5	1.746	1845.3	3.865	18.9	0.040	22.6	0.047	27.9	0.058	50.5	0.106
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	638.8	1.326	1650.0	3.439	21.4	0.045	22.2	0.046	23.4	0.049	45.6	0.095
S.D.	144.4	0.280	237.2	0.528	3.7	0.008	3.3	0.007	4.5	0.010	7.5	0.016
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-4. Organ weights of male rats at the end of the dosing period

1,2-MD 300 mg/kg																	
Male No.	Body weight (g)	Brain (mg)		Thymus (mg)		Heart (mg)		Liver (mg)		Kidney (R) (mg)		Kidney (L) (mg)		Kidney (mg)		Spleen (mg)	
M04037	417.0	1896.7	4.548	217.8	0.522	1196.0	2.868	13328.5	31.963	1652.9	3.964	1550.5	3.718	3203.4	7.682	682.0	1.635
M04038	446.3	2004.7	4.492	278.8	0.625	1478.8	3.313	17417.2	39.026	2146.1	4.809	2138.3	4.791	4284.4	9.600	848.0	1.900
M04039	479.2	2046.4	4.270	292.7	0.611	1419.4	2.962	17936.6	37.430	1829.9	3.819	1774.1	3.702	3604.0	7.521	745.5	1.556
M04040	455.6	1966.5	4.316	367.6	0.807	1402.3	3.078	15877.2	34.849	1857.6	4.077	1828.0	4.012	3685.6	8.090	987.3	2.167
M04041	456.2	2035.4	4.462	171.1	0.375	1422.1	3.117	16180.7	35.468	1747.9	3.831	1847.7	4.050	3595.6	7.882	810.5	1.777
M04042	477.5	1983.8	4.155	209.3	0.438	1407.2	2.947	16827.1	35.240	1786.2	3.741	1661.2	3.479	3447.4	7.220	754.9	1.581
M04043	452.1	1949.2	4.311	216.7	0.479	1451.4	3.210	15150.8	33.512	1801.7	3.985	1757.4	3.887	3559.1	7.872	838.4	1.854
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	454.8	1983.2	4.365	250.6	0.551	1396.7	3.071	16102.6	35.355	1831.8	4.032	1793.9	3.948	3625.6	7.981	809.5	1.781
S.D.	20.9	51.8	0.140	66.5	0.144	92.5	0.157	1542.5	2.344	153.6	0.361	183.1	0.421	330.0	0.768	97.7	0.216
Significance	*	NS	**	NS	NS	NS	*	*	**	NS	**	NS	**	NS	**	NS	NS
Statistical method	DU	AN	DU	AN	AN	AN	DU	DU	DT	DU	DU	DU	DU	DU	DU	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-4(continued). Organ weights of male rats at the end of the dosing period

1,2-MD 300 mg/kg												
Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymis	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	1681.0	4.031	1754.0	4.206	3435.0	8.237	480.5	1.152	474.0	1.137	954.5	2.289
M04038	1666.9	3.735	1704.9	3.820	3371.8	7.555	615.7	1.380	625.5	1.402	1241.2	2.781
M04039	1398.8	2.919	1489.9	3.109	2888.7	6.028	523.5	1.092	541.4	1.130	1064.9	2.222
M04040	1586.2	3.482	1589.7	3.489	3175.9	6.971	558.1	1.225	567.4	1.245	1125.5	2.470
M04041	1622.0	3.555	1640.6	3.596	3262.6	7.152	544.4	1.193	539.9	1.183	1084.3	2.377
M04042	1571.1	3.290	1523.5	3.191	3094.6	6.481	600.8	1.258	559.0	1.171	1159.8	2.429
M04043	1519.3	3.361	1520.4	3.363	3039.7	6.724	621.4	1.374	579.1	1.281	1200.5	2.655
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1577.9	3.482	1603.3	3.539	3181.2	7.021	563.5	1.239	555.2	1.221	1118.7	2.460
S.D.	96.7	0.351	100.6	0.380	191.7	0.724	52.2	0.108	46.0	0.097	95.3	0.198
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN	KW	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-1-4(continued). Organ weights of male rats at the end of the dosing period

1,2-MD 300 mg/kg												
Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	445.1	1.067	1470.0	3.525	18.7	0.045	23.3	0.056	23.1	0.055	46.4	0.111
M04038	566.4	1.269	1818.4	4.074	14.7	0.033	25.6	0.057	29.2	0.065	54.8	0.123
M04039	735.1	1.534	1798.7	3.754	19.8	0.041	25.8	0.054	27.2	0.057	53.0	0.111
M04040	569.0	1.249	1542.5	3.386	20.1	0.044	22.3	0.049	21.8	0.048	44.1	0.097
M04041	715.2	1.568	1377.2	3.019	18.9	0.041	22.7	0.050	23.8	0.052	46.5	0.102
M04042	759.9	1.591	1630.3	3.414	17.2	0.036	21.5	0.045	20.9	0.044	42.4	0.089
M04043	637.6	1.410	1974.8	4.368	17.2	0.038	21.5	0.048	19.7	0.044	41.2	0.091
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	632.6	1.384	1658.8	3.649	18.1	0.040	23.2	0.051	23.7	0.052	46.9	0.103
S.D.	113.4	0.197	213.8	0.456	1.9	0.004	1.8	0.004	3.4	0.008	5.2	0.012
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-2-1. Organ weights of male rats at the end of the recovery period

Control (vehicle: corn oil)

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidney		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	480.3	2057.3	4.283	283.2	0.590	1269.8	2.644	11062.5	23.032	1406.2	2.928	1506.5	3.137	2912.7	6.064	772.7	1.609
M01009	461.4	2052.9	4.449	250.9	0.544	1416.8	3.071	12627.5	27.368	1335.1	2.894	1486.7	3.222	2821.8	6.116	777.3	1.685
M01010	525.6	2140.1	4.072	479.3	0.912	1519.0	2.890	11734.4	22.326	1467.8	2.793	1437.3	2.735	2905.1	5.527	818.2	1.557
M01011	575.6	2180.8	3.789	320.1	0.556	1495.8	2.599	16677.8	28.975	1675.4	2.911	1634.1	2.839	3309.5	5.750	837.8	1.456
M01012	479.7	2096.1	4.370	177.0	0.369	1470.5	3.065	11610.5	24.204	1572.5	3.278	1556.0	3.244	3128.5	6.522	699.3	1.458
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	504.5	2105.4	4.193	302.1	0.594	1434.4	2.854	12742.5	25.181	1491.4	2.961	1524.1	3.035	3015.5	5.996	781.1	1.553
S.D.	46.3	54.9	0.266	112.2	0.197	99.5	0.225	2270.5	2.868	134.8	0.185	74.8	0.233	199.7	0.380	53.3	0.099

Control (vehicle: corn oil)

Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymis	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	1739.1	3.621	1712.3	3.565	3451.4	7.186	663.2	1.381	600.4	1.250	1263.6	2.631
M01009	1581.4	3.427	1614.0	3.498	3195.4	6.925	597.9	1.296	592.1	1.283	1190.0	2.579
M01010	1632.6	3.106	1568.9	2.985	3201.5	6.091	610.5	1.162	565.5	1.076	1176.0	2.237
M01011	1785.4	3.102	1793.4	3.116	3578.8	6.218	701.1	1.218	681.9	1.185	1383.0	2.403
M01012	1746.6	3.641	1816.3	3.786	3562.9	7.427	629.1	1.311	631.9	1.317	1261.0	2.629
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1697.0	3.379	1701.0	3.390	3398.0	6.769	640.4	1.274	614.4	1.222	1254.7	2.496
S.D.	86.0	0.265	108.4	0.331	188.7	0.590	41.9	0.085	44.6	0.095	82.1	0.172

Control (vehicle: corn oil)

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	481.6	1.003	1108.3	2.308	16.4	0.034	25.3	0.053	27.1	0.056	52.4	0.109
M01009	380.6	0.825	1445.8	3.134	18.7	0.041	28.6	0.062	27.4	0.059	56.0	0.121
M01010	834.8	1.588	1525.8	2.903	17.3	0.033	21.0	0.040	19.4	0.037	40.4	0.077
M01011	567.4	0.986	1598.0	2.776	29.0	0.050	25.4	0.044	26.1	0.045	51.5	0.089
M01012	713.8	1.488	1907.0	3.975	16.3	0.034	23.8	0.050	24.4	0.051	48.2	0.100
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	595.6	1.178	1517.0	3.019	19.5	0.038	24.8	0.050	24.9	0.050	49.7	0.099
S.D.	181.1	0.338	287.6	0.613	5.4	0.007	2.8	0.008	3.3	0.009	5.9	0.017

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-2-2. Organ weights of male rats at the end of the recovery period

1,2-MD 300 mg/kg

Male No.	Body weight (g)	Brain (mg)		Thymus (mg/g)		Heart (mg)		Liver (mg/g)		Kidney (R) (mg/g)		Kidney (L) (mg/g)		Kidney (mg/g)		Spleen (mg/g)	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	521.4	2067.2	3.965	310.2	0.595	1663.7	3.191	14752.6	28.294	2067.4	3.965	1987.3	3.811	4054.7	7.777	818.1	1.569
M04045	470.5	2097.2	4.457	145.8	0.310	1410.7	2.998	11941.8	25.381	1556.5	3.308	1462.3	3.108	3018.8	6.416	874.3	1.858
M04046	497.3	2046.6	4.115	175.7	0.353	1554.9	3.127	12948.2	26.037	1659.5	3.337	1714.4	3.447	3373.9	6.784	710.4	1.429
M04047	491.4	1980.8	4.031	232.8	0.474	1555.5	3.165	13827.7	28.139	1703.6	3.467	1747.0	3.555	3450.6	7.022	922.0	1.876
M04048	519.0	2092.2	4.031	331.8	0.639	1542.3	2.972	15623.7	30.103	1670.4	3.218	1578.4	3.041	3248.8	6.260	1091.8	2.104
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	499.9	2056.8	4.120	239.3	0.474	1545.4	3.091	13818.8	27.591	1731.5	3.459	1697.9	3.392	3429.4	6.852	883.3	1.767
S.D.	21.0	47.1	0.196	81.3	0.144	89.9	0.099	1450.1	1.898	195.7	0.297	197.6	0.320	385.9	0.598	140.7	0.268
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	*	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

1,2-MD 300 mg/kg

Male No.	Testis (R) (mg)		Testis (L) (mg/g)		Testis (mg)		Epididymis (R) (mg/g)		Epididymis (L) (mg/g)		Epididymis (mg/g)	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	1557.1	2.986	1555.6	2.984	3112.7	5.970	668.4	1.282	643.2	1.234	1311.6	2.516
M04045	1671.1	3.552	1666.5	3.542	3337.6	7.094	683.3	1.452	620.7	1.319	1304.0	2.772
M04046	1699.4	3.417	1582.8	3.183	3282.2	6.600	616.4	1.239	598.1	1.203	1214.5	2.442
M04047	1355.5	2.758	1395.2	2.839	2750.7	5.598	571.5	1.163	565.6	1.151	1137.1	2.314
M04048	1536.0	2.960	1522.5	2.934	3058.5	5.893	674.5	1.300	638.1	1.229	1312.6	2.529
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1563.8	3.135	1544.5	3.096	3108.3	6.231	642.8	1.287	613.1	1.227	1256.0	2.515
S.D.	136.1	0.335	99.1	0.279	230.9	0.605	47.6	0.106	31.9	0.061	78.2	0.167
Significance	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 29-2-2(continued). Organ weights of male rats at the end of the recovery period

1,2-MD 300 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	520.1	0.998	1644.0	3.153	13.8	0.026	25.8	0.049	27.9	0.054	53.7	0.103
M04045	536.8	1.141	1510.3	3.210	19.0	0.040	24.4	0.052	27.2	0.058	51.6	0.110
M04046	539.9	1.086	1751.1	3.521	21.0	0.042	24.9	0.050	23.6	0.047	48.5	0.098
M04047	536.4	1.092	1712.6	3.485	23.6	0.048	23.4	0.048	24.2	0.049	47.6	0.097
M04048	707.5	1.363	1790.1	3.449	19.1	0.037	27.9	0.054	30.6	0.059	58.5	0.113
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	568.1	1.136	1681.6	3.364	19.3	0.039	25.3	0.051	26.7	0.053	52.0	0.104
S.D.	78.3	0.137	109.9	0.169	3.6	0.008	1.7	0.002	2.9	0.005	4.4	0.007
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	AW	TT	TT	TT	AW	TT	TT	TT	TT

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 30-1-1. Organ weights of female rats at the end of the dosing period

Control (vehicle: corn oil)																	
Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidney		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	289.4	1873.7	6.474	102.6	0.355	942.8	3.258	8106.9	28.013	849.0	2.934	862.7	2.981	1711.7	5.915	725.3	2.506
F01002	269.8	1779.6	6.596	227.2	0.842	852.2	3.159	8894.1	32.966	930.8	3.450	915.4	3.393	1846.2	6.843	686.2	2.543
F01003	335.1	1852.5	5.528	246.6	0.736	1040.5	3.105	9489.2	28.318	968.2	2.889	977.9	2.918	1946.1	5.808	649.5	1.938
F01004	317.9	2003.3	6.302	218.6	0.688	1020.1	3.209	10272.6	32.314	927.3	2.917	863.1	2.715	1790.4	5.632	876.8	2.758
F01005	347.6	1901.4	5.470	201.4	0.579	1053.3	3.030	10422.6	29.984	1017.2	2.926	1044.1	3.004	2061.3	5.930	677.5	1.949
F01006	308.2	2061.1	6.688	149.6	0.485	999.5	3.243	10448.0	33.900	1075.9	3.491	964.4	3.129	2040.3	6.620	804.2	2.609
F01007	299.5	1799.7	6.009	80.4	0.268	884.9	2.955	9026.5	30.139	917.2	3.062	870.1	2.905	1787.3	5.968	596.7	1.992
F01008	315.6	1878.7	5.953	176.9	0.561	884.6	2.803	10288.8	32.601	1026.9	3.254	942.4	2.986	1969.3	6.240	989.3	3.135
F01009	285.7	2090.2	7.316	138.5	0.485	1068.8	3.741	10137.7	35.484	1114.5	3.901	1052.2	3.683	2166.7	7.584	768.3	2.689
F01010	330.8	1992.3	6.023	264.6	0.800	992.9	3.002	10156.9	30.704	890.0	2.690	863.3	2.610	1753.3	5.300	675.0	2.041
F01012	328.4	1847.3	5.625	122.4	0.373	1027.5	3.129	10706.5	32.602	1001.6	3.050	994.8	3.029	1996.4	6.079	955.6	2.910
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	311.6	1916.3	6.180	175.3	0.561	978.8	3.149	9813.6	31.548	974.4	3.142	940.9	3.032	1915.4	6.174	764.0	2.461
S.D.	23.7	104.5	0.563	61.2	0.189	75.6	0.239	819.3	2.322	81.0	0.351	71.9	0.296	146.6	0.633	128.8	0.419

Control (vehicle: corn oil)																
Female No.	Ovary (R)		Ovary (L)		Ovary		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	47.1	0.163	51.5	0.178	98.6	0.341	672.3	2.323	11.8	0.041	28.5	0.098	31.1	0.107	59.6	0.206
F01002	63.8	0.236	56.0	0.208	119.8	0.444	689.7	2.556	20.0	0.074	34.0	0.126	38.0	0.141	72.0	0.267
F01003	59.6	0.178	45.8	0.137	105.4	0.315	636.2	1.899	13.2	0.039	33.0	0.098	35.6	0.106	68.6	0.205
F01004	56.0	0.176	49.8	0.157	105.8	0.333	914.5	2.877	11.5	0.036	37.7	0.119	38.0	0.120	75.7	0.238
F01005	56.5	0.163	59.6	0.171	116.1	0.334	606.8	1.746	14.6	0.042	45.2	0.130	47.5	0.137	92.7	0.267
F01006	57.8	0.188	54.2	0.176	112.0	0.363	595.7	1.933	14.2	0.046	38.2	0.124	42.4	0.138	80.6	0.262
F01007	47.6	0.159	43.5	0.145	91.1	0.304	476.3	1.590	12.5	0.042	30.7	0.103	33.4	0.112	64.1	0.214
F01008	53.1	0.168	46.0	0.146	99.1	0.314	569.9	1.806	9.6	0.030	43.2	0.137	45.6	0.144	88.8	0.281
F01009	54.3	0.190	58.2	0.204	112.5	0.394	732.8	2.565	17.8	0.062	32.1	0.112	31.2	0.109	63.3	0.222
F01010	55.2	0.167	52.3	0.158	107.5	0.325	585.2	1.769	15.9	0.048	35.2	0.106	35.3	0.107	70.5	0.213
F01012	58.8	0.179	61.5	0.187	120.3	0.366	599.8	1.826	12.0	0.037	37.0	0.113	39.5	0.120	76.5	0.233
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	55.4	0.179	52.6	0.170	108.0	0.348	643.6	2.081	13.9	0.045	35.9	0.115	38.0	0.122	73.9	0.237
S.D.	4.9	0.022	6.0	0.024	9.3	0.041	112.6	0.424	3.0	0.013	5.1	0.013	5.5	0.015	10.4	0.028

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 30-1-2. Organ weights of female rats at the end of the dosing period

1,2-MD 30 mg/kg																	
Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidney		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	321.0	2117.7	6.597	190.0	0.592	954.8	2.974	10140.5	31.590	1035.2	3.225	985.6	3.070	2020.8	6.295	774.5	2.413
F02014	334.4	2024.1	6.053	323.3	0.967	1119.9	3.349	11029.1	32.982	1029.0	3.077	1038.7	3.106	2067.7	6.183	900.5	2.693
F02015	272.7	1947.9	7.143	120.7	0.443	860.8	3.157	8165.3	29.942	817.6	2.998	813.1	2.982	1630.7	5.980	517.6	1.898
F02016	318.8	1917.2	6.014	201.8	0.633	945.7	2.966	9841.6	30.871	858.0	2.691	832.2	2.610	1690.2	5.302	653.7	2.051
F02017	329.1	1849.8	5.621	278.4	0.846	938.2	2.851	9986.4	30.345	932.9	2.835	934.4	2.839	1867.3	5.674	896.0	2.723
F02018	328.2	1999.3	6.092	299.8	0.913	1148.7	3.500	10796.0	32.895	1097.4	3.344	1136.6	3.463	2234.0	6.807	803.6	2.449
F02020	297.8	1952.0	6.555	121.3	0.407	906.1	3.043	9005.2	30.239	1089.0	3.657	1090.8	3.663	2179.8	7.320	925.7	3.108
F02021	328.6	1864.7	5.675	102.2	0.311	940.2	2.861	10315.9	31.393	899.5	2.737	863.8	2.629	1763.3	5.366	781.4	2.378
F02022	305.8	1797.4	5.878	274.0	0.896	995.7	3.256	9387.4	30.698	897.1	2.934	826.5	2.703	1723.6	5.636	743.4	2.431
F02023	318.7	1910.3	5.994	180.1	0.565	1029.3	3.230	10379.8	32.569	965.0	3.028	914.2	2.869	1879.2	5.896	984.1	3.088
F02024	315.8	1898.6	6.012	207.0	0.655	968.1	3.066	11070.6	35.056	1138.0	3.604	1090.3	3.453	2228.3	7.056	726.3	2.300
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	315.5	1934.5	6.149	209.0	0.657	982.5	3.114	10010.7	31.689	978.1	3.103	956.9	3.035	1935.0	6.138	791.5	2.503
S.D.	17.8	89.0	0.448	76.5	0.223	86.9	0.205	886.4	1.547	106.3	0.324	118.2	0.358	222.4	0.675	133.8	0.379
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

1,2-MD 30 mg/kg																
Female No.	Ovary (R)		Ovary (L)		Ovary		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	49.5	0.154	60.2	0.188	109.7	0.342	887.9	2.766	10.6	0.033	35.8	0.112	39.0	0.121	74.8	0.233
F02014	74.2	0.222	54.6	0.163	128.8	0.385	569.2	1.702	14.8	0.044	39.2	0.117	44.5	0.133	83.7	0.250
F02015	47.6	0.175	45.0	0.165	92.6	0.340	559.0	2.050	23.1	0.085	29.3	0.107	27.5	0.101	56.8	0.208
F02016	41.1	0.129	46.8	0.147	87.9	0.276	513.0	1.609	15.4	0.048	39.6	0.124	39.4	0.124	79.0	0.248
F02017	55.5	0.169	60.2	0.183	115.7	0.352	653.7	1.986	13.9	0.042	30.6	0.093	37.4	0.114	68.0	0.207
F02018	39.2	0.119	57.0	0.174	96.2	0.293	705.3	2.149	13.6	0.041	41.5	0.126	41.1	0.125	82.6	0.252
F02020	56.0	0.188	69.3	0.233	125.3	0.421	684.3	2.298	18.7	0.063	29.8	0.100	34.0	0.114	63.8	0.214
F02021	48.8	0.149	53.8	0.164	102.6	0.312	713.2	2.170	16.6	0.051	36.6	0.111	35.1	0.107	71.7	0.218
F02022	52.7	0.172	52.6	0.172	105.3	0.344	496.4	1.623	14.1	0.046	36.3	0.119	34.9	0.114	71.2	0.233
F02023	64.2	0.201	56.9	0.179	121.1	0.380	756.6	2.374	17.9	0.056	35.5	0.111	41.8	0.131	77.3	0.243
F02024	40.2	0.127	46.4	0.147	86.6	0.274	588.7	1.864	16.8	0.053	31.6	0.100	32.5	0.103	64.1	0.203
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	51.7	0.164	54.8	0.174	106.5	0.338	647.9	2.054	16.0	0.051	35.1	0.111	37.0	0.117	72.1	0.228
S.D.	10.6	0.032	7.2	0.024	14.9	0.047	117.1	0.352	3.3	0.014	4.2	0.010	4.8	0.011	8.4	0.019
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 30-1-3. Organ weights of female rats at the end of the dosing period

1,2-MD 100 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidney		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03025	294.2	1886.9	6.414	203.0	0.690	951.6	3.235	9034.2	30.708	989.4	3.363	1022.1	3.474	2011.5	6.837	670.4	2.279
F03026	323.8	1993.8	6.158	198.1	0.612	1002.2	3.095	11039.6	34.094	941.8	2.909	928.0	2.866	1869.8	5.775	762.7	2.355
F03027	301.0	1844.8	6.129	125.6	0.417	854.3	2.838	9602.3	31.901	838.5	2.786	830.8	2.760	1669.3	5.546	615.7	2.046
F03029	311.6	1795.9	5.763	184.6	0.592	955.6	3.067	10151.3	32.578	838.2	2.690	830.0	2.664	1668.2	5.354	523.4	1.680
F03030	280.8	1768.8	6.299	129.7	0.462	878.5	3.129	9945.2	35.417	888.1	3.163	891.1	3.173	1779.2	6.336	638.8	2.275
F03033	319.2	1737.1	5.442	209.8	0.657	946.6	2.966	10778.7	33.768	897.0	2.810	893.5	2.799	1790.5	5.609	758.0	2.375
F03034	309.0	1991.4	6.445	242.2	0.784	943.3	3.053	10286.9	33.291	918.2	2.972	896.9	2.903	1815.1	5.874	701.7	2.271
F03035	317.6	1928.4	6.072	183.0	0.576	1018.9	3.208	10864.7	34.209	1024.0	3.224	1000.8	3.151	2024.8	6.375	625.9	1.971
Number of females	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	307.2	1868.4	6.090	184.5	0.599	943.9	3.074	10212.9	33.246	916.9	2.990	911.7	2.974	1828.6	5.963	662.1	2.157
S.D.	14.4	98.4	0.340	39.6	0.119	55.5	0.128	683.6	1.480	66.5	0.237	70.3	0.270	135.7	0.505	79.5	0.240
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

1,2-MD 100 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovary		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03025	57.6	0.196	43.0	0.146	100.6	0.342	513.4	1.745	17.6	0.060	24.0	0.082	28.5	0.097	52.5	0.178
F03026	44.0	0.136	56.8	0.175	100.8	0.311	742.2	2.292	11.5	0.036	32.9	0.102	33.4	0.103	66.3	0.205
F03027	40.0	0.133	48.9	0.162	88.9	0.295	525.4	1.746	12.1	0.040	32.3	0.107	35.8	0.119	68.1	0.226
F03029	52.3	0.168	46.5	0.149	98.8	0.317	559.3	1.795	14.7	0.047	32.4	0.104	34.2	0.110	66.6	0.214
F03030	39.8	0.142	46.3	0.165	86.1	0.307	517.3	1.842	19.9	0.071	30.4	0.108	36.2	0.129	66.6	0.237
F03033	42.9	0.134	54.0	0.169	96.9	0.304	526.8	1.650	15.2	0.048	34.2	0.107	35.8	0.112	70.0	0.219
F03034	38.3	0.124	45.8	0.148	84.1	0.272	569.0	1.841	11.7	0.038	32.1	0.104	33.5	0.108	65.6	0.212
F03035	49.5	0.156	56.6	0.178	106.1	0.334	611.1	1.924	12.1	0.038	31.8	0.100	30.7	0.097	62.5	0.197
Number of females	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	45.6	0.149	49.7	0.162	95.3	0.310	570.6	1.854	14.4	0.047	31.3	0.102	33.5	0.109	64.8	0.211
S.D.	6.9	0.024	5.3	0.013	7.9	0.022	76.8	0.195	3.1	0.012	3.1	0.008	2.7	0.011	5.4	0.018
Significance	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 30-1-4. Organ weights of female rats at the end of the dosing period

1,2-MD 300 mg/kg

Female No.	Body weight (g)	Brain (mg) (mg/g)		Thymus (mg) (mg/g)		Heart (mg) (mg/g)		Liver (mg) (mg/g)		Kidney (R) (mg) (mg/g)		Kidney (L) (mg) (mg/g)		Kidney (mg) (mg/g)		Spleen (mg) (mg/g)	
F04043	288.7	1865.1	6.460	191.3	0.663	900.9	3.121	12418.1	43.014	997.3	3.454	927.4	3.212	1924.7	6.667	741.3	2.568
Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mean	288.7	1865.1	6.460	191.3	0.663	900.9	3.121	12418.1	43.014	997.3	3.454	927.4	3.212	1924.7	6.667	741.3	2.568
S.D.																	
Significance	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Statistical method	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Significantly different from the control group (*: P<0.05, **: P<0.01).
 NS: Not significantly different from the control group.
 NA: Not analyzed.

1,2-MD 300 mg/kg

Female No.	Ovary (R) (mg) (mg/g)		Ovary (L) (mg) (mg/g)		Ovary (mg) (mg/g)		Uterus (mg) (mg/g)		Thyroid gland (mg) (mg/g)		Adrenal gland (R) (mg) (mg/g)		Adrenal gland (L) (mg) (mg/g)		Adrenal gland (mg) (mg/g)	
F04043	56.9	0.197	52.3	0.181	109.2	0.378	645.2	2.235	16.6	0.057	34.7	0.120	40.7	0.141	75.4	0.261
Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mean	56.9	0.197	52.3	0.181	109.2	0.378	645.2	2.235	16.6	0.057	34.7	0.120	40.7	0.141	75.4	0.261
S.D.																
Significance	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Statistical method	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Significantly different from the control group (*: P<0.05, **: P<0.01).
 NS: Not significantly different from the control group.
 NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 30-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: corn oil)																	
Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidney		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	287.8	1877.6	6.524	170.8	0.593	886.3	3.080	8026.4	27.889	972.2	3.378	919.1	3.194	1891.3	6.572	629.1	2.186
F05050	301.6	1917.9	6.359	307.0	1.018	983.2	3.260	7687.9	25.490	941.9	3.123	927.2	3.074	1869.1	6.197	602.8	1.999
F05051	295.9	1969.7	6.657	284.3	0.961	827.2	2.796	7598.3	25.679	943.3	3.188	929.1	3.140	1872.4	6.328	533.7	1.804
F05052	283.9	1919.2	6.760	222.3	0.783	852.8	3.004	7679.1	27.049	833.2	2.935	876.0	3.086	1709.2	6.020	484.4	1.706
F05053	275.1	1944.9	7.070	336.1	1.222	862.7	3.136	7095.0	25.791	934.7	3.398	916.4	3.331	1851.1	6.729	626.5	2.277
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	288.9	1925.9	6.674	264.1	0.915	882.4	3.055	7617.3	26.380	925.1	3.204	913.6	3.165	1838.6	6.369	575.3	1.994
S.D.	10.3	34.4	0.268	66.9	0.239	60.2	0.172	335.2	1.043	53.3	0.192	21.7	0.104	73.7	0.285	63.8	0.243

Control (vehicle: corn oil)																
Female No.	Ovary (R)		Ovary (L)		Ovary		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	49.0	0.170	38.4	0.133	87.4	0.304	507.5	1.763	13.2	0.046	37.6	0.131	36.0	0.125	73.6	0.256
F05050	51.5	0.171	50.5	0.167	102.0	0.338	1079.4	3.579	13.3	0.044	32.7	0.108	34.3	0.114	67.0	0.222
F05051	57.1	0.193	43.5	0.147	100.6	0.340	478.3	1.616	15.0	0.051	25.1	0.085	22.7	0.077	47.8	0.162
F05052	43.7	0.154	40.0	0.141	83.7	0.295	599.1	2.110	10.3	0.036	31.2	0.110	33.8	0.119	65.0	0.229
F05053	40.8	0.148	44.7	0.162	85.5	0.311	975.7	3.547	13.3	0.048	29.4	0.107	29.5	0.107	58.9	0.214
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	48.4	0.167	43.4	0.150	91.8	0.318	728.0	2.523	13.0	0.045	31.2	0.108	31.3	0.108	62.5	0.217
S.D.	6.4	0.018	4.7	0.014	8.7	0.020	279.5	0.966	1.7	0.006	4.6	0.016	5.4	0.019	9.7	0.034

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 30-2-2. Organ weights of female rats at the end of the dosing period, satellite group

1,2-MD 300 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidney		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	271.5	1780.4	6.558	153.5	0.565	1018.0	3.750	10998.9	40.512	1174.7	4.327	1206.9	4.445	2381.6	8.772	504.3	1.857
F06060	282.6	1905.9	6.744	184.6	0.653	1004.0	3.553	11254.4	39.824	1035.5	3.664	973.8	3.446	2009.3	7.110	537.2	1.901
F06061	266.0	1971.8	7.413	266.9	1.003	907.0	3.410	10545.6	39.645	928.3	3.490	880.0	3.308	1808.3	6.798	549.7	2.067
F06062	273.1	1828.3	6.695	193.1	0.707	1003.2	3.673	10480.5	38.376	914.9	3.350	914.7	3.349	1829.6	6.699	497.4	1.821
F06063	252.9	1874.4	7.412	156.4	0.618	853.3	3.374	10692.3	42.279	970.1	3.836	956.5	3.782	1926.6	7.618	429.5	1.698
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	269.2	1872.2	6.964	190.9	0.709	957.1	3.552	10794.3	40.127	1004.7	3.733	986.4	3.666	1991.1	7.399	503.6	1.869
S.D.	10.9	73.2	0.415	45.9	0.172	73.0	0.163	325.7	1.429	106.0	0.379	128.6	0.474	232.6	0.847	46.9	0.134
Significance	*	NS	NS	NS	NS	NS	**	**	**	NS	*	NS	*	NS	*	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	AW	AW	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

1,2-MD 300 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovary		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	45.2	0.166	38.0	0.140	83.2	0.306	521.1	1.919	15.6	0.057	28.3	0.104	30.3	0.112	58.6	0.216
F06060	56.7	0.201	63.2	0.224	119.9	0.424	437.5	1.548	16.2	0.057	40.5	0.143	42.7	0.151	83.2	0.294
F06061	45.5	0.171	42.8	0.161	88.3	0.332	300.6	1.130	12.4	0.047	33.8	0.127	34.6	0.130	68.4	0.257
F06062	43.1	0.158	35.0	0.128	78.1	0.286	1113.2	4.076	14.3	0.052	27.2	0.100	30.0	0.110	57.2	0.209
F06063	46.0	0.182	47.4	0.187	93.4	0.369	322.2	1.274	10.7	0.042	25.3	0.100	28.1	0.111	53.4	0.211
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	47.3	0.176	45.3	0.168	92.6	0.343	538.9	1.989	13.8	0.051	31.0	0.115	33.1	0.123	64.2	0.237
S.D.	5.4	0.017	11.1	0.039	16.3	0.055	333.2	1.205	2.3	0.007	6.2	0.019	5.8	0.018	12.0	0.037
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 30-3-1. Organ weights of female rats at the end of the recovery period

Control (vehicle: corn oil)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidney		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	286.1	1832.6	6.405	184.8	0.646	940.8	3.288	6612.6	23.113	881.6	3.081	869.3	3.038	1750.9	6.120	539.6	1.886
F05055	306.7	1798.7	5.865	208.0	0.678	810.6	2.643	6787.1	22.129	749.1	2.442	740.5	2.414	1489.6	4.857	428.6	1.397
F05056	311.6	1873.2	6.012	352.1	1.130	1020.2	3.274	7689.3	24.677	973.2	3.123	1025.0	3.289	1998.2	6.413	718.1	2.305
F05057	288.2	1726.2	5.990	239.8	0.832	820.6	2.847	6729.0	23.348	971.7	3.372	931.2	3.231	1902.9	6.603	405.1	1.406
F05058	305.1	1839.1	6.028	244.9	0.803	885.7	2.903	7804.3	25.579	929.2	3.046	869.4	2.850	1798.6	5.895	510.9	1.675
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	299.5	1814.0	6.060	245.9	0.818	895.6	2.991	7124.5	23.769	901.0	3.013	887.1	2.964	1788.0	5.978	520.5	1.734
S.D.	11.6	55.7	0.203	64.2	0.192	87.3	0.282	573.0	1.360	92.8	0.344	103.8	0.353	192.3	0.683	123.8	0.379

Control (vehicle: corn oil)

Female No.	Ovary (R)		Ovary (L)		Ovary		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	34.4	0.120	38.5	0.135	72.9	0.255	561.2	1.962	18.6	0.065	19.8	0.069	18.5	0.065	38.3	0.134
F05055	29.3	0.096	36.2	0.118	65.5	0.214	418.2	1.364	13.1	0.043	25.5	0.083	29.2	0.095	54.7	0.178
F05056	58.8	0.189	55.8	0.179	114.6	0.368	456.8	1.466	16.1	0.052	41.2	0.132	43.0	0.138	84.2	0.270
F05057	29.0	0.101	45.0	0.156	74.0	0.257	487.9	1.693	15.4	0.053	29.4	0.102	31.3	0.109	60.7	0.211
F05058	41.9	0.137	56.1	0.184	98.0	0.321	586.8	1.923	12.5	0.041	34.1	0.112	32.6	0.107	66.7	0.219
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	38.7	0.129	46.3	0.154	85.0	0.283	502.2	1.682	15.1	0.051	30.0	0.100	30.9	0.103	60.9	0.202
S.D.	12.4	0.037	9.4	0.028	20.6	0.061	70.6	0.267	2.5	0.010	8.2	0.025	8.7	0.026	16.8	0.050

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 30-3-2. Organ weights of female rats at the end of the recovery period

1,2-MD 300 mg/kg																	
Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidney		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06064	280.3	1872.8	6.681	245.9	0.877	903.6	3.224	7355.1	26.240	946.2	3.376	938.6	3.349	1884.8	6.724	579.3	2.067
F06065	264.2	1842.0	6.972	223.7	0.847	912.2	3.453	7298.3	27.624	907.9	3.436	888.5	3.363	1796.4	6.799	631.9	2.392
F06066	269.1	1812.7	6.736	168.4	0.626	839.9	3.121	7419.0	27.570	890.1	3.308	843.7	3.135	1733.8	6.443	542.6	2.016
F06067	269.4	1855.5	6.888	217.0	0.805	816.9	3.032	7729.3	28.691	1000.6	3.714	898.2	3.334	1898.8	7.048	494.9	1.837
F06068	291.5	1822.3	6.251	292.7	1.004	946.7	3.248	7941.4	27.243	1002.0	3.437	1010.4	3.466	2012.4	6.904	538.4	1.847
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	274.9	1841.1	6.706	229.5	0.832	883.9	3.216	7548.6	27.474	949.4	3.454	915.9	3.329	1865.2	6.784	557.4	2.032
S.D.	11.0	24.4	0.279	45.2	0.137	53.8	0.158	275.6	0.879	51.6	0.155	62.7	0.120	106.3	0.226	51.3	0.225
Significance	**	NS	**	NS	NS	NS	NS	NS	**	NS	*	NS	NS	NS	*	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

1,2-MD 300 mg/kg																
Female No.	Ovary (R)		Ovary (L)		Ovary		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06064	49.8	0.178	56.0	0.200	105.8	0.377	1210.5	4.319	15.0	0.054	28.7	0.102	29.0	0.103	57.7	0.206
F06065	45.2	0.171	40.5	0.153	85.7	0.324	675.7	2.558	15.0	0.057	24.3	0.092	29.1	0.110	53.4	0.202
F06066	37.6	0.140	40.5	0.151	78.1	0.290	394.2	1.465	17.6	0.065	31.5	0.117	30.6	0.114	62.1	0.231
F06067	39.6	0.147	38.5	0.143	78.1	0.290	455.7	1.692	14.6	0.054	29.4	0.109	32.0	0.119	61.4	0.228
F06068	51.9	0.178	35.5	0.122	87.4	0.300	397.8	1.365	12.7	0.044	30.1	0.103	34.6	0.119	64.7	0.222
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	44.8	0.163	42.2	0.154	87.0	0.316	626.8	2.280	15.0	0.055	28.8	0.105	31.1	0.113	59.9	0.218
S.D.	6.2	0.018	8.0	0.029	11.3	0.037	346.0	1.233	1.7	0.008	2.7	0.009	2.3	0.007	4.4	0.013
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	AW	AW	TT	TT	TT	TT	AW	AW	AW	AW

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 31-1. Macroscopic findings of male rats at the end of the dosing period

Findings	Group	Control (vehicle: corn oil)							1,2-MD 30 mg/kg																1,2-MD 100 mg/kg										1,2-MD 300 mg/kg																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
	Animal No.	M01	M01	M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02</

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 31-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
	Animal No.	M01	M01	M01	M01	M01	M04	M04	M04	M04	M04
		008	009	010	011	012	044	045	046	047	048
All organs		-	-	-	-	-	-	-	-	-	-

Notes) - : No abnormal changes P : Non-graded change

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 32-1. Macroscopic findings of female rats at the end of the dosing period

[illegible]

Notes) - : No abnormal changes P : Non-graded change

Fate : blanks, Subjected to autopsy on day 5 of lactation; DP, Died during pregnancy; NP, Not pregnant; TL, Total litter loss during lactation; NC, Not copulated.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 32-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		049	050	051	052	053	059	060	061	062	063
All organs											
		-	-	-	-	-	-	-	-	-	-
Notes) - : No abnormal changes P : Non-graded change											

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 32-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		054	055	056	057	058	064	065	066	067	068
All organs		-	-	-	-	-	-	-	-	-	-
Notes) - : No abnormal changes P : Non-graded change											

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 33-1. Histopathological findings of male rats at the end of the dosing period

[illegible]

Notes) - : No abnormal changes $\pm$: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Findings	Group Animal No.	Control (vehicle: corn oil)							1,2-MD 30 mg/kg																1,2-MD 100 mg/kg												1,2-MD 300 mg/kg							
		M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043					
Liver							NE	NE						NE	NE	NE	NE	NE	NE	NE	NE						NE	NE	NE	NE	NE	NE	NE											
Fatty change, hepatocyte, periportal		±	-	±	+	+			±	±	+	±	+								+	+	-	+	±	±																		
Ground glass appearance, hepatocyte, centrilobular		-	-	-	-	-			-	-	-	-	-								-	-	-	-	+	-																		
Hypertrophy, hepatocyte, centrilobular		-	-	-	-	-			-	-	-	-	-								+	±	±	±	-	±																		
Microgranuloma		-	-	±	-	-			±	±	-	+	+								±	±	±	+	+	+																		
Vacuolation, cytoplasmic, hepatocyte, centrilobular		-	-	-	-	-			-	+	-	-	±								-	-	-	-	-	-																		
Pancreas							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE							NE	NE				
Cellular infiltration, lymphocyte, interstitial		-	-	-	-	-																																						
Hemorrhage, focal		-	-	-	-	-																																						
Stomach							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE								NE	NE				
Duodenum							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE									NE	NE			
Jejunum							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE									NE	NE			
Ileum							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE									NE	NE			
Cecum							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE									NE	NE			
Colon							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE									NE	NE			
Rectum							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE									NE	NE			
Lymph node, mesenteric							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE									NE	NE			
Spleen							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE									NE	NE			
Deposit, pigment, brown		±	+	±	±	+																																						
Hematopoiesis, extramedullary		±	2+	±	2+	±																																						

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Findings	Group Animal No.	Control (vehicle: corn oil)							1,2-MD 30 mg/kg														1,2-MD 100 mg/kg														1,2-MD 300 mg/kg																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
		M01	M01	M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02</

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 33-2. Histopathological findings of male rats at the end of the recovery period

Findings	Group Animal No.	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
		M01	M01	M01	M01	M01	M04	M04	M04	M04	M04
		008	009	010	011	012	044	045	046	047	048
Brain		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		-	-	-	-	-	-	-	-	-	-
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland											
Ultimobranchial body		-	-	-	P	-	P	-	-	-	P
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 33-2(continued). Histopathological findings of male rats at the end of the recovery period

Group		Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
Findings	Animal No.	M01	M01	M01	M01	M01	M04	M04	M04	M04	M04
		008	009	010	011	012	044	045	046	047	048
Liver											
	Fatty change, hepatocyte, periportal	±	±	±	±	±	±	±	±	±	±
	Hypertrophy, hepatocyte, centrilobular	-	-	-	-	-	-	-	-	-	±
	Microgranuloma	±	-	-	-	-	-	±	-	-	-
	Vacuolation, cytoplasmic, hepatocyte, centrilobular	-	-	-	±	-	-	-	-	+	-
Pancreas											
	Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach											
	Stomach	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Duodenum											
	Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum											
	Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum											
	Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum											
	Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon											
	Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum											
	Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric											
	Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen											
	Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 33-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
	Animal No.	M01	M01	M01	M01	M01	M04	M04	M04	M04	M04
		008	009	010	011	012	044	045	046	047	048
Kidney											
Basophilic tubule, cortex		±	-	±	±	±	-	±	±	±	+
Cast, hyalin		-	±	-	±	-	±	-	-	-	±
Cellular infiltration, lymphocyte, interstitial		-	-	-	±	±	-	-	-	±	±
Mineralization, cortex/medulla		-	-	±	-	-	-	-	-	±	-
Urinary bladder											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland											
Increase, lipid content, zona fasciculata		-	-	±	±	-	-	±	-	-	±
Testis											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Epididymis											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Prostate											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Seminal vesicle											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Coagulating gland											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Appendix 34-1. Histopathological findings of female rats at the end of the dosing period

Notes) -: No abnormal changes +: Very slight ++: Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Fate : blanks, Subjected to autopsy on day 5 of lactation; DP, Died during pregnancy; NP, Not pregnant; TL, Total litter loss during lactation; NC, Not copulated.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 34-1 (continued). Histopathological findings of female rats at the end of the dosing period

[illegible]

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate : blanks, Subjected to autopsy on day 5 of lactation; DP, Died during pregnancy; NP, Not pregnant; TL, Total litter loss during lactation; NC, Not copulated.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 34-1(continued). Histopathological findings of female rats at the end of the dosing period

[illegible]

Notes) - : No abnormal changes ± Very slight + : Slight 2+ : Moderate 3+ : Marked

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Fate : blanks, Subjected to autopsy on day 5 of lactation; DP, Died during pregnancy; NP, Not pregnant; TL, Total litter loss during lactation; NC, Not copulated.

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Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 34-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Animal No.	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		049	050	051	052	053	059	060	061	062	063
Brain		-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-
Thyroid gland											
Cellular infiltration, lymphocyte, interstitial		-	-	-	-	-	+	-	-	-	-
Ultimobranchial body		-	P	-	-	-	-	-	-	-	-
Parathyroid gland											
Vacuolation, cytoplasmic		±	-		M	M	-	-	±	-	-
Thymus											
Atrophy		+	-	-	+	±	+	±	-	±	±
Heart		-	-	-	-	-	-	-	-	-	-
Trachea		-	-	-	-	-	-	-	-	-	-
Lung											
Accumulation, foam cell, alveolus		-	-	-	-	-	-	-	-	±	-
Bronchus		-	-	-	-	-	-	-	-	-	-

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Animal No.	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		049	050	051	052	053	059	060	061	062	063
Liver											
Fatty change, hepatocyte, periportal		±	±	±	±	±	±	±	+	+	±
Ground glass appearance, hepatocyte, centrilobular		-	-	-	-	-	+	±	±	±	±
Hypertrophy, hepatocyte, centrilobular		-	-	-	-	-	2+	+	2+	2+	2+
Microgranuloma		±	±	-	-	±	±	±	±	±	±
Pancreas											
		-	-	-	-	-	-	-	-	-	-
Stomach											
		-	-	-	-	-	-	-	-	-	-
Duodenum											
		-	-	-	-	-	-	-	-	-	-
Jejunum											
		-	-	-	-	-	-	-	-	-	-
Ileum											
		-	-	-	-	-	-	-	-	-	-
Cecum											
		-	-	-	-	-	-	-	-	-	-
Colon											
		-	-	-	-	-	-	-	-	-	-
Rectum											
		-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric											
		-	-	-	-	-	-	-	-	-	-
Spleen											
Deposit, pigment, brown		+	+	2+	2+	2+	+	+	2+	2+	2+
Hematopoiesis, extramedullary		2+	+	±	±	±	+	+	±	+	+

(Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Animal No.	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		049	050	051	052	053	059	060	061	062	063
Kidney											
Basophilic tubule, cortex		-	-	±	±	-	+	±	±	-	-
Cast, hyalin		-	-	-	±	-	-	-	±	±	-
Cellular infiltration, lymphocyte, interstitial		-	-	-	±	-	±	-	-	±	-
Cyst, cortex		-	-	-	-	-	-	-	P	-	-
Mineralization, cortex		-	-	-	-	-	±	±	-	-	-
Urinary bladder											
		-	-	-	-	-	-	-	-	-	-
Adrenal gland											
Hypertrophy, zona glomerulosa		-	-	±	-	-	-	-	-	±	±
Increase, lipid content, zona fasciculata		±	-	-	-	-	±	±	-	-	-
Ovary											
Cyst, follicular		±	-	-	-	-	-	-	-	±	-
Cyst, luteinized		-	-	-	-	-	+	-	-	-	-
Increase, atretic follicle		±	-	-	-	-	+	±	-	-	-
Uterus											
Dilatation, cystic, uterin gland		-	-	-	-	-	P	-	-	-	-
Dilatation, lumen		-	+	-	-	+	-	-	-	+	-
Vagina											
Cellular infiltration, lymphocyte, lamina propria		-	-	-	-	-	±	-	-	-	-
Eyeball											
		-	-	-	-	-	-	-	-	-	-
Harderian gland											
Cellular infiltration, lymphocyte, interstitial		-	-	-	-	-	-	±	-	-	±
Sciatic nerve											
		-	-	-	-	-	-	-	-	-	-
Skeletal muscle											
		-	-	-	-	-	-	-	-	-	-
Femur											
		-	-	-	-	-	-	-	-	-	-
Marrow, femur											
Increase, hematopoiesis		+	+	±	-	+	±	±	+	+	±

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 34-3. Histopathological findings of female rats at the end of the recovery period

Findings	Group Animal No.	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		054	055	056	057	058	064	065	066	067	068
Brain		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		-	-	-	-	-	-	-	-	-	-
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland											
Ectopic thymic tissue		-	-	P	-	-	-	-	-	-	-
Ultimobranchial body		-	-	-	-	-	-	P	P	-	-
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 34-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group Animal No.	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		054	055	056	057	058	064	065	066	067	068
Liver											
Fatty change, hepatocyte, periportal		±	±	±	±	±	±	±	±	±	±
Microgranuloma		±	±	±	±	±	±	±	±	±	±
Necrosis, focal		-	-	-	-	-	±	-	-	-	-
Pancreas		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Duodenum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 34-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group Animal No.	Control (vehicle: corn oil)					1,2-MD 300 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		054	055	056	057	058	064	065	066	067	068
Kidney		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland		-	-	-	-	-	-	-	-	-	-
Ovary		-	-	-	-	-	-	-	-	-	-
Uterus											
Dilatation, cystic, uterin gland		-	-	-	-	-	P	-	-	-	-
Dilatation, lumen		-	-	-	-	-	+	-	-	-	-
Vagina		-	-	-	-	-	-	-	-	-	-
Eyeball		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 35-1. Results of observations about estrous cycle

Control (vehicle: corn oil)

Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F01001	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1	
F01002	D E D D P E D D P E D D D E	4-day	4.0	D D D E D D P E D D P E D D	4-day	4.0	P PL	1	
F01003	D P E D D P E D D P E D D D	4-day	4.0	E D D D E D D P E D D D E D	4-day	4.0	D P PL	1	
F01004	D D P E D D P E D D P E D D	4-day	4.0	P E D D D E D D P E D D P E	4-day	4.0	D D P PL	1	
F01005	P E D D D P E D D D E D D P	4-5-day	4.5	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1	
F01006	D P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1	
F01007	D P E D D D E D D P E D D P	4-day	4.0	E D D P E D D P E D D D E D	4-day	4.0	D P PL	1	
F01008	D P E D D D E D D P E D D P	4-day	4.0	E D D P E D D P E D D D E D	4-day	4.0	D P PL	1	
F01009	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D D E	4-day	4.0	D D P PL	1	
F01010	E D D D E D D P E D D D E D	4-day	4.0	D D E D D P E D D P E D D D	4-day	4.0	PL	1	
F01011	D D D P E D D D E E D D D P	5-day	5.0	E D D D P E D D D P E D D D	5-day	5.0	P PL	1	
F01012	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1	
Mean			4.1			4.1		1.0	
S.D.			0.3			0.3		0.0	
(N)			(12)			(12)		(12)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 35-2. Results of observations about estrous cycle

1,2-MD 30 mg/kg

Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F02013	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1	
F02014	P E D D D E D D D E D D D E	4-day	4.0	D D D E D D D E D D D E D D	4-day	4.0	P PL	1	
F02015	D P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1	
F02016	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1	
F02017	D E D D D E D D D E D D D E	4-day	4.0	D D D E D D D E D D P E D D	4-day	4.0	P PL	1	
F02018	P E D D P E D D D E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1	
F02019	E D D D E D D D E D D D E D	4-day	4.0	D P E D D D E E D D D E E D	5-day	5.0	D D PL	1	
F02020	E D D D E D D D E D D D E D	4-day	4.0	D P E D D D E D D D E D D P	4-day	4.0	PL	1	
F02021	D P E D D D E D D D E E D D	4-5-day	4.5	D E E D D P E D D D E E D D	4-5-day	4.5	P PL	1	
F02022	D E D D D E D D D E D D P E	4-day	4.0	D D D E D D D E D D D P E D	4-5-day	4.5	D D PL	1	
F02023	E D D P E D D D E D D D E D	4-day	4.0	D P E D D P E D D D E D D D	4-day	4.0	PL	1	
F02024	D E D D D E D D P E D D D E	4-day	4.0	D D D E D D D E D D D E D D	4-day	4.0	P PL	1	
Mean			4.0			4.2		1.0	
S.D.			0.1			0.3		0.0	
(N)			(12)			(12)		(12)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 35-3. Results of observations about estrous cycle

1,2-MD 100 mg/kg

Animal no.	Pre-mating period							Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period				Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)				
F03025	D D E D D D E D D D P E D D	4-5-day	4.5	P E D D D E D D P E D D D E	4-day	4.0	D D P PL	1		
F03026	D P E D D P E D D P E D D P	4-day	4.0	E D D P E D D D E D D P E D	4-day	4.0	D P PL	1		
F03027	D E D D P E D D P E D D P E	4-day	4.0	D D D E D D D E D D P E D D	4-day	4.0	P PL	1		
F03028	D D E D D D E D D P E D D D	4-day	4.0	E E D D D E D D D E D D D E	4-day	4.0	D D P PL	1		
F03029	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1		
F03030	D P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1		
F03031	D D E D D D P E D D D P E D	5-day	5.0	D D P E D D D D E D D D E D	4-5-day	4.5	D D SP	1		
F03032	E D D D E D D P E D D D E D	4-day	4.0	D P E D D P E D D D E D D P	4-day	4.0	PL	1		
F03033	D D D E D D D P E D D D E D	4-5-day	4.5	D D E D D P E D D P E D D P	4-day	4.0	PL	1		
F03034	E D D D E D D D E D D D E D	4-day	4.0	D D E D D D E E D D D D E D	5-day	5.0	D D PL	1		
F03035	D D E D D D E D D D E D D D	4-day	4.0	E D D D E D D P E D D P E D	4-day	4.0	D P PL	1		
F03036	D D D P E D D D P E D D D E	5-day	5.0	E D D D E D D P E D D D E E	4-5-day	4.5	D D D E SP	1		
Mean			4.3			4.2		1.0		
S.D.			0.4			0.3		0.0		
(N)			(12)			(12)		(12)		

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 35-4. Results of observations about estrous cycle

1,2-MD 300 mg/kg

Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F04037	D D P E D D P E D D P E D D	4-day	4.0	P E E D D D E E D D P E E D	5-day	5.0	D P E E SP	1	
F04038	D D P E D D D E D D P E D D	4-day	4.0	P E D D P E D D D E D D D E	4-day	4.0	D D P SP	1	
F04039	E D D P E D D P E D D P E D	4-day	4.0	D P E E D P P P E D D P E D	Irregular	4.5	D P E PL	1	
F04040	E D D D E D D D E D D D E D	4-day	4.0	D D E E D D D E E P P P P P	Irregular	5.0	D D D PL	1	
F04041	D E D D P E D D P E D D D E	4-day	4.0	D D D P E D D P E E D D D E	5-day	5.0	PL	1	
F04042	P E D D D P E D D D E E D D	5-day	5.0	D P E D D D E E D D D E D D	4-5-day	4.5	P PL	1	
F04043	P E D D D E D D P E D D P E	4-day	4.0	D D P E E D D P E D D P E D	4-5-day	4.3	D P PL	1	
F04044	P E D D D E D D P E D D P E	4-day	4.0	D D D E E D D P E D D P E D	4-5-day	4.3	D P E D D P PL	2	
F04045	E D D P E D D D E D D P E D	4-day	4.0	D P E E D D D D D D D P E D	Irregular	9.0	D P PL	1	
F04046	D P E D D D E D D P E D D P	4-day	4.0	E E D D P E E D D E E D D D	4-5-day	4.5	E E D D D D E E D D P P D D	-	
F04047	D E D D D P E D D D E D D P	4-5-day	4.5	E E D D D E E D D D E E D D	5-day	5.0	D E D D SP	2	
F04048	P E D D P E D D P E D D P E	4-day	4.0	D D P E E D D P E D D P E D	4-5-day	4.3	D P PL	1	
Mean			4.1			5.0	**	1.2	
S.D.			0.3			1.3		0.4	
(N)			(12)			(12)		(11)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Significantly different from the control group (*: $p<0.05$, **: $p<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 36-1. Results of observations about reproductive performance

Control (vehicle: corn oil)

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M01001	F01001	+	+	4
M01002	F01002	+	+	2
M01003	F01003	+	+	3
M01004	F01004	+	+	4
M01005	F01005	+	+	3
M01006	F01006	+	+	3
M01007	F01007	+	+	3
M01008	F01008	+	+	3
M01009	F01009	+	+	4
M01010	F01010	+	+	1
M01011	F01011	+	+	2
M01012	F01012	+	+	2
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.8
S.D.				0.9
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 36-2. Results of observations about reproductive performance

1,2-MD 30 mg/kg

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M02013	F02013	+	+	1
M02014	F02014	+	+	2
M02015	F02015	+	+	3
M02016	F02016	+	+	2
M02017	F02017	+	+	2
M02018	F02018	+	+	2
M02019	F02019	+	-	3
M02020	F02020	+	+	1
M02021	F02021	+	+	2
M02022	F02022	+	+	3
M02023	F02023	+	+	1
M02024	F02024	+	+	2
Total		+: 12, -: 0	+: 11, -: 1	
Mean				2.0
S.D.				0.7
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 36-3. Results of observations about reproductive performance

1,2-MD 100 mg/kg

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M03025	F03025	+	+	4
M03026	F03026	+	+	3
M03027	F03027	+	+	2
M03028	F03028	+	+	4
M03029	F03029	+	+	1
M03030	F03030	+	+	3
M03031	F03031	+	+	3
M03032	F03032	+	-	1
M03033	F03033	+	+	1
M03034	F03034	+	+	3
M03035	F03035	+	+	3
M03036	F03036	+	-	5
Total		+: 12, -: 0	+: 10, -: 2	
Mean				2.8
S.D.				1.3
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 36-4. Results of observations about reproductive performance

1,2-MD 300 mg/kg

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M04037	F04037	+	-	5
M04038	F04038	+	-	4
M04039	F04039	+	+	4
M04040	F04040	+	+	4
M04041	F04041	+	+	1
M04042	F04042	+	+	2
M04043	F04043	+	+	3
M04044	F04044	+	+	7
M04045	F04045	+	-	3
M04046	F04046	-		
M04047	F04047	+	-	5
M04048	F04048	+	+	3
Total		+: 11, -: 1	+: 7, -: 4 *	
Mean				3.7
S.D.				1.6
(N)				(11)

+, confirmed

-, not confirmed

Significantly different from the control group (*: $p < 0.05$, **: $p < 0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 37-1. Observation of offspring (F₁)

Control (vehicle; corn oil)																				
Dam No.	Gestation length	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring				External abnormalities ^{b)}		
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio	Viability index	(Number)	(%)	
							Male	Female	Total											
F01001	22	14	14	100.0	+	13	7	6	13	0.54	0	92.9	92.9	100.0	7	6	0.54	100.0	0	0.0
F01002	21	16	16	100.0	+	15	7	8	15	0.47	0	93.8	93.8	100.0	7	8	0.47	100.0	0	0.0
F01003	22	14	13	92.9	+	11	5	6	11	0.45	0	84.6	84.6	100.0	5	6	0.45	100.0	0	0.0
F01004	22	15	14	93.3	+	13	5	8	13	0.38	0	92.9	92.9	100.0	5	6	0.45	84.6	0	0.0
F01005	22	19	18	94.7	+	15	10	5	15	0.67	0	83.3	83.3	100.0	10	5	0.67	100.0	0	0.0
F01006	22	19	18	94.7	+	18	6	12	18	0.33	0	100.0	100.0	100.0	6	12	0.33	100.0	0	0.0
F01007	22	14	14	100.0	+	14	7	7	14	0.50	0	100.0	100.0	100.0	7	7	0.50	100.0	0	0.0
F01008	22	16	16	100.0	+	14	9	5	14	0.64	0	87.5	87.5	100.0	9	5	0.64	100.0	0	0.0
F01009	22	18	18	100.0	+	17	10	7	17	0.59	0	94.4	94.4	100.0	10	7	0.59	100.0	0	0.0
F01010	22	16	16	100.0	+	14	7	7	14	0.50	0	87.5	87.5	100.0	7	7	0.50	100.0	0	0.0
F01011	Died on day 22 of pregnancy																			
F01012	22	16	16	100.0	+	13	7	6	13	0.54	0	81.3	81.3	100.0	7	6	0.54	100.0	0	0.0
Number of dams	11	11	11	11	11 ^{a)}	11			11	11	11	11	11	11			11	11	11	11
Total		177	173			157	80	77	157		0				80	75			0	
Mean	21.9	16.1	15.7	97.8		14.3	7.3	7.0	14.3	0.51	0.0	90.7	90.7	100.0	7.3	6.8	0.52	98.6		0.0
S.D.	0.3	1.9	1.8	3.1		2.0	1.7	1.9	2.0	0.10	0.0	6.4	6.4	0.0	1.7	1.9	0.10	4.6		0.0
%					100.0															

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

b): Number of external abnormalities in live offspring at birth.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 37-2. Observation of offspring (F₁)

1,2-MD 30 mg/kg																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implan- tation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring			External abnormalities ^{b)}			
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio			Viability index (%)	
							Male	Female	Total											
																	(Number)	(%)		
F02013	22	14	14	100.0	+	13	6	7	13	0.46	0	92.9	92.9	100.0	6	7	0.46	100.0	0	0.0
F02014	22	17	17	100.0	+	16	6	10	16	0.38	0	94.1	94.1	100.0	6	10	0.38	100.0	0	0.0
F02015	22	15	15	100.0	+	14	7	7	14	0.50	0	93.3	93.3	100.0	6	6	0.50	85.7	0	0.0
F02016	22	15	14	93.3	+	13	5	8	13	0.38	0	92.9	92.9	100.0	5	8	0.38	100.0	0	0.0
F02017	22	15	15	100.0	+	12	5	6	11	0.45	1	80.0	73.3	91.7	3	6	0.33	81.8	1	9.1
F02018	22	16	16	100.0	+	15	5	10	15	0.33	0	93.8	93.8	100.0	5	10	0.33	100.0	0	0.0
F02019	Not pregnant																			
F02020	22	17	16	94.1	+	16	7	9	16	0.44	0	100.0	100.0	100.0	7	9	0.44	100.0	0	0.0
F02021	23	15	15	100.0	+	15	8	7	15	0.53	0	100.0	100.0	100.0	8	6	0.57	93.3	0	0.0
F02022	22	19	17	89.5	+	14	3	11	14	0.21	0	82.4	82.4	100.0	3	11	0.21	100.0	0	0.0
F02023	22	15	15	100.0	+	15	5	10	15	0.33	0	100.0	100.0	100.0	5	10	0.33	100.0	0	0.0
F02024	23	19	17	89.5	+	12	5	7	12	0.42	0	70.6	70.6	100.0	5	7	0.42	100.0	0	0.0
Number of dams	11	11	11	11	11 ^{a)}	11			11	11	11	11	11	11			11	11	11	11
Total		177	171			155	62	92	154		1				59	90			1	
Mean	22.2	16.1	15.5	96.9		14.1	5.6	8.4	14.0	0.40	0.1	90.9	90.3	99.2	5.4	8.2	0.40	96.4		0.8
S.D.	0.4	1.7	1.1	4.4		1.4	1.4	1.7	1.6	0.09	0.3	9.4	10.3	2.5	1.5	1.9	0.10	6.6		2.7
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	DT	DU	DU	DT	KW	DT	DT	DT	DT	DU	DU	DU	DT		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

b): Number of external abnormalities in live offspring at birth.

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 37-3. Observation of offspring (F₁)

1,2-MD 100 mg/kg																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring				External abnormalities ^{b)}		
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio	Viability index (%)	(Number)	(%)	
							Male	Female	Total											
F03025	22	16	16	100.0	+	16	6	4	10	0.60	6	100.0	62.5	62.5	6	3	0.67	90.0	0	0.0
F03026	22	17	16	94.1	+	15	9	6	15	0.60	0	93.8	93.8	100.0	6	6	0.50	80.0	0	0.0
F03027	22	14	14	100.0	+	14	5	7	12	0.42	2	100.0	85.7	85.7	4	6	0.40	83.3	0	0.0
F03028	22	17	17	100.0	+	17	14	3	17	0.82	0	100.0	100.0	100.0	0	0		0.0	0	0.0
F03029	22	15	15	100.0	+	15	7	8	15	0.47	0	100.0	100.0	100.0	7	8	0.47	100.0	0	0.0
F03030	22	16	15	93.8	+	15	7	8	15	0.47	0	100.0	100.0	100.0	6	7	0.46	86.7	0	0.0
F03031	22	18	18	100.0	+	17	9	8	17	0.53	0	94.4	94.4	100.0	0	0		0.0	0	0.0
F03032	Not pregnant																			
F03033	23	15	14	93.3	+	14	5	6	11	0.45	3	100.0	78.6	78.6	5	6	0.45	100.0	0	0.0
F03034	22	15	15	100.0	+	15	5	8	13	0.38	2	100.0	86.7	86.7	3	7	0.30	76.9	0	0.0
F03035	22	18	14	77.8	+	12	4	8	12	0.33	0	85.7	85.7	100.0	3	7	0.30	83.3	0	0.0
F03036	Not pregnant																			
Number of dams	10	10	10	10	10 ^{a)}	10			10	10	10	10	10	10			8	10	10	10
Total		161	154			150	71	66	137		13				40	50		0		
Mean	22.1	16.1	15.4	95.9		15.0	7.1	6.6	13.7	0.51	1.3	97.4	88.7	91.4	4.0	5.0	0.44	70.0		0.0
S.D.	0.3	1.4	1.3	7.0		1.5	3.0	1.8	2.5	0.14	2.0	4.8	11.8	12.9	2.5	2.9	0.12	37.7		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	NS	*		NS
Statistical method	DU	AN	AN	AN	AN	DT	DU	DU	DT	KW	DT	DT	DT	DT	DU	DU	DU	DT		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

b): Number of external abnormalities in live offspring at birth.

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 37-4. Observation of offspring (F₁)

1,2-MD 300 mg/kg																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan- tation scars	Implan- tation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring				External abnormalities ^{b)}		
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio	Viability index (%)	(Number)	(%)	
							Male	Female	Total											
F04037	Not pregnant																			
F04038	Not pregnant																			
F04039	23	13	13	100.0	+	4	1	2	3	0.33	1	30.8	23.1	75.0	0	0		0.0	0	0.0
F04040	23	14	14	100.0	+	12	4	5	9	0.44	3	85.7	64.3	75.0	0	0		0.0	0	0.0
F04041	22	14	13	92.9	+	12	5	7	12	0.42	0	92.3	92.3	100.0	0	0		0.0	0	0.0
F04042	22	14	14	100.0	+	12	4	7	11	0.36	1	85.7	78.6	91.7	0	0		0.0	0	0.0
F04043	22	16	16	100.0	+	14	7	7	14	0.50	0	87.5	87.5	100.0	5	4	0.56	64.3	0	0.0
F04044	23	17	17	100.0	+	15	4	2	6	0.67	9	88.2	35.3	40.0	0	0		0.0	0	0.0
F04045	Not pregnant																			
F04046	Not copulated																			
F04047	Not pregnant																			
F04048	23	19	18	94.7	+	2	1	0	1	1.00	1	11.1	5.6	50.0	0	0		0.0	0	0.0
Number of dams	7	7	7	7	7 ^{a)}	7	7	7	7	7	7	7	7	7			1	7	7	7
Total		107	105			71	26	30	56		15				5	4			0	
Mean	22.6	15.3	15.0	98.2		10.1	3.7	4.3	8.0	0.53	2.1	68.8	55.2	76.0	0.7	0.6	0.56	9.2		0.0
S.D.	0.5	2.1	2.0	3.1		5.0	2.1	2.9	4.8	0.23	3.2	33.2	34.0	23.7	1.9	1.5		24.3		0.0
%					100.0															
Significance	**	NS	NS	NS	NS	NS	**	*	**	NS	**	NS	*	**	**	**	---	**		NS
Statistical method	DU	AN	AN	AN	AN	DT	DU	DU	DT	KW	DT	DT	DT	DT	DU	DU	NA	DT		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

b): Number of external abnormalities in live offspring at birth.

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 38-1. Body weights of offspring (F₁) before weaning

Control (vehicle: corn oil)						
Dam No.	Days after birth					
	Male body weight				Female body weight	
	0	4	0	4	0	4
F01001	7.0 (7)	10.9 (7)	6.5 (6)	10.3 (6)		
F01002	6.1 (7)	9.6 (7)	5.9 (8)	9.5 (8)		
F01003	6.9 (5)	12.5 (5)	6.2 (6)	11.2 (6)		
F01004	6.1 (5)	11.0 (5)	6.1 (8)	11.2 (6)		
F01005	7.0 (10)	11.4 (10)	6.4 (5)	10.6 (5)		
F01006	6.2 (6)	9.7 (6)	6.0 (12)	9.2 (12)		
F01007	7.2 (7)	11.1 (7)	6.8 (7)	10.6 (7)		
F01008	7.1 (9)	10.6 (9)	6.6 (5)	10.4 (5)		
F01009	6.6 (10)	10.0 (10)	6.0 (7)	9.2 (7)		
F01010	7.0 (7)	11.7 (7)	6.8 (7)	10.8 (7)		
F01011	Died on day 22 of pregnancy					
F01012	6.6 (7)	11.1 (7)	6.3 (6)	10.5 (6)		
Number of dams	11	11	11	11		
Mean	6.7	10.9	6.3	10.3		
S.D.	0.4	0.9	0.3	0.7		

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 38-2. Body weights of offspring (F₁) before weaning

1,2-MD 30 mg/kg

Dam No.	Days after birth					
	Male body weight				Female body weight	
	0	4			0	4
F02013	7.4 (6)	12.6 (6)			7.0 (7)	12.2 (7)
F02014	6.5 (6)	9.4 (6)			6.0 (10)	8.6 (10)
F02015	5.2 (7)	8.4 (6)			4.8 (7)	7.8 (6)
F02016	7.0 (5)	10.4 (5)			6.8 (8)	10.0 (8)
F02017	6.1 (5)	12.8 (3)			6.0 (6)	11.1 (6)
F02018	6.0 (5)	9.5 (5)			5.7 (10)	8.9 (10)
F02019	Not pregnant					
F02020	5.8 (7)	8.6 (7)			5.4 (9)	8.3 (9)
F02021	6.6 (8)	9.5 (8)			6.0 (7)	9.1 (6)
F02022	6.4 (3)	11.7 (3)			6.1 (11)	10.5 (11)
F02023	6.6 (5)	10.8 (5)			6.1 (10)	10.3 (10)
F02024	7.1 (5)	12.1 (5)			6.6 (7)	11.7 (7)
Number of dams	11	11			11	11
Mean	6.4	10.5			6.0	9.9
S.D.	0.6	1.6			0.6	1.4
Significance	NS	NS			NS	NS
Statistical method	DU	AN			DU	AN

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 38-3. Body weights of offspring (F₁) before weaning

1,2-MD 100 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F03025	5.2	(6)	8.8	(6)	4.7	(4)	7.8	(3)
F03026	5.4	(9)	11.0	(6)	6.3	(6)	10.8	(6)
F03027	5.5	(5)	10.1	(4)	5.2	(7)	9.5	(6)
F03028	5.6	(14)	Total litter loss		5.5	(3)	Total litter loss	
F03029	5.3	(7)	8.9	(7)	5.0	(8)	8.8	(8)
F03030	5.5	(7)	9.0	(6)	5.6	(8)	8.8	(7)
F03031	5.6	(9)	Total litter loss		5.5	(8)	Total litter loss	
F03032	Not pregnant							
F03033	6.0	(5)	10.5	(5)	5.8	(6)	10.6	(6)
F03034	5.1	(5)	8.8	(3)	5.1	(8)	9.1	(7)
F03035	5.2	(4)	10.0	(3)	4.9	(8)	9.5	(7)
F03036	Not pregnant							
Number of dams	10		8		10		8	
Mean	5.4		9.6		5.4		9.4	
S.D.	0.3		0.9		0.5		1.0	
Significance	**		NS		**		NS	
Statistical method	DU		AN		DU		AN	

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Significantly different from the control group (*: $P < 0.05$, **: $P < 0.01$).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,2-Methylenedioxybenzene by oral administration in rats

Appendix 38-4. Body weights of offspring (F₁) before weaning

1,2-MD 300 mg/kg

Dam No.	Days after birth			
	Male body weight		Female body weight	
	0	4	0	4
F04037	Not pregnant			
F04038	Not pregnant			
F04039	4.1	(1) Total litter loss	3.6	(2) Total litter loss
F04040	4.7	(4) Total litter loss	4.1	(5) Total litter loss
F04041	5.0	(5) Total litter loss	4.9	(7) Total litter loss
F04042	4.8	(4) Total litter loss	4.3	(7) Total litter loss
F04043	5.2	(7) 7.7 (5)	4.7	(7) 6.2 (4)
F04044	4.8	(4) Total litter loss	4.6	(2) Total litter loss
F04045	Not pregnant			
F04047	Not pregnant			
F04048	4.3	(1) Total litter loss	Total litter loss	
Number of dams	7	1	6	1
Mean	4.7	7.7	4.4	6.2
S.D.	0.4		0.5	
Significance	**	---	**	---
Statistical method	DU	NA	DU	NA

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of
1,2-Methylenedioxybenzene by oral administration in rats

Appendix 39-1. General conditions in offspring (F₁) before weaning

Control (vehicle: corn oil)						
Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F01001	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01002	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01003	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F01004	Number of offspring	13	13	13	13	11
	General appearance, No abnormality	13	13	13	11	11
	General appearance, Death	0	0	0	2	0
F01005	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01006	Number of offspring	18	18	18	18	18
	General appearance, No abnormality	18	18	18	18	18
F01007	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01008	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01009	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F01010	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01011	Died on day 22 of pregnancy					
F01012	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
	Number of offspring	157	157	157	157	155
	General appearance, No abnormality	157	157	157	155	155
	Abnormal findings of offspring, Lack of nursing					
	Skin, Cyanosis					
	Abnormal findings of offspring, Short tail					
	General appearance, Death					2

Combined repeat dose and reproductive/developmental toxicity screening test of

1,2-Methylenedioxybenzene by oral administration in rats

Appendix 39-2. General conditions in offspring (F₁) before weaning

1,2-MD 30 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
F02013	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F02014	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02015	Number of offspring	14	14	12	12	12
	General appearance, No abnormality	14	12	12	12	12
	General appearance, Death	0	2	0	0	0
F02016	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F02017	Number of offspring	11	11	10	9	9
	General appearance, No abnormality	10	10	9	9	9
	Abnormal findings of offspring, Short tail	1	0	0	0	0
	General appearance, Death	0	1	1	0	0
F02018	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02019	Not pregnant					
F02020	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02021	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	14
	General appearance, Death	0	0	0	0	1
F02022	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02023	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02024	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
	Number of offspring	154	154	151	150	150
	General appearance, No abnormality	153	151	150	150	149
	Abnormal findings of offspring, Lack of nursing Skin, Cyanosis					
	Abnormal findings of offspring, Short tail	1				
	General appearance, Death		3	1		1

Combined repeat dose and reproductive/developmental toxicity screening test of
1,2-Methylenedioxybenzene by oral administration in rats

Appendix 39-3. General conditions in offspring (F₁) before weaning

1,2-MD 100 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
F03025	Number of offspring	10	10	9	9	9
	General appearance, No abnormality	10	9	9	9	9
	General appearance, Death	0	1	0	0	0
F03026	Number of offspring	15	15	13	12	12
	General appearance, No abnormality	15	13	12	12	12
	General appearance, Death	0	2	1	0	0
F03027	Number of offspring	12	12	10	10	10
	General appearance, No abnormality	12	10	10	10	10
	General appearance, Death	0	2	0	0	0
F03028	Number of offspring	17	17	13	9	6
	General appearance, No abnormality	17	13	9	6	0
	General appearance, Death	0	4	4	3	6
F03029	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03030	Number of offspring	15	15	14	13	13
	General appearance, No abnormality	15	14	13	13	13
	General appearance, Death	0	1	1	0	0
F03031	Number of offspring	17	17	17	8	2
	General appearance, No abnormality	17	17	8	2	0
	General appearance, Death	0	0	9	6	2
F03032	Not pregnant					
F03033	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F03034	Number of offspring	13	13	10	10	10
	General appearance, No abnormality	13	10	10	10	10
	General appearance, Death	0	3	0	0	0
F03035	Number of offspring	12	12	10	10	10
	General appearance, No abnormality	12	10	10	10	10
	General appearance, Death	0	2	0	0	0
F03036	Not pregnant					
	Number of offspring	137	137	122	107	98
	General appearance, No abnormality	137	122	107	98	90
	Abnormal findings of offspring, Lack of nursing					
	Skin, Cyanosis					
	Abnormal findings of offspring, Short tail					
	General appearance, Death		15	15	9	8

Combined repeat dose and reproductive/developmental toxicity screening test of
1,2-Methylenedioxybenzene by oral administration in rats

Appendix 39-4. General conditions in offspring (F₁) before weaning

1,2-MD 300 mg/kg						
Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F04037	Not pregnant					
F04038	Not pregnant					
F04039	Number of offspring	3	3	0	0	0
	Abnormal findings of offspring, Lack of nursing	3	0	0	0	0
	General appearance, Death	0	3	0	0	0
F04040	Number of offspring	9	9	0	0	0
	Abnormal findings of offspring, Lack of nursing	9	0	0	0	0
	General appearance, Death	0	9	0	0	0
F04041	Number of offspring	12	12	0	0	0
	Abnormal findings of offspring, Lack of nursing	12	0	0	0	0
	Skin, Cyanosis	3	0	0	0	0
	General appearance, Death	0	12	0	0	0
F04042	Number of offspring	11	11	0	0	0
	Abnormal findings of offspring, Lack of nursing	11	0	0	0	0
	General appearance, Death	0	11	0	0	0
F04043	Number of offspring	14	14	9	9	9
	General appearance, No abnormality	14	9	9	9	9
	General appearance, Death	0	5	0	0	0
F04044	Number of offspring	6	6	0	0	0
	Abnormal findings of offspring, Lack of nursing	6	0	0	0	0
	General appearance, Death	0	6	0	0	0
F04045	Not pregnant					
F04047	Not pregnant					
F04048	Number of offspring	1	1	0	0	0
	Abnormal findings of offspring, Lack of nursing	1	0	0	0	0
	Skin, Cyanosis	1	0	0	0	0
	General appearance, Death	0	1	0	0	0
	Number of offspring	56	56	9	9	9
	General appearance, No abnormality	14	9	9	9	9
	Abnormal findings of offspring, Lack of nursing	42				
	Skin, Cyanosis	4				
	Abnormal findings of offspring, Short tail					
	General appearance, Death		47			

信頼性保証書

表題 1,2-メチレンジオキシベンゼンのラットを用いる反復投与毒性・生殖発生毒性併合試験

試験番号 R-12-012

この試験に関する信頼性保証部門による査察および監査状況等は下記のとおりであった。

査察・監査項目	査察・監査年月日	運営管理者および試験責任者への報告年月日
試験計画書	2012 年 9 月 14 日	2012 年 9 月 14 日
試験計画書変更書		
R-12-012-No.1	2012 年 11 月 8 日	2012 年 11 月 8 日
R-12-012-No.2	2012 年 11 月 28 日	2012 年 11 月 28 日
R-12-012-No.3	2013 年 1 月 9 日	2013 年 1 月 9 日
R-12-012-No.4	2013 年 4 月 1 日	2013 年 4 月 1 日
動物の受入れおよび検疫	2012 年 9 月 24 日	2012 年 9 月 24 日
媒体中の安定性(安定性試験開始日)	2012 年 9 月 25 日	2012 年 9 月 25 日
検体調製および含量試験	2012 年 10 月 5 日	2012 年 10 月 5 日
群分け	2012 年 10 月 8 日	2012 年 10 月 9 日
体重測定、給餌量測定、投与および一般状態の観察	2012 年 10 月 9 日	2012 年 10 月 9 日
性周期観察	2012 年 10 月 10 日	2012 年 10 月 10 日
詳細な症状観察	2012 年 10 月 16 日	2012 年 10 月 16 日
交尾確認	2012 年 10 月 24 日	2012 年 10 月 24 日
尿検査	2012 年 11 月 14、15 日	2012 年 11 月 16 日
分娩状態および出生児の観察	2012 年 11 月 15 日	2012 年 11 月 16 日
機能検査	2012 年 11 月 16、19 日	2012 年 11 月 19 日
雄動物剖検、器官重量測定、固定、血液学検査、血液生化学検査および出生児剖検	2012 年 11 月 20 日	2012 年 11 月 20 日
病理組織学的検査 (標本作製:切り出し)	2012 年 12 月 21 日	2012 年 12 月 21 日
報告書草案および生データ	2013 年 4 月 9～12、15～18 日	2013 年 4 月 18 日
最終報告書	2014 年 1 月 31 日	2014 年 1 月 31 日

試験は、「新規化学物質等に係る試験を実施する試験施設に関する基準について」(平成 23 年 3 月 31 日、薬食発 0331 第 8 号、平成 23・03・29 製局第 6 号、環企発第 110331010 号)を遵守して実施され、また、この報告書は試験に使用された方法および手順を正確に記載し、記載された結果は試験の生データを正確に反映していることを保証する。

2014 年 1 月 31 日

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信頼性保証部門責任者