

## 最終報告書訂正版

### 1,3-Benzenedicarboxylic acid, dimethyl ester のラットを用いる 反復投与毒性・生殖発生毒性併合試験

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被験物質 1,3-Benzenedicarboxylic acid, dimethyl ester

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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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。

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所長 

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。

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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

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## 要約

今回、1,3-Benzenedicarboxylic acid, dimethyl ester の雌雄動物の反復投与毒性および回復性、ならびに生殖能力に対する影響および新生児の発育に及ぼす影響を検討することを目的として、反復投与毒性ならびに生殖発生毒性試験を化審法ガイドラインに従って実施した。雌雄の CrI:CD (SD)ラットに被験物質を 0 (媒体:トウモロコシ油)、62.5、250 ならびに 1000 mg/kg の用量で経口投与した。雄は 42 日間投与した後に剖検し、雌は交配前 2 週間および交配期間、妊娠期間を通して哺育 4 日まで連日投与 (投与日数:41~45 日間)した。なお、交配雌は自然分娩させ、出生児は哺育 4 日、母動物は哺育 5 日に剖検した。また、雌の 0 および 1000 mg/kg 投与群に非交配のサテライト群を設け、42 日間投与した後に半数の 5 例を剖検した。

回復性を確認するために、雄の 0 および 1000 mg/kg 投与群の各雄 5 例、雌のサテライト群の各 5 例は、42 日間投与した後、14 日間回復させて剖検した。

得られた結果を以下に要約した。

### 1. 親動物所見

投与期間中の一般状態の変化として、1000 mg/kg 投与群の雌雄で投与 3 週以降、投与後に一過性の流涎が散見された。また、1000 mg/kg 投与群の雌 1 例で投与 15 日にのみ赤色尿が観察された。

生殖能力を検査した雌の 250 および 1000 mg/kg 投与群では、妊娠および哺育期間の体重推移が対照群に比較して低値に推移し、摂餌量の減少傾向もみられた。雄およびサテライト群 (非交配雌) では体重および摂餌量の変化は認められなかった。

尿検査では、雄の 1000 mg/kg 投与群の尿量およびナトリウム排泄量が増加した。分娩雌およびサテライト群 (非交配雌) では尿検査に異常は認められなかった。

血液生化学検査では、1000 mg/kg 投与群の分娩雌およびサテライト群 (非交配群) とともに、グルコース濃度およびトリグリセライド濃度が増加し、分娩雌では胆汁酸濃度も増加した。雄の生化学検査には、被験物質投与による影響はなかった。

器官重量測定では、1000 mg/kg 投与群の雌では肝臓および腎臓重量が増加した。また、分娩雌で副腎重量が増加した。雄の器官重量には被験物質投与による影響はなかった。

その他、詳細な症状観察、機能検査、血液学検査、病理組織学検査に雌雄のいずれの群においても被験物質投与による影響は認められなかった。

回復試験の結果、投与期間中にみられた流涎は観察されず、投与期間終了時にみられた尿検査、血液生化学検査、器官重量の変化も回復試験終了時には観察されなかった。

### 2. 生殖発生毒性学的所見および出生児所見

性周期、交配成績、出産率および妊娠期間、黄体数、着床数および着床率に被験物質投与による影響はみられなかった。出生児の生存性、体重および観察所見に被験物質投与の影響はみられなかった。

### 3. 無毒性量

以上の結果から、本試験条件下における 1,3-Benzenedicarboxylic acid, dimethyl ester の親動物に対する一般毒性学的無毒性量は、一般状態、体重、摂餌量、尿検査、血液生化学検査および器官重量の結果から、雄では 250 mg/kg/day、雌では 62.5 mg/kg/day、生殖発生毒性学的な無毒性量および次世代児に対する無毒性量は、被験物質投与による分娩および哺育異常はなく、出生児数、生存率、出生児体重にも影響は認められなかったため、1000 mg/kg/day と考えられた。

また、一般毒性学的変化は 14 日間の回復期間により回復することが明らかとなった。

### 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(投与日数:42 日間)、交配雌では妊娠期間を通して周産期(哺育 4 日まで、投与日数:41~45 日間)に、非交配群では雄と同様の期間に 1,3-Benzenedicarboxylic acid, dimethyl ester 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。

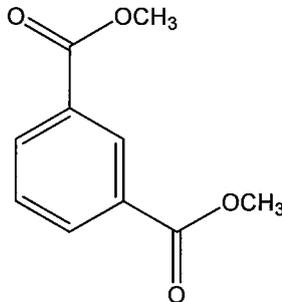
### 動物愛護

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 18 年 6 月 2 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:1110268A)。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 1,3-Benzenedicarboxylic acid, dimethyl ester (別名: Dimethyl isophthalate、CAS No.: 1459-93-4、分子式:  $C_{10}H_{10}O_4$ 、分子量: 194.18、外観: 固体、結晶～粉末、白色～ほとんど白色、純度(GC): 99.9%、沸点/沸騰範囲: 124°C/0.3kPa、融点: 68.9°C、オクタノール/水分配係数: 1.7、蒸気圧: 1.3Pa/25°C、ロット番号: FGM01、Annex A、以下、DMIP)は [REDACTED] より購入し(被験物質入手: 2011年9月27日)、使用時まで冷蔵・遮光下(実測値 3~6°C)で保管した。DMIPの構造式を次に示す。



被験物質の安定性は、投与開始前(2011年11月7日)および投与期間終了後(2012年2月2日)に秦野研究所にてフーリエ変換赤外分光光度計(FTIR-8300、島津製作所)を使用し、臭化カリウム錠剤法にて赤外吸収スペクトル(波数範囲: 4000~400  $cm^{-1}$ )を測定して調べた。投与前後の2つのスペクトルに変化がなかったことは、同被験物質を用いて実施した他試験(試験番号 G-11-032)にて確認されている。

### 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62匹、雌103匹を購入し、15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(入荷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、入荷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	: 2011年11月28日
入荷時体重	: 雄 265.1~300.5 g、雌 186.0~217.9 g
検疫終了日	: 2011年12月12日
検疫終了時体重	: 雄 360.6~447.0 g、雌 226.5~298.7 g

検疫・馴化期間中、雌動物の1例(馴化動物番号85)で外傷出血が1日のみ認められたが、その後回復しており、検疫期間中の一般状態、詳細な症状観察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、規則的な性周期の回帰が認められない7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、性別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 10 匹、雌動物 24 匹および性周期の結果により除外した 7 匹は全て余剰動物とし、他目的に使用した。

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)收容し、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(ただし、死亡例および全哺育児が死亡した例を除く全例は解剖前に絶食させた)。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 匹ずつ收容し、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 22.5~25.5℃、湿度は 48.0~72.0 %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、メノウ乳鉢で磨砕し、媒体(トウモロコシ油、製造元:ナカライテスク、製造番号:V1P6999)を少量ずつ加えながら懸濁させ、20.0 w/v%液を調製した。さらに 20.0 w/v%液を媒体によって希釈し、5.0 ならびに 1.25 w/v%液を段階的に調製した。調製した検体は室温・遮光下(実測値 22.5~25.5℃)で保管し、安定性の保証期間内に使用した。

#### 2) 安定性試験

秦野研究所で、投与に先立ち、1.25 および 20.0 w/v%濃度の投与検体について、室温、遮光条件下(実測値 22.0~24.4℃)における 8 日間の安定性を確認した後、本試験の動物実験を開始した(安定性試験開始日:2011 年 11 月 28 日、8 日目:2011 年 12 月 6 日、Annex B)。

#### 3) 含量試験および均一性試験

初回調製検体(調製日:2011 年 12 月 12 日)について、1.25、5.0 および 20.0 w/v%濃度の調製検体の含量を測定し、分散性(均一性)を確認した。その結果、平均含量は調製指示濃度の 89.5~101.8 %であり、各測定値のばらつきはそれぞれ平均値の 98.6~101.4 %で規定範囲内にあった(Annex C)。

調製検体中の被験物質濃度は以下の方法で測定した。投与検体の 1 mL を正確にとり、2-プロパノールで希釈した後、アセトニトリルで希釈し、試料溶液(約 1 µg/mL)を調製した。別に、被験物質約 10 mg を精密に量り、アセトニトリルに溶解して正確に 50 mL とした。この液 1 mL を正確にとり、アセトニトリルを加えて正確に 20 mL とし、標準原液とした。さらに、この標準原液 1、1 および 4 mL を正確にとり、アセトニトリ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、1 および 4 µg/mL、各濃度 n=1)を調製した。試料溶液および標準溶液を以下に示す高速液体クロマトグラフ(HPLC)法により測定し、標準溶液から作成した検量線を用いて調製検体中の DMIP 濃度を算出した。

## HPLC 測定条件

検出器	紫外分光光度計(測定波長210 nm)
分析カラム	XTerra RP18 (内径4.6 mm、長さ100 mm、粒子径3.5 μm、Waters)
移動相	蒸留水/アセトニトリル混液(65:35 v/v)
流量	1 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	測定開始前および測定終了後に標準溶液(約1 μg/mL)を1回ずつ測定し、ピーク保持時間および強度(ピーク面積)の変動(測定開始前に対する測定終了後の偏差%)を確認した。変動の許容基準は、ピーク保持時間が±3.0%以内、ピーク強度が±5.0%以内を目安とした。

## 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「1,3-Benzenedicarboxylic acid, dimethyl ester 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-11-004)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、0(媒体、トウモロコシ油)、500 および 1000 mg/kg の DMIP を 8 週齢の雌 SD 系ラット(各群 5 匹)に 14 日間、反復強制経口投与した結果、いずれの群においても死亡動物は観察されず、投与期間中に一般状態の変化は観察されなかった。体重にも対照群と DMIP 各投与群との間に有意差は認められなかった。500 mg/kg 投与群の 1 例で DMIP の標的器官と推測される腎臓に白色域が認められたが、1000 mg/kg 投与群の腎臓では肉眼的変化は認められず、その他の器官・組織にも変化はなかった。また、肝臓および腎臓重量は対照群と DMIP 各投与群との間に有意差は認められなかった。

従って、1000 mg/kg の DMIP を投与しても重篤な毒性は認められないと考えられたことから、本試験の高用量を 1000 mg/kg とし、以下公比 4 で減じて、中用量を 250 mg/kg、低用量を 62.5 mg/kg とした。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。

本試験では、雄動物は交配前 2 週間、交配期間(14 日間)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、非妊娠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、経口的に 1 日 1 回、1 週 7 回、午前中(9 時 01 分～11 時 59 分)に投与した。投与容量は 5 mL/kg とし、雄、サテライト群、ならびに交配前ならびに交配中の雌では週 1 回測定する体重を基に、交尾が確認された雌では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
1	トウモロコシ油 (媒体)	0	0	5	M01001~M01013*	F01001~F01013
2	DMIP	62.5	1.25	5	M02001~M02013	F02001~F02013
3	DMIP	250	5.0	5	M03001~M03013	F03001~F03013
4	DMIP	1000	20.0	5	M04001~M04013*	F04001~F04013
5(サテライト群)	トウモロコシ油 (媒体)	0	0	5	-	F05001~F05010*
6(サテライト群)	DMIP	1000	20.0	5	-	F06001~F06010*

\* 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 (F<sub>0</sub>)

#### 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)、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04分~15時10分の間に行った。

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

雄では各群の動物番号の若い5例について、刺激に対する感覚運動反応は投与42日の詳細な症状観察に引き続いて検査し、握力測定および自発運動測定は投与39日に検査した。雌では、分娩例は哺育5日に投与期間が近接した各群の動物番号の若い5例について、サテライト群では各群の動物番号の若い5例について、刺激に対する感覚運動反応は投与42日の詳細な症状観察に引き続いて検査し、握力測定および自発運動測定は投与41日に検査した。

##### (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。実施場所は14号室とし、環境条件は15号室に準じた。試験対象動物は、検査直前に14号室に運搬し、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、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、7、14日、妊娠0、7、14、20日、哺育0、4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收容し、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	オーシオンイレブン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
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(エアントイー)
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、入荷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 11 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 日と起算して同居を解消し、個別に飼育した。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 $[(交尾動物数/交配に用いた動物数) \times 100, \%)$ 、妊娠率 $[(妊娠動物数/交尾した雌動物数) \times 100, \%)$ を算出した。

## ⑩妊娠・分娩・哺育状態の観察

交尾が確認された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行い、午前 11 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。分娩した全例の妊娠期間(妊娠 0 日から分娩日までの日数)を求めた。哺育 5 日の剖検時に卵巣は妊娠黄体数を、子宮は着床数を数え、着床率 $[(着床数/妊娠黄体数) \times 100, \%)$ を算出した。

## ⑪採血

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。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例全例(5例)で採血を行った。また、雌の投与終了時剖検では、分娩例について哺育5日に投与期間が近接した各群の動物番号が若い5例、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例全例(5例)で採血を行った。

- (1) 血液学検査用:抗凝固剤 クエン酸ナトリウム
- (2) 血液学検査用:抗凝固剤 EDTA-2K
- (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)	半導体レーザー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

項目	測定法	使用機器
平均赤血球血色素濃度 (MCHC)	計算 (HGB×100/HCT)	血液自動分析装置 XT-2000iV (シスメックス)
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・HDAOS法	同上
トリグリセライド濃度 (TG)	GPO・HDAOS (グリセリン消去) 法	同上
リン脂質濃度 (PL)	コリンオキシダーゼ・DAOS法	同上
尿素窒素濃度 (BUN)	ウレアゼ・GLDH法,ウレアゼ律速系	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アミナーゼ活性 (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ノトランスフェラーゼ活性 (AST)	IFCC法	同上
アラニンアミノ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 (エイアントイー)
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

分娩中に死亡した雌 (250 mg/kg 投与群の 1 例:動物番号 F03011)は死亡確認日に、全哺育児が死亡した雌 (62.5 および 1000mg/kg 投与群の各 1 例:動物番号 F02006、F04007)では全哺育児の死亡を確認した日に、雄動物およびサテライト群の投与終了時剖検例は投与 42 日の翌日に、雌動物の分娩例は哺育 4 日の翌日に、雄動物およびサテライト群の回復観察例は回復 15 日に、血液学、血液生化学検査を実施する動物はペントバルビタールナトリウム麻酔下で採血し、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て剖検した。なお、死亡動物以外の全例について、

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、乳腺、および病変部を採取し、保存した。死亡動物以外の肺/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、全哺育児が死亡した母動物の器官重量値は評価対象からは除外した。

#### 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、雌の投与終了時剖検では分娩例について哺育5日に投与期間が近接した対照群ならびに高用量群の動物番号が若い各5例について、組織学検査対象器官のヘマトキシリン・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、剖検時に異常所見がみられた器官・組織(腎臓、胃、胸腺、肝臓、肺、脾臓、精巣上体、精巣、子宮)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、投与期間終了時屠殺例の病理組織学検査において、対照群および高用量群との間に変化の程度および頻度に有意差が認められなかったことから、回復期間終了時屠殺例の病理組織学検査は行なわなかった。

## 2) 出生児(F<sub>1</sub>)

### 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[(出産生児数/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[(出産生児数/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。外表に異常が観察された哺育児1例も同様に固定して保存した。

## 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%)。ただし、雌においては、哺育 5 日に剖検した動物の成績に関してのみ検定を実施した。

その他のデータは、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 群以上の場合には、先ず、Bartlett の方法により各群の分散の一意性について検定(有意水準:5%)を行った。分散が一意であった場合には、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意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 1 月 6 日 13 時頃、本館動物飼育施設用温水ボイラの電源が誤操作によって停止した。温水ボイラの電源を復帰させたところ、オーバーシュートにより、飼育室の温度が許容値を超え、25.5℃となった。オーバーシュートが収束した後、温度が許容範囲内で安定して推移していることを確認した。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、他の測定項目にも異常は認められていないことから、試験への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~Table 4, Appendix 1~Appendix 4)

雄では死亡動物はみられなかった。

雌では、250 mg/kg 投与群の 1 例(動物番号 F03011)が妊娠 23 日の分娩中に死亡した。サテライト群では死亡動物はみられなかった。

投与期間中の一般状態の変化として、投与3週以降に1000 mg/kg投与群の雌雄で投与後の一過性の流涎が散見された。一過性の流涎は、雄では投与18日～40日の間に1～6例、雌では投与16日以降、サテライト群では投与36日まで、交配をさせた群では妊娠期間中に1～4例で認められた。また、1000 mg/kg投与群の雌1例で投与15日のみに赤色尿が観察された。それ以外に一般状態の異常は認められなかった。

回復期間の観察では一般状態の異常は認められなかった。なお、対照群の1例(動物番号 F05008)では回復13日の尿検査時に代謝ケージに尾を挟んだため、尾の先端部が欠落した。

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

投与期間中の観察では、挙尾が、投与8日の観察で250 mg/kg投与群の雄1例、投与24日の観察で62.5 mg/kg投与群の雌1例、哺育期間中に実施した観察で対照群の雌1例に、それぞれ1回観察された。

回復期間中の観察でも、回復7日および回復14日の観察でいずれも対照群の雌各1例で、挙尾が1回観察された。それ以外に変化は観察されなかった。

その他の観察項目には、いずれの観察日にも異常は認められず、排尿および排糞数にも対照群と比較して差はなかった。

## 3) 体重 (Table 7～Table 10, Appendix 7～Appendix 10)

雄では、対照群とDMIP各投与群との間で体重推移に有意差は認められなかった。

雌では、交配前の期間では、DMIP各投与群の体重は対照群と同様に推移した。妊娠期間中は、250および1000 mg/kg投与群の体重が、統計学的には差はなかったがやや低値に推移し、250および1000 mg/kg投与群の哺育0日の体重には有意な低下( $P < 0.05$ )が認められ、哺育4日の体重も低い傾向がみられた。サテライト群では、投与期間を通して、対照群とDMIP投与群(1000 mg/kg)との間で体重に有意差は認められなかった。

回復期間の体重は、雌雄ともに対照群と1000 mg/kg 投与群との間に有意差はなかった。

## 4) 摂餌量 (Table 11～Table 14, Appendix 11～Appendix 14)

雄では、対照群とDMIP各投与群との間で摂餌量に有意差は認められなかった。

雌では、交配前の期間では、対照群とDMIP各投与群との間で摂餌量に有意差はなかった。妊娠期間中は、250および1000 mg/kg投与群の摂餌量が、妊娠中期以降、僅かであるが減少傾向を示した。哺育期間中の摂餌量には対照群とDMIP各投与群との間で有意差は認められなかった。

サテライト群では、投与期間を通して、対照群とDMIP投与群(1000 mg/kg)との間で摂餌量に有意差は認められなかった。

回復期間の摂餌量は、雌雄ともに対照群と1000 mg/kg のDMIP投与群との間に有意差はなかった。

## 5)機能検査

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

投与最終週に実施した検査では、雌雄ともにいずれの群においても異常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検査では、雌雄ともに対照群とDMIP各投与群との間で握力(前肢および後肢)に有意差は認められなかった。

## ③自発運動量測定 (Table 20~Table 22, Appendix 20~Appendix 22)

投与最終週に実施した検査では、雌雄ともに対照群とDMIP各投与群との間で自発運動量(区画移動数および立ち上がり回数)に有意差は認められなかった。

## 6)尿検査 (Table 23~Table 24, Appendix 23~Appendix 24)

投与期間終了時の検査では、雄の1000 mg/kg投与群の尿量(P<0.05)およびナトリウム排泄量(P<0.01)が対照群に比較して有意に増加した。雌では特記すべき変化は認められず、対照群とDMIP各投与群との間で尿量、比重、電解質濃度および排泄量に有意差は認められなかった。

回復期間終了時の検査では、雄では特記すべき変化は認められず、対照群とDMIP投与群との間で尿量、比重、電解質濃度および排泄量に有意差は認められなかった。雌のサテライト群の1000 mg/kg投与群で、尿比重が有意に減少した(P<0.05)。

## 7)血液学検査 (Table 25~Table 26, Appendix 25~Appendix 26)

## ①投与期間終了時

雄では、DMIP各投与群の血液学検査の結果には、対照群との間に有意差は認められなかった。

分娩雌では、250 mg/kg投与群で好酸球比率の低下(P<0.05)、リンパ球比率の上昇(P<0.05)が、1000 mg/kg投与群で白血球数の減少(P<0.01)、好中球比率の低下(P<0.05)、リンパ球比率の上昇(P<0.05)がいずれも有意に認められた。

サテライト群では、1000 mg/kg投与群で好酸球比率が有意に低下した(P<0.01)。

## ②回復期間終了時

雄では、1000 mg/kg投与群で赤血球数およびヘマトクリット値が有意に増加した(P<0.05)。

雌(サテライト群)では、1000 mg/kg投与群の血液学検査の結果には、対照群との間に有意差は認められなかった。

## 8)血液生化学検査 (Table 27~Table 28, Appendix 27~Appendix 28)

## ①投与期間終了時

雄では、62.5および250 mg/kg投与群で総コレステロール濃度が有意に増加した(P<0.05)。

分娩雌では、62.5 mg/kg投与群でグルコース濃度が有意に増加し(P<0.05)、1000 mg/kg投与群でグルコース濃度(P<0.01)、トリグリセライド濃度(P<0.01)、胆汁酸濃度(P<0.01)、カルシウム濃度(P<0.05)

がそれぞれ有意に増加した。

サテライト群では、1000 mg/kg投与群でグルコース濃度、トリグリセライド濃度が有意に増加し(P<0.05)、塩素濃度が有意に減少(P<0.05)した。

#### ②回復期間終了時

雄では、1000 mg/kg投与群で総コレステロールおよびリン脂質濃度が有意に減少した(P<0.05)。

雌(サテライト群)では、1000 mg/kg 投与群の血液生化学検査の結果には対照群との間に有意差は認められなかった。

### 9) 器官重量 (Table 29～Table 30, Appendix 29～Appendix 30)

#### ①投与期間終了時

雄では、対照群とDMIP各投与群との間でいずれの器官重量に有意差は認められなかった。

分娩雌では、62.5 mg/kg 投与群で肝臓の相対重量が有意に増加し(P<0.05)、250 mg/kg 投与群で解剖時体重(P<0.05)、胸腺の実重量および相対重量(P<0.01)が有意に減少し、1000 mg/kg 投与群で肝臓の相対重量(P<0.05)、腎臓の相対重量(P<0.01)、副腎の相対重量(P<0.01)がいずれも有意に増加した。

サテライト群では、1000 mg/kg 投与群で心臓の実重量および相対重量(P<0.01)、肝臓の実重量および相対重量(P<0.01)、腎臓の実重量および相対重量(P<0.05)が有意に増加し、甲状腺の実重量および相対重量(P<0.05)が有意に減少した。

#### ②回復期間終了時

雄では、1000 mg/kg 投与群の副腎(左側)の実重量が有意に増加した(P<0.05)。

雌(サテライト群)では、1000 mg/kg 投与群の甲状腺の実重量および相対重量が有意に増加した(P<0.05)。

### 10) 剖検所見 (Table 31～Table 32, Appendix 31～Appendix 32)

#### ①雄の投与期間終了時屠殺例

腎臓では、250 mg/kg 投与群の2例および 1000 mg/kg 投与群の1例に大型化が認められたほか、62.5 および 1000 mg/kg 投与群の各1例に陥凹部が、そのうち 1000 mg/kg 投与群の例では淡色化を呈していた。また、250 mg/kg 投与群の1例の左側精巣に大型化が、62.5 mg/kg 投与群の2例の精巣上体の左側あるいは右側の尾部に黄色の結節が観察された。その他、対照群の1例の回腸に憩室が認められた。

#### ②雄の回復期間終了時屠殺例

回復期間終了時屠殺例に、肉眼的な異常所見は認められなかった。

#### ③雌の投与期間終了時屠殺例(哺育5日剖検)

腎臓では、250 mg/kg 投与群の左側に散在する陥凹部が、1000 mg/kg 投与群には淡色化あるいは右側腎盂の拡張がそれぞれ1例観察された。また、胃では、62.5 および 1000 mg/kg 投与群の各1例

の腺胃粘膜に暗色域あるいは点が、1000 mg/kg 投与群の1例の前胃には粘膜下織が浮腫様を呈する粘膜の肥厚が認められた。その他、対照群の1例の脾臓に大型化が観察された。

④投与期間中の死亡例(妊娠23日、母動物分娩中死亡)および全哺育児が死亡した母動物

妊娠 23 日に分娩中に死亡した 250 mg/kg 投与群の母動物(動物番号 F03011)では、腎臓、肝臓および脾臓に淡色化が、肺には散在する暗色域が、胸腺には散在する暗赤色点が観察されたほか、胃の腺胃粘膜に暗色域あるいは点が観察された。また、子宮は、内膜面が暗赤色調を呈し、腔が拡張していた。この動物では 4 匹(雄 3 匹、雌 1 匹)生まれていたが、いずれも死亡していた。さらに右子宮角に 8 匹(雄 5 匹、雌 3 匹)、左子宮角に 4 匹(雄 2 匹、雌 2 匹)の死亡胎児が観察された。なお、胎児および産児の外表面には異常は認められなかった。

全哺育児が哺育 0 日に死亡したため屠殺した 62.5 mg/kg 投与群の母動物(動物番号 F02006)では、胸腺が小型化を呈しており、子宮は、内膜面が暗赤色調を呈し、腔が拡張していた。全哺育児が哺育 1 日に死亡した 1000 mg/kg 投与群の母動物(動物番号 F04007)では、胸腺の小型化に加え、肝臓の淡色化、腎臓および副腎の大型化が認められた。

⑤サテライト群の投与期間終了時屠殺例

対照群および 1000 mg/kg 投与群の各 5 例を剖検したが、肉眼的な異常所見は認められなかった。

⑥サテライト群の回復期間終了時屠殺例

尿検査時に代謝ケージに尾を挟んだために尾の先端部が欠損した対照群の 1 例以外に、肉眼的な異常所見は認められなかった。

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

①雄の投与期間終了時屠殺例

心臓では、対照群および 1000 mg/kg 投与群の各2例に限局性の心筋の変性/線維化が観察されたが、いずれの例もごく軽度な変化であり、両群間に程度の有意差は認められなかった。

肺では、対照群の1例の肺胞腔に泡沫細胞の集簇が、1000 mg/kg 投与群の2例の動脈壁に限局性の鉍質沈着が観察されたが、いずれの例もごく軽度な変化であった。

肝臓では、対照群および 1000 mg/kg 投与群の全例に門脈周囲性の肝細胞の脂肪化が、対照群および 1000 mg/kg 投与群の各3例に小肉芽腫が観察されたが、両群間に変化の程度の有意差は認められなかった。

脾臓では、対照群および 1000 mg/kg 投与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、両群間に変化の程度の有意差は認められなかった。

腎臓では、対照群の3例、1000 mg/kg 投与群においては肉眼的に異常が認められた2例を加えた7例中5例の皮質に好塩基性尿細管が観察されたが、両群間に変化の程度および頻度の有意差は認められなかった。また、肉眼的に異常が認められた 62.5 mg/kg 投与群の1例の皮質には、好塩基性尿細管および被膜下に嚢胞がみられたが、250 mg/kg 投与群の2例には、組織学的な異常所見は認められなかった。

精巣では、対照群の1例の精巣に限局性の精細管萎縮が観察された。また、肉眼的に異常が認められた 250 mg/kg 投与群の片側の精巣では、管腔は拡張し生殖細胞層が減少した精細管とともに、間質

には浮腫が観察された。

精巣上体では、1000 mg/kg 投与群の1例の間質にリンパ球浸潤が観察された。また、肉眼的に異常が認められた 62.5 mg/kg 投与群の2例の尾部には、精子肉芽腫が認められた。

その他、1000 mg/kg 投与群の甲状腺に異所性の胸腺組織が、対照群の前立腺およびハーダー腺の間質にリンパ球浸潤がそれぞれ1例観察された。

他の組織学検査対象器官・組織には、組織学的な異常所見は認められなかった。

肉眼的に異常が認められた対照群の回腸では、憩室の一部の筋層が欠如しており、漿膜面には異物巨細胞を伴う鉍質沈着が観察された。

#### ②雌の投与期間終了時屠殺例(哺育5日剖検)

肝臓では、対照群および 1000 mg/kg 投与群の各 1 例に門脈周囲性の肝細胞の脂肪化が、対照群の 3 例、1000 mg/kg 投与群の 1 例に小肉芽腫が観察されたが、いずれの所見も両群間に程度および頻度の有意差は認められなかった。

脾臓では、対照群および 1000 mg/kg 投与群の全例に髓外造血および褐色色素の沈着が観察されたが、両群間に程度および頻度の有意差は認められなかった。剖検時、肉眼的に異常(大型化)が認められた対照群の 1 例では、褐色色素の沈着に加え、顕著な髓外造血が観察された。

腎臓では、対照群の 2 例、1000 mg/kg 投与群の 1 例の皮質に好塩基性尿細管が観察されたが、両群間に程度および頻度の有意差は認められなかった。その他、対照群の 1 例の皮質被膜下に嚢胞が、1000 mg/kg 投与群で 2 例の髓質に鉍質沈着、1 例の片側に腎盂の拡張がみられた。剖検時、肉眼的に異常が認められた 250 および 1000 mg/kg 投与群の各 1 例では、組織学的な異常所見は認められなかった。

その他、対照群では、心臓に限局性の心筋の変性／線維化、甲状腺には異所性の胸腺組織が、1000 mg/kg 投与群では、肺の肺胞腔に泡沫細胞の集簇、膵臓の動脈周囲に限局性の好酸球浸潤がそれぞれ 1 例観察されたが、ごく軽度であった。

他の組織学検査対象器官・組織には、組織学的な異常所見は認められなかった。

剖検時に肉眼的な異常所見が認められた 62.5 mg/kg 投与群の 1 例および 1000 mg/kg 投与群の 2 例の胃では、1000 mg/kg 投与群の 1 例の前胃粘膜に扁平上皮細胞の過形成が観察されたが、他の 2 例には組織学的な異常所見は認められなかった。

なお、対照群および 1000 mg/kg 投与群の各 1 例の上皮小体がスライド標本上になかったため、観察することが出来なかったが、他の例では観察ができ、上皮小体に被検物質による影響はみられていないことから、試験評価に影響はないと判断した。

#### ③投与期間中の死亡例(母動物)および全哺育児が死亡した母動物

妊娠 23 日に分娩中に死亡した 250 mg/kg 投与群の母動物(動物番号 F03011)では、胸腺の萎縮、下顎および腸間膜リンパ節の濾胞の萎縮が観察されたほか、脾臓に白脾髄および赤脾髄領域の減少がみられた。また、腎臓の皮質に近位尿細管上皮の変性／壊死および好塩基性尿細管が、胃の前胃粘膜に潰瘍が観察された。その他、子宮の内膜に出血、肺の動脈壁に限局性の鉍質沈着がみられた。

全哺育児が死亡した母動物は、剖検時に肉眼的に異常が認められた器官・組織を組織学的に検査し

た。62.5 mg/kg 投与群の母動物(異常器官:胸腺、子宮)では、胸腺が萎縮しており、子宮の内膜に出血が認められた。1000 mg/kg 投与群の母動物(異常器官:胸腺、肝臓、腎臓、副腎)では、胸腺の萎縮および肝臓の小葉中間帯の肝細胞に空胞化が観察されたほか、腎臓の皮質に近位尿細管上皮の変性/壊死、副腎の皮質索状帯に細胞肥大がみられた。

#### ④サテライト群(雌)の投与期間終了時屠殺例

肝臓では、対照群の2例、1000 mg/kg 投与群の1例に門脈周囲性の肝細胞の脂肪化が、対照群の3例、1000 mg/kg 投与群の1例に小肉芽腫が観察されたが、いずれの所見も両群間に程度および頻度の有意差は認められなかった。

脾臓では、対照群および1000 mg/kg 投与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、両群間に程度の有意差は認められなかった。

腎臓では、対照群の3例の皮質に好塩基性尿細管が観察されたが、いずれもごく軽度な変化であった。

その他、肺の動脈壁に限局性の鈣質沈着が対照群および1000 mg/kg 投与群の各1例に、膵臓に膵管の増生を伴う限局性の腺房細胞の萎縮が対照群の1例に、甲状腺の間質にリンパ球浸潤が1000 mg/kg 投与群の1例にみられた。

他の組織学検査対象器官・組織には、組織学的な異常所見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~Appendix 36)

性周期には、DMIP 投与の影響を示唆する変化はみられなかった。

また、交尾までの日数およびその間の発情回数、交尾率、妊娠率にも、対照群と DMIP 各投与群との間に有意差は認められなかった。

### 2)出産率および妊娠期間 (Table 37, Appendix 37)

妊娠期間には対照群と DMIP 各投与群との間に有意差は認められなかった。

出産率には対照群と DMIP 各投与群との間に有意差は認められなかった。

### 3)分娩および哺育状態 (Table 37, Appendix 37)

250 mg/kg投与群の1例が妊娠23日に死亡した(前述)。

62.5(動物番号 F02006)および1000 mg/kg投与群(動物番号 F04007)の各1例において、それぞれ哺育0日および1日に全哺育児が死亡した。

対照群の1例(動物番号 F01009)および1000 mg/kg 投与例の1例(動物番号 F04007、哺育1日に全哺育児死亡)では、分娩終了後に出生児を集めずに児の腹部にミルクスポット(母乳が貯留している様子)がみられず、授乳している状態ではないと考えられたため分娩状態不良と判断した。また、分娩日(哺育0日)に全哺育児が死亡した62.5 mg/kg 投与群の1例(動物番号 F02006)では児に母動物による食害がみられたことから、分娩状態不良と判断した。

他の妊娠動物は、妊娠22~23日に出産し、分娩状態および哺育状態に異常は認められなかった。

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

黄体数、着床数および着床率には、対照群と DMIP 各投与群との間に有意差は認められなかった。

## 3. 出生児

## 1) 生存 (Table 37, Appendix 37)

分娩率、生児出産率、出生率、新生児生存率および性比には、対照群と DMIP 各投与群との間に有意差は認められなかった。

## 2) 体重 (Table 38, Appendix 38)

哺育 0 および 4 日における出生児の体重には、対照群と DMIP 各投与群との間に有意差は認められなかった。250 mg/kg 投与群の 1 例(動物番号 F03007)の哺育 4 日の哺育児体重は哺育 0 日に比較して減少した。この母動物の哺育期間中の体重は増加していなかった。

## 3) 出生児観察 (Table 39~Table 40, Appendix 39)

62.5 mg/kg 投与群の 1 例(動物番号 F02007)では、哺育 0 日の外表観察時に尾屈曲が 1 例の雌出生児で認められた。その他の生存児には、外表奇形は観察されなかった。

哺育 4 日の剖検の結果、前述の尾屈曲のほか、対照群の 1 例(動物番号 F01009)および 250 mg/kg 投与群の 1 例(動物番号 F03007)の出生児には、ミルクスポットがみられなかった。

死亡児は、対照群を含む各投与群に認められた。死亡児には、母動物の食害により存在が不明になったと推察される児(不明児)、あるいは死後変化が進み自己融解により内臓観察ができなかった児を含むが、剖検が可能であった死亡児には外表奇形は観察されなかった。内臓観察が可能であった死亡児については、全哺育児が死亡した 1000 mg/kg 投与群の 1 例(動物番号 F04007)の死亡児の胃にミルクスポットがみられなかった以外に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、交配雌では妊娠期間を通して周産期(哺育 4 日まで)に、非交配雌のサテライト群では雄と同様の期間に 1,3-Benzenedicarboxylic acid, dimethyl ester(DMIP)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. 親動物

1000 mg/kg 投与群の雌雄で、投与後に一過性の流涎が散見された。詳細な症状観察で神経毒性を示唆する変化は認められておらず、投与後のみにみられた変化であることから、被験物質の刺激性による変化と考えられた。

妊娠期間中および哺育期間中の体重が、250 mg/kg 以上の投与群において、対照群と比較して低値

に推移し、摂餌量も減少傾向がみられたことから、DMIP が妊娠中および哺育期間中の母動物の体重増加に影響を及ぼすと考えられた。

尿検査では、1000 mg/kg 投与群の雄で尿量およびナトリウム排泄量が増加し、同群の腎臓重量は、分娩雌および非交配雌ともに、増加した。DMIP の類似化合物であり、同じ代謝経路を持つ dimethyl terephthalate (DMTP) が terephthalic acid (TPA) に代謝される際に TPA-カルシウム沈殿物が産生され、腎臓および膀胱にカルシウム結晶あるいは結石が形成され、血尿、膀胱壁の肥厚等の泌尿器系への影響が報告されている<sup>1)</sup>。また、ラットに DMTP の 0、125、250 mg/kg/day を 103 週間混餌投与した結果、250 mg/kg 投与群にて軽度ではあるが腎臓の慢性的な炎症が認められている<sup>2)</sup>。本試験において、高用量群の雄での尿量およびナトリウム排泄量の増加、雌での腎臓重量の増加は DMIP 投与の影響と考えられたが、腎臓に DMIP 投与によると考えられる病理組織学的な変化はみられなかった。

血液学検査の結果、分娩雌では1000 mg/kg投与群において、白血球数の減少、好中球比率の低下、リンパ球比率の上昇が認められた。しかし、分娩後の白血球数は個体差が大きく、同種試験の対照群(8試験分)の背景値範囲内(40.6~183.8 x 10<sup>2</sup>/μL)であること、造血臓器の異常、栄養不良、感染症、免疫不全などの異常を示唆する変化は観察されていないことから、DMIP投与による変化ではないと判断した。その他、白血球分類に変化が認められたが、いずれも白血球数に変動はみられていないことから、毒性学的意義はないと判断した。

血液生化学検査では、雄において、総コレステロール濃度が増加したが、僅かな変化であり用量依存的な変化ではないことから、被験物質投与の影響ではないと判断した。雌では、1000 mg/kg投与群の分娩雌および非交配雌(サテライト群)にグルコース濃度およびトリグリセライド濃度の増加が認められた。さらに分娩雌では胆汁酸濃度の増加もみられた。肝臓障害を示唆する血液生化学パラメータに変動はなく、肝臓の病理組織学所見に異常は認められていないが、高用量群の分娩雌および非交配雌に共通した変化であり肝臓重量の増加も認められていることから総合的に判断し、これらの変化は被験物質投与による影響であると考えられた。1000 mg/kgのDMIP投与により、脂質代謝および糖代謝に影響を及ぼす可能性が示唆されたが、病理組織学的検索では検出できない程度の弱い変化であると考えられた。また、グルコース濃度の増加および肝臓重量の増加が62.5 mg/kg投与群の分娩雌に観察されたが、用量依存的な変化ではなく肝臓障害を示唆する血液生化学パラメータに変動がないこと、病理組織学検査においても異常所見は認められないことから偶発的な変化であると判断した。その他、1000 mg/kg投与群では、分娩雌においてカルシウム濃度の増加が、非交配雌(サテライト群)において塩素濃度の減少が認められたが、いずれも僅かな変化であり、カルシウムの吸収不良のほか、上皮小体および甲状腺機能、骨代謝の異常を示す病理組織学的所見は観察されていないこと、血中電解質の異常を来すほどの状態の変化や腎臓の病理組織学所見に変化は観察されていないことから、これらの変化は偶発的な変化であると考えられた。

投与期間終了時の器官重量測定では、前述の腎臓および肝臓の他に、分娩雌で胸腺重量の減少、副腎重量の増加がみられた。しかし、非交配雌(サテライト群)では同様の変化が認められていないことから、妊娠、分娩および哺育によるストレスに起因した変化と考えられた。非交配雌(サテライト群)の

1000 mg/kg 投与群で心臓重量の増加、甲状腺重量の減少が認められたが、これらの臓器に DMIP 投与によると考えられた病理組織学的変化は観察されなかったことから、被験物質投与の影響ではないと判断した。

詳細な症状観察、機能検査および病理組織学検査には、雌雄ともに、いずれの群においても、被験物質投与による影響と考えられた変化は認められなかった。

## 2. 毒性の回復性

2 週間の回復期間中には、投与期間中にみられた流涎は観察されず、投与期間終了時にみられた尿検査、血液生化学検査、器官重量の変化も回復試験終了時には観察されなかった。

回復 13 日に実施した尿検査の結果、雌では 1000 mg/kg 投与群で尿比重が減少したが、尿量および尿中電解質濃度に変化はみられなかったことから、被験物質投与に関連した変化ではないと判断した。

回復 15 日に実施した血液学検査の結果、雄では、1000 mg/kg 投与群において、赤血球数およびヘマトクリット値が増加したが、投与期間終了時の検査では同様の変化はみられず、血液濃縮を示唆する所見も認められていない。また、投与期間終了時の脾臓および骨髄の病理組織検査においても、造血系の異常を示唆する変化は認められていないことから、これらの変化は被験物質投与に関連した変化ではないと判断した。

血液生化学検査の結果、雄では、1000 mg/kg 投与群において、総コレステロールおよびリン脂質濃度が減少したが、投与期間終了時の検査では同様の変化はみられず、回復期間中の体重推移に影響はなく栄養状態の悪化は認められていないこと、回復期間終了時の肝臓重量にも差はないことから、これらの変化は被験物質投与に関連した変化ではないと判断した。

1000 mg/kg 投与群の雌の甲状腺重量が増加したが、投与期間終了時の検査では同様の変化はみられず、甲状腺の病理検査でも異常は認められていないことから、これらの変化は被験物質投与に関連した変化ではないと判断した。

## 3. 生殖発生毒性および出生児

性周期、交配成績、出産率および妊娠期間、黄体数、着床数および着床率に被験物質投与による影響はみられなかった。

分娩中死亡例が 250 mg/kg 投与群に 1 例、分娩後に全哺育児が死亡する例が 62.5 および 1000 mg/kg 投与群に各 1 例観察された。いずれの動物も一般状態に異常はなかったが、妊娠 20 日の摂餌量が他の妊娠動物に比較して少なかった。全哺育児が死亡した例では、病理学検査の結果および哺育状態から、分娩状態が不良であったことが示唆された。分娩中死亡例の病理学検査の結果では、分娩によるストレスおよび貧血を示唆する変化や、腎臓に急性毒性を示唆する病理組織学的変化(尿管壊死)が認められたことから、母動物の状態が悪いことが考えられた。しかし、分娩状態の不良は対照群の 1 例でも認められていること、同群の他の動物に分娩および哺育状態の異常はなく、母動物の体重推移も対照群と比較して有意差はなかったことから、DMIP の投与により、分娩および哺育状態へ影響は及ぼさないと判断した。

出生児の生存性および体重に被験物質投与の影響はみられなかった。

62.5 mg/kg 投与群の 1 例の母動物で尾屈曲が雌の哺育児 1 例で認められたが、それ以外の出産児に外表および内臓異常は認められなかったことから、被験物質投与による奇形ではないと考えられた。

死亡児が対照群を含む各投与群に認められたが、死亡児の外表および内臓に異常が認められず、用量依存性に死亡児数も増加していないことから、DMIP 投与により、児の生存率には影響はないと判断した。

#### 4. 無毒性量

以上の結果から、1000 mg/kg 投与群の雌雄で投与後の一過性の流涎が散見され、また、腎臓への影響が示唆された。1000 mg/kg 投与群の分娩雌および非交配雌では血漿中トリグリセライド濃度の増加が、分娩雌では胆汁酸濃度の増加もみられた。同投与群の分娩雌および非交配雌では肝臓重量の増加も観察された。また、妊娠動物の 250 および 1000 mg/kg 投与群では、妊娠後期と哺育期間中に体重増加抑制が認められた。しかし、分娩および哺育状態に異常はなく出生児にも DMIP の影響は認められなかった。従って、本試験条件下における DMIP の親動物に対する一般毒性学的無毒性量は、雄では 250 mg/kg/day、雌では 62.5 mg/kg/day、生殖発生毒性学的な無毒性量は 1000 mg/kg/day と考えられた。

また、一般毒性学的変化は 14 日間の回復期間により回復することが明らかとなった。

#### 参考文献

- 1) U.S. EPA High production volume (HPV) chemicals challenge program, Assessment of data availability and test plan for Dimethyl Isophthalate (DMIP; CAS RN 1459-93-4) (2006)
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Annex A



## 試験成績書

2011年09月27日

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製品名: Dimethyl Isophthalate			
製品コード: I0157	等級: EP	製品ロット: FGM01	判定: 合格

項目	結果	規格値
メノール溶状	澄明	ほとんど澄明以内
純度(GC)	99.9 %	99.0 %以上
融点	68.9 deg-C	67.0 ~ 71.0 deg-C
酸価	0.1	0.5 以下

Annex B

### 安定性試験結果

試験番号	R-11-005
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被験(対照)物質: 1,3-Benzenedicarboxylic acid, dimethyl ester  
 ロット番号:FGM01  
 媒体: トウモロコシ油

調製年月日 2011年11月28日  
 測定年月日 A 2011年11月28日(調製直後)  
 B 2011年12月6日(調製後8日)  
 保存条件 室温、遮光

調製濃度 (mg/mL)	A				B				
	試料 番号	測定濃度 (mg/mL)	含量 <sup>a)</sup> (%)	ばらつき <sup>b)</sup> (%)	試料 番号	測定濃度 (mg/mL)	含量 <sup>a)</sup> (%)	ばらつき <sup>b)</sup> (%)	残存率 <sup>c)</sup> (%)
12.5	1	11.36	90.9	99.1	7	11.68	93.4	100.9	101.9
	2	11.47	91.8	100.1	8	11.53	92.2	99.6	100.6
	3	11.55	92.4	100.8	9	11.55	92.4	99.7	100.8
	平均	11.46	91.7	/	平均	11.58	92.7	/	101.1
200	4	192.4	96.2	100.0	10	197.5	98.8	102.3	102.7
	5	192.7	96.4	100.2	11	190.6	95.3	98.7	99.1
	6	192.2	96.1	99.9	12	191.2	95.6	99.0	99.4
	平均	192.4	96.2	/	平均	193.1	96.6	/	100.4

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

#### 安定性の判断基準(懸濁液検体)

各試料採取時点の平均含量がそれぞれ調製濃度の85.0~115.0%以内であり、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、調製直後の測定平均値に対する各保管期間後の残存率の平均値が90.0%以上を示す期間とする。

Annex C

試験番号	R - 11 - 005
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### 含量・均一性試験結果

被験(対照)物質: 1,3-Benzenedicarboxylic acid, dimethyl ester 調製年月日: 2011年12月12日  
 ロット番号: FGM01 測定年月日: 2011年12月12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×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
13	12.5	11.26	11.23	90.1	89.8	100.3
14		11.14		89.1		99.2
15		11.29		90.3		100.5
16	50.0	44.12	44.75	88.2	89.5	98.6
17		44.75		89.5		100.0
18		45.38		90.8		101.4
19	200	203.8	203.4	101.9	101.8	100.2
20		204.7		102.4		100.6
21		201.9		101.0		99.3

#### 含量・均一性の判断基準(懸濁液検体)

平均含量が調製濃度の85.0~115.0%、また各測定値のばらつきがそれぞれ平均値の90.0~110.0%以内とする。

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 1-1. General conditions of male rats

Group	Number of males 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	Pre	Post			
Corn oil (control)	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13		
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
DMIP 62.5 mg/kg	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13		
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
DMIP 250 mg/kg	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DMIP 1000 mg/kg	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 1-1(continued). General conditions of male rats

Group	Number of males 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
Corn oil (control)	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
DMIP 62.5 mg/kg	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13		
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13		
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
DMIP 250 mg/kg	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13		
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13		
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
DMIP 1000 mg/kg	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8		
	General appearance, No abnormality	13	10	13	11	13	13	13	11	13	11	13	13	12	13	11	13	7	13	12	13	13	13	13	13	13	13	13	12	13	12	13	13	13	8		
	Mouth, Salivation	0	3	0	2	0	0	0	2	0	2	0	0	0	1	0	2	0	6	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0		

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Corn oil (control)	Number of males	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
DMIP 1000 mg/kg	Number of males	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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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			
		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		
Corn oil (control)	Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DMIP 62.5 mg/kg	Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	9	9	4	4	4	4	2	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	9	9	4	4	4	4	2	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
DMIP 250 mg/kg	Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	10	10	6	6	6	1		
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	10	10	6	6	6	1
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DMIP 1000 mg/kg	Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	12	12	10	10	9	9	9	4
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	12	12	10	10	9	8	9	3
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
	Excretion, Reddish urine	0	0	0	0	0	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	1	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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	Pre	Post			
Corn oil (control)	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	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
DMIP 1000 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	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

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
Corn oil (control)	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
	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	5
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DMIP 1000 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	5	
	General appearance, No abnormality	10	9	10	10	10	10	10	10	10	10	10	10	9	10	10	10	6	10	9	10	9	10	10	10	10	10	10	10	10	10	10	10	10	10	5	
	Mouth, Salivation	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	4	0	1	0	1	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 1,3-Benzenedicarboxylic acid, dimethyl ester 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														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Corn oil (control)	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	4	4	4
	Skin, Loss of tail	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
DMIP 1000 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
	Skin, Loss of tail	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 3. General conditions in dams during pregnancy

Group	Number of dams 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
Corn oil (control)	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
DMIP 62.5 mg/kg	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
DMIP 250 mg/kg	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
DMIP 1000 mg/kg	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	9	13	13	13	13	13	13	13	13	13	13	13	12	13	13	13	12	13	12	13	13	13	13	13	11	13	12
	Mouth, Salivation	0	4	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0	0	0	0	0	2	0	1

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Table 3(continued). General conditions in dams during pregnancy

Group	Number of dams and general conditions	Days of pregnancy																		
		14		15		16		17		18		19		20		21		22		23
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Corn oil (control)	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	2	2	0
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	2	2	0
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0
DMIP 62.5 mg/kg	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	5	5	0	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	5	5	0	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	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	0	0	0	
DMIP 250 mg/kg	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	7	7	1		
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	7	7	0		
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	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	0	0		
DMIP 1000 mg/kg	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	5	5	0		
	General appearance, No abnormality	13	12	13	12	13	11	13	11	13	13	13	13	13	13	5	5	0		
	Mouth, Salivation	0	1	0	1	0	2	0	2	0	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	0	0		

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 4. General conditions in dams during lactation

Group	Number of dams and general conditions	Days of lactation											
		0		1		2		3		4		5	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Corn oil (control)	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0
DMIP 62.5 mg/kg	Number of dams	13	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	13	12	12	12	12	12	12	12	12	12	12	12
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0
DMIP 250 mg/kg	Number of dams	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
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0
DMIP 1000 mg/kg	Number of dams	13	13	13	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	13	13	13	12	12	12	12	12	12	11	12	12
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	1	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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 <sup>a</sup>	
				8	15	24	30	36	42	7	14
[Straub tail]	Corn oil (control)	13	0 <sup>b</sup>	0	0	0	0	0	0	0	0
Tail elevation	DMIP (62.5 mg/kg)	13	0	0	0	0	0	0	0		
	DMIP (250 mg/kg)	13	0	1	0	0	0	0	0		
	DMIP (1000 mg/kg)	13	0	0	0	0	0	0	0	0	0
[Urination] (frequency/30sec)	Corn oil (control)	13	1 <sup>c</sup>	0	1	1	1	0	1	1	0
	DMIP (62.5 mg/kg)	13	0	2	1	1	3	1	1		
	DMIP (250 mg/kg)	13	0	7	0	4	3	2	2		
	DMIP (1000 mg/kg)	13	0	4	1	2	1	1	3	2	1
[Defecation] (frequency/30sec)	Corn oil (control)	13	1 <sup>c</sup>	0	0	0	0	0	0	0	0
	DMIP (62.5 mg/kg)	13	1	0	0	0	0	0	0		
	DMIP (250 mg/kg)	13	0	1	0	0	0	0	0		
	DMIP (1000 mg/kg)	13	0	1	0	0	0	0	0	0	0

<sup>a</sup> The recovery test was performed in 5 animals for each of the 0 and 1000 mg/kg groups.

<sup>b</sup> Values represent number of animals with the findings.

<sup>c</sup> Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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	
[Straub tail]	Corn oil (control)	13	0 <sup>a</sup>	0	0	0	0	0	1
Tail elevation	DMIP (62.5 mg/kg)	13	0	0	0	1	0	0	0 (12)
	DMIP (250 mg/kg)	13	0	0	0	0	0	0	0 (12)
	DMIP (1000 mg/kg)	13	0	0	0	0	0	0	0 (12)
[Urination]	Corn oil (control)	13	0 <sup>b</sup>	0	0	0	0	1	0
(frequency/30sec)	DMIP (62.5 mg/kg)	13	0	1	0	0	0	1	2 (12)
	DMIP (250 mg/kg)	13	1	1	0	0	0	0	0 (12)
	DMIP (1000 mg/kg)	13	0	0	0	0	0	0	0 (12)
[Defecation]	Corn oil (control)	13	0 <sup>b</sup>	0	0	0	0	0	0
(frequency/30sec)	DMIP (62.5 mg/kg)	13	0	0	0	0	0	0	0 (12)
	DMIP (250 mg/kg)	13	0	0	0	0	0	0	0 (12)
	DMIP (1000 mg/kg)	13	0	0	0	0	0	0	0 (12)

<sup>a</sup> Values represent number of animals with the findings.

<sup>b</sup> Values represent total score of each group.

Figures in parentheses indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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 <sup>a</sup>	
				8	15	24	30	36	42	7	14
[Straub tail] Tail elevation	Corn oil (control)	5	0 <sup>b</sup>	0	0	0	0	0	0	1	1
	DMIP (1000 mg/kg)	5	0	0	0	0	0	0	0	0	0
[Urination] (frequency/30sec)	Corn oil (control)	5	1 <sup>c</sup>	0	0	0	0	0	1	0	1
	DMIP (1000 mg/kg)	5	1	1	0	2	2	2	1	0	3
[Defecation] (frequency/30sec)	Corn oil (control)	5	0 <sup>c</sup>	0	0	0	0	0	0	0	0
	DMIP (1000 mg/kg)	5	0	0	2	0	0	0	0	0	0

<sup>a</sup> the recovery test was performed in 5 animals for each of the 0 and 1000 mg/kg groups.

<sup>b</sup> Values represent number of animals with the findings.

<sup>c</sup> Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 7-1. Body weights of male rats

Group	Corn oil (control)	DMIP 62.5 mg/kg	DMIP 250 mg/kg	DMIP 1000 mg/kg
Number of males	13	13	13	13
Days of administration				
1	410.8 ± 17.4	412.7 ± 14.6	414.2 ± 15.1	410.7 ± 15.7
7	434.2 ± 20.7	434.7 ± 19.5	435.2 ± 16.6	433.5 ± 21.7
14	463.4 ± 24.1	462.4 ± 22.0	460.0 ± 20.6	462.9 ± 25.9
21	487.1 ± 27.5	486.9 ± 21.0	485.0 ± 20.4	480.3 ± 26.2
28	517.4 ± 31.8	513.7 ± 25.1	511.2 ± 24.3	504.0 ± 30.4
35	541.8 ± 36.0	533.7 ± 25.6	533.6 ± 27.5	524.2 ± 32.8
42	558.6 ± 41.2	551.4 ± 25.9	551.2 ± 32.2	541.6 ± 38.5

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)	DMIP 1000 mg/kg
Number of males	5	5
Days of recovery period		
1	557.0 ± 51.9	541.4 ± 44.8
7	568.5 ± 52.2	557.1 ± 46.8
14	578.3 ± 54.5	570.0 ± 53.4

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 8-1. Body weights of female rats

Group	Corn oil (control)		DMIP 62.5 mg/kg		DMIP 250 mg/kg		DMIP 1000 mg/kg	
Number of females	13		13		13		13	
Days of administration								
	1	255.4 ± 10.3	255.1 ± 12.8	251.0 ± 9.6	257.9 ± 7.9			
	7	267.9 ± 13.6	269.4 ± 11.9	260.5 ± 12.9	262.6 ± 11.0			
	14	277.2 ± 17.4	280.0 ± 13.3	268.3 ± 14.1	271.8 ± 11.6			

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP 1000 mg/kg	
Number of females	10		10	
Days of administration				
1	252.6	± 10.3	259.0	± 9.7
7	267.1	± 15.5	259.4	± 12.5
14	277.7	± 18.5	268.9	± 11.2
21	286.0	± 16.9	281.7	± 13.5
28	293.0	± 18.1	287.6	± 17.2
35	299.2	± 17.4	292.2	± 14.1
42	306.4	± 17.4	302.6	± 16.1

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Table 8-3. Body weights of female rats at the recovery period

Group	Corn oil (control)	DMIP 1000 mg/kg
Number of females	5	5
Days of recovery period		
1	313.4 ± 18.1	303.4 ± 21.1
7	324.9 ± 16.1	320.3 ± 19.8
14	317.5 ± 24.2	320.2 ± 22.7

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 9. Body weights of dams during pregnancy

Group	Corn oil (control)	DMIP 62.5 mg/kg	DMIP 250 mg/kg	DMIP 1000 mg/kg
Number of dams	13	13	13	13
Days of pregnancy				
0	287.5 ± 18.1	290.4 ± 17.7	276.8 ± 16.0	281.7 ± 11.2
7	322.1 ± 22.2	325.3 ± 20.9	310.9 ± 14.8	312.7 ± 11.4
14	360.4 ± 27.6	367.4 ± 24.6	343.1 ± 17.7	347.7 ± 14.8
20	446.1 ± 36.9	452.6 ± 31.9	424.8 ± 26.2	426.0 ± 20.1

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 10. Body weights of dams during lactation

Group	Corn oil (control)	DMIP 62.5 mg/kg	DMIP 250 mg/kg	DMIP 1000 mg/kg
Number of dams	13	13	12	13
Days of lactation				
0	344.3 ± 34.6	335.7 ± 31.7	309.6 ± 27.1 *	312.2 ± 18.0 *
4	352.0 ± 25.1	354.5 ± 26.2 (12)	324.1 ± 29.8	338.0 ± 11.0 (12)

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 11-1. Food consumption of male rats

Group	Corn oil (control)		DMIP 62.5 mg/kg		DMIP 250 mg/kg		DMIP 1000 mg/kg	
Number of males	13		13		13		13	
Days of administration								
1	24.4	± 2.6	25.9	± 3.6	24.4	± 3.0	24.7	± 3.8
7	24.3	± 2.6	23.0	± 2.2	24.6	± 2.5	24.3	± 2.8
14	24.5	± 3.2	23.1	± 2.6	22.9	± 3.1	23.4	± 3.2
29	24.8	± 3.7	24.6	± 3.5	23.9	± 2.2	24.6	± 3.7
35	24.5	± 3.5	24.3	± 3.4	24.3	± 2.5	24.5	± 2.5
41	23.7	± 2.6	21.9	± 2.5	23.3	± 2.7	23.8	± 3.0

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP 1000 mg/kg	
Number of males	5		5	
Days of recovery period				
	6	31.3 ± 3.1	32.0 ± 4.1	
	12	30.6 ± 3.6	32.3 ± 3.2	

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 12-1. Food consumption of female rats

Group	Corn oil (control)	DMIP 62.5 mg/kg	DMIP 250 mg/kg	DMIP 1000 mg/kg
Number of females	13	13	13	13
Days of administration				
1	18.1 ± 4.4	17.6 ± 2.6	16.8 ± 3.3	17.0 ± 2.5
7	18.0 ± 2.2	16.5 ± 2.0	16.3 ± 3.8	15.8 ± 3.2
14	16.7 ± 3.4	16.5 ± 2.9	16.4 ± 2.8	15.8 ± 3.9

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP 1000 mg/kg	
	10		10	
Number of females				
Days of administration				
1	16.8	± 2.8	17.4	± 2.3
7	17.5	± 3.1	14.8	± 3.3
14	14.7	± 3.9	14.4	± 2.8
21	17.9	± 2.8	16.7	± 1.5
29	18.1	± 2.9	17.5	± 2.7
35	15.8	± 2.9	16.3	± 2.6
41	16.2	± 3.0	15.9	± 2.0

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP 1000 mg/kg	
Number of females	5		5	
Days of recovery period				
	6	23.9 ± 1.8	24.6 ± 1.9	
	12	19.9 ± 3.1	21.1 ± 2.0	

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 13. Food consumption in dams during pregnancy

Group	Corn oil (control)		DMIP 62.5 mg/kg		DMIP 250 mg/kg		DMIP 1000 mg/kg	
Number of dams	13		13		13		13	
Days of pregnancy								
	0	17.9 ± 2.2	17.5 ± 2.1	16.1 ± 2.3	17.9 ± 3.0			
	7	22.5 ± 3.8	22.9 ± 3.8	20.7 ± 3.0	21.0 ± 3.1			
	14	24.4 ± 4.8	24.0 ± 3.2	21.9 ± 2.6	21.2 ± 1.8			
	20	18.2 ± 5.0	17.6 ± 4.9	15.0 ± 6.0	16.4 ± 4.3			

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 14. Food consumption in dams during lactation

Group	Corn oil (control)	DMIP 62.5 mg/kg	DMIP 250 mg/kg	DMIP 1000 mg/kg	
Number of dams	13	12	12	12	
Days of lactation	3	36.7 ± 6.8	41.7 ± 6.0	35.3 ± 12.4	42.6 ± 3.4

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Table 15. Functional findings of male rats at the last week of the dosing period

Group	Corn oil (control)	DMIP (62.5 mg/kg)	DMIP (250 mg/kg)	DMIP (1000 mg/kg)
<u>Male</u>				
Number of animals	5	5	5	4
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Prayer'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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 16. Functional findings of female rats at the last week of the dosing period

Group	Corn oil (control)	DMIP (62.5 mg/kg)	DMIP (250 mg/kg)	DMIP (1000 mg/kg)
<u>Female, dam</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	100
Prayer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
<u>Female, satellite group</u>				
Number of animals	5			5
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Prayer'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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Table 17. Assessment of grip strength of male rats at the last week of the dosing period

Group	Corn oil (control)	DMIP (62.5 mg/kg)	DMIP (250 mg/kg)	DMIP (1000 mg/kg)
Number of males	5	5	5	4
Forelimb	1.066 ± 0.116	1.105 ± 0.132	1.207 ± 0.048	1.182 ± 0.064
Hindlimb	0.603 ± 0.088	0.558 ± 0.110	0.570 ± 0.095	0.567 ± 0.079

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 18. Assessment of grip strength of female rats at the last week of the dosing period

Group	Corn oil (control)	DMIP (62.5 mg/kg)	DMIP (250 mg/kg)	DMIP (1000 mg/kg)
Number of females	5	5	5	5
Forelimb	1.154 ± 0.095	1.194 ± 0.047	1.203 ± 0.108	1.220 ± 0.060
Hindlimb	0.792 ± 0.089	0.734 ± 0.089	0.729 ± 0.044	0.707 ± 0.141

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 19. Assessment of grip strength of female rats at the last week of the dosing period, satellite group

Group	Corn oil (control)	DMIP (1000 mg/kg)
Number of females	5	5
Forelimb	1.102 ± 0.048	1.061 ± 0.104
Hindlimb	0.727 ± 0.111	0.803 ± 0.093

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Table 20. Motor activity of male rats at the last week of the dosing period

Group	Corn oil (control)	DMIP (62.5 mg/kg)	DMIP (250 mg/kg)	DMIP (1000 mg/kg)
Number of males	5	5	5	4
Ambulation (counts)				
5min	1113 ± 107	1067 ± 130	1203 ± 212	1029 ± 166
10min	911 ± 56	1030 ± 42	1177 ± 347	932 ± 129
15min	907 ± 126	956 ± 117	1057 ± 374	865 ± 167
20min	877 ± 112	748 ± 51	842 ± 516	1441 ± 1856
Total	3808 ± 318	3801 ± 231	4279 ± 1418	4267 ± 2187
Rearing (counts)				
5min	33 ± 7	37 ± 2	29 ± 6	30 ± 7
10min	23 ± 9	34 ± 13	24 ± 4	23 ± 7
15min	22 ± 14	27 ± 11	20 ± 8	17 ± 7
20min	21 ± 10	17 ± 5	11 ± 6	33 ± 45
Total	99 ± 35	115 ± 25	85 ± 18	102 ± 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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 21. Motor activity of female rats at the last week of the dosing period

Group	Corn oil (control)	DMIP (62.5 mg/kg)	DMIP (250 mg/kg)	DMIP (1000 mg/kg)
Number of males	5	5	5	4
Ambulation (counts)				
5min	1139 ± 75	1037 ± 98	1182 ± 391	1028 ± 160
10min	942 ± 120	783 ± 64	904 ± 402	795 ± 139
15min	765 ± 211	521 ± 49	800 ± 299	604 ± 233
20min	756 ± 171	660 ± 177	727 ± 231	1121 ± 1368
Total	3603 ± 310	3002 ± 330	3613 ± 1280	3548 ± 1487
Rearing (counts)				
5min	29 ± 4	31 ± 8	23 ± 8	27 ± 7
10min	26 ± 10	16 ± 4	17 ± 11	14 ± 5
15min	16 ± 10	8 ± 7	5 ± 3	8 ± 9
20min	13 ± 8	12 ± 6	4 ± 2	23 ± 40
Total	84 ± 17	67 ± 15	48 ± 17	72 ± 48

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 22. Motor activity of female rats at the last week of the dosing period, satellite group

Group	Corn oil (control)		DMIP (1000 mg/kg)	
Number of females	5		5	
Ambulation (counts)				
5min	1301	± 127	1146	± 87
10min	1114	± 139	999	± 65
15min	1094	± 99	909	± 109
20min	941	± 45	883	± 165
Total	4451	± 337	3936	± 351
Rearing (counts)				
5min	43	± 13	32	± 4
10min	31	± 8	28	± 6
15min	27	± 3	18	± 8
20min	21	± 6	20	± 6
Total	121	± 27	98	± 19

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 23-1. Urinalysis in male rats

Group	Number of males	Quality <sup>a)</sup>																						
		Color		Turbidity	pH						Protein			Glucose	Ketone			Bilirubin	Occult blood	Urobilinogen				
		Light yellow	Yellow	-	5.5	6.0	6.5	7.0	7.5	8.0	8.5	±	+	2+	-	-	±	+	2+	-	-	±	+	2+
Corn oil (control)	5	4	1	5	0	0	0	0	3	2	0	0	1	4	5	0	1	4	0	5	5	2	3	0
DMIP (62.5 mg/kg)	5	4	1	5	0	0	0	3	1	0	1	0	3	2	5	0	1	3	1	5	5	2	1	2
DMIP (250 mg/kg)	5	5	0	5	1	1	1	2	0	0	0	0	4	1	5	0	3	2	0	5	5	3	2	0
DMIP (1000 mg/kg)	5	5	0	5	0	5	0	0	0	0	0	1	4	0	5	4	1	0	0	5	5	5	0	0

Group	Number of males	Urinary sediments <sup>a)</sup>					Urine volume <sup>b)</sup> (mL/24hr)	Specific gravity <sup>b)</sup>	Electrolyte, density <sup>b)</sup> (mEq/L)			Electrolyte, gross volume <sup>b)</sup> (mEq/24 hr)			
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells			Na	K	Cl	Na	K	Cl	
		-	-	-	±	-									
Corn oil (control)	5	5	5	5	0	5	5	12.2 ±3.1	1.056 ±0.016	75.8 ±29.0	206.6 ±55.3	91.1 ±41.6	0.89 ±0.34	2.46 ±0.77	1.06 ±0.52
DMIP (62.5 mg/kg)	5	5	5	5	1	4	5	11.3 ±2.8	1.064 ±0.011	91.5 ±25.2	224.9 ±45.5	112.5 ±24.8	1.04 ±0.35	2.48 ±0.51	1.27 ±0.36
DMIP (250 mg/kg)	5	5	5	5	2	3	5	16.8 ±10.1	1.055 ±0.020	82.1 ±28.7	191.2 ±58.2	88.1 ±36.5	1.17 ±0.16	2.85 ±0.80	1.26 ±0.31
DMIP (1000 mg/kg)	5	5	5	5	3	2	5	21.4 * ±3.3	1.048 ±0.006	77.8 ±10.9	140.8 ±28.5	61.6 ±17.4	1.64 ** ±0.12	3.04 ±1.06	1.32 ±0.50

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Number of males	Quality <sup>a)</sup>																		
		Color	Turbidity	pH					Protein			Glucose	Ketone		Bilirubin	Occult blood		Urobilinogen		
		Light yellow	-	6.5	7.0	7.5	8.0	8.5	±	+	2+	-	-	±	+	-	-	±	+	
Corn oil (control)	5	5	5	1	0	2	2	0	1	3	1	5	1	2	2	5	5	0	4	1
DMIP (1000 mg/kg)	5	5	5	0	0	4	0	1	0	3	2	5	0	3	2	5	4	1	2	3

Group	Number of males	Urinary sediments <sup>a)</sup>							Urine volume <sup>b)</sup> (mL/24hr)	Specific gravity <sup>b)</sup>	Electrolyte, density <sup>b)</sup> (mEq/L)			Electrolyte, gross volume <sup>b)</sup> (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells		Na			K	Cl	Na	K	Cl	
		-	-	-	-	±	-	±								
Corn oil (control)	5	5	5	5	1	4	5	0	20.2 ±9.2	1.057 ±0.021	104.5 ±55.8	309.5 ±138.2	118.8 ±46.8	1.79 ±0.61	5.42 ±0.99	2.12 ±0.43
DMIP (1000 mg/kg)	5	5	5	5	0	5	4	1	17.0 ±3.3	1.067 ±0.009	134.1 ±7.5	288.7 ±66.9	153.4 ±14.5	2.27 ±0.38	4.92 ±1.48	2.57 ±0.24

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Number of females	Quality <sup>a)</sup>															
		Color	Turbidity	pH			Protein			Glucose	Ketone			Bilirubin	Occult blood	Urobilinogen	
		Light yellow	-	5.5	6.0	6.5	-	±	+	-	-	±	+	-	-	±	+
Corn oil (control)	5	5	5	0	1	4	1	0	4	5	1	1	3	5	5	4	1
DMIP (1000 mg/kg)	5	5	5	1	3	1	1	2	2	5	4	1	0	5	5	4	1

Group	Number of females	Urinary sediments <sup>a)</sup>						Urine volume <sup>b)</sup> (mL/24hr)	Specific gravity <sup>b)</sup>	Electrolyte, density <sup>b)</sup> (mEq/L)			Electrolyte, gross volume <sup>b)</sup> (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	Na			K	Cl	Na	K	Cl	
		-	-	-	-	±	-			-	-	-	-	-	-
Corn oil (control)	5	5	5	5	3	2	5	9.4 ±3.0	1.048 ±0.012	79.1 ±38.9	190.7 ±60.9	96.6 ±41.7	0.69 ±0.27	1.76 ±0.66	0.89 ±0.43
DMIP (1000 mg/kg)	5	5	5	5	3	2	5	12.7 ±4.4	1.054 ±0.012	84.2 ±22.1	165.7 ±46.1	75.7 ±39.7	1.03 ±0.30	2.11 ±0.87	0.99 ±0.61

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Number of females	Quality <sup>a)</sup>																		
		Color	Turbidity	pH				Protein				Glucose		Ketone		Bilirubin	Occult blood		Urobilinogen	
				Light yellow	-	6.5	7.0	7.5	8.0	-	±	+	2+	-	-		±	+	-	-
Corn oil (control)	5	5	5	3	0	1	1	1	1	1	2	1	5	2	2	1	5	5	2	3
DMIP (1000 mg/kg)	5	5	5	0	4	0	1	4	1	0	0	5	5	0	0	5	5	5	0	

Group	Number of females	Urinary sediments <sup>a)</sup>						Urine volume <sup>b)</sup> (mL/24hr)	Specific gravity <sup>b)</sup>	Electrolyte, density <sup>b)</sup> (mEq/L)			Electrolyte, gross volume <sup>b)</sup> (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	Na			K	Cl	Na	K	Cl	
															-
Corn oil (control)	5	5	5	5	1	4	5	10.3 ±5.4	1.063 ±0.015	111.9 ±24.5	257.8 ±122.1	121.5 ±35.1	1.19 ±0.67	2.55 ±1.37	1.25 ±0.68
DMIP (1000 mg/kg)	5	5	5	5	0	5	5	17.0 ±5.5	1.041 * ±0.011	80.8 ±18.1	179.2 ±53.6	85.4 ±28.1	1.35 ±0.41	3.05 ±1.10	1.48 ±0.61

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP (62.5 mg/kg)		DMIP (250 mg/kg)		DMIP (1000 mg/kg)	
	Number of males		Number of males		Number of males		Number of males	
	5	5	5	5	5	5	4	4
RBC ( $\times 10^4/\mu\text{L}$ )	862 ± 35	862 ± 35	848 ± 32	848 ± 32	866 ± 13	866 ± 13	874 ± 30	874 ± 30
Hemoglobin (g/dL)	15.1 ± 0.4	15.1 ± 0.4	15.0 ± 0.6	15.0 ± 0.6	15.3 ± 0.5	15.3 ± 0.5	15.5 ± 0.3	15.5 ± 0.3
Hematocrit (%)	44.5 ± 0.8	44.5 ± 0.8	43.5 ± 1.8	43.5 ± 1.8	45.5 ± 1.7	45.5 ± 1.7	44.8 ± 0.8	44.8 ± 0.8
MCV (fL)	51.7 ± 2.3	51.7 ± 2.3	51.3 ± 2.2	51.3 ± 2.2	52.5 ± 2.2	52.5 ± 2.2	51.3 ± 2.2	51.3 ± 2.2
MCH (pg)	17.5 ± 0.8	17.5 ± 0.8	17.6 ± 0.6	17.6 ± 0.6	17.7 ± 0.6	17.7 ± 0.6	17.8 ± 0.4	17.8 ± 0.4
MCHC (g/dL)	33.9 ± 0.3	33.9 ± 0.3	34.4 ± 0.5	34.4 ± 0.5	33.7 ± 0.4	33.7 ± 0.4	34.6 ± 0.7	34.6 ± 0.7
Platelet ( $\times 10^4/\mu\text{L}$ )	112.5 ± 10.6	112.5 ± 10.6	107.3 ± 8.0	107.3 ± 8.0	99.7 ± 7.5	99.7 ± 7.5	102.4 ± 10.7	102.4 ± 10.7
PT (sec)	16.2 ± 2.0	16.2 ± 2.0	14.8 ± 0.8	14.8 ± 0.8	16.4 ± 4.4	16.4 ± 4.4	15.7 ± 4.3	15.7 ± 4.3
APTT (sec)	23.6 ± 1.6	23.6 ± 1.6	22.8 ± 3.1	22.8 ± 3.1	23.6 ± 3.6	23.6 ± 3.6	22.9 ± 0.9	22.9 ± 0.9
WBC ( $\times 10^2/\mu\text{L}$ )	97.4 ± 24.6	97.4 ± 24.6	101.0 ± 25.7	101.0 ± 25.7	83.4 ± 21.3	83.4 ± 21.3	94.2 ± 14.6	94.2 ± 14.6
Differential leukocyte count (%)								
Neutrophil	14.8 ± 4.2	14.8 ± 4.2	17.4 ± 3.1	17.4 ± 3.1	15.6 ± 4.0	15.6 ± 4.0	14.4 ± 3.5	14.4 ± 3.5
Eosinophil	1.5 ± 0.3	1.5 ± 0.3	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.3	1.5 ± 0.4	1.5 ± 0.4
Basophil	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1
Monocyte	4.1 ± 0.9	4.1 ± 0.9	3.9 ± 1.2	3.9 ± 1.2	4.7 ± 1.3	4.7 ± 1.3	3.9 ± 0.7	3.9 ± 0.7
Lymphocyte	79.6 ± 5.1	79.6 ± 5.1	77.5 ± 3.1	77.5 ± 3.1	78.6 ± 5.4	78.6 ± 5.4	80.2 ± 3.4	80.2 ± 3.4
Reticulocyte count (%)	2.57 ± 0.59	2.57 ± 0.59	3.04 ± 0.43	3.04 ± 0.43	2.87 ± 0.34	2.87 ± 0.34	2.79 ± 0.42	2.79 ± 0.42

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Table 25-2. Hematological findings of male rats at the end of the recovery period

Group	Corn oil (control)		DMIP (1000 mg/kg)	
	5		5	
Number of males	5		5	
RBC ( $\times 10^4/\mu\text{L}$ )	827	$\pm 36$	870	$\pm 21$ *
Hemoglobin (g/dL)	14.7	$\pm 0.6$	15.3	$\pm 0.7$
Hematocrit (%)	41.9	$\pm 1.0$	44.3	$\pm 2.0$ *
MCV (fL)	50.8	$\pm 2.3$	50.9	$\pm 1.3$
MCH (pg)	17.7	$\pm 0.5$	17.6	$\pm 0.6$
MCHC (g/dL)	35.0	$\pm 1.0$	34.7	$\pm 0.6$
Platelet ( $\times 10^4/\mu\text{L}$ )	113.5	$\pm 32.9$	117.9	$\pm 8.2$
PT (sec)	19.2	$\pm 4.1$	16.4	$\pm 3.8$
APTT (sec)	26.8	$\pm 2.2$	24.3	$\pm 0.7$
WBC ( $\times 10^2/\mu\text{L}$ )	103.8	$\pm 15.9$	97.6	$\pm 25.3$
Differential leukocyte count (%)				
Neutrophil	13.7	$\pm 7.7$	13.5	$\pm 2.7$
Eosinophil	1.2	$\pm 0.3$	1.4	$\pm 0.5$
Basophil	0.0	$\pm 0.1$	0.0	$\pm 0.1$
Monocyte	3.0	$\pm 0.7$	3.3	$\pm 1.2$
Lymphocyte	82.0	$\pm 8.4$	81.8	$\pm 3.5$
Reticulocyte count (%)	3.09	$\pm 0.52$	2.56	$\pm 0.21$

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP (62.5 mg/kg)		DMIP (250 mg/kg)		DMIP (1000 mg/kg)	
	5		5		5		4	
Number of males	5		5		5		4	
RBC ( $\times 10^4/\mu\text{L}$ )	660	$\pm 57$	698	$\pm 48$	672	$\pm 59$	704	$\pm 46$
Hemoglobin (g/dL)	12.5	$\pm 1.2$	13.3	$\pm 0.7$	12.6	$\pm 1.0$	13.2	$\pm 0.8$
Hematocrit (%)	38.3	$\pm 2.7$	40.5	$\pm 2.4$	38.7	$\pm 2.8$	39.8	$\pm 2.0$
MCV (fL)	58.1	$\pm 2.0$	58.1	$\pm 1.9$	57.8	$\pm 2.2$	56.7	$\pm 1.7$
MCH (pg)	19.0	$\pm 0.5$	19.1	$\pm 0.6$	18.8	$\pm 0.6$	18.8	$\pm 0.1$
MCHC (g/dL)	32.7	$\pm 0.8$	32.8	$\pm 0.4$	32.6	$\pm 0.4$	33.2	$\pm 0.9$
Platelet ( $\times 10^4/\mu\text{L}$ )	111.1	$\pm 16.2$	112.6	$\pm 4.4$	96.2	$\pm 13.5$	112.0	$\pm 16.1$
PT (sec)	12.0	$\pm 0.6$	12.2	$\pm 0.6$	12.4	$\pm 0.3$	12.4	$\pm 0.7$
APTT (sec)	18.2	$\pm 1.3$	19.7	$\pm 2.0$	17.9	$\pm 1.0$	18.3	$\pm 1.8$
WBC ( $\times 10^2/\mu\text{L}$ )	105.0	$\pm 13.8$	93.8	$\pm 18.4$	84.2	$\pm 14.7$	69.0	$\pm 17.0$ **
Differential leukocyte count (%)								
Neutrophil	31.6	$\pm 8.7$	32.1	$\pm 4.2$	22.9	$\pm 5.0$	21.5	$\pm 3.8$ *
Eosinophil	1.0	$\pm 0.5$	0.6	$\pm 0.3$	0.4	$\pm 0.2$ *	0.9	$\pm 0.2$
Basophil	0.0	$\pm 0.0$	0.0	$\pm 0.1$	0.0	$\pm 0.0$	0.0	$\pm 0.0$
Monocyte	4.1	$\pm 0.7$	4.0	$\pm 1.1$	3.2	$\pm 1.0$	4.2	$\pm 1.5$
Lymphocyte	63.3	$\pm 8.7$	63.2	$\pm 4.2$	73.6	$\pm 4.7$ *	73.4	$\pm 2.7$ *
Reticulocyte count (%)	6.81	$\pm 1.03$	7.41	$\pm 1.47$	6.49	$\pm 0.76$	7.19	$\pm 0.54$

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP (1000 mg/kg)	
	5		5	
Number of females	5		5	
RBC ( $\times 10^4/\mu\text{L}$ )	787	$\pm 68$	807	$\pm 33$
Hemoglobin (g/dL)	14.4	$\pm 0.8$	14.9	$\pm 0.6$
Hematocrit (%)	42.3	$\pm 2.1$	43.4	$\pm 2.1$
MCV (fL)	53.8	$\pm 3.0$	53.7	$\pm 1.2$
MCH (pg)	18.3	$\pm 0.8$	18.4	$\pm 0.3$
MCHC (g/dL)	34.0	$\pm 0.7$	34.4	$\pm 0.3$
Platelet ( $\times 10^4/\mu\text{L}$ )	98.2	$\pm 3.1$	102.3	$\pm 13.8$
PT (sec)	11.5	$\pm 0.7$	11.4	$\pm 0.4$
APTT (sec)	18.1	$\pm 2.7$	17.8	$\pm 2.8$
WBC ( $\times 10^2/\mu\text{L}$ )	54.2	$\pm 13.1$	53.2	$\pm 13.4$
Differential leukocyte count (%)				
Neutrophil	14.7	$\pm 9.8$	12.1	$\pm 3.7$
Eosinophil	1.5	$\pm 0.2$	0.9	$\pm 0.3$ **
Basophil	0.0	$\pm 0.0$	0.0	$\pm 0.0$
Monocyte	2.4	$\pm 0.4$	2.6	$\pm 0.9$
Lymphocyte	81.5	$\pm 10.1$	84.5	$\pm 3.7$
Reticulocyte count (%)	2.58	$\pm 0.50$	3.11	$\pm 0.47$

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP (1000 mg/kg)	
Number of males	5		5	
RBC ( $\times 10^4/\mu\text{L}$ )	828	± 40	815	± 34
Hemoglobin (g/dL)	15.0	± 0.6	15.1	± 0.5
Hematocrit (%)	42.6	± 2.2	42.6	± 1.0
MCV (fL)	51.6	± 3.7	52.4	± 1.5
MCH (pg)	18.1	± 0.8	18.6	± 0.4
MCHC (g/dL)	35.2	± 1.0	35.5	± 0.4
Platelet ( $\times 10^4/\mu\text{L}$ )	105.7	± 10.2	110.8	± 13.8
PT (sec)	11.6	± 0.8	11.2	± 0.4
APTT (sec)	18.0	± 0.5	18.2	± 0.7
WBC ( $\times 10^2/\mu\text{L}$ )	77.1	± 21.4	62.4	± 20.1
Differential leukocyte count (%)				
Neutrophil	14.7	± 7.9	8.9	± 3.7
Eosinophil	1.5	± 0.2	1.9	± 0.8
Basophil	0.0	± 0.0	0.0	± 0.0
Monocyte	4.0	± 1.4	3.1	± 0.5
Lymphocyte	79.8	± 9.2	86.1	± 3.7
Reticulocyte count (%)	2.57	± 0.40	2.50	± 0.58

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP (62.5 mg/kg)		DMIP (250 mg/kg)		DMIP (1000 mg/kg)	
	5		5		5		5	
Number of males	5		5		5		5	
Total protein (g/dL)	5.6 ± 0.2		5.7 ± 0.3		5.4 ± 0.4		5.6 ± 0.3	
Albumin (g/dL)	3.7 ± 0.1		3.7 ± 0.2		3.6 ± 0.3		3.7 ± 0.1	
A/G	1.96 ± 0.17		1.82 ± 0.18		1.98 ± 0.12		1.88 ± 0.19	
Glucose (mg/dL)	152 ± 14		156 ± 11		163 ± 13		167 ± 11	
Total cholesterol (mg/dL)	53 ± 8		69 ± 9 *		68 ± 11 *		61 ± 6	
Triglyceride (mg/dL)	57 ± 20		66 ± 16		75 ± 46		72 ± 27	
Phospholipid (mg/dL)	83 ± 9		98 ± 13		95 ± 18		97 ± 4	
AST (U/L)	55 ± 4		61 ± 8		51 ± 4		59 ± 7	
ALT (U/L)	24 ± 3		29 ± 3		25 ± 3		28 ± 3	
γ -GTP (U/L)	0 ± 0		0 ± 0		0 ± 0		0 ± 0	
LDH (U/L)	158 ± 130		113 ± 57		106 ± 64		104 ± 58	
Bile acid ( μ mol/L)	16.5 ± 11.7		9.3 ± 3.6		10.2 ± 5.4		19.4 ± 16.5	
Blood urea nitrogen (mg/dL)	13 ± 0		13 ± 2		11 ± 1		11 ± 1	
Creatinine (mg/dL)	0.5 ± 0.1		0.5 ± 0.0		0.4 ± 0.1		0.5 ± 0.1	
Total bilirubin (mg/dL)	0.06 ± 0.03		0.06 ± 0.01		0.06 ± 0.01		0.06 ± 0.02	
ALP (U/L)	389 ± 83		378 ± 74		378 ± 77		402 ± 109	
Inorganic phosphorus (mg/dL)	6.4 ± 0.5		6.1 ± 0.3		6.2 ± 0.6		6.4 ± 0.6	
Ca (mg/dL)	9.8 ± 0.1		10.1 ± 0.3		9.7 ± 0.3		9.7 ± 0.2	
Na (mEq/L)	144.6 ± 0.7		143.8 ± 0.5		144.8 ± 1.4		144.5 ± 0.6	
K (mEq/L)	3.79 ± 0.13		3.91 ± 0.25		3.86 ± 0.18		3.81 ± 0.23	
Cl (mEq/L)	107.6 ± 0.2		106.6 ± 1.0		107.1 ± 1.6		106.2 ± 0.8	

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP (1000 mg/kg)	
	5		5	
Number of females				
Total protein (g/dL)	6.1 ± 0.4		6.0 ± 0.2	
Albumin (g/dL)	3.6 ± 0.3		3.6 ± 0.1	
A/G	1.48 ± 0.14		1.53 ± 0.06	
Glucose (mg/dL)	154 ± 33		137 ± 4	
Total cholesterol (mg/dL)	66 ± 9		46 ± 11 *	
Triglyceride (mg/dL)	52 ± 33		35 ± 14	
Phospholipid (mg/dL)	96 ± 13		72 ± 11 *	
AST (U/L)	63 ± 7		60 ± 6	
ALT (U/L)	27 ± 2		28 ± 2	
γ -GTP (U/L)	0 ± 0		0 ± 1	
LDH (U/L)	113 ± 49		84 ± 46	
Bile acid ( μ mol/L)	35.9 ± 39.6		15.0 ± 7.7	
Blood urea nitrogen (mg/dL)	14 ± 2		14 ± 2	
Creatinine (mg/dL)	0.5 ± 0.0		0.5 ± 0.0	
Total bilirubin (mg/dL)	0.05 ± 0.01		0.05 ± 0.01	
ALP (U/L)	283 ± 23		282 ± 60	
Inorganic phosphorus (mg/dL)	5.9 ± 0.9		5.9 ± 0.4	
Ca (mg/dL)	9.3 ± 0.4		9.4 ± 0.2	
Na (mEq/L)	144.9 ± 0.6		143.9 ± 0.8	
K (mEq/L)	3.78 ± 0.44		3.89 ± 0.20	
Cl (mEq/L)	107.7 ± 1.1		106.7 ± 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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP (62.5 mg/kg)		DMIP (250 mg/kg)		DMIP (1000 mg/kg)	
	5		5		5		5	
Number of males								
Total protein (g/dL)	5.6 ± 0.2		5.8 ± 0.3		5.8 ± 0.2		5.8 ± 0.2	
Albumin (g/dL)	3.8 ± 0.2		4.0 ± 0.2		3.8 ± 0.1		3.9 ± 0.1	
A/G	2.00 ± 0.12		2.19 ± 0.18		1.99 ± 0.17		2.02 ± 0.10	
Glucose (mg/dL)	114 ± 9		130 ± 9 *		121 ± 9		136 ± 11 **	
Total cholesterol (mg/dL)	63 ± 4		61 ± 12		68 ± 6		66 ± 13	
Triglyceride (mg/dL)	28 ± 4		45 ± 23		35 ± 12		71 ± 28 **	
Phospholipid (mg/dL)	102 ± 6		104 ± 11		111 ± 11		115 ± 16	
AST (U/L)	169 ± 63		136 ± 64		95 ± 16		82 ± 19	
ALT (U/L)	53 ± 10		52 ± 15		50 ± 12		40 ± 4	
γ -GTP (U/L)	0 ± 0		0 ± 1		0 ± 0		0 ± 0	
LDH (U/L)	78 ± 26		140 ± 79		58 ± 20		85 ± 53	
Bile acid ( μ mol/L)	9.5 ± 4.8		12.5 ± 2.3		12.7 ± 5.9		21.7 ± 5.8 **	
Blood urea nitrogen (mg/dL)	12 ± 3		13 ± 1		10 ± 5		14 ± 5	
Creatinine (mg/dL)	0.5 ± 0.1		0.5 ± 0.1		0.5 ± 0.0		0.5 ± 0.1	
Total bilirubin (mg/dL)	0.05 ± 0.01		0.06 ± 0.01		0.06 ± 0.02		0.06 ± 0.02	
ALP (U/L)	177 ± 24		223 ± 91		177 ± 57		169 ± 40	
Inorganic phosphorus (mg/dL)	6.1 ± 0.5		6.4 ± 0.5		6.4 ± 0.8		6.9 ± 1.4	
Ca (mg/dL)	9.8 ± 0.4		10.0 ± 0.3		10.4 ± 0.2		10.5 ± 0.5 *	
Na (mEq/L)	142.0 ± 1.3		142.3 ± 2.0		142.7 ± 0.6		142.3 ± 1.5	
K (mEq/L)	3.62 ± 0.49		3.53 ± 0.26		3.62 ± 0.24		4.20 ± 0.86	
Cl (mEq/L)	107.4 ± 2.2		107.7 ± 2.3		107.7 ± 1.1		106.2 ± 2.1	

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP (1000 mg/kg)	
	5		5	
Number of females				
Total protein (g/dL)	6.1	± 0.3	6.1	± 0.6
Albumin (g/dL)	4.2	± 0.2	4.3	± 0.4
A/G	2.20	± 0.12	2.33	± 0.06
Glucose (mg/dL)	129	± 7	159	± 18 *
Total cholesterol (mg/dL)	68	± 12	77	± 16
Triglyceride (mg/dL)	13	± 2	33	± 14 *
Phospholipid (mg/dL)	111	± 14	125	± 20
AST (U/L)	59	± 9	51	± 5
ALT (U/L)	20	± 2	20	± 2
γ -GTP (U/L)	0	± 0	0	± 1
LDH (U/L)	93	± 31	82	± 31
Bile acid ( μ mol/L)	12.4	± 7.6	11.6	± 6.5
Blood urea nitrogen (mg/dL)	16	± 1	15	± 0
Creatinine (mg/dL)	0.6	± 0.1	0.6	± 0.1
Total bilirubin (mg/dL)	0.06	± 0.01	0.06	± 0.00
ALP (U/L)	171	± 25	173	± 28
Inorganic phosphorus (mg/dL)	4.4	± 0.8	5.5	± 0.9
Ca (mg/dL)	9.8	± 0.4	9.9	± 0.3
Na (mEq/L)	143.8	± 0.7	143.9	± 1.1
K (mEq/L)	3.45	± 0.21	3.60	± 0.13
Cl (mEq/L)	108.7	± 1.1	107.0	± 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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group	Corn oil (control)		DMIP (1000 mg/kg)	
	5		5	
Number of females				
Total protein (g/dL)	6.1 ±	0.3	6.5 ±	0.2
Albumin (g/dL)	3.8 ±	0.2	4.2 ±	0.2
A/G	1.70 ±	0.11	1.80 ±	0.21
Glucose (mg/dL)	122 ±	16	126 ±	6
Total cholesterol (mg/dL)	66 ±	12	66 ±	13
Triglyceride (mg/dL)	17 ±	4	25 ±	17
Phospholipid (mg/dL)	98 ±	12	112 ±	23
AST (U/L)	71 ±	23	57 ±	17
ALT (U/L)	32 ±	16	25 ±	8
γ -GTP (U/L)	0 ±	1	0 ±	0
LDH (U/L)	73 ±	53	84 ±	42
Bile acid ( μ mol/L)	21.0 ±	16.5	9.4 ±	2.9
Blood urea nitrogen (mg/dL)	13 ±	1	16 ±	3
Creatinine (mg/dL)	0.6 ±	0.0	0.6 ±	0.0
Total bilirubin (mg/dL)	0.07 ±	0.02	0.07 ±	0.02
ALP (U/L)	155 ±	49	144 ±	34
Inorganic phosphorus (mg/dL)	4.7 ±	1.3	4.8 ±	0.4
Ca (mg/dL)	9.3 ±	0.3	9.6 ±	0.4
Na (mEq/L)	143.2 ±	1.9	142.7 ±	1.2
K (mEq/L)	3.65 ±	0.35	3.69 ±	0.30
Cl (mEq/L)	107.4 ±	2.3	107.6 ±	2.4

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group		Corn oil (control)		DMIP 62.5 mg/kg		DMIP 250 mg/kg		DMIP 1000 mg/kg	
Number of males		8		13		13		8	
Body weight	(g)	534.3	± 36.6	528.9	± 23.8	528.4	± 31.6	510.4	± 36.3
Brain	(mg)	2019.5	± 96.7	2029.7	± 77.5	2032.3	± 124.4	2028.8	± 54.0
	(mg/g)	3.790	± 0.230	3.842	± 0.183	3.860	± 0.343	3.989	± 0.247
Thymus	(mg)	273.5	± 69.1	308.9	± 53.4	296.8	± 67.6	288.5	± 51.2
	(mg/g)	0.515	± 0.140	0.586	± 0.108	0.563	± 0.132	0.569	± 0.117
Heart	(mg)	1469.0	± 115.3	1490.4	± 144.7	1567.9	± 135.8	1432.5	± 106.6
	(mg/g)	2.753	± 0.177	2.815	± 0.207	2.967	± 0.192	2.809	± 0.141
Liver	(mg)	15388.4	± 2656.7	14432.4	± 1769.8	14301.8	± 1618.5	14058.8	± 1496.2
	(mg/g)	28.658	± 3.279	27.237	± 2.627	27.024	± 2.079	27.500	± 1.364
Kidney (R)	(mg)	1608.9	± 162.0	1594.3	± 173.9	1690.9	± 164.9	1599.0	± 135.4
	(mg/g)	3.008	± 0.173	3.016	± 0.320	3.203	± 0.276	3.136	± 0.208
Kidney (L)	(mg)	1626.6	± 191.9	1604.9	± 152.0	1691.4	± 167.6	1582.9	± 141.5
	(mg/g)	3.038	± 0.206	3.035	± 0.255	3.203	± 0.268	3.104	± 0.209
Kidney	(mg)	3235.5	± 348.4	3199.2	± 321.1	3382.3	± 325.9	3181.9	± 270.9
	(mg/g)	6.046	± 0.360	6.051	± 0.567	6.405	± 0.529	6.240	± 0.400
Spleen	(mg)	793.9	± 127.7	874.9	± 99.2	847.6	± 135.4	841.3	± 75.9
	(mg/g)	1.487	± 0.228	1.657	± 0.202	1.602	± 0.222	1.655	± 0.174
Testis (R)	(mg)	1709.9	± 105.5	1621.4	± 165.5	1622.9	± 166.7	1629.3	± 92.1
	(mg/g)	3.208	± 0.208	3.065	± 0.274	3.090	± 0.438	3.200	± 0.186
Testis (L)	(mg)	1737.1	± 150.8	1633.7	± 137.2	1762.1	± 397.7	1615.2	± 90.0
	(mg/g)	3.255	± 0.241	3.091	± 0.245	3.339	± 0.715	3.171	± 0.150
Testis	(mg)	3446.9	± 252.9	3255.1	± 299.5	3385.0	± 429.7	3244.5	± 179.4
	(mg/g)	6.463	± 0.436	6.156	± 0.511	6.429	± 0.891	6.370	± 0.331
Epididymis (R)	(mg)	650.2	± 55.0	627.5	± 63.1	599.0	± 50.9	608.8	± 40.6
	(mg/g)	1.220	± 0.104	1.187	± 0.109	1.140	± 0.140	1.199	± 0.124
Epididymis (L)	(mg)	648.0	± 70.0	627.6	± 64.5	605.4	± 52.8	593.3	± 37.0
	(mg/g)	1.217	± 0.135	1.187	± 0.116	1.150	± 0.124	1.168	± 0.113
Epididymides	(mg)	1298.2	± 123.7	1255.2	± 123.9	1204.3	± 72.3	1202.1	± 76.4
	(mg/g)	2.436	± 0.238	2.374	± 0.218	2.290	± 0.229	2.367	± 0.235
Prostate, ventral	(mg)	602.5	± 141.7	717.2	± 119.4	661.0	± 144.4	644.6	± 106.8
	(mg/g)	1.138	± 0.314	1.359	± 0.234	1.253	± 0.271	1.268	± 0.218
Seminal vesicles	(mg)	1761.5	± 223.6	1707.8	± 309.8	1894.0	± 199.0	1695.7	± 161.8
	(mg/g)	3.296	± 0.334	3.237	± 0.614	3.594	± 0.413	3.340	± 0.435

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group		Corn oil (control)		DMIP 62.5 mg/kg		DMIP 250 mg/kg		DMIP 1000 mg/kg	
Number of males		8		13		13		8	
Body weight	(g)	534.3	± 36.6	528.9	± 23.8	528.4	± 31.6	510.4	± 36.3
Thyroid gland	(mg)	22.7	± 5.7	18.3	± 5.2	21.6	± 4.4	20.4	± 5.4
	(mg/g)	0.043	± 0.012	0.034	± 0.009	0.041	± 0.008	0.040	± 0.009
Adrenal gland (R)	(mg)	28.3	± 5.7	27.3	± 5.3	28.3	± 3.7	29.2	± 8.0
	(mg/g)	0.053	± 0.012	0.052	± 0.011	0.054	± 0.008	0.057	± 0.014
Adrenal gland (L)	(mg)	29.5	± 6.3	29.2	± 5.4	30.5	± 4.5	31.6	± 7.6
	(mg/g)	0.056	± 0.013	0.055	± 0.010	0.058	± 0.010	0.062	± 0.013
Adrenal gland	(mg)	57.8	± 11.9	56.5	± 10.6	58.8	± 8.0	60.8	± 15.4
	(mg/g)	0.109	± 0.025	0.107	± 0.021	0.112	± 0.018	0.119	± 0.026

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group		Corn oil (control)		DMIP 1000 mg/kg	
Number of males		5		5	
Body weight	(g)	548.4	± 52.8	536.4	± 49.1
Brain	(mg)	1986.5	± 67.6	2015.7	± 134.8
	(mg/g)	3.645	± 0.320	3.781	± 0.418
Thymus	(mg)	270.7	± 34.8	272.5	± 57.8
	(mg/g)	0.502	± 0.105	0.505	± 0.078
Heart	(mg)	1542.6	± 145.9	1611.7	± 156.3
	(mg/g)	2.825	± 0.298	3.007	± 0.179
Liver	(mg)	15801.4	± 3438.5	14133.8	± 2092.5
	(mg/g)	28.577	± 3.643	26.266	± 2.073
Kidney (R)	(mg)	1743.8	± 221.6	1698.5	± 100.0
	(mg/g)	3.184	± 0.335	3.177	± 0.189
Kidney (L)	(mg)	1717.2	± 209.3	1732.2	± 151.1
	(mg/g)	3.136	± 0.309	3.234	± 0.190
Kidney	(mg)	3461.0	± 428.1	3430.8	± 237.4
	(mg/g)	6.320	± 0.638	6.411	± 0.335
Spleen	(mg)	882.0	± 111.2	816.4	± 127.5
	(mg/g)	1.609	± 0.139	1.526	± 0.244
Testis (R)	(mg)	1674.5	± 99.9	1714.1	± 137.0
	(mg/g)	3.063	± 0.164	3.224	± 0.450
Testis (L)	(mg)	1643.2	± 112.7	1717.7	± 136.8
	(mg/g)	3.003	± 0.112	3.228	± 0.426
Testis	(mg)	3317.7	± 209.8	3431.8	± 269.5
	(mg/g)	6.066	± 0.273	6.452	± 0.871
Epididymis (R)	(mg)	685.6	± 67.0	640.0	± 27.6
	(mg/g)	1.255	± 0.123	1.201	± 0.123
Epididymis (L)	(mg)	652.0	± 46.4	624.1	± 41.2
	(mg/g)	1.194	± 0.106	1.174	± 0.157
Epididymis	(mg)	1337.6	± 113.3	1264.1	± 66.2
	(mg/g)	2.449	± 0.226	2.376	± 0.280
Prostate, ventral	(mg)	668.7	± 229.3	731.0	± 165.9
	(mg/g)	1.200	± 0.328	1.356	± 0.255
Seminal vesicles	(mg)	1904.3	± 451.8	2015.4	± 255.4
	(mg/g)	3.463	± 0.710	3.763	± 0.422

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group		Corn oil (control)		DMIP 1000 mg/kg	
Number of males		5		5	
Body weight	(g)	548.4 ±	52.8	536.4 ±	49.1
Thyroid gland	(mg)	20.7 ±	3.5	20.5 ±	3.1
	(mg/g)	0.038 ±	0.006	0.038 ±	0.004
Adrenal gland (R)	(mg)	26.6 ±	4.8	32.0 ±	3.7
	(mg/g)	0.048 ±	0.007	0.060 ±	0.011
Adrenal gland (L)	(mg)	27.5 ±	3.5	33.6 ±	4.4 *
	(mg/g)	0.051 ±	0.006	0.063 ±	0.011
Adrenal gland	(mg)	54.2 ±	7.9	65.6 ±	8.0
	(mg/g)	0.099 ±	0.012	0.124 ±	0.022

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group		Corn oil (control)		DMIP 62.5 mg/kg		DMIP 250 mg/kg		DMIP 1000 mg/kg	
Number of females		13		12		12		12	
Body weight	(g)	322.9 ± 22.8		323.8 ± 25.8		297.9 ± 22.4 *		302.0 ± 8.7	
Brain	(mg)	1889.1 ± 39.1		1898.8 ± 67.2		1858.6 ± 62.3		1898.7 ± 75.3	
	(mg/g)	5.877 ± 0.427		5.902 ± 0.544		6.281 ± 0.634		6.291 ± 0.271	
Thymus	(mg)	221.8 ± 52.7		188.4 ± 62.5		143.4 ± 57.0 **		184.0 ± 51.9	
	(mg/g)	0.686 ± 0.159		0.573 ± 0.153		0.472 ± 0.162 **		0.609 ± 0.169	
Heart	(mg)	1001.7 ± 104.4		1016.1 ± 99.0		923.0 ± 89.3		978.1 ± 46.6	
	(mg/g)	3.101 ± 0.206		3.140 ± 0.210		3.100 ± 0.218		3.242 ± 0.176	
Liver	(mg)	9807.2 ± 858.1		10551.3 ± 830.1		9511.0 ± 1172.6		9900.0 ± 488.2	
	(mg/g)	30.382 ± 1.760		32.660 ± 2.348 *		31.895 ± 2.653		32.808 ± 1.789 *	
Kidney (R)	(mg)	974.6 ± 104.7		1015.8 ± 127.8		934.3 ± 120.4		1036.4 ± 70.4	
	(mg/g)	3.026 ± 0.321		3.145 ± 0.370		3.139 ± 0.339		3.432 ± 0.203 **	
Kidney (L)	(mg)	944.9 ± 96.3		1000.8 ± 119.9		926.4 ± 121.1		1009.1 ± 75.4	
	(mg/g)	2.933 ± 0.292		3.097 ± 0.326		3.112 ± 0.336		3.342 ± 0.228 **	
Kidney	(mg)	1919.5 ± 195.5		2016.6 ± 244.7		1860.7 ± 240.4		2045.5 ± 141.5	
	(mg/g)	5.959 ± 0.595		6.241 ± 0.686		6.252 ± 0.670		6.774 ± 0.416 **	
Spleen	(mg)	794.5 ± 300.4		738.4 ± 111.2		640.5 ± 107.3		745.0 ± 150.9	
	(mg/g)	2.451 ± 0.854		2.284 ± 0.316		2.144 ± 0.281		2.468 ± 0.496	
Ovary (R)	(mg)	53.3 ± 16.9		54.2 ± 7.8		52.6 ± 8.0		50.7 ± 9.2	
	(mg/g)	0.165 ± 0.050		0.168 ± 0.022		0.177 ± 0.023		0.167 ± 0.028	
Ovary (L)	(mg)	50.5 ± 6.4		51.5 ± 8.7		48.3 ± 6.5		46.0 ± 7.6	
	(mg/g)	0.156 ± 0.016		0.159 ± 0.026		0.162 ± 0.014		0.152 ± 0.026	
Ovary	(mg)	103.9 ± 19.6		105.7 ± 13.6		100.9 ± 13.1		96.6 ± 11.7	
	(mg/g)	0.321 ± 0.055		0.327 ± 0.038		0.338 ± 0.032		0.320 ± 0.036	
Uterus	(mg)	652.8 ± 120.5		638.3 ± 82.3		645.0 ± 108.8		659.7 ± 103.7	
	(mg/g)	2.023 ± 0.348		1.970 ± 0.182		2.159 ± 0.262		2.184 ± 0.337	
Thyroid gland	(mg)	15.4 ± 3.2		15.1 ± 3.4		14.6 ± 3.3		14.5 ± 3.5	
	(mg/g)	0.048 ± 0.009		0.047 ± 0.009		0.049 ± 0.011		0.048 ± 0.012	
Adrenal gland (R)	(mg)	33.6 ± 4.0		34.6 ± 3.2		34.5 ± 5.2		37.2 ± 4.7	
	(mg/g)	0.104 ± 0.012		0.107 ± 0.009		0.116 ± 0.014		0.123 ± 0.016 **	
Adrenal gland (L)	(mg)	36.5 ± 3.4		35.5 ± 5.1		36.7 ± 6.6		39.0 ± 5.0	
	(mg/g)	0.114 ± 0.012		0.110 ± 0.016		0.123 ± 0.019		0.129 ± 0.017 *	
Adrenal gland	(mg)	70.1 ± 6.6		70.1 ± 7.4		71.2 ± 11.5		76.1 ± 9.5	
	(mg/g)	0.218 ± 0.022		0.217 ± 0.023		0.239 ± 0.032		0.252 ± 0.033 **	

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group		Corn oil (control)		DMIP 1000 mg/kg	
Number of females		5		5	
Body weight	(g)	282.5	± 13.3	283.4	± 10.9
Brain	(mg)	1895.7	± 99.1	1929.5	± 89.7
	(mg/g)	6.710	± 0.149	6.815	± 0.387
Thymus	(mg)	275.0	± 33.1	291.7	± 36.0
	(mg/g)	0.977	± 0.145	1.028	± 0.101
Heart	(mg)	808.6	± 14.8	933.7	± 58.0 **
	(mg/g)	2.866	± 0.107	3.295	± 0.185 **
Liver	(mg)	6907.6	± 247.9	8233.1	± 604.9 **
	(mg/g)	24.500	± 1.575	29.036	± 1.500 **
Kidney (R)	(mg)	866.2	± 68.0	980.8	± 44.4 *
	(mg/g)	3.079	± 0.363	3.461	± 0.113 *
Kidney (L)	(mg)	855.8	± 59.3	958.0	± 54.2 *
	(mg/g)	3.038	± 0.300	3.379	± 0.103 *
Kidney	(mg)	1722.0	± 121.5	1938.8	± 92.5 *
	(mg/g)	6.117	± 0.651	6.840	± 0.176 *
Spleen	(mg)	522.8	± 36.5	601.8	± 71.6
	(mg/g)	1.857	± 0.194	2.124	± 0.241
Ovary (R)	(mg)	42.8	± 4.7	44.5	± 4.0
	(mg/g)	0.152	± 0.018	0.157	± 0.018
Ovary (L)	(mg)	41.3	± 5.2	43.7	± 4.1
	(mg/g)	0.146	± 0.018	0.154	± 0.012
Ovary	(mg)	84.0	± 8.2	88.1	± 2.1
	(mg/g)	0.298	± 0.029	0.311	± 0.013
Uterus	(mg)	504.8	± 103.0	751.6	± 369.0
	(mg/g)	1.799	± 0.429	2.636	± 1.257
Thyroid gland	(mg)	16.6	± 2.5	13.3	± 0.9 *
	(mg/g)	0.059	± 0.010	0.047	± 0.004 *
Adrenal gland (R)	(mg)	30.9	± 2.5	32.7	± 4.0
	(mg/g)	0.110	± 0.010	0.116	± 0.015
Adrenal gland (L)	(mg)	32.4	± 2.2	34.8	± 4.0
	(mg/g)	0.115	± 0.011	0.123	± 0.014
Adrenal gland	(mg)	63.3	± 4.1	67.5	± 7.8
	(mg/g)	0.225	± 0.019	0.238	± 0.029

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Group		Corn oil (control)		DMIP 1000 mg/kg	
Number of females		5		5	
Body weight	(g)	301.6	± 15.4	304.5	± 18.7
Brain	(mg)	1840.5	± 114.3	1922.0	± 58.4
	(mg/g)	6.106	± 0.303	6.328	± 0.392
Thymus	(mg)	270.1	± 70.0	280.1	± 74.3
	(mg/g)	0.895	± 0.222	0.916	± 0.219
Heart	(mg)	925.3	± 29.9	963.8	± 47.8
	(mg/g)	3.071	± 0.097	3.168	± 0.109
Liver	(mg)	7348.2	± 655.8	7871.4	± 555.2
	(mg/g)	24.357	± 1.655	25.837	± 0.386
Kidney (R)	(mg)	941.2	± 36.3	941.1	± 37.0
	(mg/g)	3.126	± 0.164	3.098	± 0.199
Kidney (L)	(mg)	937.5	± 55.1	916.2	± 58.3
	(mg/g)	3.112	± 0.187	3.013	± 0.178
Kidney	(mg)	1878.6	± 85.2	1857.3	± 92.5
	(mg/g)	6.237	± 0.328	6.111	± 0.363
Spleen	(mg)	605.5	± 146.7	514.4	± 37.4
	(mg/g)	2.013	± 0.494	1.693	± 0.149
Ovary (R)	(mg)	59.1	± 9.2	49.9	± 10.1
	(mg/g)	0.195	± 0.022	0.166	± 0.043
Ovary (L)	(mg)	49.2	± 4.4	45.5	± 10.5
	(mg/g)	0.163	± 0.012	0.150	± 0.036
Ovary	(mg)	108.4	± 13.3	95.4	± 19.1
	(mg/g)	0.359	± 0.032	0.316	± 0.075
Uterus	(mg)	439.9	± 99.3	591.0	± 273.1
	(mg/g)	1.473	± 0.389	1.923	± 0.816
Thyroid gland	(mg)	13.1	± 0.8	17.6	± 3.2 *
	(mg/g)	0.044	± 0.003	0.058	± 0.010 *
Adrenal gland (R)	(mg)	32.8	± 3.5	34.2	± 5.7
	(mg/g)	0.109	± 0.010	0.114	± 0.026
Adrenal gland (L)	(mg)	35.7	± 4.7	33.6	± 6.6
	(mg/g)	0.118	± 0.015	0.111	± 0.027
Adrenal gland	(mg)	68.5	± 8.0	67.8	± 12.1
	(mg/g)	0.227	± 0.024	0.225	± 0.052

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Findings	Group Grade	Corn oil (control)		DMIP 62.5 mg/kg		DMIP 250 mg/kg		DMIP 1000 mg/kg		
		-	P	-	P	-	P	-	P	
Epididymis										
Nodule, yellowish, cauda, left/right side		8	0	11	2	13	0	8	0	
Ileum										
Diverticulum		7	1	13	0	13	0	8	0	
Kidney										
Discoloration, pale colored		8	0	13	0	13	0	7	1	
Enlargement		8	0	13	0	11	2	7	1	
Recessed area		8	0	12	1	13	0	7	1	
Testis										
Enlargement, left side		8	0	13	0	12	1	8	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Table 31-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group Grade	Corn oil (control)		DMIP 1000 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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Table 32-1. Macroscopic findings of female rats at the end of the dosing period

Findings	Group Grade	Corn oil (control)		DMIP 62.5 mg/kg		DMIP 250 mg/kg		DMIP 1000 mg/kg	
		-	P	-	P	-	P	-	P
Kidney									
Dilatation, pelvis, right side		13	0	12	0	12	0	11	1
Discoloration, pale colored		13	0	12	0	12	0	11	1
Recessed area, scattered, left side		13	0	12	0	11	1	12	0
Spleen									
Enlargement		12	1	12	0	12	0	12	0
Stomach									
Dark colored spot/area, mucosa, glandular stomach		13	0	11	1	12	0	11	1
Edematous, subserosa, forestomach		13	0	12	0	12	0	11	1
Thickening, mucosa, forestomach		13	0	12	0	12	0	11	1

Notes) - : No abnormal changes P : Non-graded change  
 Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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	Corn oil (control)		DMIP 1000 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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Table 32-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group Grade	Corn oil (control)		DMIP 1000 mg/kg	
		-	P	-	P
External appearance					
Defect, in the end of the tail		4	1	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Findings	Group Grade	Corn oil (control)						DMIP 62.5 mg/kg						DMIP 250 mg/kg						DMIP 1000 mg/kg																	
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE								
Brain		5																																			
Spinal cord		5																																			
Pituitary gland		5																																			
Submandibular gland		5																																			
Sublingual gland		5																																			
Lymph node, submandibular		5																																			
Thyroid gland		5																																			
Ectopic thymus		0						4																								1					
Parathyroid gland		5																																			
Thymus		5																																			
Heart		5																																			
Degeneration/fibrosis, myocardial, focal		3	2	0	0	0	3																								2	0	0	0			
Trachea		5																																			
Lung		5																																			
Accumulation, foam cell, alveolus		4	1	0	0	0	5																								0	0	0	0			
Mineralization, focal, arterial wall		5	0	0	0	0	3																								2	0	0	0			
Bronchus		5																																			
Liver		5																																			
Fatty change, hepatocyte, periportal		0	3	2	0	0	0																								4	1	0	0			
Microgranuloma		2	3	0	0	0	2																								3	0	0	0			
Pancreas		5																																			
Stomach		5																																			
Duodenum		5																																			
Jejunum		5																																			
Ileum		5																																			
Defect, muscular layer, focal, in diverticulum		5	0	1	0	0	5																								0	0	0	0			
Mineralization, with foreign body giant cell, serosa, in diverticulum		5	0	1	0	0	5																								0	0	0	0			
Cecum		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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Table 33(continued). Histopathological findings of male rats at the end of the dosing period

Findings	Group Grade	Corn oil (control)						DMIP 62.5 mg/kg						DMIP 250 mg/kg						DMIP 1000 mg/kg							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+
Colon		5																									
Rectum		5																									
Lymph node, mesenteric		5																									
Spleen																											
Deposit, pigment, brown		0	4	1	0	0		0	1	0	0	0		2	0	0	0	0		0	5	0	0	0			
Hematopoiesis, extramedullary		0	0	5	0	0														0	0	5	0	0			
Kidney																											
Basophilic tubule, cortex		2	3	0	0	0		0	1	0	0	0		2	0	0	0	0		2	4	1	0	0			
Cyst, cortex, subserosa		5					0	0				1		2				0		7					0		
Urinary bladder		5																									
Adrenal gland		5																									
Testis																											
Atrophy, seminiferous tubule, focal		4	1	0	0	0								1	0	0	0	0		5	0	0	0	0			
Decrease, germ cell layer,																											
seminiferous tubule, unilateral		5	0	0	0	0								0	0	1	0	0		5	0	0	0	0			
Dilatation, lumen,																											
seminiferous tubule, unilateral		5	0	0	0	0								0	0	0	1	0		5	0	0	0	0			
Edema, interstitial, unilateral		5	0	0	0	0								0	0	1	0	0		5	0	0	0	0			
Epididymis																											
Cellular infiltration, lymphocyte, interstitial		5	0	0	0	0		2	0	0	0	0								4	1	0	0	0			
Granuloma, spermatic		5	0	0	0	0		0	2	0	0	0								5	0	0	0	0			
Prostate																											
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0														5	0	0	0	0			
Seminal vesicle		5																									
Coagulating gland		5																									
Eyeball		5																									
Harderian gland																											
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0														5	0	0	0	0			
Sciatic nerve		5																									
Skeletal muscle		5																									
Femur		5																									
Marrow, femur		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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Findings	Group Grade	Corn oil (control)						DMIP 62.5 mg/kg						DMIP 250 mg/kg						DMIP 1000 mg/kg									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5						0							0								5						
Spinal cord		5						0							0								5						
Pituitary gland		5						0							0								5						
Submandibular gland		5						0							0								5						
Sublingual gland		5						0							0								5						
Lymph node, submandibular		5						0							0								5						
Thyroid gland																													
Ectopic thymus		4					1	0						0							0		5						0
Parathyroid gland		4						1	0					0									4						1
Thymus		5						0							0								5						
Heart																													
Degeneration/fibrosis, myocardial, focal		4	1	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
Trachea		5						0							0								5						
Lung																													
Accumulation, foam cell, alveolus		5	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	1	0	0	0	0	0	
Bronchus		5						0							0								5						
Liver																													
Fatty change, hepatocyte, periportal		4	1	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	1	0	0	0	0	0	
Microgranuloma		2	3	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	1	0	0	0	0	0	
Pancreas																													
Cellular infiltration, eosinophil, around artery		5	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	1	0	0	0	0	0	
Stomach																													
Hyperplasia, squamous cell, mucosa, forestomach		5	0	0	0	0		1	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	1	0	0	0	0	
Duodenum		5						0							0								5						
Jejunum		5						0							0								5						
Ileum		5						0							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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Table 34-1(continued). Histopathological findings of female rats at the end of the dosing period

Findings	Group Grade	Corn oil (control)							DMIP 62.5 mg/kg							DMIP 250 mg/kg							DMIP 1000 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Cecum		5						0						0						5									
Colon		5						0						0						5									
Rectum		5						0						0						5									
Lymph node, mesenteric		5						0						0						5									
Spleen																													
Deposit, pigment, brown		0	2	4	0	0		0	0	0	0	0		0	0	0	0	0		0	1	4	0	0					
Hematopoiesis, extramedullary		0	0	4	1	1		0	0	0	0	0		0	0	0	0	0		0	0	3	2	0					
Kidney																													
Basophilic tubule, cortex		3	2	0	0	0		0	0	0	0	0		1	0	0	0	0		5	1	0	0	0					
Cyst, cortex, subserosa		4					1	0					0	1					0	6						0			
Dilatation, pelvis, unilateral		5	0	0	0	0		0	0	0	0	0		1	0	0	0	0		5	0	1	0	0					
Mineralization, medulla		5	0	0	0	0		0	0	0	0	0		1	0	0	0	0		4	2	0	0	0					
Urinary bladder		5						0						0						5									
Adrenal gland		5						0						0						5									
Ovary		5						0						0						5									
Uterus		5						0						0						5									
Vagina		5						0						0						5									
Eyeball		5						0						0						5									
Harderian gland		5						0						0						5									
Sciatic nerve		5						0						0						5									
Skeletal muscle		5						0						0						5									
Femur		5						0						0						5									
Marrow, femur		5						0						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 1,3-Benzenedicarboxylic acid, dimethyl ester 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	Corn oil (control)						DMIP 1000 mg/kg							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		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	1	0	0	0			
Parathyroid gland		5						5							
Thymus		5						5							
Heart		5						5							
Trachea		5						5							
Lung															
Mineralization, focal, arterial wall		4	1	0	0	0		4	1	0	0	0			
Bronchus		5						5							
Liver															
Fatty change, hepatocyte, periportal		3	2	0	0	0		4	1	0	0	0			
Microgranuloma		2	3	0	0	0		4	1	0	0	0			
Pancreas															
Atrophy, acinar cell, focal, with ductal proliferation		4	1	0	0	0		5	0	0	0	0			
Stomach		5						5							
Duodenum		5						5							
Jejunum		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.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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	Corn oil (control)						DMIP 1000 mg/kg								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Ileum		5							5							
Cecum		5							5							
Colon		5							5							
Rectum		5							5							
Lymph node, mesenteric		5							5							
Spleen																
Deposit, pigment, brown		0	0	3	2	0			0	1	2	2	0			
Hematopoiesis, extramedullary		0	0	5	0	0			0	0	5	0	0			
Kidney																
Basophilic tubule, cortex		2	3	0	0	0			5	0	0	0	0			
Urinary bladder		5							5							
Adrenal gland		5							5							
Ovary		5							5							
Uterus		5							5							
Vagina		5							5							
Eyeball		5							5							
Harderian gland		5							5							
Sciatic nerve		5							5							
Skeletal muscle		5							5							
Femur		5							5							
Marrow, femur		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.  
Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 35. Results of observations about estrous cycle

Dose	Corn oil (control)	DMIP (62.5 mg/kg)	DMIP (250 mg/kg)	DMIP (1000 mg/kg)
Number of animals examined	13	13	13	13
<u>Pre-treatment period</u>				
Number of animals showing type of cycle				
4-day cycle	9	11	11	11
4-5-day cycle	1	0	1	0
5-day cycle	3	2	1	2
Mean length of estrous cycle in days; Mean±S.D. (N)	4.3 ± 0.4 (13)	4.2 ± 0.4 (13)	4.1 ± 0.3 (13)	4.2 ± 0.4 (13)
<u>Treatment period</u>				
Number of animals showing each type of cycle				
4-day cycle	9	11	11	12
4-5-day cycle	1	1	0	0
5-day cycle	3	1	2	1
Mean length of estrous cycle in days; Mean±S.D. (N)	4.3 ± 0.4 (13)	4.1 ± 0.3 (13)	4.2 ± 0.4 (13)	4.1 ± 0.3 (12)
Frequency of animals of which type of estrus cycle				
was changed after the treatment	0 / 13	1 / 13	2 / 13	1 / 13
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.0 ± 0.0 (13)	1.0 ± 0.0 (13)	1.0 ± 0.0 (13)	1.0 ± 0.0 (13)

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 36. Results of observations about reproductive performance

Dose	Corn oil (control)	DMIP (62.5 mg/kg)	DMIP (250 mg/kg)	DMIP (1000 mg/kg)
Number of mated pairs [A]	13	13	13	13
Number of copulated pairs [B]	13	13	13	13
Copulation index [(B/A) × 100,%]	100.0	100.0	100.0	100.0
Number of fertile males [C]	13	13	13	13
Fertility index [(C/B) × 100,%]	100.0	100.0	100.0	100.0
Pairing days until copulation ; Mean ± S.D. (N)	2.8 ± 1.1 (13)	2.2 ± 1.1 (13)	2.3 ± 0.9 (13)	2.8 ± 1.2 (13)

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 37. Observation of offspring (F<sub>1</sub>)

Group	Corn oil (control)	DMIP 62.5 mg/kg	DMIP 250 mg/kg	DMIP 1000 mg/kg
Number of dams	13	13	13	13
Gestation length (days)				
Mean ± S.D. per dam	22.2 ± 0.4	22.4 ± 0.5	22.5 ± 0.5 (12)	22.4 ± 0.5
Number of corpora lutea				
Total	208	214	212	207
Mean ± S.D. per dam	16.0 ± 2.3	16.5 ± 1.1	16.3 ± 1.4	15.9 ± 1.2
Number of implantation scars				
Total	201	210	202	200
Mean ± S.D. per dam	15.5 ± 2.4	16.2 ± 0.9	15.5 ± 1.3	15.4 ± 1.4
Implantation index (%) <sup>a)</sup>	96.6 ± 5.8	98.2 ± 3.6	95.4 ± 4.7	96.7 ± 6.0
Delivery index (dams,%) <sup>b)</sup>	100.0	100.0	92.3	100.0
Number of offspring at birth				
Total	184	201	173	191
Mean ± S.D. per dam	14.2 ± 2.3	15.5 ± 0.9	14.4 ± 1.3 (12)	14.7 ± 1.8
Number of live offspring at birth				
Male	83	93	71	98
Female	89	93	89	91
Total	172	186	160	189
Mean ± S.D. per dam	13.2 ± 3.8	14.3 ± 4.4	13.3 ± 2.1 (12)	14.5 ± 2.0
Sex ratio <sup>c)</sup>				
Mean ± S.D. per dam	0.49 ± 0.17	0.50 ± 0.10 (12)	0.44 ± 0.10 (12)	0.52 ± 0.12
Number of dead offspring				
Total	12	15	13	2
Mean ± S.D. per dam	0.9 ± 2.2	1.2 ± 3.9	1.1 ± 2.1 (12)	0.2 ± 0.6
Delivery index (offspring) <sup>d)</sup>				
Mean% ± S.D. per dam	91.6 ± 6.6	95.9 ± 6.7	93.1 ± 4.9 (12)	95.2 ± 4.6
Birth index <sup>e)</sup>				
Mean% ± S.D. per dam	85.1 ± 20.5	89.5 ± 27.2	86.1 ± 12.1 (12)	94.2 ± 6.2
Live birth index <sup>f)</sup>				
Mean% ± S.D. per dam	92.1 ± 19.8	91.8 ± 27.6	92.9 ± 13.9 (12)	98.9 ± 4.0
Number of offspring on day 4				
Male	83	92	68	93
Female	88	92	83	82
Sex ratio <sup>g)</sup>				
Mean ± S.D. per dam	0.51 ± 0.22	0.50 ± 0.10 (12)	0.44 ± 0.10 (12)	0.54 ± 0.13 (12)
Viability index <sup>h)</sup>				
Mean% ± S.D. per dam	97.4 ± 9.2	98.9 ± 3.8 (12)	94.2 ± 16.6 (12)	91.4 ± 27.5
Number of external abnormalities <sup>i)</sup>	0	1	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.5 ± 1.8 (12)	0.0 ± 0.0 (12)	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 live offspring 21 days after birth/number of live offspring after culling) × 100.

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

Figures in parentheses indicate number of dams.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 38. Body weights of offspring (F<sub>1</sub>) before weaning

Group	Corn oil (control)	DMIP 62.5 mg/kg	DMIP 250 mg/kg	DMIP 1000 mg/kg
Number of dams	13	12	12	13
Male				
Days after birth				
0	6.7 ± 0.4	6.7 ± 0.5	6.7 ± 0.5	6.5 ± 0.4
4	11.1 ± 0.9	10.7 ± 0.8	10.7 ± 1.9	10.3 ± 0.9 (12)
Number of dams	13	12	12	13
Female				
Days after birth				
0	6.2 ± 0.3	6.2 ± 0.6	6.3 ± 0.6	6.1 ± 0.5
4	10.5 ± 0.7 (12)	10.1 ± 1.0	10.1 ± 1.7	9.8 ± 0.9 (12)

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 39. General conditions in offspring (F<sub>1</sub>) before weaning

Group	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
Corn oil (control)	Number of offspring	172	172	171	171	171
	General appearance, No abnormality	172	171	171	171	171
	General appearance, Death		1			
	Abnormal findings of offspring, Bent tail					
DMIP 62.5 mg/kg	Number of offspring	186	186	185	184	184
	General appearance, No abnormality	185	184	183	183	183
	General appearance, Death		1	1		
	Abnormal findings of offspring, Bent tail	1	1	1	1	1
DMIP 250 mg/kg	Number of offspring	160	160	155	155	152
	General appearance, No abnormality	160	155	155	152	151
	General appearance, Death		5		3	1
	Abnormal findings of offspring, Bent tail					
DMIP 1000 mg/kg	Number of offspring	189	189	176	175	175
	General appearance, No abnormality	189	176	175	175	175
	General appearance, Death		13	1		
	Abnormal findings of offspring, Bent tail					

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Table 40. Morphological observations of offspring (F<sub>1</sub>)

Group	Corn oil (control)	DMIP 62.5 mg/kg	DMIP 250 mg/kg	DMIP 1000 mg/kg
Dead pups				
Number of dead pups <sup>a)</sup>	12	15	13	2
Number of missing pups	2	6	0	0
Number of dead pups examined	10	9	13	2
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)	172	186	160	189
Number of live pups with external changes	0	1	0	0
Number of live pups examined (postnatal day 4)	171	184	151	175
Number of live pups with external changes	0	1	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)

<sup>a)</sup>including missing pups



Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 1-1-1(continued). General conditions of male rats

Corn oil (control)

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				
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8	
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8	
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	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.



Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 1-1-2(continued). General conditions of male rats

DMP 62.5 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
M02001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
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: Mouth, Salivation.



Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 1-1-3(continued). General conditions of male rats

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		
M03001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13		
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13		
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		

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.



Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 1-1-4(continued). General conditions of male rats

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	
M04001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04005	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04006	-	a	-	a	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04008	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04009	-	-	-	a	-	-	-	-	-	a	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04010	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8	
-	13	10	13	11	13	13	13	11	13	11	13	13	13	12	13	11	13	7	13	12	13	13	13	13	13	13	13	13	12	13	12	13	13	13	13	13	8	
a	0	3	0	2	0	0	0	2	0	2	0	0	0	1	0	2	0	6	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)															
Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 1000 mg/kg

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M04009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Female No.		Days of administration																																				
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		
		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	
F01001		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01002		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01003		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01004		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01005		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01006		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01007		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01008		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01009		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01010		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01011		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01012		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01013		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females		13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
-		13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
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
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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

b: Excretion, Reddish urine.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Female No.	Days of administration																																					
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18			
	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
F02001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
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
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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

b: Excretion, Reddish urine.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Female No.	Days of administration																																							
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18					
	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		
F03001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	10	10	6	6	6	1
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	10	10	6	6	6	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	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	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

b: Excretion, Reddish urine.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Female No.	DMIP 1000 mg/kg																																						
	Days of administration																																						
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18				
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		
F04001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a
F04003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b	b
F04009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-
F04010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
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	
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	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

b: Excretion, Reddish urine.



Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

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
F05001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	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	5
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: Mouth, Salivation.



Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Female No.	DMIP 1000 mg/kg																																			
	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	
F06001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06002	-	a	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
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	9	10	10	10	10	10	10	10	10	10	10	10	9	10	10	10	6	10	9	10	9	10	10	10	10	10	10	10	10	10	10	10	10	10	5
a	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	4	0	1	0	1	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: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)															
Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F05006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05008	-	-	-	-	-	-	-	-	-	-	-	-	a	a	a
F05009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	4	4	4
a	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1

-: General appearance, No abnormality.

a: Skin, Loss of tail.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 1000 mg/kg															
Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F06006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

-: General appearance, No abnormality.

a: Skin, Loss of tail.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 3-1. General conditions in dams during pregnancy

Corn oil (control)																												
Dam 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)																				
Dam No.	Days of pregnancy																			
	14		15		16		17		18		19		20		21		22		23	
	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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	2	2	0
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	2	2	0
a	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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

c: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 3-2. General conditions in dams during pregnancy

DMP 62.5 mg/kg

Dam 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
F02001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 62.5 mg/kg

Dam No.	Days of pregnancy																				
	14		15		16		17		18		19		20		21		22		23		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F02001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	5	5	0	0
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	5	5	0	0
a	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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

c: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 3-3. General conditions in dams during pregnancy

Dam 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	Pre
F03001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 250 mg/kg

Dam No.	Days of pregnancy																				
	14		15		16		17		18		19		20		21		22		23		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F03001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	c
F03012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	7	7	1		
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	7	7	0		
a	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	1		

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

c: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 3-4. General conditions in dams during pregnancy

DMP 1000 mg/kg

Dam 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
F04001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04002	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04008	-	a	-	-	-	-	-	-	-	-	-	-	a	-	-	-	a	-	a	-	-	-	-	-	-	a	-	-
F04009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04010	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-
F04012	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
-	13	9	13	13	13	13	13	13	13	13	13	13	12	13	13	13	12	13	12	13	13	13	13	13	13	11	13	12
a	0	4	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0	0	0	0	0	0	2	0	1

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 3-4(continued). General conditions in dams during pregnancy

DMIP 1000 mg/kg

Dam No.	Days of pregnancy																			
	14		15		16		17		18		19		20		21		22		23	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04005	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04008	-	a	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-
F04009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04010	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-
F04011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	5	5	0	0
-	13	12	13	12	13	11	13	11	13	13	13	13	13	13	13	13	5	5	0	0
a	0	1	0	1	0	2	0	2	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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

c: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 4-1. General conditions in dams during lactation

Corn oil (control)

Dam 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	-	-	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-
F01013	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13
-	13	13	13	13	13	13	13	13	13	13	13	13
a	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 4-2. General conditions in dams during lactation

DMIP 62.5 mg/kg

Dam No.	Days of lactation											
	0		1		2		3		4		5	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
F02001	-	-	-	-	-	-	-	-	-	-	-	-
F02002	-	-	-	-	-	-	-	-	-	-	-	-
F02003	-	-	-	-	-	-	-	-	-	-	-	-
F02004	-	-	-	-	-	-	-	-	-	-	-	-
F02005	-	-	-	-	-	-	-	-	-	-	-	-
F02006	-	Total litter loss.										
F02007	-	-	-	-	-	-	-	-	-	-	-	-
F02008	-	-	-	-	-	-	-	-	-	-	-	-
F02009	-	-	-	-	-	-	-	-	-	-	-	-
F02010	-	-	-	-	-	-	-	-	-	-	-	-
F02011	-	-	-	-	-	-	-	-	-	-	-	-
F02012	-	-	-	-	-	-	-	-	-	-	-	-
F02013	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	12	12	12	12	12	12	12	12	12	12	12
-	13	12	12	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 4-3. General conditions in dams during lactation

DMIP 250 mg/kg											
Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F03001	-	-	-	-	-	-	-	-	-	-	-
F03002	-	-	-	-	-	-	-	-	-	-	-
F03003	-	-	-	-	-	-	-	-	-	-	-
F03004	-	-	-	-	-	-	-	-	-	-	-
F03005	-	-	-	-	-	-	-	-	-	-	-
F03006	-	-	-	-	-	-	-	-	-	-	-
F03007	-	-	-	-	-	-	-	-	-	-	-
F03008	-	-	-	-	-	-	-	-	-	-	-
F03009	-	-	-	-	-	-	-	-	-	-	-
F03010	-	-	-	-	-	-	-	-	-	-	-
F03011	Dam died on the gestation day 23.										
F03012	-	-	-	-	-	-	-	-	-	-	-
F03013	-	-	-	-	-	-	-	-	-	-	-
Number of dams	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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 4-4. General conditions in dams during lactation

DMIP 1000 mg/kg													
Dam No.	Days of lactation												
	0		1		2		3		4		5		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre		
F04001	-	-	-	-	-	-	-	-	-	-	-	-	
F04002	-	-	-	-	-	-	-	-	-	-	-	-	
F04003	-	-	-	-	-	-	-	-	-	-	-	-	
F04004	-	-	-	-	-	-	-	-	-	-	-	-	
F04005	-	-	-	-	-	-	-	-	-	-	-	-	
F04006	-	-	-	-	-	-	-	-	-	-	-	-	
F04007	-	-	-	Total litter loss.								-	-
F04008	-	-	-	-	-	-	-	-	-	-	-	-	
F04009	-	-	-	-	-	-	-	-	-	-	-	-	
F04010	-	-	-	-	-	-	-	-	-	-	-	-	
F04011	-	-	-	-	-	-	-	-	-	-	-	-	
F04012	-	-	-	-	-	-	-	-	-	a	-	-	
F04013	-	-	-	-	-	-	-	-	-	-	-	-	
Number of dams	13	13	13	12	12	12	12	12	12	12	12	12	
-	13	13	13	12	12	12	12	12	12	11	12	12	
a	0	0	0	0	0	0	0	0	0	1	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 5-1. Detailed clinical observations of male rats

Corn oil (control)

Male No.	Open-field observations <sup>a)</sup>										Urination								Defecation							
	Straub tail																									
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	T42	R7 <sup>c</sup>	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7
M01001	2	2	2	2	2	2	2	2		0	0	0	1	0	0	0		0	0	0	0	0	0	0		
M01002	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0		
M01003	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0		1	0	0	0	0	0	0		
M01004	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0		
M01005	2	2	2	2	2	2	2	2		0	0	0	0	0	0	1		0	0	0	0	0	0	0		
M01006	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0		
M01007	2	2	2	2	2	2	2	2		1	0	1	0	1	0	0		0	0	0	0	0	0	0		
M01008	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0		
M01009	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
M01010	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01011	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01012	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01013	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1	0	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> day 7 of recovery

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

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, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 5-2. Detailed clinical observations of male rats

DMP (62.5 mg/kg)

Male No.	Open-field observations <sup>c)</sup>							Urination							Defecation						
	Straub tail																				
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M02001	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02002	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02003	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02004	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02005	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02006	2	2	2	2	2	2	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0
M02007	2	2	2	2	2	2	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0
M02008	2	2	2	2	2	2	2	0	1	1	0	3	0	0	0	0	0	0	0	0	0
M02009	2	2	2	2	2	2	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M02010	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02011	2	2	2	2	2	2	2	0	0	0	0	0	0	1	0	0	0	0	0	0	0
M02012	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02013	2	2	2	2	2	2	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	0	2	1	1	3	1	1	1	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> day 7 of recovery

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

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, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 5-3. Detailed clinical observations of male rats

DMIP (250 mg/kg)

Male No.	Open-field observations <sup>c)</sup>																				
	Straub tail							Urination							Defecation						
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M03001	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03002	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03003	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03004	2	2	2	2	2	2	2	0	2	0	1	0	0	2	0	0	0	0	0	0	0
M03005	2	3	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03006	2	2	2	2	2	2	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0
M03007	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03008	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03009	2	2	2	2	2	2	2	0	2	0	1	0	0	0	0	0	0	0	0	0	0
M03010	2	2	2	2	2	2	2	0	1	0	1	1	1	0	0	1	0	0	0	0	0
M03011	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03012	2	2	2	2	2	2	2	0	1	0	1	2	0	0	0	0	0	0	0	0	0
M03013	2	2	2	2	2	2	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Total score	3:0	3:1	3:0	3:0	3:0	3:0	3:0	0	7	0	4	3	2	2	0	1	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> day 7 of recovery

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

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, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Appendix 5-4. Detailed clinical observations of male rats

DMP (1000 mg/kg)

Male No.	Open-field observations <sup>o)</sup>										Urination								Defecation									
	Straub tail																											
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	T42	R7 <sup>c</sup>	R14		Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M04001	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04002	2	2	2	2	2	2	2	2			0	0	0	1	1	0	2			0	0	0	0	0	0	0		
M04003	2	2	2	2	2	2	2	2			0	2	0	0	0	0	1			0	0	0	0	0	0	0		
M04004	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04005	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04006	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04007	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04008	2	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04009	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04010	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04011	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04012	2	2	2	2	2	2	2	2	2	2	0	2	1	1	0	0	0	2	1	0	1	0	0	0	0	0	0	0
M04013	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	0	4	1	2	1	1	3	2	1	0	1	0	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)		(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> day 7 of recovery

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

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, fur, 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, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)

Female No.	Open-field observations <sup>o)</sup>																				
	Straub tail							Urination						Defecation							
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	L <sup>c</sup>	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L
F01001	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01002	2	2	2	2	2	2	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0
F01003	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01004	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01005	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01006	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01007	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01008	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01009	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01010	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01011	2	2	2	2	2	2	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01012	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01013	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> lactation period

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

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, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP (62.5 mg/kg)

Female No.	Open-field observations <sup>o</sup>																				
	Straub tail							Urination							Defecation						
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	L <sup>c</sup>	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L
F02001	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02002	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02003	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02004	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02005	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02006	2	2	2	2	2	2	Total litter loss.	0	0	0	0	0	0	Total litter loss.	0	0	0	0	0	0	Total litter loss.
F02007	2	2	2	2	2	2	2	0	0	0	0	0	1	2	0	0	0	0	0	0	0
F02008	2	2	2	3	2	2	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0
F02009	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02010	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02011	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02012	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02013	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	3:0	3:0	3:0	3:1	3:0	3:0	3:0	0	1	0	0	0	1	2	0	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> lactation period

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

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, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 6-1-3. Detailed clinical observations of female rats

DMIP (250 mg/kg)

Female No.	Open-field observations <sup>o)</sup>							Urination							Defecation						
	Straub tail																				
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	L <sup>c</sup>	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L
F03001	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03002	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03003	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03004	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03005	2	2	2	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0
F03006	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03007	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03008	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03009	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03010	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03011	2	2	2	2	2	2	Died	0	1	0	0	0	0	Died	0	0	0	0	0	0	Died
F03012	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03013	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(13)	(12)

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> lactation period

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

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, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMP (1000 mg/kg)

Female No.	Open-field observations <sup>o</sup>																				
	Straub tail							Urination						Defecation							
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	L <sup>c</sup>	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L
F04001	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04002	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04003	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04004	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04005	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04006	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04007	2	2	2	2	2	2	Total litter loss.	0	0	0	0	0	0	Total litter loss.	0	0	0	0	0	0	Total litter loss.
F04008	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04009	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04010	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04011	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04012	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04013	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> lactation period

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

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, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)

Female No.	Open-field observations <sup>o)</sup>										Open-field observations																			
	Straub tail										Urination										Defecation									
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	T42	R7 <sup>c</sup>	R14		Pre	T8	T15	T24	T30	T36	T42	R7 <sup>c</sup>	R14		Pre	T8	T15	T24	T30	T36	T42	R7	R14	
F05001	2	2	2	2	2	2	2				0	0	0	0	0	0	0				0	0	0	0	0	0	0			
F05002	2	2	2	2	2	2	2				0	0	0	0	0	0	0				0	0	0	0	0	0	0			
F05003	2	2	2	2	2	2	2				0	0	0	0	0	0	0				0	0	0	0	0	0	0			
F05004	2	2	2	2	2	2	2				0	0	0	0	0	0	0				0	0	0	0	0	0	0			
F05005	2	2	2	2	2	2	2				0	0	0	0	0	0	1				0	0	0	0	0	0	0			
F05006	2	2	2	2	2	2	2	2	2		1	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0
F05007	2	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0
F05008	2	2	2	2	2	2	2	3	2		0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0
F05009	2	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0
F05010	2	2	2	2	2	2	2	2	3		0	0	0	0	0	0	0	0	1		0	0	0	0	0	0	0	0	0	0
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:1	3:1		1	0	0	0	0	0	1	0	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)		(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> day 7 of recovery

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

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, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMP (1000 mg/kg)

Female No.	Open-field observations <sup>a)</sup>										Open-field observations																			
	Straub tail										Urination										Defecation									
	Pre <sup>a</sup>	T8 <sup>b</sup>	T15	T24	T30	T36	T42	R7 <sup>c</sup>	R14	Pre	T8	T15	T24	T30	T36	T42	R7 <sup>c</sup>	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14			
F06001	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0					
F06002	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0					
F06003	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0					
F06004	2	2	2	2	2	2	2			1	0	0	0	2	1	1			0	0	0	0	0	0	0					
F06005	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0					
F06006	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F06007	2	2	2	2	2	2	2	2	2	0	1	0	2	0	1	0	0	2	0	0	2	0	0	0	0	0	0			
F06008	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0			
F06009	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F06010	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1	1	0	2	2	2	1	0	3	0	0	2	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)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)				

<sup>a</sup> pre-treatment; <sup>b</sup> day 8 of treatment; <sup>c</sup> day 7 of recovery

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

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, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)							
Male No.	Days of administration						
	1	7	14	21	28	35	42
M01001	384.2	410.9	436.3	460.1	494.2	521.3	520.7
M01002	402.4	427.7	457.2	487.4	524.4	543.2	550.1
M01003	407.1	424.1	449.3	486.3	509.8	538.3	546.0
M01004	436.5	464.3	494.7	508.9	537.7	557.8	566.0
M01005	392.8	415.1	449.3	463.8	488.3	507.9	511.1
M01006	428.9	458.8	488.9	508.5	542.7	563.0	590.3
M01007	423.7	452.4	487.4	524.0	564.9	604.2	625.6
M01008	428.9	437.7	461.0	481.8	504.3	526.3	552.2
M01009	407.4	437.5	474.4	508.1	536.0	569.0	594.5
M01010	407.2	428.1	444.4	463.2	486.0	495.2	510.4
M01011	382.8	394.5	419.6	431.5	459.4	487.1	510.3
M01012	411.9	435.2	463.6	484.2	511.1	532.4	555.6
M01013	426.2	458.5	498.2	524.0	566.9	597.7	628.4
Number of males	13	13	13	13	13	13	13
Mean	410.8	434.2	463.4	487.1	517.4	541.8	558.6
S.D.	17.4	20.7	24.1	27.5	31.8	36.0	41.2

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Male No.	Days of administration						
	1	7	14	21	28	35	42
M02001	405.7	423.5	447.6	474.0	498.3	522.6	532.4
M02002	395.6	417.2	443.0	461.1	478.1	510.1	518.2
M02003	410.0	433.8	461.9	485.0	516.6	538.4	553.0
M02004	434.0	466.8	501.5	521.3	552.3	579.2	589.4
M02005	429.3	459.2	492.7	514.2	546.2	559.3	574.7
M02006	416.6	423.8	457.8	483.2	516.1	527.1	549.0
M02007	424.8	448.2	480.5	501.9	537.3	564.0	583.0
M02008	416.2	444.0	470.7	491.7	508.5	526.4	544.1
M02009	412.4	442.5	456.5	504.3	530.5	543.3	571.9
M02010	432.3	456.4	482.9	501.7	532.1	554.3	576.6
M02011	389.8	406.0	428.9	459.2	488.4	510.6	528.0
M02012	394.7	413.7	449.2	473.1	496.9	513.8	538.4
M02013	403.7	416.5	438.5	458.5	476.6	489.5	509.7
Number of males	13	13	13	13	13	13	13
Mean	412.7	434.7	462.4	486.9	513.7	533.7	551.4
S.D.	14.6	19.5	22.0	21.0	25.1	25.6	25.9
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 250 mg/kg

Male No.	Days of administration						
	1	7	14	21	28	35	42
M03001	390.1	405.9	426.3	449.3	471.5	492.2	498.5
M03002	408.4	424.6	455.2	480.7	510.9	527.1	539.1
M03003	416.5	442.6	460.3	481.6	503.9	528.5	538.5
M03004	414.7	430.7	468.6	478.7	506.9	522.3	533.1
M03005	419.7	444.9	465.1	501.3	534.4	564.4	576.0
M03006	429.9	453.3	499.0	522.0	552.6	580.1	609.4
M03007	396.8	420.3	450.0	464.2	476.0	495.6	509.6
M03008	411.6	428.2	440.6	474.9	491.2	504.5	527.2
M03009	434.7	454.1	483.4	511.2	540.0	564.7	585.1
M03010	435.2	454.5	487.0	506.8	529.3	556.3	586.3
M03011	399.5	426.0	455.5	482.2	517.0	542.5	564.8
M03012	428.6	455.7	439.4	485.8	517.8	537.4	558.1
M03013	398.5	417.2	450.1	466.8	493.9	520.9	539.7
Number of males	13	13	13	13	13	13	13
Mean	414.2	435.2	460.0	485.0	511.2	533.6	551.2
S.D.	15.1	16.6	20.6	20.4	24.3	27.5	32.2
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 1000 mg/kg

Male No.	Days of administration						
	1	7	14	21	28	35	42
M04001	425.8	459.8	498.4	514.5	537.0	567.2	579.5
M04002	394.7	420.4	449.7	470.4	498.9	525.4	534.5
M04003	385.3	408.0	439.2	463.8	492.8	503.1	511.4
M04004	433.9	458.6	486.6	495.4	527.8	550.1	569.0
M04005	401.9	413.1	440.0	463.7	479.8	499.3	507.0
M04006	424.9	455.9	489.3	515.3	539.7	559.4	586.4
M04007	421.4	446.7	478.5	494.7	523.0	534.1	550.6
M04008	400.5	414.1	428.8	436.8	457.0	477.4	488.6
M04009	433.9	468.9	506.2	520.3	557.2	583.3	619.6
M04010	401.6	422.3	443.5	468.2	486.7	501.8	518.8
M04011	403.3	416.5	452.0	469.9	485.7	507.2	532.0
M04012	400.5	415.1	441.1	448.8	466.8	485.3	499.0
M04013	411.7	436.4	464.0	481.8	499.3	521.2	543.9
Number of males	13	13	13	13	13	13	13
Mean	410.7	433.5	462.9	480.3	504.0	524.2	541.6
S.D.	15.7	21.7	25.9	26.2	30.4	32.8	38.5
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 7-2-1. Body weights of male rats at the recovery period

Corn oil (control)

Male No.	Days of recovery period		
	1	7	14
M01009	583.6	593.1	592.1
M01010	510.7	519.2	532.0
M01011	507.5	524.9	530.3
M01012	552.3	559.9	573.6
M01013	630.7	645.3	663.3
Number of males	5	5	5
Mean	557.0	568.5	578.3
S.D.	51.9	52.2	54.5

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Male No.	Days of recovery period		
	1	7	14
M04009	614.2	636.7	660.0
M04010	512.0	532.6	547.1
M04011	538.7	550.1	562.9
M04012	498.3	515.3	518.3
M04013	543.9	550.9	561.9
Number of males	5	5	5
Mean	541.4	557.1	570.0
S.D.	44.8	46.8	53.4
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 8-1-1. Body weights of female rats

Corn oil (control)			
Female No.	Days of administration		
	1	7	14
F01001	264.8	274.6	289.8
F01002	241.1	239.7	244.3
F01003	277.3	293.7	308.5
F01004	244.4	264.1	276.5
F01005	254.8	264.1	289.7
F01006	246.0	255.5	254.9
F01007	252.4	276.3	281.6
F01008	259.2	268.7	271.4
F01009	265.6	279.9	281.7
F01010	253.8	262.6	283.2
F01011	245.2	255.1	253.5
F01012	262.7	278.9	284.2
F01013	252.7	269.4	284.8
Number of females	13	13	13
Mean	255.4	267.9	277.2
S.D.	10.3	13.6	17.4

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 8-1-2. Body weights of female rats

DMIP 62.5 mg/kg

Female No.	Days of administration		
	1	7	14
F02001	236.3	252.7	255.8
F02002	271.3	284.4	296.9
F02003	248.1	255.4	266.5
F02004	265.8	266.5	279.1
F02005	250.3	258.4	274.0
F02006	241.6	263.5	275.0
F02007	268.9	274.2	276.8
F02008	243.3	258.5	267.1
F02009	250.2	269.9	287.0
F02010	263.1	283.5	302.4
F02011	277.4	291.2	295.9
F02012	252.4	268.9	278.7
F02013	247.6	274.9	285.0
Number of females	13	13	13
Mean	255.1	269.4	280.0
S.D.	12.8	11.9	13.3
Significance	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 8-1-3. Body weights of female rats

Female No.	Days of administration		
	1	7	14
F03001	248.2	265.7	271.3
F03002	252.4	262.9	269.1
F03003	245.6	247.8	247.5
F03004	262.9	279.5	283.3
F03005	237.9	242.8	242.9
F03006	234.9	254.8	264.7
F03007	249.1	253.9	257.6
F03008	247.8	250.2	259.5
F03009	262.3	256.2	273.6
F03010	262.9	275.1	275.6
F03011	262.0	267.7	275.6
F03012	254.7	282.8	295.1
F03013	242.8	247.6	272.6
Number of females	13	13	13
Mean	251.0	260.5	268.3
S.D.	9.6	12.9	14.1
Significance	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 8-1-4. Body weights of female rats

Female No.	Days of administration		
	1	7	14
F04001	250.8	256.1	261.8
F04002	263.9	262.4	279.5
F04003	244.5	245.2	252.1
F04004	254.6	251.4	270.5
F04005	254.2	256.1	259.1
F04006	269.6	275.6	294.1
F04007	257.1	268.1	276.6
F04008	261.8	267.6	266.9
F04009	263.7	254.7	273.7
F04010	256.8	270.7	274.1
F04011	244.9	254.0	266.2
F04012	264.0	268.2	269.9
F04013	266.2	284.3	289.2
Number of females	13	13	13
Mean	257.9	262.6	271.8
S.D.	7.9	11.0	11.6
Significance	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 8-2-1. Body weights of female rats, satellite group

Corn oil (control)							
Female No.	Days of administration						
	1	7	14	21	28	35	42
F05001	242.3	255.3	262.0	278.7	284.3	290.4	295.4
F05002	229.8	251.6	262.0	261.6	271.8	279.6	278.9
F05003	261.2	270.4	280.2	298.9	307.2	314.5	316.3
F05004	251.1	274.5	281.0	284.1	298.3	301.9	306.5
F05005	251.0	256.8	260.3	267.9	272.0	282.0	291.2
F05006	264.6	278.7	295.5	308.7	321.0	330.7	333.6
F05007	260.2	274.3	284.8	295.7	297.0	308.2	317.2
F05008	260.0	299.2	317.4	306.1	308.7	303.4	316.3
F05009	253.5	261.5	274.0	291.3	301.7	306.3	320.8
F05010	252.4	248.3	260.1	266.8	268.2	275.0	287.9
Number of females	10	10	10	10	10	10	10
Mean	252.6	267.1	277.7	286.0	293.0	299.2	306.4
S.D.	10.3	15.5	18.5	16.9	18.1	17.4	17.4

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Female No.	Days of administration						
	1	7	14	21	28	35	42
F06001	249.2	244.9	255.9	270.4	275.0	278.9	281.4
F06002	260.6	263.2	272.3	277.8	280.5	290.1	301.7
F06003	272.0	247.7	270.1	287.9	291.0	294.9	311.9
F06004	264.5	271.3	273.3	287.1	300.6	306.4	313.4
F06005	252.4	263.5	268.5	276.7	271.1	286.4	292.3
F06006	252.7	265.9	275.0	277.2	300.2	291.3	310.4
F06007	270.4	264.0	275.0	297.2	304.4	304.9	320.0
F06008	268.0	277.8	287.3	307.2	314.2	311.7	316.9
F06009	243.1	237.2	246.3	260.2	259.5	263.6	271.3
F06010	256.8	258.0	265.2	275.2	279.0	294.0	306.9
Number of females	10	10	10	10	10	10	10
Mean	259.0	259.4	268.9	281.7	287.6	292.2	302.6
S.D.	9.7	12.5	11.2	13.5	17.2	14.1	16.1
Significance	NS	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 8-3-1. Body weights of female rats at the recovery period

Corn oil (control)

Female No.	Days of recovery period		
	1	7	14
F05006	336.4	338.4	346.8
F05007	313.7	321.9	318.6
F05008	310.6	332.6	307.6
F05009	319.7	333.6	331.4
F05010	286.4	298.2	282.9
Number of females	5	5	5
Mean	313.4	324.9	317.5
S.D.	18.1	16.1	24.2

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 8-3-2. Body weights of female rats at the recovery period

DMIP 1000 mg/kg

Female No.	Days of recovery period		
	1	7	14
F06006	306.5	318.4	300.3
F06007	318.7	344.6	345.9
F06008	320.7	329.3	336.3
F06009	268.2	290.4	293.4
F06010	302.8	318.9	325.2
Number of females	5	5	5
Mean	303.4	320.3	320.2
S.D.	21.1	19.8	22.7
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 9-1. Body weights of dams during pregnancy

Corn oil (control)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	302.5	331.9	369.6	466.8
F01002	256.6	280.9	305.2	357.3
F01003	318.2	367.5	413.5	501.2
F01004	294.2	331.4	368.3	457.1
F01005	295.4	327.1	356.9	431.2
F01006	263.8	294.3	329.0	417.6
F01007	290.5	319.0	361.8	444.9
F01008	291.8	313.4	355.4	460.7
F01009	297.4	338.2	381.3	455.2
F01010	285.0	318.2	345.3	430.9
F01011	258.3	299.1	336.6	416.5
F01012	300.2	337.9	381.9	470.3
F01013	283.6	328.8	380.3	489.4
Number of dams	13	13	13	13
Mean	287.5	322.1	360.4	446.1
S.D.	18.1	22.2	27.6	36.9

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 9-2. Body weights of dams during pregnancy

Dam No.	Days of pregnancy			
	0	7	14	20
F02001	256.8	288.6	317.2	395.5
F02002	312.4	333.8	371.6	453.6
F02003	272.9	302.1	347.3	423.9
F02004	299.3	331.3	368.8	464.3
F02005	286.3	316.7	354.8	437.3
F02006	278.5	327.3	374.8	434.0
F02007	306.8	333.7	373.9	473.0
F02008	263.9	293.6	335.7	414.8
F02009	291.5	331.8	382.5	494.2
F02010	307.5	354.1	398.4	482.7
F02011	303.3	340.8	391.9	475.3
F02012	294.2	319.3	358.1	436.9
F02013	302.1	356.0	401.4	498.9
Number of dams	13	13	13	13
Mean	290.4	325.3	367.4	452.6
S.D.	17.7	20.9	24.6	31.9
Significance	NS	NS	NS	NS
Statistical method	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 9-3. Body weights of dams during pregnancy

Dam No.	Days of pregnancy			
	0	7	14	20
F03001	280.8	316.3	343.4	427.3
F03002	290.0	314.2	346.5	425.6
F03003	264.7	290.1	316.4	383.5
F03004	284.8	320.5	342.6	429.1
F03005	249.1	287.0	317.0	396.7
F03006	272.3	305.5	341.8	425.9
F03007	266.9	309.3	340.4	415.2
F03008	254.2	293.0	319.2	396.0
F03009	290.0	320.0	365.1	469.4
F03010	289.6	315.7	349.6	450.0
F03011	284.7	319.0	351.9	430.9
F03012	304.5	342.1	376.4	467.2
F03013	266.2	308.7	349.5	406.0
Number of dams	13	13	13	13
Mean	276.8	310.9	343.1	424.8
S.D.	16.0	14.8	17.7	26.2
Significance	NS	NS	NS	NS
Statistical method	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 9-4. Body weights of dams during pregnancy

DMIP 1000 mg/kg				
Dam No.	Days of pregnancy			
	0	7	14	20
F04001	268.5	302.8	331.5	397.3
F04002	291.8	323.5	365.6	444.5
F04003	256.0	288.7	321.4	392.8
F04004	279.5	322.5	359.4	436.9
F04005	274.2	296.3	329.9	414.1
F04006	290.6	320.4	358.0	435.4
F04007	279.1	303.6	336.7	411.1
F04008	278.2	310.1	334.6	411.1
F04009	286.1	320.1	351.8	426.9
F04010	288.2	320.8	359.1	437.8
F04011	283.1	317.6	350.3	420.3
F04012	287.6	315.9	361.6	455.3
F04013	299.0	323.3	360.6	453.9
Number of dams	13	13	13	13
Mean	281.7	312.7	347.7	426.0
S.D.	11.2	11.4	14.8	20.1
Significance	NS	NS	NS	NS
Statistical method	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 10-1. Body weights of dams during lactation

Dam No.	Days of lactation	
	0	4
F01001	341.6	377.7
F01002	289.8	313.6
F01003	395.0	389.4
F01004	353.7	361.3
F01005	337.8	353.3
F01006	291.6	316.4
F01007	350.9	339.7
F01008	325.1	351.9
F01009	385.2	369.1
F01010	304.5	319.1
F01011	344.4	337.5
F01012	379.8	374.6
F01013	376.2	372.6
Number of dams	13	13
Mean	344.3	352.0
S.D.	34.6	25.1

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 10-2. Body weights of dams during lactation

Dam No.	Days of lactation	
	0	4
F02001	291.0	306.7
F02002	322.5	359.6
F02003	296.3	324.1
F02004	358.7	376.4
F02005	312.5	336.4
F02006	328.6	Total litter loss
F02007	329.5	352.9
F02008	327.4	326.5
F02009	356.8	378.6
F02010	372.8	382.5
F02011	354.5	374.7
F02012	311.2	350.9
F02013	401.7	384.9
Number of dams	13	12
Mean	335.7	354.5
S.D.	31.7	26.2
Significance	NS	NS
Statistical method	DU	DT

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.

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 10-3. Body weights of dams during lactation

Dam No.	Days of lactation	
	0	4
F03001	298.4	324.1
F03002	330.5	313.0
F03003	302.2	305.1
F03004	298.7	321.0
F03005	266.1	286.7
F03006	304.6	342.0
F03007	273.2	266.4
F03008	302.9	310.9
F03009	359.3	352.9
F03010	306.0	342.2
F03011	Dam died on the gestation day 23.	
F03012	344.0	364.9
F03013	329.6	359.5
Number of dams	12	12
Mean	309.6	324.1
S.D.	27.1	29.8
Significance	*	NS
Statistical method	DU	DT

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.

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 10-4. Body weights of dams during lactation

DMIP 1000 mg/kg		
Dam No.	Days of lactation	
	0	4
F04001	298.8	328.6
F04002	336.2	331.9
F04003	290.6	319.3
F04004	311.8	353.6
F04005	316.2	346.6
F04006	308.5	334.7
F04007	275.2	Total litter loss
F04008	321.2	344.3
F04009	323.6	340.7
F04010	334.2	333.1
F04011	316.4	337.2
F04012	296.1	328.5
F04013	329.5	357.0
Number of dams	13	12
Mean	312.2	338.0
S.D.	18.0	11.0
Significance	*	NS
Statistical method	DU	DT

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.

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 11-1-1. Food consumption of male rats

Corn oil (control)						
Male No.	Days of administration					
	1	7	14	29	35	41
M01001	23.9	20.1	23.7	25.4	22.0	22.0
M01002	24.0	24.1	24.0	26.0	22.8	20.4
M01003	23.6	23.4	25.5	27.3	26.6	23.5
M01004	25.7	25.5	21.9	25.3	22.2	22.9
M01005	22.8	25.1	22.6	19.8	20.5	20.6
M01006	28.4	27.8	27.8	25.7	27.1	26.3
M01007	26.6	26.6	26.8	31.7	29.3	25.0
M01008	24.9	25.6	22.3	23.2	23.1	27.0
M01009	23.8	26.0	26.8	25.6	26.1	25.3
M01010	27.5	23.4	20.8	20.0	21.6	21.4
M01011	17.7	20.1	23.7	19.9	21.7	24.3
M01012	24.9	21.0	20.7	22.3	22.8	20.8
M01013	23.1	27.5	31.9	30.3	32.1	28.6
Number of males	13	13	13	13	13	13
Mean	24.4	24.3	24.5	24.8	24.5	23.7
S.D.	2.6	2.6	3.2	3.7	3.5	2.6

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 11-1-2. Food consumption of male rats

DMIP 62.5 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02001	22.5	22.3	23.2	22.5	22.6	21.3
M02002	26.6	23.7	23.1	22.6	25.8	19.0
M02003	26.5	23.9	22.2	20.3	23.0	21.7
M02004	30.5	26.4	27.7	32.5	30.6	23.5
M02005	25.5	25.5	22.9	25.8	20.0	21.1
M02006	26.8	20.0	23.6	23.2	24.6	24.1
M02007	29.7	24.2	27.0	28.7	27.2	25.8
M02008	30.5	24.4	23.0	23.4	23.1	19.1
M02009	29.1	24.5	23.7	28.5	25.2	26.0
M02010	26.1	22.2	22.1	23.6	28.6	22.0
M02011	21.6	22.2	24.7	25.3	25.3	23.0
M02012	20.1	20.4	20.1	21.1	18.3	18.4
M02013	21.1	19.0	17.3	22.8	22.1	19.7
Number of males	13	13	13	13	13	13
Mean	25.9	23.0	23.1	24.6	24.3	21.9
S.D.	3.6	2.2	2.6	3.5	3.4	2.5
Significance	NS	NS	NS	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 11-1-3. Food consumption of male rats

Male No.	Days of administration					
	1	7	14	29	35	41
M03001	21.7	22.7	21.8	23.6	26.1	23.1
M03002	18.1	20.7	20.2	22.4	23.9	19.4
M03003	23.3	21.7	21.2	22.0	21.9	21.1
M03004	26.8	26.5	23.9	23.6	26.0	22.7
M03005	24.4	24.0	24.5	23.4	24.5	23.3
M03006	25.7	30.4	29.7	27.9	28.2	26.1
M03007	26.0	24.1	19.4	20.1	18.5	19.2
M03008	22.7	22.2	23.0	21.4	24.7	23.5
M03009	27.2	25.6	26.7	23.9	24.0	23.7
M03010	29.3	24.7	21.6	25.7	27.3	28.5
M03011	26.6	26.7	22.8	26.9	24.6	26.2
M03012	24.2	25.9	18.6	25.6	22.5	21.2
M03013	21.6	24.7	24.8	24.8	23.8	25.1
Number of males	13	13	13	13	13	13
Mean	24.4	24.6	22.9	23.9	24.3	23.3
S.D.	3.0	2.5	3.1	2.2	2.5	2.7
Significance	NS	NS	NS	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 11-1-4. Food consumption of male rats

DMIP 1000 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04001	29.4	25.4	23.2	26.2	23.3	24.2
M04002	26.1	27.2	26.2	27.8	24.9	24.0
M04003	19.4	22.8	21.0	21.0	22.5	18.7
M04004	26.7	22.9	25.7	24.4	23.9	25.5
M04005	19.6	20.6	23.7	26.3	26.2	21.9
M04006	26.6	25.1	24.3	26.5	25.4	26.8
M04007	24.1	21.4	20.5	21.6	23.4	21.0
M04008	24.4	21.5	18.1	18.1	19.6	20.8
M04009	31.1	29.6	29.0	30.5	27.9	28.2
M04010	20.0	20.9	21.6	22.8	25.1	22.2
M04011	22.1	26.1	21.3	23.1	26.7	24.1
M04012	23.0	24.5	21.7	21.9	21.0	22.5
M04013	28.0	27.3	28.5	30.2	28.2	29.0
Number of males	13	13	13	13	13	13
Mean	24.7	24.3	23.4	24.6	24.5	23.8
S.D.	3.8	2.8	3.2	3.7	2.5	3.0
Significance	NS	NS	NS	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 11-2-1. Food consumption of male rats at the recovery period

Corn oil (control)

Male No.	Days of recovery period	
	6	12
M01009	31.1	30.5
M01010	28.0	29.3
M01011	31.9	27.6
M01012	29.4	28.9
M01013	36.1	36.8
Number of males	5	5
Mean	31.3	30.6
S.D.	3.1	3.6

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 1000 mg/kg

Male No.	Days of recovery period	
	6	12
M04009	39.0	38.0
M04010	31.7	30.5
M04011	30.9	30.4
M04012	29.7	30.7
M04013	28.5	32.1
Number of males	5	5
Mean	32.0	32.3
S.D.	4.1	3.2
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 12-1-1. Food consumption of female rats

Corn oil (control)

Female No.	Days of administration		
	1	7	14
F01001	15.9	20.2	19.2
F01002	14.0	14.7	8.1
F01003	25.1	19.2	19.7
F01004	19.2	20.3	17.5
F01005	22.2	19.1	12.4
F01006	12.5	17.1	16.7
F01007	20.5	17.8	19.3
F01008	10.4	19.7	19.5
F01009	19.1	19.2	17.0
F01010	14.7	20.4	18.6
F01011	17.4	17.1	13.8
F01012	22.6	14.4	16.9
F01013	21.4	14.9	18.3
Number of females	13	13	13
Mean	18.1	18.0	16.7
S.D.	4.4	2.2	3.4

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 12-1-2. Food consumption of female rats

Female No.	Days of administration		
	1	7	14
F02001	17.0	15.0	16.0
F02002	15.4	17.5	18.0
F02003	16.3	13.5	13.2
F02004	18.8	17.7	11.8
F02005	20.2	19.5	12.5
F02006	17.2	16.0	17.0
F02007	11.6	18.6	17.7
F02008	18.7	14.2	16.3
F02009	16.8	19.1	15.6
F02010	20.4	15.1	19.6
F02011	20.3	15.1	17.4
F02012	20.1	15.4	17.2
F02013	15.5	17.7	22.4
Number of females	13	13	13
Mean	17.6	16.5	16.5
S.D.	2.6	2.0	2.9
Significance	NS	NS	NS
Statistical method	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).

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 12-1-3. Food consumption of female rats

DMIP 250 mg/kg

Female No.	Days of administration		
	1	7	14
F03001	18.7	16.8	13.8
F03002	14.0	18.7	15.9
F03003	12.5	15.7	16.1
F03004	20.7	18.5	18.2
F03005	15.6	7.0	12.4
F03006	19.6	18.3	18.7
F03007	12.1	20.1	17.8
F03008	18.2	10.2	16.5
F03009	19.7	17.4	10.8
F03010	18.8	13.5	18.4
F03011	14.3	18.4	19.2
F03012	21.1	18.4	20.0
F03013	12.5	18.4	15.3
Number of females	13	13	13
Mean	16.8	16.3	16.4
S.D.	3.3	3.8	2.8
Significance	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 12-1-4. Food consumption of female rats

Female No.	Days of administration		
	1	7	14
F04001	13.9	9.8	15.9
F04002	21.3	17.0	11.0
F04003	13.7	11.2	15.0
F04004	19.7	19.1	8.8
F04005	16.1	18.8	16.9
F04006	17.2	13.3	19.3
F04007	20.1	15.4	21.9
F04008	15.7	12.1	15.4
F04009	17.1	17.1	10.1
F04010	13.7	18.3	18.3
F04011	18.2	18.2	14.4
F04012	15.6	17.8	17.9
F04013	18.6	17.5	20.0
Number of females	13	13	13
Mean	17.0	15.8	15.8
S.D.	2.5	3.2	3.9
Significance	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 12-2-1. Food consumption of female rats, satellite group

Corn oil (control)

Female No.	Days of administration						
	1	7	14	21	29	35	41
F05001	11.4	19.5	10.3	17.0	18.1	10.9	16.1
F05002	18.2	17.0	17.0	16.8	17.5	15.6	12.6
F05003	13.6	19.3	16.6	14.1	12.3	17.7	11.0
F05004	17.4	17.3	17.8	18.5	17.7	18.0	14.4
F05005	18.3	11.6	14.4	17.8	17.3	10.4	16.5
F05006	17.4	16.5	20.7	20.6	23.0	16.8	18.7
F05007	20.5	14.5	18.3	19.6	21.2	15.2	19.7
F05008	17.4	22.9	10.5	16.7	16.3	17.6	16.7
F05009	19.2	19.5	10.9	23.3	19.8	18.0	20.3
F05010	14.3	16.7	10.2	14.6	17.6	17.3	16.1
Number of females	10	10	10	10	10	10	10
Mean	16.8	17.5	14.7	17.9	18.1	15.8	16.2
S.D.	2.8	3.1	3.9	2.8	2.9	2.9	3.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06001	15.6	15.3	10.4	16.0	17.9	17.7	13.1
F06002	16.5	10.8	16.1	16.6	17.6	12.3	14.6
F06003	17.1	14.0	12.1	16.6	18.2	20.5	15.7
F06004	15.6	17.3	16.5	14.9	16.9	16.4	14.9
F06005	19.4	10.2	15.9	17.5	20.3	13.8	16.3
F06006	19.4	19.2	19.7	19.8	14.3	16.3	19.3
F06007	21.9	17.1	11.7	18.0	19.8	19.5	18.9
F06008	18.4	18.3	15.9	14.8	11.6	15.3	14.3
F06009	15.0	14.6	12.7	17.1	18.7	17.3	14.6
F06010	15.5	10.8	13.2	15.7	19.4	14.0	17.1
Number of females	10	10	10	10	10	10	10
Mean	17.4	14.8	14.4	16.7	17.5	16.3	15.9
S.D.	2.3	3.3	2.8	1.5	2.7	2.6	2.0
Significance	NS	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 12-3-1. Food consumption of female rats at the recovery period

Corn oil (control)

Female No.	Days of recovery period	
	6	12
F05006	21.6	22.3
F05007	24.3	21.6
F05008	22.7	20.8
F05009	26.2	20.2
F05010	24.5	14.5
Number of females	5	5
Mean	23.9	19.9
S.D.	1.8	3.1

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 12-3-2. Food consumption of female rats at the recovery period

Female No.	Days of recovery period	
	6	12
F06006	24.8	19.3
F06007	27.6	21.1
F06008	22.3	20.1
F06009	24.6	20.3
F06010	23.9	24.5
Number of females	5	5
Mean	24.6	21.1
S.D.	1.9	2.0
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 13-1. Food consumption in dams during pregnancy

Corn oil (control)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	18.8	24.2	23.0	20.6
F01002	16.5	17.4	17.6	15.3
F01003	20.7	28.8	28.6	26.3
F01004	18.5	24.9	25.0	17.8
F01005	18.9	21.3	21.5	17.4
F01006	12.1	19.7	19.8	13.2
F01007	20.3	18.8	26.9	11.3
F01008	18.5	16.7	21.7	16.2
F01009	18.9	22.2	32.6	15.2
F01010	18.5	20.9	17.5	12.2
F01011	15.9	24.6	24.4	24.9
F01012	18.6	24.6	27.3	21.1
F01013	16.4	28.1	31.0	24.8
Number of dams	13	13	13	13
Mean	17.9	22.5	24.4	18.2
S.D.	2.2	3.8	4.8	5.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 13-2. Food consumption in dams during pregnancy

DMP 62.5 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02001	16.9	17.4	18.2	13.8
F02002	15.1	24.0	18.8	14.5
F02003	13.6	20.7	22.6	20.2
F02004	18.3	21.0	27.1	20.3
F02005	17.7	24.0	25.5	17.3
F02006	18.3	19.6	24.3	6.9
F02007	17.8	24.8	24.4	15.1
F02008	15.2	21.1	22.8	23.1
F02009	17.0	24.0	30.3	25.7
F02010	18.6	29.0	23.9	20.0
F02011	20.1	23.7	25.2	17.8
F02012	17.5	18.0	22.9	13.7
F02013	21.6	30.3	26.0	20.8
Number of dams	13	13	13	13
Mean	17.5	22.9	24.0	17.6
S.D.	2.1	3.8	3.2	4.9
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 13-3. Food consumption in dams during pregnancy

Dam No.	Days of pregnancy			
	0	7	14	20
F03001	15.3	20.1	21.6	17.5
F03002	16.5	18.9	21.9	12.6
F03003	17.4	17.4	17.1	15.5
F03004	19.7	17.2	20.7	11.1
F03005	14.8	17.6	18.2	8.7
F03006	17.7	17.4	23.9	15.9
F03007	12.7	23.3	22.8	12.1
F03008	16.8	25.2	19.0	22.6
F03009	15.3	24.7	23.7	19.1
F03010	17.3	19.0	21.9	15.2
F03011	17.4	21.6	24.1	1.9
F03012	17.1	22.2	26.3	17.5
F03013	11.0	23.9	23.6	25.4
Number of dams	13	13	13	13
Mean	16.1	20.7	21.9	15.0
S.D.	2.3	3.0	2.6	6.0
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 13-4. Food consumption in dams during pregnancy

Dam No.	Days of pregnancy			
	0	7	14	20
F04001	13.7	16.1	20.6	15.4
F04002	20.8	16.0	20.7	17.3
F04003	15.6	18.2	19.0	20.7
F04004	23.5	21.7	22.8	16.1
F04005	16.0	20.1	24.6	20.7
F04006	18.8	24.1	19.5	18.3
F04007	14.5	22.7	20.1	6.2
F04008	15.5	18.9	20.3	21.5
F04009	18.0	22.0	20.9	16.7
F04010	18.9	24.3	21.9	16.4
F04011	19.5	25.5	20.5	15.3
F04012	16.0	23.7	24.5	9.7
F04013	22.0	19.1	19.7	19.1
Number of dams	13	13	13	13
Mean	17.9	21.0	21.2	16.4
S.D.	3.0	3.1	1.8	4.3
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 14-1. Food consumption in dams during lactation

Corn oil (control)	
Dam No.	Days of lactation
	3
F01001	47.8
F01002	35.8
F01003	32.6
F01004	41.0
F01005	29.9
F01006	34.6
F01007	34.5
F01008	49.2
F01009	25.6
F01010	30.6
F01011	39.1
F01012	35.6
F01013	40.3
Number of dams	13
Mean	36.7
S.D.	6.8

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 14-2. Food consumption in dams during lactation

DMIP 62.5 mg/kg	
Dam No.	Days of lactation
	3
F02001	40.1
F02002	44.5
F02003	37.1
F02004	51.1
F02005	44.3
F02006	Total litter loss.
F02007	40.0
F02008	35.7
F02009	47.9
F02010	36.6
F02011	47.1
F02012	45.5
F02013	30.6
Number of dams	12
Mean	41.7
S.D.	6.0
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 14-3. Food consumption in dams during lactation

DMIP 250 mg/kg	
Dam No.	Days of lactation
	3
F03001	33.7
F03002	21.4
F03003	32.7
F03004	42.2
F03005	27.9
F03006	48.7
F03007	5.8
F03008	40.3
F03009	36.3
F03010	49.5
F03011	Dam died on the gestation day 23.
F03012	39.6
F03013	45.0
Number of dams	12
Mean	35.3
S.D.	12.4
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 14-4. Food consumption in dams during lactation

DMIP 1000 mg/kg	
Dam No.	Days of lactation
	3
F04001	43.5
F04002	34.9
F04003	40.8
F04004	44.1
F04005	43.7
F04006	41.4
F04007	Total litter loss.
F04008	38.5
F04009	44.3
F04010	45.8
F04011	42.6
F04012	43.8
F04013	47.9
Number of dams	12
Mean	42.6
S.D.	3.4
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 15-1. Functional findings of male rats at the end of the dosing period

Corn oil (control)

Male

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer'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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 15-2. Functional findings of male rats at the end of the dosing period

DMP (62.5 mg/kg)

Male

Male No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M02001	2	2	2	2	+	+	+
M02002	2	2	2	2	+	+	+
M02003	2	2	2	2	+	+	+
M02004	2	2	2	2	+	+	+
M02005	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 15-3. Functional findings of male rats at the end of the dosing period

DMIP (250 mg/kg)

Male

Male No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M03001	2	2	2	2	+	+	+
M03002	2	2	2	2	+	+	+
M03003	2	2	2	2	+	+	+
M03004	2	2	2	2	+	+	+
M03005	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 15-4. Functional findings of male rats at the end of the dosing period

DMIP (1000 mg/kg)

Male

Male No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M04001	2	2	2	2	+	+	+
M04002	2	2	2	2	+	+	+
M04003	2	2	2	2	+	+	+
M04004	2	2	2	2	+	+	+
M04005	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 16-1. Functional findings of female rats at the end of the dosing period

Corn oil (control)

Female, dam

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F01003	2	2	2	2	+	+	+
F01004	2	2	2	2	+	+	+
F01006	2	2	2	2	+	+	+
F01007	2	2	2	2	+	+	+
F01010	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 16-2. Functional findings of female rats at the end of the dosing period

DMIP (62.5 mg/kg)

Female, dam

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F02001	2	2	2	2	+	+	+
F02003	2	2	2	2	+	+	+
F02008	2	2	2	2	+	+	+
F02009	2	2	2	2	+	+	+
F02010	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 16-3. Functional findings of female rats at the end of the dosing period

DMIP (250 mg/kg)

Female, dam

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F03001	2	2	2	2	+	+	+
F03002	2	2	2	2	+	+	+
F03004	2	2	2	2	+	+	+
F03005	2	2	2	2	+	+	+
F03008	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 16-4. Functional findings of female rats at the end of the dosing period

DMIP (1000 mg/kg)

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F04003	2	2	2	2	+	+	+
F04005	2	2	2	2	+	+	+
F04006	2	2	2	2	+	+	+
F04008	2	2	2	2	+	+	+
F04010	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 16-5. Functional findings of female rats at the end of the dosing period

Com oil (control)

Female, satellite group

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F05001	2	2	2	2	+	+	+
F05002	2	2	2	2	+	+	+
F05003	2	2	2	2	+	+	+
F05004	2	2	2	2	+	+	+
F05005	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 16-6. Functional findings of female rats at the end of the dosing period

DMIP (1000 mg/kg)

Female, satellite group

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F06001	2	2	2	2	+	+	+
F06002	2	2	2	2	+	+	+
F06003	2	2	2	2	+	+	+
F06004	2	2	2	2	+	+	+
F06005	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 17. Assessment of grip strength of male rats

Corn oil (control)		
Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M01001	0.924	0.697
M01002	0.957	0.490
M01003	1.167	0.658
M01004	1.156	0.637
M01005	1.127	0.531
Number of males	5	5
Mean	1.066	0.603
S.D.	0.116	0.088

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

DMIP (250 mg/kg)		
Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M03001	1.274	0.729
M03002	1.143	0.564
M03003	1.227	0.562
M03004	1.199	0.482
M03005	1.190	0.513
Number of males	5	5
Mean	1.207	0.570
S.D.	0.048	0.095

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

DMIP (62.5 mg/kg)		
Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M02001	1.137	0.601
M02002	0.902	0.466
M02003	1.239	0.683
M02004	1.054	0.618
M02005	1.191	0.421
Number of males	5	5
Mean	1.105	0.558
S.D.	0.132	0.110

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

DMIP (1000 mg/kg)		
Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M04001	1.124	0.449
M04002	1.147	0.644
M04003	1.200	0.539
M04004	1.286	0.569
M04005	1.152	0.635
Number of males	5	5
Mean	1.182	0.567
S.D.	0.064	0.079

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 18. Assessment of grip strength of female rats

Corn oil (control)		
Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F01003	1.195	0.925
F01004	1.018	0.828
F01006	1.122	0.693
F01007	1.276	0.738
F01010	1.161	0.776
Number of females	5	5
Mean	1.154	0.792
S.D.	0.095	0.089

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

DMIP (250 mg/kg)		
Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F03001	1.316	0.716
F03002	1.267	0.729
F03004	1.139	0.665
F03005	1.246	0.780
F03008	1.048	0.757
Number of females	5	5
Mean	1.203	0.729
S.D.	0.108	0.044

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

DMIP (62.5 mg/kg)		
Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F02001	1.179	0.774
F02003	1.203	0.659
F02008	1.133	0.726
F02009	1.263	0.865
F02010	1.191	0.647
Number of females	5	5
Mean	1.194	0.734
S.D.	0.047	0.089

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

DMIP (1000 mg/kg)		
Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F04003	1.212	0.695
F04005	1.179	0.689
F04006	1.273	0.606
F04008	1.147	0.598
F04010	1.287	0.945
Number of females	5	5
Mean	1.220	0.707
S.D.	0.060	0.141

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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)
F05001	1.044	0.760
F05002	1.103	0.569
F05003	1.174	0.712
F05004	1.080	0.878
F05005	1.111	0.714
Number of females	5	5
Mean	1.102	0.727
S.D.	0.048	0.111

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

DMIP (1000 mg/kg)		
Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F06001	0.945	0.736
F06002	1.149	0.902
F06003	1.121	0.686
F06004	1.139	0.885
F06005	0.951	0.806
Number of females	5	5
Mean	1.061	0.803
S.D.	0.104	0.093

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 20-1. Motor activity of male rats

Corn oil (control)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1162	873	1054	1048	4137	37	26	34	29	126
M01002	1055	901	992	839	3787	31	17	22	14	84
M01003	1187	949	863	790	3789	33	26	10	31	100
M01004	1206	985	900	930	4021	42	34	38	24	138
M01005	953	848	726	780	3307	23	11	6	9	49
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1113	911	907	877	3808	33	23	22	21	99
S.D.	107	56	126	112	318	7	9	14	10	35

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 20-2. Motor activity of male rats

DMIP (62.5 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02001	980	979	914	779	3652	39	50	24	14	127
M02002	1031	1065	1091	681	3868	36	45	45	25	151
M02003	1024	1081	815	704	3624	35	29	15	13	92
M02004	1298	1022	1062	795	4177	39	19	21	14	93
M02005	1004	1003	896	779	3682	36	27	30	20	113
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1067	1030	956	748	3801	37	34	27	17	115
S.D.	130	42	117	51	231	2	13	11	5	25

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 20-3. Motor activity of male rats

DMIP (250 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03001	1106	992	1014	857	3969	33	20	17	16	86
M03002	1108	1033	683	297	3121	23	27	23	3	76
M03003	1028	892	810	456	3186	28	20	10	8	66
M03004	1208	1204	1131	986	4529	25	25	20	14	84
M03005	1564	1764	1649	1614	6591	37	28	32	16	113
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1203	1177	1057	842	4279	29	24	20	11	85
S.D.	212	347	374	516	1418	6	4	8	6	18

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 20-4. Motor activity of male rats

DMIP (1000 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04001	1079	874	761	753	3467	33	35	25	27	120
M04002	1041	979	976	748	3744	30	18	17	5	70
M04003	965	1002	879	288	3134	18	22	5	0	45
M04004	801	738	646	673	2858	32	19	19	21	91
M04005	1257	1069	1065	4743	8134	36	22	17	111	186
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1029	932	865	1441	4267	30	23	17	33	102
S.D.	166	129	167	1856	2187	7	7	7	45	54

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 21-1. Motor activity of female rats

Corn oil (control)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01003	1228	1084	815	647	3774	31	31	23	13	98
F01004	1166	956	667	583	3372	28	20	28	15	91
F01006	1039	757	454	966	3216	24	37	2	26	89
F01007	1089	993	993	913	3988	33	30	14	8	85
F01010	1173	920	897	673	3663	27	12	11	5	55
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1139	942	765	756	3603	29	26	16	13	84
S.D.	75	120	211	171	310	4	10	10	8	17

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 21-2. Motor activity of female rats

DMIP (62.5 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02001	967	757	471	461	2656	37	15	5	12	69
F02003	1043	892	498	630	3063	23	17	2	3	45
F02008	997	735	500	666	2898	23	11	5	21	60
F02009	1204	786	598	944	3532	42	19	8	12	81
F02010	975	746	539	599	2859	31	20	19	11	81
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1037	783	521	660	3002	31	16	8	12	67
S.D.	98	64	49	177	330	8	4	7	6	15

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 21-3. Motor activity of female rats

DMIP (250 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03001	1006	792	528	670	2996	27	14	7	6	54
F03002	1027	910	799	713	3449	26	24	1	4	55
F03004	1002	442	621	436	2501	18	5	9	2	34
F03005	995	830	751	736	3312	12	9	4	3	28
F03008	1881	1547	1299	1081	5808	31	31	4	3	69
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1182	904	800	727	3613	23	17	5	4	48
S.D.	391	402	299	231	1280	8	11	3	2	17

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 21-4. Motor activity of female rats

DMIP (1000 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04003	971	659	220	383	2233	20	15	0	7	42
F04005	1107	980	674	423	3184	27	8	0	0	35
F04006	1261	799	855	707	3622	22	13	5	4	44
F04008	843	661	624	536	2664	39	21	20	9	89
F04010	960	874	646	3558	6038	25	12	16	95	148
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1028	795	604	1121	3548	27	14	8	23	72
S.D.	160	139	233	1368	1487	7	5	9	40	48

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 22-1. Motor activity of female rats, satellite group

Corn oil (control)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05001	1443	1140	1152	906	4641	51	39	24	18	132
F05002	1105	1017	1030	884	4036	31	27	27	21	106
F05003	1270	930	951	984	4135	43	21	25	19	108
F05004	1316	1260	1180	980	4736	60	40	32	30	162
F05005	1372	1222	1158	953	4705	28	27	25	15	95
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1301	1114	1094	941	4451	43	31	27	21	121
S.D.	127	139	99	45	337	13	8	3	6	27

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 22-2. Motor activity of female rats, satellite group

DMIP (1000 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06001	1057	1002	802	718	3579	38	36	20	27	121
F06002	1138	997	870	1053	4058	35	31	16	25	107
F06003	1075	922	887	702	3586	27	20	9	14	70
F06004	1272	973	891	924	4060	32	27	15	17	91
F06005	1186	1101	1093	1018	4398	29	24	31	17	101
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1146	999	909	883	3936	32	28	18	20	98
S.D.	87	65	109	165	351	4	6	8	6	19

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 23-1-1. Urinalysis in male rats

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
M01001	Light yellow	-	8.0	2+	-	±	-	-	±	-	-	-	±	-
M01002	Light yellow	-	8.0	+	-	+	-	-	±	-	-	-	±	-
M01003	Light yellow	-	7.5	2+	-	+	-	-	+	-	-	-	±	-
M01004	Light yellow	-	7.5	2+	-	+	-	-	+	-	-	-	±	-
M01005	Yellow	-	7.5	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
M01001	14.8	1.031	29.7	109.9	19.2	0.44	1.63	0.28
M01002	15.0	1.056	84.5	237.1	107.5	1.27	3.56	1.61
M01003	13.4	1.054	76.0	211.5	100.0	1.02	2.83	1.34
M01004	9.9	1.075	109.8	241.5	127.0	1.09	2.39	1.26
M01005	8.1	1.065	78.8	232.9	101.8	0.64	1.89	0.82
Number of males	5	5	5	5	5	5	5	5
Mean	12.2	1.056	75.8	206.6	91.1	0.89	2.46	1.06
±S.D.	3.1	0.016	29.0	55.3	41.6	0.34	0.77	0.52

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 23-1-2. Urinalysis in male rats

DMIP (62.5 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
M02001	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M02002	Light yellow	-	8.5	+	-	+	-	-	2+	-	-	-	±	-
M02003	Light yellow	-	7.0	+	-	+	-	-	±	-	-	-	-	-
M02004	Light yellow	-	7.0	2+	-	+	-	-	+	-	-	-	±	-
M02005	Yellow	-	7.0	2+	-	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
M02001	14.4	1.048	80.5	202.1	105.5	1.16	2.91	1.52
M02002	10.2	1.075	129.8	285.5	152.5	1.32	2.91	1.56
M02003	10.4	1.066	95.6	248.3	117.5	0.99	2.58	1.22
M02004	13.9	1.059	90.9	165.4	98.7	1.26	2.30	1.37
M02005	7.6	1.072	60.9	223.2	88.1	0.46	1.70	0.67
Number of males	5	5	5	5	5	5	5	5
Mean	11.3	1.064	91.5	224.9	112.5	1.04	2.48	1.27
±S.D.	2.8	0.011	25.2	45.5	24.8	0.35	0.51	0.36

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 23-1-3. Urinalysis in male rats

DMIP (250 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
M03001	Light yellow	-	6.0	+	-	±	-	-	±	-	-	-	-	-
M03002	Light yellow	-	7.0	2+	-	+	-	-	+	-	-	-	±	-
M03003	Light yellow	-	5.5	+	-	±	-	-	±	-	-	-	-	-
M03004	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	±	-
M03005	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
			M03001	34.3	1.023	39.9	108.8	42.0
M03002	16.5	1.050	68.5	203.7	83.8	1.13	3.36	1.38
M03003	10.3	1.062	100.5	183.5	109.0	1.04	1.89	1.12
M03004	11.5	1.076	112.9	272.1	136.9	1.30	3.13	1.57
M03005	11.4	1.062	88.9	187.9	68.6	1.01	2.14	0.78
Number of males	5	5	5	5	5	5	5	5
Mean	16.8	1.055	82.1	191.2	88.1	1.17	2.85	1.26
±S.D.	10.1	0.020	28.7	58.2	36.5	0.16	0.80	0.31

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 23-1-4. Urinalysis in male rats

DMIP (1000 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
M04001	Light yellow	-	6.0	+	-	-	-	-	±	-	-	-	-	-
M04002	Light yellow	-	6.0	+	-	-	-	-	±	-	-	-	±	-
M04003	Light yellow	-	6.0	±	-	-	-	-	±	-	-	-	-	-
M04004	Light yellow	-	6.0	+	-	-	-	-	±	-	-	-	-	-
M04005	Light yellow	-	6.0	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M04001	19.7	1.055	89.6	164.0	81.6	1.77	3.23	1.61
M04002	20.2	1.042	77.8	110.4	44.0	1.57	2.23	0.89
M04003	18.0	1.052	87.7	141.5	68.3	1.58	2.55	1.23
M04004	26.6	1.047	65.8	173.8	71.4	1.75	4.62	1.90
M04005	22.4	1.043	68.1	114.5	42.5	1.53	2.56	0.95
Number of males	5	5	5	5	5	4	4	4
Mean	21.4*	1.048	77.8	140.8	61.6	1.64**	3.04	1.32
±S.D.	3.3	0.006	10.9	28.5	17.4	0.12	1.06	0.50

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 23-2-1. Urinalysis in male rats of the recovery period

Corn oil (control)

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
M01009	Light yellow	-	8.0	+	-	+	-	-	±	-	-	-	±	-
M01010	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M01011	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	±	-
M01012	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M01013	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
M01009	12.8	1.074	100.4	375.6	119.6	1.29	4.81	1.53
M01010	18.1	1.053	97.1	262.5	111.2	1.76	4.75	2.01
M01011	35.8	1.027	31.9	149.7	55.2	1.14	5.36	1.98
M01012	20.3	1.051	104.1	248.8	121.1	2.11	5.05	2.46
M01013	14.0	1.080	188.8	511.0	187.1	2.64	7.15	2.62
Number of males	5	5	5	5	5	5	5	5
Mean	20.2	1.057	104.5	309.5	118.8	1.79	5.42	2.12
±S.D.	9.2	0.021	55.8	138.2	46.8	0.61	0.99	0.43

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP (1000 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
M04009	Light yellow	-	7.5	2+	-	±	-	±	+	-	-	-	±	±
M04010	Light yellow	-	7.5	+	-	±	-	-	+	-	-	-	±	-
M04011	Light yellow	-	8.5	+	-	±	-	-	±	-	-	-	±	-
M04012	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M04013	Light yellow	-	7.5	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
			M04009	17.7	1.067	133.0	404.4	149.9
M04010	15.8	1.068	135.4	287.9	155.1	2.14	4.55	2.45
M04011	22.3	1.054	125.7	249.4	131.5	2.80	5.56	2.93
M04012	15.7	1.066	145.9	242.7	159.6	2.29	3.81	2.51
M04013	13.5	1.079	130.6	259.2	170.9	1.76	3.50	2.31
Number of males	5	5	5	5	5	5	5	5
Mean	17.0	1.067	134.1	288.7	153.4	2.27	4.92	2.57
±S.D.	3.3	0.009	7.5	66.9	14.5	0.38	1.48	0.24

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)

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
F05001	Light yellow	-	6.5	+	-	+	-	-	±	-	-	-	-	-
F05002	Light yellow	-	6.0	-	-	-	-	-	±	-	-	-	-	-
F05003	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	±	-
F05004	Light yellow	-	6.5	+	-	+	-	-	±	-	-	-	±	-
F05005	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05001	7.5	1.055	105.8	227.5	127.4	0.79	1.71	0.96
F05002	14.2	1.047	58.1	187.4	102.8	0.83	2.66	1.46
F05003	7.6	1.065	134.0	272.9	144.8	1.02	2.07	1.10
F05004	7.2	1.041	54.7	128.8	54.4	0.39	0.93	0.39
F05005	10.3	1.034	43.0	136.9	53.5	0.44	1.41	0.55
Number of females	5	5	5	5	5	5	5	5
Mean	9.4	1.048	79.1	190.7	96.6	0.69	1.76	0.89
±S.D.	3.0	0.012	38.9	60.9	41.7	0.27	0.66	0.43

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 24-1-2. Urinalysis in female rats, satellite group

DMIP (1000 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
F06001	Light yellow	-	6.0	+	-	-	-	-	±	-	-	-	±	-
F06002	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	±	-
F06003	Light yellow	-	6.0	±	-	-	-	-	±	-	-	-	-	-
F06004	Light yellow	-	6.0	±	-	-	-	-	±	-	-	-	-	-
F06005	Light yellow	-	5.5	+	-	±	-	-	+	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			F06001	11.7	1.060	115.1	216.6	123.2
F06002	19.9	1.041	68.3	154.0	80.3	1.36	3.06	1.60
F06003	12.0	1.065	75.8	211.8	103.6	0.91	2.54	1.24
F06004	12.1	1.041	62.9	121.4	30.9	0.76	1.47	0.37
F06005	7.7	1.065	99.1	124.6	40.6	0.76	0.96	0.31
Number of females	5	5	5	5	5	5	5	5
Mean	12.7	1.054	84.2	165.7	75.7	1.03	2.11	0.99
±S.D.	4.4	0.012	22.1	46.1	39.7	0.30	0.87	0.61

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 24-2-1. Urinalysis in female rats of the recovery period

Corn oil (control)

Female No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells <sup>a)</sup>	White blood cells <sup>a)</sup>	Casts <sup>a)</sup>	Crystals <sup>b)</sup>	Epithelial cells <sup>b)</sup>
F05006	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	±	-
F05007	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	±	-
F05008	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	±	-
F05009	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	±	-
F05010	Light 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
			F05006	15.8	1.056	112.5	241.6	118.5
F05007	16.2	1.046	118.7	192.6	117.8	1.92	3.12	1.91
F05008	7.3	1.053	112.3	173.7	93.9	0.82	1.27	0.69
F05009	7.7	1.078	142.1	471.6	180.7	1.09	3.63	1.39
F05010	4.3	1.080	73.9	209.6	96.4	0.32	0.90	0.41
Number of females	5	5	5	5	5	5	5	5
Mean	10.3	1.063	111.9	257.8	121.5	1.19	2.55	1.25
±S.D.	5.4	0.015	24.5	122.1	35.1	0.67	1.37	0.68

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP (1000 mg/kg)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells <sup>a)</sup>	White blood cells <sup>a)</sup>	Casts <sup>a)</sup>	Crystals <sup>b)</sup>	Epithelial cells <sup>b)</sup>
F06006	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	±	-
F06007	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	±	-
F06008	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	±	-
F06009	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	±	-
F06010	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
			F06006	10.6	1.034	69.6	109.3	41.3
F06007	23.4	1.030	63.0	172.8	78.4	1.47	4.04	1.83
F06008	13.0	1.054	88.6	250.4	112.4	1.15	3.26	1.46
F06009	21.8	1.033	74.5	154.4	89.4	1.62	3.37	1.95
F06010	16.4	1.052	108.4	209.0	105.7	1.78	3.43	1.73
Number of females	5	5	5	5	5	5	5	5
Mean	17.0	1.041*	80.8	179.2	85.4	1.35	3.05	1.48
±S.D.	5.5	0.011	18.1	53.6	28.1	0.41	1.10	0.61

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)

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	824	15.5	45.5	55.2	18.8	34.1	102.7	15.3	21.7
M01002	869	15.3	45.0	51.8	17.6	34.0	116.4	16.0	22.3
M01003	917	15.3	44.7	48.7	16.7	34.2	122.3	19.7	24.2
M01004	853	14.9	43.9	51.5	17.5	33.9	121.3	14.8	25.5
M01005	846	14.5	43.4	51.3	17.1	33.4	99.7	15.0	24.2
Number of males	5	5	5	5	5	5	5	5	5
Mean	862	15.1	44.5	51.7	17.5	33.9	112.5	16.2	23.6
S.D.	35	0.4	0.8	2.3	0.8	0.3	10.6	2.0	1.6

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
M01001	116.5	18.2	1.5	0.1	4.1	76.1	3.39
M01002	126.8	12.0	1.3	0.0	3.0	83.7	2.84
M01003	84.3	19.8	1.5	0.0	5.6	73.1	2.49
M01004	93.8	9.7	1.1	0.0	3.9	85.3	2.32
M01005	65.6	14.3	2.0	0.0	4.1	79.6	1.80
Number of males	5	5	5	5	5	5	5
Mean	97.4	14.8	1.5	0.0	4.1	79.6	2.57
S.D.	24.6	4.2	0.3	0.0	0.9	5.1	0.59

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 25-1-2. Hematological findings of male rats at the end of the dosing period

DMIP (62.5 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)
M02001	814	14.6	41.9	51.5	17.9	34.8	109.8	15.1	17.8
M02002	892	15.8	45.4	50.9	17.7	34.8	110.1	14.1	22.7
M02003	857	15.1	43.9	51.2	17.6	34.4	105.1	16.0	22.7
M02004	858	14.3	41.4	48.3	16.7	34.5	116.4	14.5	26.3
M02005	820	15.0	44.8	54.6	18.3	33.5	95.0	14.4	24.3
Number of males	5	5	5	5	5	5	5	5	5
Mean	848	15.0	43.5	51.3	17.6	34.4	107.3	14.8	22.8
S.D.	32	0.6	1.8	2.2	0.6	0.5	8.0	0.8	3.1

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
M02001	145.3	19.5	1.0	0.0	3.3	76.2	3.61
M02002	86.0	19.2	0.8	0.0	4.0	76.0	3.34
M02003	99.5	13.3	1.0	0.0	2.8	82.9	2.78
M02004	93.3	14.9	1.8	0.1	5.9	77.3	2.93
M02005	81.1	20.2	1.0	0.0	3.5	75.3	2.56
Number of males	5	5	5	5	5	5	5
Mean	101.0	17.4	1.1	0.0	3.9	77.5	3.04
S.D.	25.7	3.1	0.4	0.0	1.2	3.1	0.43

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 25-1-3. Hematological findings of male rats at the end of the dosing period

DMIP (250 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)
M03001	870	16.0	47.5	54.6	18.4	33.7	108.3	22.5	27.9
M03002	859	15.0	43.9	51.1	17.5	34.2	91.4	12.4	19.7
M03003	847	15.4	46.3	54.7	18.2	33.3	105.3	15.4	24.6
M03004	881	15.4	46.2	52.4	17.5	33.3	100.9	19.0	25.8
M03005	873	14.8	43.5	49.8	17.0	34.0	92.6	12.5	20.2
Number of males	5	5	5	5	5	5	5	5	5
Mean	866	15.3	45.5	52.5	17.7	33.7	99.7	16.4	23.6
S.D.	13	0.5	1.7	2.2	0.6	0.4	7.5	4.4	3.6

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
M03001	115.6	16.5	1.0	0.0	4.4	78.1	3.04
M03002	87.1	9.2	0.9	0.0	2.6	87.3	2.37
M03003	61.5	19.9	1.3	0.0	6.0	72.8	3.00
M03004	66.6	15.3	1.5	0.0	4.7	78.5	2.69
M03005	86.0	17.3	0.8	0.0	5.7	76.2	3.24
Number of males	5	5	5	5	5	5	5
Mean	83.4	15.6	1.1	0.0	4.7	78.6	2.87
S.D.	21.3	4.0	0.3	0.0	1.3	5.4	0.34

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 25-1-4. Hematological findings of male rats at the end of the dosing period

DMIP (1000 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)
M04001	857	15.4	45.0	52.5	18.0	34.2	113.9	23.0	22.8
M04002	891	15.4	43.7	49.0	17.3	35.2	105.1	15.7	23.5
M04003	845	15.2	44.6	52.8	18.0	34.1	88.7	12.4	22.9
M04004	917	15.9	44.8	48.9	17.3	35.5	110.3	12.9	21.4
M04005	859	15.6	45.9	53.4	18.2	34.0	94.1	14.4	23.8
Number of males	5	5	5	5	5	5	5	5	5
Mean	874	15.5	44.8	51.3	17.8	34.6	102.4	15.7	22.9
S.D.	30	0.3	0.8	2.2	0.4	0.7	10.7	4.3	0.9

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
M04001	89.9	15.8	1.2	0.0	4.7	78.3	3.45
M04002	117.7	18.3	1.4	0.1	3.1	77.1	2.86
M04003	96.2	11.7	1.7	0.1	3.2	83.3	2.79
M04004	78.4	9.8	1.3	0.0	4.5	84.4	2.39
M04005	88.8	16.2	2.1	0.1	3.8	77.8	2.48
Number of males	5	5	5	5	5	5	5
Mean	94.2	14.4	1.5	0.1	3.9	80.2	2.79
S.D.	14.6	3.5	0.4	0.1	0.7	3.4	0.42

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 25-2-1. Hematological findings of male rats at the end of the recovery period

Corn oil (control)

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)
M01009	835	14.8	41.2	49.3	17.7	35.9	96.2	22.3	26.1
M01010	850	14.8	41.7	49.1	17.4	35.5	167.6	16.4	25.8
M01011	779	14.4	42.6	54.7	18.5	33.8	82.2	18.4	27.1
M01012	868	15.4	43.2	49.8	17.7	35.6	103.7	14.6	24.5
M01013	801	13.9	40.8	50.9	17.4	34.1	117.8	24.4	30.3
Number of males	5	5	5	5	5	5	5	5	5
Mean	827	14.7	41.9	50.8	17.7	35.0	113.5	19.2	26.8
S.D.	36	0.6	1.0	2.3	0.5	1.0	32.9	4.1	2.2

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^3/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
M01009	126.0	14.5	0.8	0.1	3.4	81.2	3.47
M01010	96.6	8.8	1.1	0.0	2.8	87.3	3.08
M01011	86.2	8.9	1.2	0.0	2.3	87.6	2.34
M01012	113.9	9.7	1.5	0.0	2.5	86.3	2.88
M01013	96.5	26.8	1.2	0.1	4.1	67.8	3.66
Number of males	5	5	5	5	5	5	5
Mean	103.8	13.7	1.2	0.0	3.0	82.0	3.09
S.D.	15.9	7.7	0.3	0.1	0.7	8.4	0.52

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP (1000 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)
M04009	850	15.4	43.6	51.3	18.1	35.3	129.7	17.2	24.9
M04010	878	15.2	44.6	50.8	17.3	34.1	115.4	22.7	24.7
M04011	868	15.1	44.6	51.4	17.4	33.9	121.1	13.4	24.4
M04012	901	16.5	47.0	52.2	18.3	35.1	107.6	14.7	24.4
M04013	854	14.5	41.6	48.7	17.0	34.9	115.9	13.9	23.0
Number of males	5	5	5	5	5	5	5	5	5
Mean	870 *	15.3	44.3 *	50.9	17.6	34.7	117.9	16.4	24.3
S.D.	21	0.7	2.0	1.3	0.6	0.6	8.2	3.8	0.7

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
M04009	104.7	9.7	1.7	0.0	3.9	84.7	2.78
M04010	91.1	12.7	1.1	0.0	3.3	82.9	2.22
M04011	135.1	13.5	1.0	0.1	2.1	83.3	2.69
M04012	65.4	14.7	1.1	0.0	2.1	82.1	2.51
M04013	91.8	17.0	2.2	0.1	4.9	75.8	2.59
Number of males	5	5	5	5	5	5	5
Mean	97.6	13.5	1.4	0.0	3.3	81.8	2.56
S.D.	25.3	2.7	0.5	0.1	1.2	3.5	0.21

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)

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)
F01003	608	12.0	37.3	61.3	19.7	32.2	102.0	12.3	19.2
F01004	745	14.4	42.8	57.4	19.3	33.6	102.3	11.0	16.3
F01006	631	11.9	36.2	57.4	18.9	32.9	124.6	11.8	18.5
F01007	693	12.9	38.8	56.0	18.6	33.2	132.0	12.4	19.4
F01010	625	11.5	36.5	58.4	18.4	31.5	94.5	12.4	17.6
Number of males	5	5	5	5	5	5	5	5	5
Mean	660	12.5	38.3	58.1	19.0	32.7	111.1	12.0	18.2
S.D.	57	1.2	2.7	2.0	0.5	0.8	16.2	0.6	1.3

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
F01003	84.5	27.1	0.8	0.0	3.3	68.8	5.86
F01004	106.7	33.2	1.4	0.1	4.0	61.3	7.35
F01006	112.0	20.9	1.6	0.0	4.6	72.9	8.27
F01007	121.4	44.4	0.6	0.0	4.9	50.1	6.70
F01010	100.2	32.4	0.5	0.0	3.7	63.4	5.88
Number of males	5	5	5	5	5	5	5
Mean	105.0	31.6	1.0	0.0	4.1	63.3	6.81
S.D.	13.8	8.7	0.5	0.0	0.7	8.7	1.03

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 26-1-2. Hematological findings of female rats at the end of the dosing period

DMIP (62.5 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)
F02001	737	13.7	41.8	56.7	18.6	32.8	112.4	12.4	19.7
F02003	640	12.8	39.0	60.9	20.0	32.8	105.7	11.5	17.5
F02008	652	12.3	37.6	57.7	18.9	32.7	112.8	12.6	19.0
F02009	738	14.1	43.7	59.2	19.1	32.3	114.9	11.6	19.4
F02010	722	13.5	40.5	56.1	18.7	33.3	117.4	12.9	22.9
Number of males	5	5	5	5	5	5	5	5	5
Mean	698	13.3	40.5	58.1	19.1	32.8	112.6	12.2	19.7
S.D.	48	0.7	2.4	1.9	0.6	0.4	4.4	0.6	2.0

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
F02001	123.9	38.5	0.4	0.1	3.5	57.5	8.27
F02003	78.6	28.4	0.8	0.0	3.9	66.9	8.03
F02008	86.6	32.2	0.8	0.0	5.9	61.1	7.05
F02009	98.2	28.4	0.3	0.1	3.7	67.5	8.67
F02010	81.9	33.1	0.9	0.0	3.2	62.8	5.01
Number of males	5	5	5	5	5	5	5
Mean	93.8	32.1	0.6	0.0	4.0	63.2	7.41
S.D.	18.4	4.2	0.3	0.1	1.1	4.2	1.47

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 26-1-3. Hematological findings of female rats at the end of the dosing period

DMIP (250 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)
F03001	705	13.3	40.6	57.6	18.9	32.8	101.0	12.4	18.7
F03002	655	12.3	37.8	57.7	18.8	32.5	93.0	12.5	16.5
F03004	726	13.9	42.2	58.1	19.1	32.9	115.0	12.4	18.9
F03005	697	12.5	38.1	54.7	17.9	32.8	94.0	12.0	17.4
F03008	576	11.2	35.0	60.8	19.4	32.0	77.9	12.7	18.0
Number of males	5	5	5	5	5	5	5	5	5
Mean	672	12.6	38.7	57.8	18.8	32.6	96.2	12.4	17.9
S.D.	59	1.0	2.8	2.2	0.6	0.4	13.5	0.3	1.0

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
F03001	81.1	25.7	0.7	0.0	3.7	69.9	7.62
F03002	91.8	24.8	0.2	0.0	2.1	72.9	5.94
F03004	92.0	25.9	0.3	0.0	3.6	70.2	6.92
F03005	96.2	14.0	0.1	0.0	4.4	81.5	5.86
F03008	59.9	24.0	0.5	0.0	2.2	73.3	6.13
Number of males	5	5	5	5	5	5	5
Mean	84.2	22.9	0.4 *	0.0	3.2	73.6 *	6.49
S.D.	14.7	5.0	0.2	0.0	1.0	4.7	0.76

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 26-1-4. Hematological findings of female rats at the end of the dosing period

DMP (1000 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)
F04003	638	12.0	36.8	57.7	18.8	32.6	102.9	13.4	20.9
F04005	713	13.3	40.3	56.5	18.7	33.0	103.9	11.3	19.5
F04006	762	14.2	41.0	53.8	18.6	34.6	99.2	12.3	17.5
F04008	722	13.6	42.0	58.2	18.8	32.4	115.2	12.4	16.4
F04010	685	13.0	39.1	57.1	19.0	33.2	138.7	12.4	17.3
Number of males	5	5	5	5	5	5	5	5	5
Mean	704	13.2	39.8	56.7	18.8	33.2	112.0	12.4	18.3
S.D.	46	0.8	2.0	1.7	0.1	0.9	16.1	0.7	1.8

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
F04003	45.7	27.3	1.1	0.0	2.2	69.4	7.09
F04005	78.6	20.6	1.0	0.0	5.2	73.2	6.86
F04006	91.0	23.0	0.7	0.0	3.2	73.1	6.58
F04008	66.3	18.4	0.8	0.0	6.0	74.8	7.46
F04010	63.2	18.1	0.8	0.0	4.4	76.7	7.97
Number of males	5	5	5	5	5	5	5
Mean	69.0 **	21.5 *	0.9	0.0	4.2	73.4 *	7.19
S.D.	17.0	3.8	0.2	0.0	1.5	2.7	0.54

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 26-2-1. Hematological findings of female rats at the end of the dosing period, satellite group

Corn oil (control)

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)
F05001	819	14.1	41.4	50.5	17.2	34.1	94.8	11.7	16.3
F05002	715	13.8	41.5	58.0	19.3	33.3	99.9	11.7	17.6
F05003	769	14.3	40.9	53.2	18.6	35.0	98.6	10.8	18.1
F05004	888	15.8	46.1	51.9	17.8	34.3	102.2	12.3	22.5
F05005	746	13.9	41.5	55.6	18.6	33.5	95.6	10.8	15.8
Number of females	5	5	5	5	5	5	5	5	5
Mean	787	14.4	42.3	53.8	18.3	34.0	98.2	11.5	18.1
S.D.	68	0.8	2.1	3.0	0.8	0.7	3.1	0.7	2.7

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
F05001	71.7	31.5	1.7	0.0	2.6	64.2	2.13
F05002	64.6	8.6	1.4	0.0	2.2	87.8	3.22
F05003	43.2	9.3	1.6	0.0	2.3	86.8	2.27
F05004	48.6	9.0	1.2	0.0	1.9	87.9	2.28
F05005	43.1	15.1	1.4	0.0	2.8	80.7	3.01
Number of females	5	5	5	5	5	5	5
Mean	54.2	14.7	1.5	0.0	2.4	81.5	2.58
S.D.	13.1	9.8	0.2	0.0	0.4	10.1	0.50

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 26-2-2. Hematological findings of female rats at the end of the dosing period, satellite group

DMIP (1000 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)
F06001	844	15.8	46.1	54.6	18.7	34.3	91.0	11.5	22.3
F06002	811	14.7	42.7	52.7	18.1	34.4	101.9	11.7	15.8
F06003	826	15.3	44.9	54.4	18.5	34.1	123.0	10.7	17.6
F06004	798	14.5	41.6	52.1	18.2	34.9	107.0	11.6	18.4
F06005	758	14.2	41.5	54.7	18.7	34.2	88.8	11.3	15.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	807	14.9	43.4	53.7	18.4	34.4	102.3	11.4	17.8
S.D.	33	0.6	2.1	1.2	0.3	0.3	13.8	0.4	2.8

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
F06001	56.7	7.8	0.5	0.0	3.9	87.8	3.44
F06002	43.0	11.0	0.7	0.0	2.3	86.0	3.32
F06003	63.8	11.7	1.1	0.0	2.7	84.5	3.51
F06004	35.8	12.0	0.8	0.0	1.4	85.8	2.88
F06005	66.9	18.0	1.3	0.0	2.5	78.2	2.39
Number of females	5	5	5	5	5	5	5
Mean	53.2	12.1	0.9 **	0.0	2.6	84.5	3.11
S.D.	13.4	3.7	0.3	0.0	0.9	3.7	0.47

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 26-3-1. Hematological findings of female rats at the end of the recovery period

Corn oil (control)

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)
F05006	792	14.8	43.8	55.3	18.7	33.8	97.0	11.0	17.4
F05007	871	15.1	41.7	47.9	17.3	36.2	108.4	10.6	18.0
F05008	802	15.5	44.7	55.7	19.3	34.7	99.5	12.4	17.8
F05009	873	15.5	43.7	50.1	17.8	35.5	101.4	11.7	18.8
F05010	803	14.1	39.3	48.9	17.6	35.9	122.3	12.3	18.1
Number of females	5	5	5	5	5	5	5	5	5
Mean	828	15.0	42.6	51.6	18.1	35.2	105.7	11.6	18.0
S.D.	40	0.6	2.2	3.7	0.8	1.0	10.2	0.8	0.5

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
F05006	96.6	10.1	1.6	0.0	3.2	85.1	3.05
F05007	101.4	7.5	1.4	0.0	3.2	87.9	2.03
F05008	66.8	26.5	1.3	0.0	6.3	65.9	2.81
F05009	70.0	10.2	1.7	0.0	3.0	85.1	2.61
F05010	50.7	19.1	1.6	0.0	4.3	75.0	2.34
Number of females	5	5	5	5	5	5	5
Mean	77.1	14.7	1.5	0.0	4.0	79.8	2.57
S.D.	21.4	7.9	0.2	0.0	1.4	9.2	0.40

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 26-3-2. Hematological findings of female rats at the end of the recovery period

DMIP (1000 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)
F06006	872	15.7	43.6	50.0	18.0	36.0	129.0	10.9	17.9
F06007	791	14.5	41.1	52.0	18.3	35.3	121.7	10.8	17.3
F06008	788	14.8	42.4	53.8	18.8	34.9	100.2	11.0	19.1
F06009	812	15.4	43.6	53.7	19.0	35.3	105.8	11.4	18.4
F06010	811	15.2	42.5	52.4	18.7	35.8	97.5	11.7	18.1
Number of females	5	5	5	5	5	5	5	5	5
Mean	815	15.1	42.6	52.4	18.6	35.5	110.8	11.2	18.2
S.D.	34	0.5	1.0	1.5	0.4	0.4	13.8	0.4	0.7

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	( $\times 10^2/\mu\text{L}$ )	(%)	(%)	(%)	(%)	(%)	(%)
F06006	92.4	3.6	2.4	0.1	2.8	91.1	1.80
F06007	68.9	12.8	2.3	0.0	3.6	81.3	3.02
F06008	59.2	12.1	1.0	0.0	2.9	84.0	3.19
F06009	38.4	8.3	2.6	0.0	2.6	86.5	2.23
F06010	53.3	7.9	1.1	0.0	3.6	87.4	2.27
Number of females	5	5	5	5	5	5	5
Mean	62.4	8.9	1.9	0.0	3.1	86.1	2.50
S.D.	20.1	3.7	0.8	0.0	0.5	3.7	0.58

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)

Male No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ-GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
M01001	5.9	3.8	1.81	138	47	42	76	60	30	0	62	35.3
M01002	5.5	3.7	2.06	167	63	39	94	50	23	0	84	18.2
M01003	5.5	3.5	1.75	163	44	82	72	55	25	0	63	3.9
M01004	5.5	3.7	2.06	137	58	45	84	55	22	0	357	11.3
M01005	5.6	3.8	2.11	157	55	76	91	54	22	0	226	13.7
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.7	1.96	152	53	57	83	55	24	0	158	16.5
S.D.	0.2	0.1	0.17	14	8	20	9	4	3	0	130	11.7

Male No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
M01001	13	0.5	0.10	440	5.8	9.7	145.0	3.76	107.3
M01002	13	0.5	0.05	315	7.1	9.9	145.2	3.73	107.8
M01003	13	0.4	0.03	509	6.5	9.7	143.6	3.99	107.7
M01004	12	0.4	0.05	341	5.9	10.0	144.3	3.64	107.8
M01005	13	0.6	0.07	338	6.5	9.9	145.1	3.82	107.6
Number of males	5	5	5	5	5	5	5	5	5
Mean	13	0.5	0.06	389	6.4	9.8	144.6	3.79	107.6
S.D.	0	0.1	0.03	83	0.5	0.1	0.7	0.13	0.2

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 27-1-2. Biochemical findings of male rats at the end of the dosing period

DMP (62.5 mg/kg)

Male No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
M02001	6.1	3.8	1.65	161	65	76	100	57	26	0	72	6.6
M02002	6.0	4.0	2.00	151	70	64	100	62	33	0	197	8.4
M02003	5.6	3.7	1.95	172	80	86	110	75	31	0	144	12.9
M02004	5.5	3.6	1.89	150	74	63	102	53	29	0	91	5.3
M02005	5.5	3.4	1.62	146	57	43	76	60	28	0	60	13.1
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.7	1.82	156	69 *	66	98	61	29	0	113	9.3
S.D.	0.3	0.2	0.18	11	9	16	13	8	3	0	57	3.6

Male No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
M02001	13	0.5	0.06	418	6.5	10.1	143.3	4.11	105.0
M02002	15	0.5	0.07	334	5.6	10.5	144.6	3.51	107.0
M02003	11	0.5	0.05	409	6.2	10.0	143.8	3.98	107.8
M02004	13	0.4	0.05	455	6.1	9.7	143.6	3.84	106.5
M02005	12	0.5	0.05	272	6.0	10.1	143.8	4.10	106.7
Number of males	5	5	5	5	5	5	5	5	5
Mean	13	0.5	0.06	378	6.1	10.1	143.8	3.91	106.6
S.D.	2	0.0	0.01	74	0.3	0.3	0.5	0.25	1.0

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 27-1-3. Biochemical findings of male rats at the end of the dosing period

DMIP (250 mg/kg)

Male No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
M03001	6.0	4.0	2.00	170	60	62	91	57	30	0	118	19.0
M03002	4.9	3.3	2.06	158	67	49	83	52	24	0	211	5.4
M03003	5.5	3.6	1.89	145	72	42	87	51	24	0	86	6.3
M03004	5.3	3.6	2.12	165	58	65	87	51	27	0	57	8.9
M03005	5.4	3.5	1.84	179	85	155	127	46	22	0	56	11.3
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.6	1.98	163	68 *	75	95	51	25	0	106	10.2
S.D.	0.4	0.3	0.12	13	11	46	18	4	3	0	64	5.4

Male No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
M03001	11	0.5	0.08	444	6.8	9.9	143.3	4.17	105.0
M03002	11	0.4	0.05	251	6.3	9.3	146.6	3.72	108.0
M03003	12	0.5	0.05	372	5.3	9.5	144.9	3.81	108.4
M03004	11	0.4	0.05	390	6.4	9.7	145.4	3.81	108.3
M03005	12	0.4	0.05	431	6.3	10.0	143.6	3.81	105.9
Number of males	5	5	5	5	5	5	5	5	5
Mean	11	0.4	0.06	378	6.2	9.7	144.8	3.86	107.1
S.D.	1	0.1	0.01	77	0.6	0.3	1.4	0.18	1.6

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 27-1-4. Biochemical findings of male rats at the end of the dosing period

DMP (1000 mg/kg)

Male No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
M04001	5.7	3.7	1.85	182	63	98	102	69	26	0	91	11.6
M04002	5.8	3.7	1.76	159	52	81	96	57	27	0	60	18.2
M04003	5.9	3.7	1.68	168	69	57	100	51	24	0	184	11.4
M04004	5.4	3.7	2.18	172	58	91	95	63	31	0	141	48.1
M04005	5.3	3.5	1.94	154	63	32	93	56	30	0	44	7.5
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.7	1.88	167	61	72	97	59	28	0	104	19.4
S.D.	0.3	0.1	0.19	11	6	27	4	7	3	0	58	16.5

Male No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
M04001	11	0.5	0.06	385	6.7	9.8	144.6	3.73	106.8
M04002	10	0.5	0.05	540	7.0	9.8	144.3	4.20	105.5
M04003	11	0.5	0.06	305	5.4	9.9	144.9	3.61	105.8
M04004	13	0.4	0.09	487	6.3	9.7	143.6	3.70	105.6
M04005	11	0.4	0.06	293	6.4	9.5	145.2	3.79	107.3
Number of males	5	5	5	5	5	5	5	5	5
Mean	11	0.5	0.06	402	6.4	9.7	144.5	3.81	106.2
S.D.	1	0.1	0.02	109	0.6	0.2	0.6	0.23	0.8

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 27-2-1. Biochemical findings of male rats at the end of the recovery period

Corn oil (control)

Male No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
M01009	5.6	3.2	1.33	209	74	42	103	71	27	0	135	95.9
M01010	6.2	3.8	1.58	141	64	36	90	67	30	0	161	10.9
M01011	5.8	3.6	1.64	132	62	36	92	63	24	1	66	57.4
M01012	6.1	3.5	1.35	129	55	33	80	52	25	0	55	8.2
M01013	6.7	4.0	1.48	157	76	111	115	62	27	0	147	7.1
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	3.6	1.48	154	66	52	96	63	27	0	113	35.9
S.D.	0.4	0.3	0.14	33	9	33	13	7	2	0	49	39.6

Male No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
M01009	11	0.6	0.05	313	7.4	9.0	145.3	4.52	109.0
M01010	15	0.5	0.06	290	6.0	9.5	144.4	3.86	106.7
M01011	14	0.5	0.05	286	5.7	9.2	145.8	3.47	108.4
M01012	15	0.5	0.04	276	5.5	9.1	144.7	3.46	107.9
M01013	13	0.5	0.04	250	5.1	9.9	144.5	3.60	106.6
Number of males	5	5	5	5	5	5	5	5	5
Mean	14	0.5	0.05	283	5.9	9.3	144.9	3.78	107.7
S.D.	2	0.0	0.01	23	0.9	0.4	0.6	0.44	1.1

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Appendix 27-2-2. Biochemical findings of male rats at the end of the recovery period

DMIP (1000 mg/kg)

Male No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ-GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
M04009	6.3	3.8	1.52	142	54	54	80	55	24	0	72	7.0
M04010	6.0	3.6	1.50	138	50	22	70	57	29	0	64	12.3
M04011	5.8	3.6	1.64	132	40	47	70	55	28	0	46	16.6
M04012	6.0	3.6	1.50	136	31	23	55	62	28	0	76	27.3
M04013	5.7	3.4	1.48	139	56	31	83	70	29	2	163	11.8
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.0	3.6	1.53	137	46 *	35	72 *	60	28	0	84	15.0
S.D.	0.2	0.1	0.06	4	11	14	11	6	2	1	46	7.7

Male No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
M04009	11	0.5	0.05	276	5.4	9.7	143.1	4.21	104.9
M04010	15	0.6	0.06	264	6.3	9.4	144.5	3.90	106.5
M04011	16	0.5	0.04	316	5.7	9.2	143.0	3.89	106.0
M04012	12	0.5	0.05	356	5.8	9.4	144.7	3.70	107.4
M04013	15	0.5	0.03	196	6.1	9.4	144.3	3.76	108.9
Number of males	5	5	5	5	5	5	5	5	5
Mean	14	0.5	0.05	282	5.9	9.4	143.9	3.89	106.7
S.D.	2	0.0	0.01	60	0.4	0.2	0.8	0.20	1.5

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)

Female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
F01003	5.8	3.9	2.05	105	64	23	105	256	70	0	75	8.6
F01004	5.8	3.9	2.05	126	56	27	97	149	51	0	93	5.8
F01006	5.8	3.9	2.05	106	67	30	111	87	43	0	41	17.7
F01007	5.5	3.7	2.06	119	64	33	100	157	51	0	70	6.5
F01010	5.3	3.4	1.79	116	62	26	98	198	52	1	109	8.8
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.8	2.00	114	63	28	102	169	53	0	78	9.5
S.D.	0.2	0.2	0.12	9	4	4	6	63	10	0	26	4.8

Female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F01003	15	0.5	0.07	183	6.0	10.2	142.2	3.65	108.2
F01004	14	0.5	0.05	163	6.2	10.2	143.0	3.62	108.7
F01006	13	0.4	0.04	168	6.5	9.8	139.8	4.41	106.7
F01007	13	0.5	0.06	216	6.3	9.3	141.7	3.19	103.9
F01010	7	0.4	0.04	157	5.3	9.6	143.1	3.21	109.5
Number of males	5	5	5	5	5	5	5	5	5
Mean	12	0.5	0.05	177	6.1	9.8	142.0	3.62	107.4
S.D.	3	0.1	0.01	24	0.5	0.4	1.3	0.49	2.2

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 28-1-2. Biochemical findings of female rats at the end of the dosing period

DMIP (62.5 mg/kg)

Female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
F02001	5.5	3.7	2.06	125	67	34	106	217	55	1	99	13.2
F02003	5.7	4.0	2.35	129	58	31	96	87	50	1	71	8.7
F02008	6.3	4.2	2.00	145	71	38	123	191	76	0	79	13.6
F02009	5.9	4.0	2.11	130	66	36	99	105	42	0	231	14.8
F02010	5.8	4.1	2.41	123	42	85	97	78	36	0	219	12.0
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	4.0	2.19	130 *	61	45	104	136	52	0	140	12.5
S.D.	0.3	0.2	0.18	9	12	23	11	64	15	1	79	2.3

Female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F02001	13	0.6	0.07	156	6.7	9.6	140.4	3.66	104.3
F02003	13	0.5	0.04	345	5.8	10.0	141.0	3.32	108.9
F02008	15	0.5	0.07	165	6.8	10.3	141.4	3.82	107.3
F02009	12	0.5	0.07	297	6.0	10.0	145.4	3.64	110.4
F02010	13	0.4	0.07	153	6.9	10.2	143.1	3.20	107.4
Number of males	5	5	5	5	5	5	5	5	5
Mean	13	0.5	0.06	223	6.4	10.0	142.3	3.53	107.7
S.D.	1	0.1	0.01	91	0.5	0.3	2.0	0.26	2.3

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 28-1-3. Biochemical findings of female rats at the end of the dosing period

DMIP (250 mg/kg)

Female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
F03001	6.1	3.9	1.77	129	61	53	109	85	52	0	49	10.7
F03002	5.7	3.8	2.00	118	65	32	105	93	52	0	36	8.3
F03004	5.5	3.8	2.24	131	64	40	105	84	38	1	64	23.0
F03005	5.7	3.8	2.00	119	73	22	107	89	39	0	51	9.3
F03008	5.9	3.9	1.95	110	75	28	131	123	68	0	89	12.2
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.8	1.99	121	68	35	111	95	50	0	58	12.7
S.D.	0.2	0.1	0.17	9	6	12	11	16	12	0	20	5.9

Female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F03001	9	0.4	0.05	148	6.2	10.7	142.0	3.94	107.9
F03002	5	0.5	0.04	150	5.4	10.3	142.2	3.74	108.5
F03004	10	0.5	0.09	134	6.2	10.3	143.4	3.34	108.4
F03005	9	0.5	0.05	275	6.5	10.1	143.1	3.44	107.8
F03008	19	0.5	0.06	180	7.6	10.4	142.7	3.64	105.7
Number of males	5	5	5	5	5	5	5	5	5
Mean	10	0.5	0.06	177	6.4	10.4	142.7	3.62	107.7
S.D.	5	0.0	0.02	57	0.8	0.2	0.6	0.24	1.1

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 28-1-4. Biochemical findings of female rats at the end of the dosing period

DMIP (1000 mg/kg)

Female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ-GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
F04003	5.8	3.8	1.90	151	48	48	93	96	42	0	86	26.1
F04005	5.6	3.8	2.11	131	61	113	109	67	36	0	44	20.7
F04006	5.6	3.8	2.11	138	66	87	120	105	46	0	176	27.4
F04008	6.1	4.1	2.05	138	85	56	138	61	38	0	52	21.6
F04010	5.9	3.9	1.95	122	69	50	114	83	38	0	69	12.6
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.9	2.02	136 **	66	71 **	115	82	40	0	85	21.7 **
S.D.	0.2	0.1	0.10	11	13	28	16	19	4	0	53	5.8

Female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F04003	23	0.6	0.04	133	9.3	11.2	143.3	5.66	106.1
F04005	13	0.5	0.06	138	7.0	10.5	140.0	4.13	103.3
F04006	12	0.5	0.09	165	6.1	9.8	142.5	4.01	107.4
F04008	14	0.5	0.06	233	6.4	10.4	141.8	3.69	105.3
F04010	10	0.4	0.05	175	5.7	10.4	143.8	3.49	108.9
Number of males	5	5	5	5	5	5	5	5	5
Mean	14	0.5	0.06	169	6.9	10.5 *	142.3	4.20	106.2
S.D.	5	0.1	0.02	40	1.4	0.5	1.5	0.86	2.1

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 28-2-1. Biochemical findings of female rats at the end of the dosing period, satellite group

Corn oil (control)

Female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
F05001	5.9	4.1	2.28	129	53	10	92	56	20	0	61	7.3
F05002	6.1	4.1	2.05	122	80	15	127	48	19	0	77	8.5
F05003	6.5	4.4	2.10	127	81	16	122	56	24	0	125	12.9
F05004	5.7	4.0	2.35	126	64	14	108	73	18	0	74	25.4
F05005	6.1	4.2	2.21	140	61	12	105	64	21	0	126	8.0
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	4.2	2.20	129	68	13	111	59	20	0	93	12.4
S.D.	0.3	0.2	0.12	7	12	2	14	9	2	0	31	7.6

Female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F05001	16	0.7	0.05	188	5.4	10.0	142.9	3.78	107.8
F05002	15	0.6	0.07	170	5.1	10.2	143.4	3.26	107.8
F05003	17	0.7	0.06	129	4.2	9.8	144.0	3.29	110.1
F05004	18	0.6	0.07	179	3.6	9.2	144.9	3.44	108.1
F05005	15	0.6	0.06	191	3.9	9.9	143.9	3.50	109.8
Number of females	5	5	5	5	5	5	5	5	5
Mean	16	0.6	0.06	171	4.4	9.8	143.8	3.45	108.7
S.D.	1	0.1	0.01	25	0.8	0.4	0.7	0.21	1.1

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Appendix 28-2-2. Biochemical findings of female rats at the end of the dosing period, satellite group

DMIP (1000 mg/kg)

Female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
F06001	6.4	4.5	2.37	162	59	30	101	53	19	0	75	8.7
F06002	5.2	3.6	2.25	150	92	32	137	48	20	0	66	6.1
F06003	6.6	4.6	2.30	175	92	31	138	47	20	2	44	9.0
F06004	6.6	4.6	2.30	175	78	55	143	49	17	0	122	22.7
F06005	5.8	4.1	2.41	132	62	16	107	59	22	0	105	11.6
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	4.3	2.33	159 *	77	33 *	125	51	20	0	82	11.6
S.D.	0.6	0.4	0.06	18	16	14	20	5	2	1	31	6.5

Female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F06001	15	0.7	0.05	185	6.0	10.2	143.8	3.71	106.4
F06002	15	0.7	0.06	147	5.4	9.4	145.5	3.50	108.0
F06003	15	0.6	0.06	148	5.8	10.2	143.9	3.43	106.6
F06004	14	0.6	0.06	173	3.9	10.0	142.4	3.61	106.7
F06005	15	0.6	0.06	213	6.2	9.7	144.0	3.74	107.5
Number of females	5	5	5	5	5	5	5	5	5
Mean	15	0.6	0.06	173	5.5	9.9	143.9	3.60	107.0 *
S.D.	0	0.1	0.00	28	0.9	0.3	1.1	0.13	0.7

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 28-3-1. Biochemical findings of female rats at the end of the recovery period

Corn oil (control)

Female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	$\gamma$ -GTP (U/L)	LDH (U/L)	Bile acid ( $\mu$ mol/L)
F05006	6.3	4.0	1.74	149	75	21	101	58	20	1	45	45.8
F05007	6.3	4.1	1.86	119	74	18	110	107	44	0	165	30.2
F05008	6.1	3.8	1.65	114	71	18	103	79	54	0	68	10.2
F05009	5.6	3.5	1.67	108	45	17	78	56	19	1	37	11.2
F05010	6.2	3.8	1.58	118	63	11	100	54	22	0	49	7.7
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	3.8	1.70	122	66	17	98	71	32	0	73	21.0
S.D.	0.3	0.2	0.11	16	12	4	12	23	16	1	53	16.5

Female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F05006	13	0.6	0.08	142	6.4	9.6	140.8	4.13	104.6
F05007	15	0.6	0.10	217	5.6	9.5	141.4	3.86	105.2
F05008	13	0.6	0.07	129	4.2	9.3	145.0	3.44	108.8
F05009	13	0.5	0.05	193	3.7	8.8	144.5	3.24	109.8
F05010	13	0.6	0.07	96	3.5	9.2	144.1	3.56	108.4
Number of females	5	5	5	5	5	5	5	5	5
Mean	13	0.6	0.07	155	4.7	9.3	143.2	3.65	107.4
S.D.	1	0.0	0.02	49	1.3	0.3	1.9	0.35	2.3

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 28-3-2. Biochemical findings of female rats at the end of the recovery period

DMP (1000 mg/kg)

Female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ-GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
F06006	6.6	4.2	1.75	134	68	16	103	86	38	0	139	10.2
F06007	6.4	4.1	1.78	124	68	27	116	41	21	0	67	12.4
F06008	6.5	4.4	2.10	129	65	23	116	55	25	0	64	11.8
F06009	6.3	3.8	1.52	119	47	7	81	51	19	0	35	6.6
F06010	6.8	4.4	1.83	125	83	52	143	50	21	0	115	6.2
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.5	4.2	1.80	126	66	25	112	57	25	0	84	9.4
S.D.	0.2	0.2	0.21	6	13	17	23	17	8	0	42	2.9

Female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F06006	14	0.6	0.09	97	5.0	9.9	141.3	4.13	105.2
F06007	18	0.6	0.06	179	5.3	9.5	142.0	3.71	105.3
F06008	15	0.6	0.06	145	4.4	9.5	144.6	3.30	110.9
F06009	20	0.6	0.05	172	4.7	9.1	142.6	3.58	108.1
F06010	15	0.6	0.08	127	4.6	10.1	143.1	3.72	108.3
Number of females	5	5	5	5	5	5	5	5	5
Mean	16	0.6	0.07	144	4.8	9.6	142.7	3.69	107.6
S.D.	3	0.0	0.02	34	0.4	0.4	1.2	0.30	2.4

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)																	
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)
M01001	498.0	1946.1	3.908	340.8	0.684	1408.8	2.829	12537.1	25.175	1435.0	2.882	1467.9	2.948	2902.9	5.829	666.0	1.337
M01002	525.1	1894.0	3.607	296.6	0.565	1578.5	3.006	15666.9	29.836	1647.3	3.137	1598.2	3.044	3245.5	6.181	1025.0	1.952
M01003	522.3	1960.9	3.754	334.6	0.641	1456.8	2.789	15869.6	30.384	1525.4	2.921	1553.2	2.974	3078.6	5.894	715.9	1.371
M01004	545.1	2127.8	3.904	313.3	0.575	1511.3	2.773	14534.1	26.663	1741.9	3.196	1717.6	3.151	3459.5	6.347	758.6	1.392
M01005	489.3	1975.0	4.036	264.3	0.540	1286.9	2.630	12625.6	25.803	1347.7	2.754	1362.7	2.785	2710.4	5.539	697.8	1.426
M01006	566.1	2170.9	3.835	204.8	0.362	1652.8	2.920	19138.2	33.807	1820.4	3.216	1971.4	3.482	3791.8	6.698	954.1	1.685
M01007	602.2	1999.9	3.321	293.7	0.488	1480.1	2.458	19251.1	31.968	1727.3	2.868	1784.1	2.963	3511.4	5.831	749.4	1.244
M01008	526.2	2081.6	3.956	140.0	0.266	1376.8	2.616	13484.8	25.627	1625.8	3.090	1557.8	2.960	3183.6	6.050	784.6	1.491
Number of males	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	534.3	2019.5	3.790	273.5	0.515	1469.0	2.753	15388.4	28.658	1608.9	3.008	1626.6	3.038	3235.5	6.046	793.9	1.487
S.D.	36.6	96.7	0.230	69.1	0.140	115.3	0.177	2656.7	3.279	162.0	0.173	191.9	0.206	348.4	0.360	127.7	0.228

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Corn oil (control)																
Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	1589.1	3.191	1561.1	3.135	3150.2	6.326	626.2	1.257	594.3	1.193	1220.5	2.451	491.9	0.988	1713.3	3.440
M01002	1747.1	3.327	1760.7	3.353	3507.8	6.680	698.3	1.330	716.7	1.365	1415.0	2.695	558.2	1.063	1860.6	3.543
M01003	1627.1	3.115	1657.9	3.174	3285.0	6.289	639.8	1.225	644.3	1.234	1284.1	2.459	637.1	1.220	1470.8	2.816
M01004	1828.6	3.355	1819.2	3.337	3647.8	6.692	676.5	1.241	680.8	1.249	1357.3	2.490	720.7	1.322	1646.5	3.021
M01005	1659.1	3.391	1629.1	3.329	3288.2	6.720	576.2	1.178	580.1	1.186	1156.3	2.363	880.5	1.800	1720.2	3.516
M01006	1895.6	3.349	2052.1	3.625	3947.7	6.974	746.5	1.319	758.4	1.340	1504.9	2.658	450.3	0.795	2130.5	3.763
M01007	1659.8	2.756	1676.2	2.783	3336.0	5.540	599.4	0.995	554.4	0.921	1153.8	1.916	579.4	0.962	2000.6	3.322
M01008	1672.6	3.179	1740.2	3.307	3412.8	6.486	638.8	1.214	654.9	1.245	1293.7	2.459	501.9	0.954	1549.2	2.944
Number of males	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	1709.9	3.208	1737.1	3.255	3446.9	6.463	650.2	1.220	648.0	1.217	1298.2	2.436	602.5	1.138	1761.5	3.296
S.D.	105.5	0.208	150.8	0.241	252.9	0.436	55.0	0.104	70.0	0.135	123.7	0.238	141.7	0.314	223.6	0.334

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-1-2. Organ weights of male rats at the end of the dosing period

DMIP 62.5 mg/kg																	
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)
M02001	513.3	2008.1	3.912	358.5	0.698	1369.5	2.668	13621.8	26.538	1590.7	3.099	1578.3	3.075	3169.0	6.174	750.2	1.462
M02002	501.7	1940.4	3.868	294.7	0.587	1525.3	3.040	13362.3	26.634	1404.9	2.800	1376.7	2.744	2781.6	5.544	929.8	1.853
M02003	533.4	2121.8	3.978	310.8	0.583	1512.7	2.836	14915.4	27.963	1795.3	3.366	1707.0	3.200	3502.3	6.566	903.2	1.693
M02004	558.8	2173.2	3.889	290.7	0.520	1775.7	3.178	15376.4	27.517	1687.3	3.020	1693.9	3.031	3381.2	6.051	1023.4	1.831
M02005	557.9	2096.1	3.757	265.9	0.477	1478.9	2.651	14767.3	26.469	1409.2	2.526	1462.9	2.622	2872.1	5.148	808.5	1.449
M02006	526.6	2092.8	3.974	407.2	0.773	1468.1	2.788	13459.4	25.559	1845.0	3.504	1827.0	3.469	3672.0	6.973	786.7	1.494
M02007	555.2	2035.7	3.667	250.8	0.452	1460.1	2.630	15863.0	28.572	1466.2	2.641	1544.3	2.782	3010.5	5.422	769.6	1.386
M02008	520.5	1957.8	3.761	344.6	0.662	1434.2	2.755	14588.6	28.028	1486.1	2.855	1559.8	2.997	3045.9	5.852	918.4	1.764
M02009	546.5	1951.1	3.570	235.7	0.431	1713.0	3.134	18029.1	32.990	1887.9	3.455	1887.4	3.454	3775.3	6.908	882.5	1.615
M02010	552.9	2005.7	3.628	354.1	0.640	1639.5	2.965	15733.5	28.456	1634.6	2.956	1715.7	3.103	3350.3	6.060	862.7	1.560
M02011	507.3	1933.6	3.812	363.9	0.717	1342.7	2.647	14808.8	29.191	1641.4	3.236	1569.4	3.094	3210.8	6.329	814.6	1.606
M02012	515.4	1984.6	3.851	297.2	0.577	1294.8	2.512	11307.9	21.940	1354.7	2.628	1443.2	2.800	2797.9	5.429	1089.6	2.114
M02013	486.7	2084.6	4.283	242.0	0.497	1360.4	2.795	11787.6	24.219	1522.6	3.128	1498.7	3.079	3021.3	6.208	834.7	1.715
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	528.9	2029.7	3.842	308.9	0.586	1490.4	2.815	14432.4	27.237	1594.3	3.016	1604.9	3.035	3199.2	6.051	874.9	1.657
S.D.	23.8	77.5	0.183	53.4	0.108	144.7	0.207	1769.8	2.627	173.9	0.320	152.0	0.255	321.1	0.567	99.2	0.202
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).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-1-2(continued). Organ weights of male rats at the end of the dosing period

Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02001	1553.0	3.026	1593.5	3.104	3146.5	6.130	615.9	1.200	600.9	1.171	1216.8	2.371	790.8	1.541	1495.9	2.914
M02002	1632.8	3.255	1639.1	3.267	3271.9	6.522	634.1	1.264	599.2	1.194	1233.3	2.458	762.1	1.519	1921.9	3.831
M02003	1604.9	3.009	1626.1	3.049	3231.0	6.057	691.6	1.297	726.9	1.363	1418.5	2.659	870.4	1.632	2362.5	4.429
M02004	1839.2	3.291	1760.0	3.150	3599.2	6.441	661.8	1.184	661.7	1.184	1323.5	2.368	495.6	0.887	1265.6	2.265
M02005	1869.6	3.351	1852.5	3.320	3722.1	6.672	750.8	1.346	691.5	1.239	1442.3	2.585	723.3	1.296	1523.9	2.731
M02006	1843.5	3.501	1837.8	3.490	3681.3	6.991	712.2	1.352	750.0	1.424	1462.2	2.777	858.6	1.630	2082.2	3.954
M02007	1628.1	2.932	1660.0	2.990	3288.1	5.922	598.8	1.079	633.0	1.140	1231.8	2.219	615.5	1.109	1659.5	2.989
M02008	1249.1	2.400	1339.0	2.573	2588.1	4.972	521.9	1.003	552.5	1.061	1074.4	2.064	818.0	1.572	1302.9	2.503
M02009	1594.8	2.918	1505.5	2.755	3100.3	5.673	577.6	1.057	558.3	1.022	1135.9	2.078	852.4	1.560	1613.2	2.952
M02010	1590.8	2.877	1598.4	2.891	3189.2	5.768	603.8	1.092	577.2	1.044	1181.0	2.136	672.7	1.217	1871.6	3.385
M02011	1622.5	3.198	1655.6	3.264	3278.1	6.462	606.5	1.196	609.9	1.202	1216.4	2.398	590.9	1.165	1880.9	3.708
M02012	1581.0	3.068	1649.5	3.200	3230.5	6.268	622.0	1.207	640.5	1.243	1262.5	2.450	662.2	1.285	1688.9	3.277
M02013	1469.3	3.019	1521.2	3.126	2990.5	6.144	560.7	1.152	557.8	1.146	1118.5	2.298	610.9	1.255	1532.8	3.149
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	1621.4	3.065	1633.7	3.091	3255.1	6.156	627.5	1.187	627.6	1.187	1255.2	2.374	717.2	1.359	1707.8	3.237
S.D.	165.5	0.274	137.2	0.245	299.5	0.511	63.1	0.109	64.5	0.116	123.9	0.218	119.4	0.234	309.8	0.614
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	KW	KW	AN	KW	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).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-1-3. Organ weights of male rats at the end of the dosing period

DMP 250 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)	
M03001	476.1	2098.3	4.407	231.5	0.486	1458.2	3.063	12135.5	25.489	1527.1	3.208	1600.0	3.361	3127.1	6.568	625.9	1.315
M03002	523.4	2058.1	3.932	310.8	0.594	1534.1	2.931	15547.8	29.705	1583.5	3.025	1674.8	3.200	3258.3	6.225	901.5	1.722
M03003	517.2	2073.2	4.009	226.0	0.437	1566.1	3.028	13260.9	25.640	1624.3	3.141	1671.4	3.232	3295.7	6.372	790.0	1.527
M03004	508.9	1848.9	3.633	256.7	0.504	1606.7	3.157	14541.0	28.573	1760.6	3.460	1748.0	3.435	3508.6	6.894	917.5	1.803
M03005	554.3	1843.8	3.326	370.9	0.669	1705.6	3.077	16360.8	29.516	1665.9	3.005	1632.2	2.945	3298.1	5.950	814.1	1.469
M03006	587.6	1981.1	3.372	272.9	0.464	1709.3	2.909	16617.7	28.281	1675.1	2.851	1733.7	2.950	3408.8	5.801	799.1	1.360
M03007	488.6	2064.0	4.224	342.4	0.701	1321.3	2.704	13053.3	26.716	1610.1	3.295	1541.6	3.155	3151.7	6.450	825.1	1.689
M03008	501.1	2127.2	4.245	262.5	0.524	1511.0	3.015	12150.9	24.248	1749.7	3.492	1617.9	3.229	3367.6	6.720	692.2	1.381
M03009	557.8	2313.6	4.148	268.2	0.481	1738.7	3.117	16326.3	29.269	2017.5	3.617	1954.4	3.504	3971.9	7.121	1024.6	1.837
M03010	554.9	1990.0	3.586	199.9	0.360	1755.3	3.163	14947.6	26.937	2012.8	3.627	2086.1	3.759	4098.9	7.387	1067.5	1.924
M03011	546.7	2102.1	3.845	319.0	0.584	1404.2	2.569	14377.3	26.298	1580.1	2.890	1558.3	2.850	3138.4	5.741	796.3	1.457
M03012	538.5	1937.5	3.598	361.9	0.672	1463.9	2.718	12369.5	22.970	1697.2	3.152	1699.7	3.156	3396.9	6.308	1035.9	1.924
M03013	514.5	1982.4	3.853	436.3	0.848	1608.1	3.126	14234.5	27.667	1478.2	2.873	1470.1	2.857	2948.3	5.730	729.3	1.417
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	528.4	2032.3	3.860	296.8	0.563	1567.9	2.967	14301.8	27.024	1690.9	3.203	1691.4	3.203	3382.3	6.405	847.6	1.602
S.D.	31.6	124.4	0.343	67.6	0.132	135.8	0.192	1618.5	2.079	164.9	0.276	167.6	0.268	325.9	0.529	135.4	0.222
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).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-1-3(continued). Organ weights of male rats at the end of the dosing period

Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
	M03001	1628.6	3.421	1601.0	3.363	3229.6	6.783	616.3	1.294	602.1	1.265	1218.4	2.559	670.6	1.409	2092.5
M03002	1760.0	3.363	1827.6	3.492	3587.6	6.854	602.8	1.152	590.4	1.128	1193.2	2.280	787.3	1.504	1814.7	3.467
M03003	1722.1	3.330	1713.3	3.313	3435.4	6.642	650.9	1.259	656.9	1.270	1307.8	2.529	562.1	1.087	2067.1	3.997
M03004	1709.6	3.359	1708.1	3.356	3417.7	6.716	640.9	1.259	590.4	1.160	1231.3	2.420	647.3	1.272	1753.2	3.445
M03005	1506.5	2.718	3022.5	5.453	4529.0	8.171	566.5	1.022	561.7	1.013	1128.2	2.035	416.9	0.752	1806.6	3.259
M03006	1530.6	2.605	1525.0	2.595	3055.6	5.200	569.6	0.969	556.4	0.947	1126.0	1.916	722.3	1.229	1949.6	3.318
M03007	1875.3	3.838	1797.9	3.680	3673.2	7.518	661.0	1.353	647.0	1.324	1308.0	2.677	760.4	1.556	1780.6	3.644
M03008	1729.2	3.451	1715.9	3.424	3445.1	6.875	616.1	1.229	624.3	1.246	1240.4	2.475	479.9	0.958	1921.9	3.835
M03009	1726.3	3.095	1746.3	3.131	3472.6	6.226	636.6	1.141	624.0	1.119	1260.6	2.260	920.7	1.651	2377.5	4.262
M03010	1239.0	2.233	1668.1	3.006	2907.1	5.239	479.3	0.864	726.8	1.310	1206.1	2.174	717.0	1.292	1881.4	3.391
M03011	1671.7	3.058	1668.5	3.052	3340.2	6.110	621.4	1.137	583.0	1.066	1204.4	2.203	483.8	0.885	1722.7	3.151
M03012	1432.1	2.659	1388.1	2.578	2820.2	5.237	588.6	1.093	591.4	1.098	1180.0	2.191	785.9	1.459	1862.3	3.458
M03013	1566.7	3.045	1525.0	2.964	3091.7	6.009	536.6	1.043	515.4	1.002	1052.0	2.045	638.2	1.240	1592.3	3.095
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	1622.9	3.090	1762.1	3.339	3385.0	6.429	599.0	1.140	605.4	1.150	1204.3	2.290	661.0	1.253	1894.0	3.594
S.D.	166.7	0.438	397.7	0.715	429.7	0.891	50.9	0.140	52.8	0.124	72.3	0.229	144.4	0.271	199.0	0.413
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	KW	KW	AN	KW	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).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-1-3(continued). Organ weights of male rats at the end of the dosing period

DMIP 250 mg/kg

Male No.	Body weight (g)	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03001	476.1	23.1	0.049	27.7	0.058	28.5	0.060	56.2	0.118
M03002	523.4	20.5	0.039	33.5	0.064	38.2	0.073	71.7	0.137
M03003	517.2	20.0	0.039	28.8	0.056	33.7	0.065	62.5	0.121
M03004	508.9	19.2	0.038	25.5	0.050	26.6	0.052	52.1	0.102
M03005	554.3	17.6	0.032	20.9	0.038	22.9	0.041	43.8	0.079
M03006	587.6	28.3	0.048	25.5	0.043	26.6	0.045	52.1	0.089
M03007	488.6	16.4	0.034	30.7	0.063	31.1	0.064	61.8	0.126
M03008	501.1	24.5	0.049	30.6	0.061	35.8	0.071	66.4	0.133
M03009	557.8	17.3	0.031	29.7	0.053	30.5	0.055	60.2	0.108
M03010	554.9	28.2	0.051	26.8	0.048	28.9	0.052	55.7	0.100
M03011	546.7	21.3	0.039	34.5	0.063	34.5	0.063	69.0	0.126
M03012	538.5	16.8	0.031	28.8	0.053	33.5	0.062	62.3	0.116
M03013	514.5	27.5	0.053	24.8	0.048	25.3	0.049	50.1	0.097
Number of males	13	13	13	13	13	13	13	13	13
Mean	528.4	21.6	0.041	28.3	0.054	30.5	0.058	58.8	0.112
S.D.	31.6	4.4	0.008	3.7	0.008	4.5	0.010	8.0	0.018
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-1-4. Organ weights of male rats at the end of the dosing period

DMIP 1000 mg/kg																	
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)
M04001	550.6	2101.3	3.816	312.3	0.567	1435.8	2.608	15415.2	27.997	1609.0	2.922	1638.9	2.977	3247.9	5.899	763.7	1.387
M04002	498.5	2061.2	4.135	244.3	0.490	1343.0	2.694	14044.9	28.174	1539.9	3.089	1475.3	2.959	3015.2	6.049	815.4	1.636
M04003	488.9	1988.4	4.067	401.6	0.821	1440.0	2.945	13809.3	28.246	1406.3	2.876	1400.3	2.864	2806.6	5.741	789.6	1.615
M04004	541.2	2066.5	3.818	276.3	0.511	1554.0	2.871	14789.1	27.326	1615.4	2.985	1684.5	3.113	3299.9	6.097	771.2	1.425
M04005	473.8	2054.0	4.335	295.4	0.623	1332.4	2.812	11922.0	25.163	1539.7	3.250	1450.8	3.062	2990.5	6.312	875.4	1.848
M04006	552.0	1986.9	3.599	260.7	0.472	1488.8	2.697	16398.7	29.708	1882.3	3.410	1836.1	3.326	3718.4	6.736	989.4	1.792
M04007	521.3	2035.9	3.905	246.0	0.472	1580.4	3.032	13800.7	26.474	1641.7	3.149	1581.0	3.033	3222.7	6.182	895.0	1.717
M04008	456.7	1935.8	4.239	271.5	0.594	1285.5	2.815	12290.6	26.912	1557.4	3.410	1596.5	3.496	3153.9	6.906	830.5	1.818
Number of males	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	510.4	2028.8	3.989	288.5	0.569	1432.5	2.809	14058.8	27.500	1599.0	3.136	1582.9	3.104	3181.9	6.240	841.3	1.655
S.D.	36.3	54.0	0.247	51.2	0.117	106.6	0.141	1496.2	1.364	135.4	0.208	141.5	0.209	270.9	0.400	75.9	0.174
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).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-1-4(continued). Organ weights of male rats at the end of the dosing period

Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
	M04001	1679.2	3.050	1660.7	3.016	3339.9	6.066	606.5	1.102	595.1	1.081	1201.6	2.182	540.7	0.982	1630.1
M04002	1636.8	3.283	1639.4	3.289	3276.2	6.572	619.0	1.242	607.2	1.218	1226.2	2.460	729.2	1.463	1671.5	3.353
M04003	1492.9	3.054	1494.8	3.057	2987.7	6.111	564.7	1.155	540.6	1.106	1105.3	2.261	734.9	1.503	1363.8	2.790
M04004	1615.7	2.985	1636.5	3.024	3252.2	6.009	563.0	1.040	546.3	1.009	1109.3	2.050	775.6	1.433	1780.2	3.289
M04005	1588.8	3.353	1590.9	3.358	3179.7	6.711	584.0	1.233	593.4	1.252	1177.4	2.485	534.0	1.127	1722.6	3.636
M04006	1678.2	3.040	1678.4	3.041	3356.6	6.081	605.8	1.097	598.2	1.084	1204.0	2.181	704.8	1.277	1665.4	3.017
M04007	1794.7	3.443	1741.6	3.341	3536.3	6.784	682.4	1.309	657.7	1.262	1340.1	2.571	500.7	0.960	1838.7	3.527
M04008	1548.0	3.390	1479.0	3.238	3027.0	6.628	645.2	1.413	607.9	1.331	1253.1	2.744	637.2	1.395	1893.0	4.145
Number of males	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	1629.3	3.200	1615.2	3.171	3244.5	6.370	608.8	1.199	593.3	1.168	1202.1	2.367	644.6	1.268	1695.7	3.340
S.D.	92.1	0.186	90.0	0.150	179.4	0.331	40.6	0.124	37.0	0.113	76.4	0.235	106.8	0.218	161.8	0.435
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	KW	KW	AN	KW	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).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 29-1-4(continued). Organ weights of male rats at the end of the dosing period

DMIP 1000 mg/kg

Male No.	Body weight (g)	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04001	550.6	16.6	0.030	22.6	0.041	25.4	0.046	48.0	0.087
M04002	498.5	22.1	0.044	35.8	0.072	33.9	0.068	69.7	0.140
M04003	488.9	16.1	0.033	29.9	0.061	30.1	0.062	60.0	0.123
M04004	541.2	21.0	0.039	25.4	0.047	30.9	0.057	56.3	0.104
M04005	473.8	19.6	0.041	25.8	0.054	30.1	0.064	55.9	0.118
M04006	552.0	32.2	0.058	44.4	0.080	46.8	0.085	91.2	0.165
M04007	521.3	15.5	0.030	30.5	0.059	34.3	0.066	64.8	0.124
M04008	456.7	19.7	0.043	19.1	0.042	21.0	0.046	40.1	0.088
Number of males	8	8	8	8	8	8	8	8	8
Mean	510.4	20.4	0.040	29.2	0.057	31.6	0.062	60.8	0.119
S.D.	36.3	5.4	0.009	8.0	0.014	7.6	0.013	15.4	0.026
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-2-1. Organ weights of male rats at the end of the recovery period

Corn oil (control)																	
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)
M01009	557.7	1881.5	3.374	263.4	0.472	1630.2	2.923	18052.5	32.370	2066.6	3.706	2036.3	3.651	4102.9	7.357	772.9	1.386
M01010	504.2	1986.4	3.940	298.6	0.592	1640.4	3.253	12907.6	25.600	1520.7	3.016	1558.2	3.090	3078.9	6.107	823.1	1.632
M01011	502.7	1972.8	3.924	301.3	0.599	1428.3	2.841	13031.2	25.922	1549.0	3.081	1510.3	3.004	3059.3	6.086	815.4	1.622
M01012	545.5	2042.5	3.744	274.8	0.504	1345.3	2.466	14317.8	26.247	1795.4	3.291	1694.8	3.107	3490.2	6.398	966.6	1.772
M01013	632.1	2049.2	3.242	215.5	0.341	1668.9	2.640	20697.9	32.745	1787.3	2.828	1786.2	2.826	3573.5	5.653	1032.0	1.633
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	548.4	1986.5	3.645	270.7	0.502	1542.6	2.825	15801.4	28.577	1743.8	3.184	1717.2	3.136	3461.0	6.320	882.0	1.609
S.D.	52.8	67.6	0.320	34.8	0.105	145.9	0.298	3438.5	3.643	221.6	0.335	209.3	0.309	428.1	0.638	111.2	0.139

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-2-1(continued). Organ weights of male rats at the end of the recovery period

Corn oil (control)																
Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymis		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01009	1726.4	3.096	1659.8	2.976	3386.2	6.072	662.9	1.189	636.4	1.141	1299.3	2.330	821.2	1.472	2528.9	4.535
M01010	1588.4	3.150	1557.4	3.089	3145.8	6.239	661.5	1.312	643.9	1.277	1305.4	2.589	376.1	0.746	1428.6	2.833
M01011	1545.9	3.075	1508.2	3.000	3054.1	6.075	606.6	1.207	592.7	1.179	1199.3	2.386	481.1	0.957	1862.6	3.705
M01012	1751.3	3.210	1699.9	3.116	3451.2	6.327	785.4	1.440	719.5	1.319	1504.9	2.759	752.8	1.380	1540.2	2.823
M01013	1760.5	2.785	1790.6	2.833	3551.1	5.618	711.7	1.126	667.4	1.056	1379.1	2.182	912.1	1.443	2161.0	3.419
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1674.5	3.063	1643.2	3.003	3317.7	6.066	685.6	1.255	652.0	1.194	1337.6	2.449	668.7	1.200	1904.3	3.463
S.D.	99.9	0.164	112.7	0.112	209.8	0.273	67.0	0.123	46.4	0.106	113.3	0.226	229.3	0.328	451.8	0.710

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 29-2-1(continued). Organ weights of male rats at the end of the recovery period

Corn oil (control)

Male No.	Body weight (g)	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01009	557.7	25.4	0.046	26.7	0.048	29.4	0.053	56.1	0.101
M01010	504.2	19.2	0.038	18.6	0.037	22.6	0.045	41.2	0.082
M01011	502.7	20.8	0.041	27.3	0.054	26.1	0.052	53.4	0.106
M01012	545.5	15.8	0.029	30.0	0.055	32.0	0.059	62.0	0.114
M01013	632.1	22.1	0.035	30.5	0.048	27.6	0.044	58.1	0.092
Number of males	5	5	5	5	5	5	5	5	5
Mean	548.4	20.7	0.038	26.6	0.048	27.5	0.051	54.2	0.099
S.D.	52.8	3.5	0.006	4.8	0.007	3.5	0.006	7.9	0.012

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 1000 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)	
M04009	619.5	2092.7	3.378	335.5	0.542	1783.7	2.879	16879.3	27.247	1785.7	2.882	1930.1	3.116	3715.8	5.998	826.3	1.334
M04010	510.9	2136.3	4.181	254.1	0.497	1448.6	2.835	12394.3	24.260	1595.5	3.123	1517.5	2.970	3113.0	6.093	895.4	1.753
M04011	528.6	1934.0	3.659	292.9	0.554	1623.4	3.071	14702.1	27.813	1788.0	3.383	1733.3	3.279	3521.3	6.662	946.5	1.791
M04012	491.7	2097.2	4.265	183.0	0.372	1457.8	2.965	11705.3	23.806	1587.2	3.228	1685.7	3.428	3272.9	6.656	612.5	1.246
M04013	531.4	1818.5	3.422	297.2	0.559	1744.9	3.284	14987.8	28.204	1736.3	3.267	1794.6	3.377	3530.9	6.645	801.1	1.508
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	536.4	2015.7	3.781	272.5	0.505	1611.7	3.007	14133.8	26.266	1698.5	3.177	1732.2	3.234	3430.8	6.411	816.4	1.526
S.D.	49.1	134.8	0.418	57.8	0.078	156.3	0.179	2092.5	2.073	100.0	0.189	151.1	0.190	237.4	0.335	127.5	0.244
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Male No.	Testis (R)		Testis (L)		Testis		Epididymis (R)		Epididymis (L)		Epididymis		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04009	1571.3	2.536	1617.0	2.610	3188.3	5.147	619.1	0.999	569.1	0.919	1188.2	1.918	857.6	1.384	2208.5	3.565
M04010	1847.8	3.617	1901.7	3.722	3749.5	7.339	660.7	1.293	670.6	1.313	1331.3	2.606	549.9	1.076	2046.6	4.006
M04011	1588.4	3.005	1597.7	3.023	3186.1	6.027	678.3	1.283	657.3	1.243	1335.6	2.527	790.2	1.495	2311.0	4.372
M04012	1704.2	3.466	1647.3	3.350	3351.5	6.816	621.1	1.263	621.6	1.264	1242.7	2.527	558.7	1.136	1750.9	3.561
M04013	1858.7	3.498	1824.9	3.434	3683.6	6.932	620.9	1.168	602.0	1.133	1222.9	2.301	898.5	1.691	1759.9	3.312
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1714.1	3.224	1717.7	3.228	3431.8	6.452	640.0	1.201	624.1	1.174	1264.1	2.376	731.0	1.356	2015.4	3.763
S.D.	137.0	0.450	136.8	0.426	269.5	0.871	27.6	0.123	41.2	0.157	66.2	0.280	165.9	0.255	255.4	0.422
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	AW	TT	AW	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 1000 mg/kg

Male No.	Body weight (g)	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04009	619.5	25.0	0.040	28.1	0.045	28.3	0.046	56.4	0.091
M04010	510.9	19.3	0.038	28.6	0.056	29.4	0.058	58.0	0.114
M04011	528.6	21.7	0.041	31.8	0.060	36.0	0.068	67.8	0.128
M04012	491.7	20.0	0.041	35.0	0.071	35.8	0.073	70.8	0.144
M04013	531.4	16.6	0.031	36.5	0.069	38.3	0.072	74.8	0.141
Number of males	5	5	5	5	5	5	5	5	5
Mean	536.4	20.5	0.038	32.0	0.060	33.6	0.063	65.6	0.124
S.D.	49.1	3.1	0.004	3.7	0.011	4.4	0.011	8.0	0.022
Significance	NS	NS	NS	NS	NS	*	NS	NS	NS
Statistical method	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

Com oil (control)																	
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)
F01001	330.4	1873.2	5.669	247.4	0.749	1032.3	3.124	10875.8	32.917	1110.4	3.361	997.6	3.019	2108.0	6.380	788.4	2.386
F01002	289.9	1935.0	6.675	232.3	0.801	876.9	3.025	9184.3	31.681	976.0	3.367	939.3	3.240	1915.3	6.607	740.1	2.553
F01003	368.1	1941.5	5.274	277.2	0.753	1080.3	2.935	10603.0	28.805	905.1	2.459	876.0	2.380	1781.1	4.839	705.3	1.916
F01004	332.0	1861.5	5.607	235.1	0.708	1069.0	3.220	9975.6	30.047	922.3	2.778	914.8	2.755	1837.1	5.533	784.6	2.363
F01005	326.7	1844.4	5.646	201.0	0.615	890.0	2.724	8994.9	27.533	869.7	2.662	850.7	2.604	1720.4	5.266	821.8	2.515
F01006	291.2	1874.2	6.436	216.9	0.745	889.3	3.054	8502.7	29.199	884.3	3.037	901.0	3.094	1785.3	6.131	498.3	1.711
F01007	310.2	1953.2	6.297	150.0	0.484	906.5	2.922	8623.3	27.799	1042.1	3.359	899.8	2.901	1941.9	6.260	543.5	1.752
F01008	327.3	1913.1	5.845	227.6	0.695	996.8	3.046	10820.2	33.059	1079.9	3.299	1095.9	3.348	2175.8	6.648	829.1	2.533
F01009	340.7	1920.8	5.638	217.0	0.637	1218.9	3.578	10174.6	29.864	1133.6	3.327	1131.8	3.322	2265.4	6.649	1728.3	5.073
F01010	293.3	1859.9	6.341	105.4	0.359	946.7	3.228	9187.4	31.324	834.3	2.845	820.7	2.798	1655.0	5.643	669.9	2.284
F01011	311.7	1847.6	5.927	321.8	1.032	938.5	3.011	9411.6	30.194	884.8	2.839	881.9	2.829	1766.7	5.668	862.6	2.767
F01012	336.3	1844.3	5.484	230.6	0.686	1084.2	3.224	10654.4	31.681	1099.4	3.269	1055.1	3.137	2154.5	6.406	674.2	2.005
F01013	339.8	1889.3	5.560	220.7	0.649	1093.0	3.217	10486.1	30.860	928.3	2.732	918.5	2.703	1846.8	5.435	682.8	2.009
Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	322.9	1889.1	5.877	221.8	0.686	1001.7	3.101	9807.2	30.382	974.6	3.026	944.9	2.933	1919.5	5.959	794.5	2.451
S.D.	22.8	39.1	0.427	52.7	0.159	104.4	0.206	858.1	1.760	104.7	0.321	96.3	0.292	195.5	0.595	300.4	0.854

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-1-1(continued). Organ weights of female rats at the end of the dosing period

Corn oil (control)																
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	64.5	0.195	53.5	0.162	118.0	0.357	518.4	1.569	17.6	0.053	37.3	0.113	37.5	0.113	74.8	0.226
F01002	28.6	0.099	39.7	0.137	68.3	0.236	531.4	1.833	18.1	0.062	27.8	0.096	31.0	0.107	58.8	0.203
F01003	50.2	0.136	54.8	0.149	105.0	0.285	740.5	2.012	17.3	0.047	29.4	0.080	37.8	0.103	67.2	0.183
F01004	44.9	0.135	49.9	0.150	94.8	0.286	606.9	1.828	12.0	0.036	34.9	0.105	37.1	0.112	72.0	0.217
F01005	44.3	0.136	48.4	0.148	92.7	0.284	658.7	2.016	19.9	0.061	30.7	0.094	35.9	0.110	66.6	0.204
F01006	43.1	0.148	47.8	0.164	90.9	0.312	721.1	2.476	11.2	0.038	30.0	0.103	33.7	0.116	63.7	0.219
F01007	34.0	0.110	46.8	0.151	80.8	0.260	482.5	1.555	11.2	0.036	40.8	0.132	40.4	0.130	81.2	0.262
F01008	47.2	0.144	59.9	0.183	107.1	0.327	536.3	1.639	14.2	0.043	37.4	0.114	40.1	0.123	77.5	0.237
F01009	90.5	0.266	55.9	0.164	146.4	0.430	839.9	2.465	14.0	0.041	34.8	0.102	39.0	0.114	73.8	0.217
F01010	69.4	0.237	40.3	0.137	109.7	0.374	675.6	2.303	13.5	0.046	30.3	0.103	39.3	0.134	69.6	0.237
F01011	60.7	0.195	58.3	0.187	119.0	0.382	636.4	2.042	13.7	0.044	32.1	0.103	34.7	0.111	66.8	0.214
F01012	69.4	0.206	46.5	0.138	115.9	0.345	872.5	2.594	20.9	0.062	38.0	0.113	39.0	0.116	77.0	0.229
F01013	46.4	0.137	55.1	0.162	101.5	0.299	666.8	1.962	16.5	0.049	33.1	0.097	29.5	0.087	62.6	0.184
Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	53.3	0.165	50.5	0.156	103.9	0.321	652.8	2.023	15.4	0.048	33.6	0.104	36.5	0.114	70.1	0.218
S.D.	16.9	0.050	6.4	0.016	19.6	0.055	120.5	0.348	3.2	0.009	4.0	0.012	3.4	0.012	6.6	0.022

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-1-2. Organ weights of female rats at the end of the dosing period

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)
F02001	281.2		1942.4	6.908	92.2	0.328	851.7	3.029	8134.4	28.927	855.7	3.043	858.3	3.052	1714.0	6.095	602.8	2.144
F02002	335.6		2004.8	5.974	197.9	0.590	1093.1	3.257	10745.7	32.019	1133.2	3.377	1158.1	3.451	2291.3	6.827	837.2	2.495
F02003	299.7		1971.0	6.577	136.2	0.454	846.9	2.826	10325.0	34.451	889.3	2.967	879.3	2.934	1768.6	5.901	607.1	2.026
F02004	324.3		1907.7	5.883	206.5	0.637	1100.8	3.394	11422.8	35.223	984.2	3.035	919.6	2.836	1903.8	5.870	881.0	2.717
F02005	312.9		1914.1	6.117	112.0	0.358	1028.9	3.288	10609.8	33.908	1047.3	3.347	983.8	3.144	2031.1	6.491	618.0	1.975
F02006	330.9 <sup>a)</sup>		2023.1 <sup>a)</sup>	6.114 <sup>a)</sup>	96.6 <sup>a)</sup>	0.292 <sup>a)</sup>	973.8 <sup>a)</sup>	2.943 <sup>a)</sup>	12472.2 <sup>a)</sup>	37.692 <sup>a)</sup>	948.9 <sup>a)</sup>	2.868 <sup>a)</sup>	929.1 <sup>a)</sup>	2.808 <sup>a)</sup>	1878.0 <sup>a)</sup>	5.675 <sup>a)</sup>	486.8 <sup>a)</sup>	1.471 <sup>a)</sup>
F02007	318.8		1945.8	6.104	178.5	0.560	1075.6	3.374	10795.2	33.862	1033.4	3.242	1060.1	3.325	2093.5	6.567	863.9	2.710
F02008	296.1		1790.9	6.048	152.7	0.516	905.1	3.057	10599.2	35.796	963.1	3.253	908.6	3.069	1871.7	6.321	670.8	2.265
F02009	343.0		1812.2	5.283	282.3	0.823	1042.5	3.039	11118.8	32.416	957.6	2.792	980.3	2.858	1937.9	5.650	808.6	2.357
F02010	371.3		1926.8	5.189	306.7	0.826	1010.4	2.721	11115.0	29.935	931.1	2.508	930.6	2.506	1861.7	5.014	739.3	1.991
F02011	331.9		1861.9	5.610	194.8	0.587	1072.2	3.230	10876.4	32.770	1338.1	4.032	1257.5	3.789	2595.6	7.820	866.1	2.610
F02012	313.5		1896.0	6.048	190.3	0.607	1011.4	3.226	10599.0	33.809	980.6	3.128	984.4	3.140	1965.0	6.268	746.5	2.381
F02013	356.7		1811.9	5.080	210.5	0.590	1154.1	3.235	10274.7	28.805	1075.7	3.016	1089.4	3.054	2165.1	6.070	619.5	1.737
Number of females	12		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	323.8		1898.8	5.902	188.4	0.573	1016.1	3.140	10551.3	32.660	1015.8	3.145	1000.8	3.097	2016.6	6.241	738.4	2.284
S.D.	25.8		67.2	0.544	62.5	0.153	99.0	0.210	830.1	2.348	127.8	0.370	119.9	0.326	244.7	0.686	111.2	0.316
Significance	NS		NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT		AN	AN	DU	DU	AN	AN	DU	DU	AN	DU	AN	DU	AN	DU	KW	KW

a) Excluded from data analysis (total litter loss).  
 Significantly different from the control group (\*: P<0.05, \*\*: P<0.01).  
 NS: Not significantly different from the control group.  
 DT: Analysis by Dunnett type mean rank test.  
 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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-1-2(continued). Organ weights of female rats at the end of the dosing period

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)
	F02001	46.9	0.167	34.2	0.122	81.1	0.288	508.0	1.807	11.9	0.042	34.3	0.122	36.3	0.129	70.6
F02002	61.3	0.183	50.8	0.151	112.1	0.334	616.4	1.837	13.7	0.041	31.3	0.093	23.3	0.069	54.6	0.163
F02003	45.9	0.153	49.9	0.166	95.8	0.320	549.6	1.834	10.7	0.036	32.5	0.108	36.3	0.121	68.8	0.230
F02004	59.9	0.185	50.8	0.157	110.7	0.341	651.3	2.008	13.2	0.041	33.3	0.103	35.2	0.109	68.5	0.211
F02005	51.0	0.163	48.2	0.154	99.2	0.317	646.2	2.065	18.1	0.058	31.1	0.099	34.1	0.109	65.2	0.208
F02006	54.7 <sup>a)</sup>	0.165 <sup>a)</sup>	54.2 <sup>a)</sup>	0.164 <sup>a)</sup>	108.9 <sup>a)</sup>	0.329 <sup>a)</sup>	3285.9 <sup>a)</sup>	9.930 <sup>a)</sup>	16.9 <sup>a)</sup>	0.051 <sup>a)</sup>	53.6 <sup>a)</sup>	0.162 <sup>a)</sup>	57.1 <sup>a)</sup>	0.173 <sup>a)</sup>	110.7 <sup>a)</sup>	0.335 <sup>a)</sup>
F02007	51.4	0.161	44.8	0.141	96.2	0.302	621.0	1.948	15.5	0.049	32.1	0.101	32.8	0.103	64.9	0.204
F02008	47.0	0.159	54.8	0.185	101.8	0.344	573.2	1.936	10.2	0.034	34.3	0.116	37.6	0.127	71.9	0.243
F02009	62.6	0.183	66.0	0.192	128.6	0.375	756.0	2.204	18.2	0.053	33.6	0.098	42.3	0.123	75.9	0.221
F02010	55.8	0.150	47.6	0.128	103.4	0.278	686.7	1.849	18.5	0.050	39.5	0.106	37.8	0.102	77.3	0.208
F02011	68.4	0.206	50.9	0.153	119.3	0.359	800.8	2.413	20.8	0.063	39.0	0.118	35.1	0.106	74.1	0.223
F02012	57.0	0.182	66.8	0.213	123.8	0.395	598.9	1.910	13.7	0.044	33.7	0.107	32.6	0.104	66.3	0.211
F02013	43.4	0.122	53.5	0.150	96.9	0.272	651.4	1.826	16.9	0.047	40.5	0.114	43.1	0.121	83.6	0.234
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	54.2	0.168	51.5	0.159	105.7	0.327	638.3	1.970	15.1	0.047	34.6	0.107	35.5	0.110	70.1	0.217
S.D.	7.8	0.022	8.7	0.026	13.6	0.038	82.3	0.182	3.4	0.009	3.2	0.009	5.1	0.016	7.4	0.023
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	KW	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	DU	AN	DU

a) Excluded from data analysis (total litter loss).  
 Significantly different from the control group (\*: P<0.05, \*\*: P<0.01).  
 NS: Not significantly different from the control group.  
 DT: Analysis by Dunnett type mean rank test.  
 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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-1-3. Organ weights of female rats at the end of the dosing period

DMIP 250 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)	
F03001	296.4	1835.9	6.194	116.0	0.391	939.8	3.171	9160.4	30.906	894.0	3.016	908.9	3.066	1802.9	6.083	668.2	2.254	
F03002	303.2	1831.3	6.040	125.8	0.415	834.3	2.752	8500.5	28.036	724.6	2.390	716.8	2.364	1441.4	4.754	547.8	1.807	
F03003	281.8	1983.7	7.039	101.3	0.359	866.9	3.076	7952.4	28.220	884.4	3.138	865.3	3.071	1749.7	6.209	597.0	2.119	
F03004	290.6	1821.2	6.267	177.9	0.612	873.3	3.005	8956.6	30.821	834.7	2.872	872.3	3.002	1707.0	5.874	619.5	2.132	
F03005	264.3	1848.4	6.994	91.0	0.344	945.2	3.576	8379.0	31.703	890.9	3.371	889.1	3.364	1780.0	6.735	638.1	2.414	
F03006	305.8	1839.4	6.015	188.2	0.615	900.4	2.944	9705.1	31.737	958.9	3.136	918.8	3.005	1877.7	6.140	581.9	1.903	
F03007	257.5	1926.3	7.481	51.7	0.201	793.3	3.081	8414.8	32.679	911.1	3.538	890.7	3.459	1801.8	6.997	414.0	1.608	
F03008	293.2	1938.1	6.610	108.1	0.369	858.9	2.929	10300.3	35.131	959.2	3.271	935.0	3.189	1894.2	6.460	615.5	2.099	
F03009	323.6	1748.3	5.403	171.4	0.530	1087.7	3.361	12030.4	37.177	1022.7	3.160	1046.6	3.234	2069.3	6.395	816.6	2.523	
F03010	310.3	1845.9	5.949	129.3	0.417	911.9	2.939	10506.1	33.858	1009.5	3.253	992.7	3.199	2002.2	6.452	767.3	2.473	
F03011	Died on the gestation day 23.																	
F03012	332.7	1832.6	5.508	256.2	0.770	1054.9	3.171	9974.8	29.981	1222.6	3.675	1217.7	3.660	2440.3	7.335	671.7	2.019	
F03013	315.5	1852.0	5.870	203.4	0.645	1009.0	3.198	10251.6	32.493	898.4	2.848	863.3	2.736	1761.7	5.584	748.3	2.372	
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
Mean	297.9	1858.6	6.281	143.4	0.472	923.0	3.100	9511.0	31.895	934.3	3.139	926.4	3.112	1860.7	6.252	640.5	2.144	
S.D.	22.4	62.3	0.634	57.0	0.162	89.3	0.218	1172.6	2.653	120.4	0.339	121.1	0.336	240.4	0.670	107.3	0.281	
Significance	*	NS	NS	**	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
Statistical method	DT	AN	AN	DU	DU	AN	AN	DU	DU	AN	DU	AN	DU	AN	DU	KW	KW	

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

NS: Not significantly different from the control group.

DT: Analysis by Dunnett type mean rank test.

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-1-3(continued). Organ weights of female rats at the end of the dosing period

DMIP 250 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)
F03001	64.0	0.216	49.8	0.168	113.8	0.384	658.4	2.221	11.0	0.037	39.8	0.134	40.0	0.135	79.8	0.269
F03002	54.1	0.178	45.4	0.150	99.5	0.328	549.9	1.814	15.2	0.050	27.3	0.090	27.5	0.091	54.8	0.181
F03003	38.3	0.136	43.7	0.155	82.0	0.291	519.3	1.843	18.4	0.065	29.9	0.106	28.8	0.102	58.7	0.208
F03004	53.5	0.184	47.1	0.162	100.6	0.346	658.7	2.267	13.9	0.048	33.7	0.116	37.3	0.128	71.0	0.244
F03005	51.1	0.193	41.7	0.158	92.8	0.351	539.3	2.040	13.3	0.050	30.4	0.115	33.2	0.126	63.6	0.241
F03006	59.5	0.195	52.2	0.171	111.7	0.365	679.6	2.222	16.2	0.053	34.8	0.114	37.1	0.121	71.9	0.235
F03007	40.0	0.155	40.3	0.157	80.3	0.312	590.7	2.294	11.9	0.046	31.0	0.120	33.8	0.131	64.8	0.252
F03008	48.4	0.165	39.5	0.135	87.9	0.300	578.4	1.973	14.6	0.050	34.0	0.116	37.4	0.128	71.4	0.244
F03009	55.2	0.171	50.7	0.157	105.9	0.327	875.0	2.704	13.5	0.042	44.4	0.137	53.0	0.164	97.4	0.301
F03010	57.1	0.184	51.9	0.167	109.0	0.351	675.2	2.176	11.6	0.037	30.5	0.098	34.0	0.110	64.5	0.208
F03011	Died on the gestation day 23.															
F03012	47.9	0.144	56.2	0.169	104.1	0.313	816.6	2.454	12.7	0.038	37.3	0.112	36.2	0.109	73.5	0.221
F03013	62.0	0.197	60.8	0.193	122.8	0.389	599.4	1.900	22.8	0.072	41.1	0.130	41.5	0.132	82.6	0.262
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	52.6	0.177	48.3	0.162	100.9	0.338	645.0	2.159	14.6	0.049	34.5	0.116	36.7	0.123	71.2	0.239
S.D.	8.0	0.023	6.5	0.014	13.1	0.032	108.8	0.262	3.3	0.011	5.2	0.014	6.6	0.019	11.5	0.032
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	KW	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	DU	AN	DU

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

NS: Not significantly different from the control group.

DT: Analysis by Dunnett type mean rank test.

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-1-4. Organ weights of female rats at the end of the dosing period

DMIP 1000 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)
F04001	292.6	1875.8	6.411	230.8	0.789	998.0	3.411	9392.1	32.099	961.8	3.287	898.6	3.071	1860.4	6.358	599.4	2.049
F04002	304.8	1925.6	6.318	198.5	0.651	991.8	3.254	9205.6	30.202	1056.4	3.466	1028.3	3.374	2084.7	6.840	800.2	2.625
F04003	281.8	1817.9	6.451	180.6	0.641	934.3	3.315	9967.7	35.372	1008.3	3.578	979.4	3.476	1987.7	7.054	730.7	2.593
F04004	303.9	1933.6	6.363	153.9	0.506	996.0	3.277	9977.4	32.831	1107.2	3.643	1076.4	3.542	2183.6	7.185	789.1	2.597
F04005	302.9	1935.4	6.390	241.3	0.797	1062.3	3.507	10477.3	34.590	974.3	3.217	956.3	3.157	1930.6	6.374	703.3	2.322
F04006	297.0	1900.0	6.397	146.7	0.494	1007.5	3.392	9511.6	32.026	1081.6	3.642	1076.3	3.624	2157.9	7.266	553.2	1.863
F04007	278.6 <sup>a)</sup>	1858.0 <sup>a)</sup>	6.669 <sup>a)</sup>	56.0 <sup>a)</sup>	0.201 <sup>a)</sup>	922.2 <sup>a)</sup>	3.310 <sup>a)</sup>	10701.9 <sup>a)</sup>	38.413 <sup>a)</sup>	1081.7 <sup>a)</sup>	3.883 <sup>a)</sup>	1090.9 <sup>a)</sup>	3.916 <sup>a)</sup>	2172.6 <sup>a)</sup>	7.798 <sup>a)</sup>	660.9 <sup>a)</sup>	2.372 <sup>a)</sup>
F04008	315.6	1930.7	6.118	237.9	0.754	970.5	3.075	9773.9	30.969	1148.3	3.638	1043.8	3.307	2192.1	6.946	590.5	1.871
F04009	304.2	2022.5	6.649	170.2	0.560	941.9	3.096	10120.8	33.270	1033.3	3.397	1010.2	3.321	2043.5	6.718	1020.4	3.354
F04010	305.0	1729.5	5.670	150.6	0.494	923.6	3.028	9743.4	31.946	996.3	3.267	1034.4	3.391	2030.7	6.658	613.4	2.011
F04011	307.9	1848.6	6.004	269.0	0.874	897.5	2.915	9437.3	30.651	969.2	3.148	926.3	3.008	1895.5	6.156	689.0	2.238
F04012	298.2	1966.2	6.594	97.4	0.327	990.4	3.321	10357.6	34.734	955.6	3.205	923.9	3.098	1879.5	6.303	932.9	3.128
F04013	309.5	1898.0	6.132	131.5	0.425	1023.9	3.308	10834.8	35.007	1144.5	3.698	1155.1	3.732	2299.6	7.430	918.1	2.966
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	302.0	1898.7	6.291	184.0	0.609	978.1	3.242	9900.0	32.808	1036.4	3.432	1009.1	3.342	2045.5	6.774	745.0	2.468
S.D.	8.7	75.3	0.271	51.9	0.169	46.6	0.176	488.2	1.789	70.4	0.203	75.4	0.228	141.5	0.416	150.9	0.496
Significance	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	**	NS	**	NS	**	NS	NS
Statistical method	DT	AN	AN	DU	DU	AN	AN	DU	DU	AN	DU	AN	DU	AN	DU	KW	KW

a) Excluded from data analysis (total litter loss).  
 Significantly different from the control group (\*: P<0.05, \*\*: P<0.01).  
 NS: Not significantly different from the control group.  
 DT: Analysis by Dunnett type mean rank test.  
 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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-1-4(continued). Organ weights of female rats at the end of the dosing period

DMIP 1000 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)
F04001	37.6	0.129	55.3	0.189	92.9	0.317	445.9	1.524	13.2	0.045	32.6	0.111	33.7	0.115	66.3	0.227
F04002	50.4	0.165	50.3	0.165	100.7	0.330	759.6	2.492	17.8	0.058	40.5	0.133	46.1	0.151	86.6	0.284
F04003	43.0	0.153	38.9	0.138	81.9	0.291	602.9	2.139	13.1	0.046	35.0	0.124	40.2	0.143	75.2	0.267
F04004	46.2	0.152	49.6	0.163	95.8	0.315	575.0	1.892	10.0	0.033	41.9	0.138	44.0	0.145	85.9	0.283
F04005	49.8	0.164	51.5	0.170	101.3	0.334	790.5	2.610	22.4	0.074	41.0	0.135	40.2	0.133	81.2	0.268
F04006	59.7	0.201	43.0	0.145	102.7	0.346	647.3	2.179	17.2	0.058	38.0	0.128	41.1	0.138	79.1	0.266
F04007	51.1 <sup>a)</sup>	0.183 <sup>a)</sup>	70.0 <sup>a)</sup>	0.251 <sup>a)</sup>	121.1 <sup>a)</sup>	0.435 <sup>a)</sup>	1697.1 <sup>a)</sup>	6.092 <sup>a)</sup>	15.0 <sup>a)</sup>	0.054 <sup>a)</sup>	40.3 <sup>a)</sup>	0.145 <sup>a)</sup>	47.3 <sup>a)</sup>	0.170 <sup>a)</sup>	87.6 <sup>a)</sup>	0.314 <sup>a)</sup>
F04008	49.7	0.157	32.0	0.101	81.7	0.259	589.3	1.867	12.4	0.039	30.4	0.096	33.3	0.106	63.7	0.202
F04009	46.9	0.154	50.6	0.166	97.5	0.321	672.7	2.211	10.9	0.036	41.2	0.135	43.4	0.143	84.6	0.278
F04010	59.0	0.193	41.5	0.136	100.5	0.330	644.3	2.112	11.7	0.038	32.2	0.106	33.4	0.110	65.6	0.215
F04011	52.8	0.171	35.4	0.115	88.2	0.286	755.6	2.454	15.9	0.052	30.2	0.098	30.5	0.099	60.7	0.197
F04012	41.6	0.140	48.8	0.164	90.4	0.303	800.2	2.683	13.1	0.044	41.4	0.139	41.4	0.139	82.8	0.278
F04013	71.2	0.230	54.5	0.176	125.7	0.406	632.8	2.045	16.4	0.053	41.6	0.134	40.1	0.130	81.7	0.264
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	50.7	0.167	46.0	0.152	96.6	0.320	659.7	2.184	14.5	0.048	37.2	0.123	39.0	0.129	76.1	0.252
S.D.	9.2	0.028	7.6	0.026	11.7	0.036	103.7	0.337	3.5	0.012	4.7	0.016	5.0	0.017	9.5	0.033
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	*	NS	**
Statistical method	KW	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	DU	AN	DU

a) Excluded from data analysis (total litter loss).  
 Significantly different from the control group (\*: P<0.05, \*\*: P<0.01).  
 NS: Not significantly different from the control group.  
 DT: Analysis by Dunnett type mean rank test.  
 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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Corn oil (control)																	
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)
F05001	281.7	1930.8	6.854	291.3	1.034	800.2	2.841	6540.8	23.219	825.7	2.931	784.5	2.785	1610.2	5.716	547.9	1.945
F05002	268.4	1797.7	6.698	262.5	0.978	799.5	2.979	7215.7	26.884	935.1	3.484	874.3	3.257	1809.4	6.741	539.3	2.009
F05003	303.7	2015.3	6.636	238.7	0.786	819.1	2.697	7015.9	23.101	769.4	2.533	802.7	2.643	1572.1	5.176	492.0	1.620
F05004	283.9	1946.5	6.856	258.7	0.911	829.2	2.921	6842.1	24.100	914.4	3.221	919.3	3.238	1833.7	6.459	476.1	1.677
F05005	274.8	1788.1	6.507	323.7	1.178	794.8	2.892	6923.5	25.195	886.6	3.226	898.0	3.268	1784.6	6.494	558.8	2.033
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	282.5	1895.7	6.710	275.0	0.977	808.6	2.866	6907.6	24.500	866.2	3.079	855.8	3.038	1722.0	6.117	522.8	1.857
S.D.	13.3	99.1	0.149	33.1	0.145	14.8	0.107	247.9	1.575	68.0	0.363	59.3	0.300	121.5	0.651	36.5	0.194

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-2-1(continued). Organ weights of female rats at the end of the dosing period, satellite group

Corn oil (control)																
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)
F05001	34.6	0.123	36.4	0.129	71.0	0.252	431.7	1.532	14.1	0.050	27.1	0.096	31.2	0.111	58.3	0.207
F05002	43.1	0.161	46.4	0.173	89.5	0.333	568.3	2.117	16.6	0.062	30.2	0.113	31.4	0.117	61.6	0.230
F05003	45.1	0.149	47.2	0.155	92.3	0.304	423.5	1.394	14.1	0.046	30.9	0.102	31.3	0.103	62.2	0.205
F05004	44.4	0.156	39.8	0.140	84.2	0.297	444.5	1.566	19.2	0.068	33.7	0.119	31.9	0.112	65.6	0.231
F05005	46.6	0.170	36.6	0.133	83.2	0.303	655.9	2.387	18.8	0.068	32.6	0.119	36.4	0.132	69.0	0.251
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	42.8	0.152	41.3	0.146	84.0	0.298	504.8	1.799	16.6	0.059	30.9	0.110	32.4	0.115	63.3	0.225
S.D.	4.7	0.018	5.2	0.018	8.2	0.029	103.0	0.429	2.5	0.010	2.5	0.010	2.2	0.011	4.1	0.019

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

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

DMIP 1000 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)
F06001	268.2	1860.1	6.935	273.7	1.021	910.9	3.396	7826.7	29.182	919.3	3.428	862.8	3.217	1782.1	6.645	508.7	1.897
F06002	284.7	2073.5	7.283	307.5	1.080	897.4	3.152	7858.4	27.602	1002.0	3.519	980.2	3.443	1982.2	6.962	627.1	2.203
F06003	291.7	1851.4	6.347	290.1	0.995	1036.8	3.554	9185.8	31.491	1039.6	3.564	984.0	3.373	2023.6	6.937	665.0	2.280
F06004	295.0	1914.7	6.491	341.5	1.158	914.3	3.099	8490.8	28.782	967.2	3.279	995.6	3.375	1962.8	6.654	544.2	1.845
F06005	277.5	1947.6	7.018	245.5	0.885	909.2	3.276	7804.0	28.123	975.9	3.517	967.6	3.487	1943.5	7.004	664.1	2.393
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	283.4	1929.5	6.815	291.7	1.028	933.7	3.295	8233.1	29.036	980.8	3.461	958.0	3.379	1938.8	6.840	601.8	2.124
S.D.	10.9	89.7	0.387	36.0	0.101	58.0	0.185	604.9	1.500	44.4	0.113	54.2	0.103	92.5	0.176	71.6	0.241
Significance	NS	NS	NS	NS	NS	**	**	**	**	*	*	*	*	*	*	NS	NS
Statistical method	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	AW	TT	TT	TT	TT	AW	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Appendix 30-2-2(continued). Organ weights of female rats at the end of the dosing period, satellite group

DMIP 1000 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)
F06001	45.2	0.169	40.7	0.152	85.9	0.320	487.1	1.816	13.8	0.051	36.2	0.135	36.5	0.136	72.7	0.271
F06002	47.6	0.167	39.5	0.139	87.1	0.306	1276.6	4.484	13.8	0.048	27.8	0.098	29.8	0.105	57.6	0.202
F06003	45.3	0.155	43.3	0.148	88.6	0.304	511.4	1.753	14.1	0.048	36.8	0.126	39.6	0.136	76.4	0.262
F06004	37.6	0.127	50.0	0.169	87.6	0.297	1007.0	3.414	12.0	0.041	33.0	0.112	36.4	0.123	69.4	0.235
F06005	46.6	0.168	44.9	0.162	91.5	0.330	475.8	1.715	12.7	0.046	29.6	0.107	31.7	0.114	61.3	0.221
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	44.5	0.157	43.7	0.154	88.1	0.311	751.6	2.636	13.3	0.047	32.7	0.116	34.8	0.123	67.5	0.238
S.D.	4.0	0.018	4.1	0.012	2.1	0.013	369.0	1.257	0.9	0.004	4.0	0.015	4.0	0.014	7.8	0.029
Significance	NS	NS	NS	NS	NS	NS	NS	NS	*	*	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	AW	TT	AW	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-3-1. Organ weights of female rats at the end of the recovery period

Corn oil (control)																	
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)
F05006	320.3	1882.6	5.878	337.0	1.052	932.9	2.913	7962.7	24.860	969.2	3.026	946.3	2.954	1915.5	5.980	485.6	1.516
F05007	302.0	1964.5	6.505	328.8	1.089	935.9	3.099	7975.0	26.407	986.0	3.265	1025.9	3.397	2011.9	6.662	514.4	1.703
F05008	302.9	1741.0	5.748	261.2	0.862	952.3	3.144	7473.4	24.673	932.3	3.078	896.5	2.960	1828.8	6.038	850.3	2.807
F05009	305.4	1914.4	6.269	162.7	0.533	931.2	3.049	6673.7	21.852	896.2	2.935	931.8	3.051	1828.0	5.986	626.9	2.053
F05010	277.4	1700.0	6.128	260.9	0.941	874.0	3.151	6656.0	23.994	922.1	3.324	886.9	3.197	1809.0	6.521	550.3	1.984
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	301.6	1840.5	6.106	270.1	0.895	925.3	3.071	7348.2	24.357	941.2	3.126	937.5	3.112	1878.6	6.237	605.5	2.013
S.D.	15.4	114.3	0.303	70.0	0.222	29.9	0.097	655.8	1.655	36.3	0.164	55.1	0.187	85.2	0.328	146.7	0.494

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-3-1(continued). Organ weights of female rats at the end of the recovery period

Corn oil (control)																
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)
F05006	74.1	0.231	56.1	0.175	130.2	0.406	293.3	0.916	12.7	0.040	37.3	0.116	39.8	0.124	77.1	0.241
F05007	59.0	0.195	48.5	0.161	107.5	0.356	395.4	1.309	14.0	0.046	34.2	0.113	37.5	0.124	71.7	0.237
F05008	59.1	0.195	49.4	0.163	108.5	0.358	524.9	1.733	13.9	0.046	32.9	0.109	39.0	0.129	71.9	0.237
F05009	52.8	0.173	44.0	0.144	96.8	0.317	453.8	1.486	12.7	0.042	27.9	0.091	28.2	0.092	56.1	0.184
F05010	50.7	0.183	48.1	0.173	98.8	0.356	532.3	1.919	12.1	0.044	31.6	0.114	34.2	0.123	65.8	0.237
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	59.1	0.195	49.2	0.163	108.4	0.359	439.9	1.473	13.1	0.044	32.8	0.109	35.7	0.118	68.5	0.227
S.D.	9.2	0.022	4.4	0.012	13.3	0.032	99.3	0.389	0.8	0.003	3.5	0.010	4.7	0.015	8.0	0.024

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 30-3-2. Organ weights of female rats at the end of the recovery period

DMIP 1000 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)
F06006	294.0	1868.5	6.355	247.5	0.842	941.5	3.202	7448.3	25.334	900.4	3.063	885.4	3.012	1785.8	6.074	504.2	1.715
F06007	324.3	1982.5	6.113	249.6	0.770	1030.9	3.179	8552.1	26.371	995.2	3.069	1019.1	3.142	2014.3	6.211	498.6	1.537
F06008	317.8	1859.9	5.852	327.0	1.029	996.9	3.137	8157.5	25.669	913.5	2.874	878.8	2.765	1792.3	5.640	576.0	1.812
F06009	278.0	1920.0	6.906	194.1	0.698	920.6	3.312	7174.7	25.808	951.6	3.423	894.0	3.216	1845.6	6.639	516.8	1.859
F06010	308.6	1978.9	6.413	382.4	1.239	929.3	3.011	8024.5	26.003	945.0	3.062	903.5	2.928	1848.5	5.990	476.5	1.544
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	304.5	1922.0	6.328	280.1	0.916	963.8	3.168	7871.4	25.837	941.1	3.098	916.2	3.013	1857.3	6.111	514.4	1.693
S.D.	18.7	58.4	0.392	74.3	0.219	47.8	0.109	555.2	0.386	37.0	0.199	58.3	0.178	92.5	0.363	37.4	0.149
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 30-3-2(continued). Organ weights of female rats at the end of the recovery period

DMIP 1000 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)
F06006	45.4	0.154	40.1	0.136	85.5	0.291	429.7	1.462	15.5	0.053	41.1	0.140	42.3	0.144	83.4	0.284
F06007	51.0	0.157	58.9	0.182	109.9	0.339	571.9	1.763	17.8	0.055	27.7	0.085	24.5	0.076	52.2	0.161
F06008	45.1	0.142	41.9	0.132	87.0	0.274	1068.3	3.362	15.3	0.048	30.4	0.096	32.4	0.102	62.8	0.198
F06009	66.9	0.241	53.6	0.193	120.5	0.433	451.9	1.626	16.2	0.058	39.1	0.141	36.8	0.132	75.9	0.273
F06010	41.2	0.134	33.1	0.107	74.3	0.241	433.3	1.404	23.1	0.075	32.8	0.106	31.8	0.103	64.6	0.209
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	49.9	0.166	45.5	0.150	95.4	0.316	591.0	1.923	17.6	0.058	34.2	0.114	33.6	0.111	67.8	0.225
S.D.	10.1	0.043	10.5	0.036	19.1	0.075	273.1	0.816	3.2	0.010	5.7	0.026	6.6	0.027	12.1	0.052
Significance	NS	NS	NS	NS	NS	NS	NS	NS	*	*	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	AW	AW	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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 31-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group Animal No.	Corn oil (control)					DMIP 1000 mg/kg				
		M01-					M04-				
		009	010	011	012	013	009	010	011	012	013
All organs		-	-	-	-	-	-	-	-	-	-

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



Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 32-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Group		Corn oil (control)					DMIP 1000 mg/kg				
		F05-					F06-				
Findings	Animal No.	001	002	003	004	005	001	002	003	004	005
All organs		-	-	-	-	-	-	-	-	-	-

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 32-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group Animal No.	Corn oil (control)					DMIP 1000 mg/kg				
		F05-					F06-				
		006	007	008	009	010	006	007	008	009	010
External appearance											
Defect, in the end of the tail		-	-	P	-	-	-	-	-	-	-

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 33. Histopathological findings of male rats at the end of the dosing period

Findings	Group Animal No.	Corn oil (control)											DMIP 62.5 mg/kg		DMIP 250 mg/kg			DMIP 1000 mg/kg														
		M01-											M02-		M03-			M04-														
		001	002	003	004	005	006	007	008	009	010	011	012	013	005	006	005	008	010	001	002	003	004	005	006	007	008	009	010	011	012	013
Brain		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thyroid gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ectopic thymus		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-
Parathyroid gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thymus		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Heart		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Degeneration/fibrosis, myocardial, focal		-	-	±	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±	-	-	±	-	-	-	-	-	-	-	-	-
Trachea		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lung		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Accumulation, foam cell, alveolus		-	-	-	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mineralization, focal, arterial wall		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±	-	±	-	-	-	-	-	-	-	-	-
Bronchus		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatty change, hepatocyte, periportal		±	+	+	±	±	-	-	-	-	-	-	-	-	-	-	-	-	-	±	+	±	±	±	-	-	-	-	-	-	-	-
Microgranuloma		-	-	±	±	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±	±	±	-	-	-	-	-	-	-	-
Pancreas		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stomach		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duodenum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Jejunum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ileum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Defect, muscular layer, focal, in diverticul		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mineralization, with foreign body giant cell, serosa, , in diverticulum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cecum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 33(continued). Histopathological findings of male rats at the end of the dosing period

		Study No. : R11005																																	
Group		Com oil (control)											DMIP 62.5 mg/kg		DMIP 250 mg/kg			DMIP 1000 mg/kg																	
Findings	Animal No.	M01-											M02-		M03-			M04-																	
		001	002	003	004	005	006	007	008	009	010	011	012	013	005	006	005	008	010	001	002	003	004	005	006	007	008	009	010	011	012	013			
Colon		-	-	-	-	-													-	-	-	-	-												
Rectum		-	-	-	-	-													-	-	-	-	-												
Lymph node, mesenteric		-	-	-	-	-													-	-	-	-	-												
Spleen																																			
Deposit, pigment, brown		+	±	±	±	±													±	±	±	±	±												
Hematopoiesis, extramedullary		+	+	+	+	+													+	+	+	+	+												
Kidney																																			
Basophilic tubule, cortex		±	±	±	-	-									±		-	-	+	±	±	±	-	±											
Cyst, cortex, subserosa		-	-	-	-	-									P		-	-	-	-	-	-	-	-											
Urinary bladder		-	-	-	-	-													-	-	-	-	-												
Adrenal gland		-	-	-	-	-													-	-	-	-	-												
Testis																																			
Atrophy, seminiferous tubule, focal		-	-	-	-	±											-		-	-	-	-	-												
Decrease, germ cell layer,																																			
seminiferous tubule, unilateral		-	-	-	-	-											+		-	-	-	-	-												
Dilatation, lumen,																																			
seminiferous tubule, unilateral		-	-	-	-	-											2+		-	-	-	-	-												
Edema, interstitial, unilateral		-	-	-	-	-											+		-	-	-	-	-												
Epididymis																																			
Cellular infiltration, lymphocyte, interstitial		-	-	-	-	-									-	-			-	±	-	-	-												
Granuloma, spermatic		-	-	-	-	-									±	±			-	-	-	-	-												
Prostate																																			
Cellular infiltration, lymphocyte, interstitial		-	-	±	-	-													-	-	-	-	-												
Seminal vesicle		-	-	-	-	-													-	-	-	-	-												
Coagulating gland		-	-	-	-	-													-	-	-	-	-												
Eyeball		-	-	-	-	-													-	-	-	-	-												
Harderian gland																																			
Cellular infiltration, lymphocyte, interstitial		-	±	-	-	-													-	-	-	-	-												
Sciatic nerve		-	-	-	-	-													-	-	-	-	-												
Skeletal muscle		-	-	-	-	-													-	-	-	-	-												
Femur		-	-	-	-	-													-	-	-	-	-												
Marrow, femur		-	-	-	-	-													-	-	-	-	-												

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
Appendix 34-1. Histopathological findings of female rats at the end of the dosing period

Findings	Group Animal No. Fate	Corn oil (control)										DMIP 62.5 mg/kg		DMIP 250 mg/kg		DMIP 1000 mg/kg													
		F01-										F02-		F03-		F04-													
		001	002	003	004	005	006	007	008	009	010	011	012	013	006	011	009	011	001	002	003	004	005	006	007	008	009	010	011
Brain		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular Atrophy, follicle		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thyroid gland Ectopic thymus		-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parathyroid gland		-	-	-	-	-	-	-	-	M	-	-	-	-	-	-	-	-	-	-	-	-	-	M	-	-	-	-	-
Thymus Atrophy		-	-	-	-	-	-	-	-	-	-	-	-	2+	2+	-	-	-	-	-	-	-	2+	-	-	-	-	-	-
Heart Degeneration/fibrosis, myocardial, focal		-	-	-	-	-	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Trachea		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lung Accumulation, foam cell, alveolus Mineralization, focal, arterial wall		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±
Bronchus		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver Fatty change, hepatocyte, periportal Microgranuloma Vacuolation, hepatocyte, midzonal		-	-	-	-	-	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±
Pancreas Cellular infiltration, eosinophil, around artery		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±
Stomach Hyperplasia, squamous cell, mucosa, forestomach Ulcer, mucosa, forestomach		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Duodenum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Jejunum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ileum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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 lactation; TL, Total litter loss during lactation; DD, Died during delivery.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 34-1(continued). Histopathological findings of female rats at the end of the dosing period

Findings	Group Animal No. Fate	Corn oil (control) F01-										DMIP 62.5 mg/kg F02-		DMIP 250 mg/kg F03-		DMIP 1000 mg/kg F04-															
		001	002	003	004	005	006	007	008	009	010	011	012	013	006	011	009	011	001	002	003	004	005	006	007	008	009	010	011	012	013
		TL													DD		TL														
Cecum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Colon		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Rectum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Lymph node, mesenteric Atrophy, follicle		-	-	-	-	-	-	-	-	-	-	-	-	-	-	2+	-	-	-	-	-	-	-	-	-	-	-	-	-		
Spleen		-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-		
Decrease, red pulp		-	-	-	-	-	-	-	-	-	-	-	-	-	-	2+	-	-	-	-	-	-	-	-	-	-	-	-	-		
Decrease, white pulp		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Deposit, pigment, brown		+	+	+	±	+	±	+	±	+	±	+	±	-	-	-	-	+	±	+	+	+	+	+	+	+	+	+	+		
Hematopoiesis, extramedullary		+	2+	+	+	+	+	3+	+	+	+	+	+	-	-	-	-	+	+	2+	+	+	+	+	+	+	+	+	2+		
Kidney		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Basophilic tubule, cortex		-	-	-	-	-	-	-	-	-	-	-	-	-	-	±	+	-	-	-	-	-	-	-	-	-	-	-	-	-	
Cyst, cortex, subserosa		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Degeneration/necrosis, proximal tubular epithelium, cortex		-	-	-	-	-	-	-	-	-	-	-	-	-	-	2+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Dilatation, pelvis, unilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Mineralization, medulla		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±	-	-	-	-	-	-	-	-	-	-	-	-	
Urinary bladder		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Adrenal gland Hypertrophy, zona fasciculata, cortex		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	
Ovary		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Uterus Hemorrhage, endometrium		-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Vagina		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Eyeball		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Harderian gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Sciatic nerve		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Skeletal muscle		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Femur		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Marrow, femur		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

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 lactation; TL, Total litter loss during lactation; DD, Died during delivery.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester 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.	Corn oil (control) F05-					DMIP 1000 mg/kg F06-				
		001	002	003	004	005	001	002	003	004	005
Brain		-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-
Thyroid gland											
Cellular infiltration, lymphocyte, interstitial		-	-	-	-	-	±	-	-	-	-
Parathyroid gland		-	-	-	-	-	-	-	-	-	-
Thymus		-	-	-	-	-	-	-	-	-	-
Heart		-	-	-	-	-	-	-	-	-	-
Trachea		-	-	-	-	-	-	-	-	-	-
Lung											
Mineralization, focal, arterial wall		-	-	-	-	±	-	-	±	-	-
Bronchus		-	-	-	-	-	-	-	-	-	-
Liver											
Fatty change, hepatocyte, periportal		-	-	-	±	±	±	-	-	-	-
Microgranuloma		±	±	-	-	±	-	±	-	-	-
Pancreas											
Atrophy, acinar cell, focal, with ductal proliferation		-	-	-	-	±	-	-	-	-	-
Stomach		-	-	-	-	-	-	-	-	-	-
Duodenum		-	-	-	-	-	-	-	-	-	-
Jejunum		-	-	-	-	-	-	-	-	-	-

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 1,3-Benzenedicarboxylic acid, dimethyl ester 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.	Corn oil (control)					DMIP 1000 mg/kg				
		F05-					F06-				
		001	002	003	004	005	001	002	003	004	005
Ileum		-	-	-	-	-	-	-	-	-	-
Cecum		-	-	-	-	-	-	-	-	-	-
Colon		-	-	-	-	-	-	-	-	-	-
Rectum		-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric		-	-	-	-	-	-	-	-	-	-
Spleen											
Deposit, pigment, brown		2+	+	+	2+	+	±	2+	2+	+	
Hematopoiesis, extramedullary		+	+	+	+	+	+	+	+	+	
Kidney											
Basophilic tubule, cortex		-	-	±	±	±	-	-	-	-	
Urinary bladder		-	-	-	-	-	-	-	-	-	
Adrenal gland		-	-	-	-	-	-	-	-	-	
Ovary		-	-	-	-	-	-	-	-	-	
Uterus		-	-	-	-	-	-	-	-	-	
Vagina		-	-	-	-	-	-	-	-	-	
Eyeball		-	-	-	-	-	-	-	-	-	
Harderian gland		-	-	-	-	-	-	-	-	-	
Sciatic nerve		-	-	-	-	-	-	-	-	-	
Skeletal muscle		-	-	-	-	-	-	-	-	-	
Femur		-	-	-	-	-	-	-	-	-	
Marrow, femur		-	-	-	-	-	-	-	-	-	

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 35-1. Results of observations about estrous cycle

Corn oil (control)

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 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 D	4-day	4.0	D P PL	1	
F01002	D D D E D D P E D D P E D	4-day	4.0	D P E D D P E D D D E D D P E	4-day	4.0	D D D PL	1	
F01003	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 P	4-day	4.0	PL	1	
F01004	D E D D D E D D D E D D D	4-day	4.0	E D D D E D D D E D D P E D D	4-day	4.0	D PL	1	
F01005	D D D 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 D E	4-day	4.0	D D D PL	1	
F01006	D E 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 D	4-day	4.0	D P PL	1	
F01007	D 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 D	4-day	4.0	P PL	1	
F01008	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 D E D	4-day	4.0	D P PL	1	
F01009	D D P E D D P E D D P P E	4-5-day	4.5	D D D E D D D P E D D D E D D	4-5day	4.5	D P P PL	1	
F01010	D D D P E D D P E E D D D	5-day	5.0	P E D D D E E D D P E E D D D	5-day	5.0	E PL	1	
F01011	D E D D D P E D D P E E D	5-day	5.0	D P P E D D P E E D D D E E D	5-day	5.0	D D P PL	1	
F01012	D E D D D P E D D D E E D	5-day	5.0	D D P E D D P E E D D D P E D	5-day	5.0	D P PL	1	
F01013	E D D P E D D P E D D P E	4-day	4.0	D D D E D D P E D D P E D D P	4-day	4.0	PL	1	
Mean			4.3			4.3		1.0	
S.D.			0.4			0.4		0.0	
(N)			(13)			(13)		(13)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 35-2. Results of observations about estrous cycle

DMIP (62.5 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)			
F02001	E 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 P E D D	4-day	4.0	P PL	1	
F02002	P E D D D E E D D D E E D	5-day	5.0	D D E E D D D E E D D P E E D	5-day	5.0	D P PL	1	
F02003	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 P	4-day	4.0	PL	1	
F02004	D D E 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 E	4-day	4.0	D D D PL	1	
F02005	D D D E D D P E D D P E D	4-day	4.0	D P E D D D E D D P E D D P E	4-day	4.0	D D D PL	1	
F02006	E 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 P E D D	4-day	4.0	P PL	1	
F02007	D E E D D P E D D D E D D	4-day	4.0	P E D D P E D D D E D D D E D	4-day	4.0	D P PL	1	
F02008	E D D P E D D D E D D D E	4-day	4.0	D D P E D D D E D D D E D D P	4-day	4.0	PL	1	
F02009	P E D D D E D D D E D D P	4-day	4.0	E D D P E D D P E D D D E D D	4-day	4.0	P PL	1	
F02010	E D D P E D D D E D D P E	4-day	4.0	D D P E D D D E D D D E D D D	4-day	4.0	PL	1	
F02011	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 P	4-day	4.0	PL	1	
F02012	P E D D D P E D D D E E D	5-day	5.0	D D P E D D D E D D D D E D D	4-5-day	4.5	D PL	1	
F02013	E 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 D	4-day	4.0	P PL	1	
Mean			4.2			4.1		1.0	
S.D.			0.4			0.3		0.0	
(N)			(13)			(13)		(13)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 35-3. Results of observations about estrous cycle

DMIP (250 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)			
F03001	P E D D P E D D P E D D D	4-day	4.0	E D D P E D D P E D D D E D D	4-day	4.0	P PL	1	
F03002	D P E D D P E D D D E D D	4-day	4.0	D E D D P E D D D E D D D E D	4-day	4.0	D P PL	1	
F03003	D E D D D P E D D P E D D	4-5-day	4.5	P E D D P E D D P E D D D E D	4-day	4.0	D P PL	1	
F03004	E 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 P E D D	4-day	4.0	P PL	1	
F03005	E D D P E D D P E D D P E	4-day	4.0	D D P E D D D E D D P E D D P	4-day	4.0	PL	1	
F03006	D E D D P E D D D E D D P	4-day	4.0	E D D P E D D D E D D P E D D	4-day	4.0	P PL	1	
F03007	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 P E D	4-day	4.0	D P PL	1	
F03008	E D D D 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 P	4-day	4.0	PL	1	
F03009	D D P E D D D E D D P E D	4-day	4.0	D P E D D D E D D P E D D P E	4-day	4.0	D D D PL	1	
F03010	D D P E D D P E D D P E D	4-day	4.0	D P E E D D D P E D D P E E D	5-day	5.0	D P PL	1	
F03011	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 D	4-day	4.0	D P PL	1	
F03012	D E D D P E D D P E D D D	4-day	4.0	E D D P E D D D E D D P E D D	4-day	4.0	P PL	1	
F03013	D D D E E D D D P E D D P	5-day	5.0	P E D D D D E D D D P E D D D	5-day	5.0	PL	1	
Mean			4.1			4.2		1.0	
S.D.			0.3			0.4		0.0	
(N)			(13)			(13)		(13)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 35-4. Results of observations about estrous cycle

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)			
F04001	E D D D P E D D D P E D D	5-day	5.0	D P E D D D E E D D D P E D D	5-day	5.0	D E PL	1	
F04002	D D P E D D P E D D P E D	4-day	4.0	D P E D D D E D D P E D D P E	4-day	4.0	D D D PL	1	
F04003	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 P	4-day	4.0	PL	1	
F04004	D D P 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 D E	4-day	4.0	D D D PL	1	
F04005	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 D	4-day	4.0	D P PL	1	
F04006	P E D D D E E D D D E E D	5-day	5.0	D P E E D D D E D D D E D D D	4-day	4.0	PL	1	
F04007	E D D D 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 P	4-day	4.0	PL	1	
F04008	D D E D D D E D D P E D D	4-day	4.0	D E D D P E D D D E D D P E D	4-day	4.0	D P PL	1	
F04009	D D P E D D P E D D P E D	4-day	4.0	D P E D D D E D D P E D D P E	4-day	4.0	D D D PL	1	
F04010	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 D	4-day	4.0	D P PL	1	
F04011	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 E	4-day	4.0	D D D PL	1	
F04012	D P E D D P E D D D E D D	4-day	4.0	P E D D P E D D D E D D D E D	4-day	4.0	D D PL	1	
F04013	E E D D P E D D D E D D D	4-day	4.0	E D D P E D D P E D D D E D D	4-day	4.0	P PL	1	
Mean			4.2			4.1		1.0	
S.D.			0.4			0.3		0.0	
(N)			(13)			(13)		(13)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 36-1. Results of observations about reproductive performance

Corn oil (control)

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M01001	F01001	+	+	3
M01002	F01002	+	+	4
M01003	F01003	+	+	1
M01004	F01004	+	+	2
M01005	F01005	+	+	4
M01006	F01006	+	+	3
M01007	F01007	+	+	2
M01008	F01008	+	+	3
M01009	F01009	+	+	4
M01010	F01010	+	+	2
M01011	F01011	+	+	4
M01012	F01012	+	+	3
M01013	F01013	+	+	1
Total		+: 13, -: 0	+: 13, -: 0	
Mean				2.8
S.D.				1.1
(N)				(13)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 36-2. Results of observations about reproductive performance

DMIP (62.5 mg/kg)

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M02001	F02001	+	+	2
M02002	F02002	+	+	3
M02003	F02003	+	+	1
M02004	F02004	+	+	4
M02005	F02005	+	+	4
M02006	F02006	+	+	2
M02007	F02007	+	+	3
M02008	F02008	+	+	1
M02009	F02009	+	+	2
M02010	F02010	+	+	1
M02011	F02011	+	+	1
M02012	F02012	+	+	2
M02013	F02013	+	+	2
Total		+: 13, -: 0	+: 13, -: 0	
Mean				2.2
S.D.				1.1
(N)				(13)

+, confirmed  
 -, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 36-3. Results of observations about reproductive performance

DMIP (250 mg/kg)					
Male no.	Female no.	Copulation	Conception	Pairing days until copulation	
M03001	F03001	+	+	2	
M03002	F03002	+	+	3	
M03003	F03003	+	+	3	
M03004	F03004	+	+	2	
M03005	F03005	+	+	1	
M03006	F03006	+	+	2	
M03007	F03007	+	+	3	
M03008	F03008	+	+	1	
M03009	F03009	+	+	4	
M03010	F03010	+	+	3	
M03011	F03011	+	+	3	
M03012	F03012	+	+	2	
M03013	F03013	+	+	1	
Total		+: 13, -: 0	+: 13, -: 0		
Mean				2.3	
S.D.				0.9	
(N)				(13)	

+, confirmed  
 -, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats  
 Appendix 36-4. Results of observations about reproductive performance

DMIP (1000 mg/kg)					
Male no.	Female no.	Copulation	Conception	Pairing days until copulation	
M04001	F04001	+	+	3	
M04002	F04002	+	+	4	
M04003	F04003	+	+	1	
M04004	F04004	+	+	4	
M04005	F04005	+	+	3	
M04006	F04006	+	+	1	
M04007	F04007	+	+	1	
M04008	F04008	+	+	3	
M04009	F04009	+	+	4	
M04010	F04010	+	+	3	
M04011	F04011	+	+	4	
M04012	F04012	+	+	3	
M04013	F04013	+	+	2	
Total		+: 13, -: 0	+: 13, -: 0		
Mean				2.8	
S.D.				1.2	
(N)				(13)	

+, confirmed  
 -, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 37-1. Observation of offspring (F<sub>1</sub>)

Corn oil (control)																					
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 <sup>b)</sup>				
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio	Viability index (%)	(Number)	(%)		
							Male	Female	Total												
F01001	23	18	16	88.9	+	15	10	5	15	0.67	0	93.8	93.8	100.0	10	5	0.67	100.0	0	0.0	
F01002	22	11	10	90.9	+	9	1	7	8	0.13	1	90.0	80.0	88.9	1	7	0.13	100.0	0	0.0	
F01003	22	18	18	100.0	+	15	7	8	15	0.47	0	83.3	83.3	100.0	7	8	0.47	100.0	0	0.0	
F01004	22	15	15	100.0	+	14	7	7	14	0.50	0	93.3	93.3	100.0	7	7	0.50	100.0	0	0.0	
F01005	22	15	15	100.0	+	13	9	3	12	0.75	1	86.7	80.0	92.3	9	3	0.75	100.0	0	0.0	
F01006	22	15	15	100.0	+	15	4	11	15	0.27	0	100.0	100.0	100.0	4	11	0.27	100.0	0	0.0	
F01007	22	14	14	100.0	+	14	6	8	14	0.43	0	100.0	100.0	100.0	6	8	0.43	100.0	0	0.0	
F01008	23	19	19	100.0	+	17	10	6	16	0.63	1	89.5	84.2	94.1	10	6	0.63	100.0	0	0.0	
F01009	22	17	14	82.4	+	11	2	1	3	0.67	8	78.6	21.4	27.3	2	0	1.00	66.7	0	0.0	
F01010	22	17	16	94.1	+	15	8	7	15	0.53	0	93.8	93.8	100.0	8	7	0.53	100.0	0	0.0	
F01011	22	15	15	100.0	+	13	6	7	13	0.46	0	86.7	86.7	100.0	6	7	0.46	100.0	0	0.0	
F01012	22	15	15	100.0	+	15	6	9	15	0.40	0	100.0	100.0	100.0	6	9	0.40	100.0	0	0.0	
F01013	22	19	19	100.0	+	18	7	10	17	0.41	1	94.7	89.5	94.4	7	10	0.41	100.0	0	0.0	
Number of dams	13	13	13	13	13 <sup>a)</sup>	13			13	13	13	13	13	13			13	13	13	13	
Total		208	201			184	83	89	172		12				83	88			0		
Mean	22.2	16.0	15.5	96.6		14.2	6.4	6.8	13.2	0.49	0.9	91.6	85.1	92.1	6.4	6.8	0.51	97.4		0.0	
S.D.	0.4	2.3	2.4	5.8		2.3	2.8	2.7	3.8	0.17	2.2	6.6	20.5	19.8	2.8	2.9	0.22	9.2		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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 37-2. Observation of offspring (F<sub>1</sub>)

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 <sup>b)</sup>		
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio	Viability index (%)	(Number)	%	
							Male	Female	Total											
							Male	Female	ratio											index
F02001	22	15	15	100.0	+	15	10	5	15	0.67	0	100.0	100.0	100.0	10	5	0.67	100.0	0	0.0
F02002	23	17	17	100.0	+	15	7	8	15	0.47	0	88.2	88.2	100.0	7	8	0.47	100.0	0	0.0
F02003	23	15	15	100.0	+	15	8	7	15	0.53	0	100.0	100.0	100.0	8	7	0.53	100.0	0	0.0
F02004	22	17	17	100.0	+	16	10	6	16	0.63	0	94.1	94.1	100.0	10	6	0.63	100.0	0	0.0
F02005	22	17	16	94.1	+	15	5	10	15	0.33	0	93.8	93.8	100.0	5	10	0.33	100.0	0	0.0
F02006	23	18	18	100.0	+	14	0	0	0	c)	14	77.8	0.0	0.0	c)					
F02007	23	17	16	94.1	+	16	5	11	16	0.31	0	100.0	100.0	100.0	5	11	0.31	100.0	1	6.3
F02008	22	16	16	100.0	+	16	8	8	16	0.50	0	100.0	100.0	100.0	8	8	0.50	100.0	0	0.0
F02009	22	16	16	100.0	+	16	8	8	16	0.50	0	100.0	100.0	100.0	8	8	0.50	100.0	0	0.0
F02010	22	15	15	100.0	+	14	7	7	14	0.50	0	93.3	93.3	100.0	7	7	0.50	100.0	0	0.0
F02011	22	17	17	100.0	+	17	8	9	17	0.47	0	100.0	100.0	100.0	8	9	0.47	100.0	0	0.0
F02012	23	18	16	88.9	+	16	9	7	16	0.56	0	100.0	100.0	100.0	9	7	0.56	100.0	0	0.0
F02013	22	16	16	100.0	+	16	8	7	15	0.53	1	100.0	93.8	93.8	7	6	0.54	86.7	0	0.0
Number of dams	13	13	13	13	13 <sup>a)</sup>	13			13	12	13	13	13	13			12	12	12	12
Total		214	210			201	93	93	186		15				92	92			1	
Mean	22.4	16.5	16.2	98.2		15.5	7.2	7.2	14.3	0.50	1.2	95.9	89.5	91.8	7.7	7.7	0.50	98.9		0.5
S.D.	0.5	1.1	0.9	3.6		0.9	2.6	2.7	4.4	0.10	3.9	6.7	27.2	27.6	1.6	1.7	0.10	3.8		1.8
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	KW	AN	KW	KW	AN	AN	KW	AN	KW	AN	DT	KW	AN	AN	KW	KW		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.

c): Total litter loss on the lactation day 0.

NS: Not significantly different from the control group.

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

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 37-3. Observation of offspring (F<sub>1</sub>)

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 <sup>b)</sup>				
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio	Viability index (%)	abnormalities <sup>b)</sup>			
							Male	Female	Total									Male	Female	(Number)	%
F03001	23	15	15	100.0	+	13	7	6	13	0.54	0	86.7	86.7	100.0	7	6	0.54	100.0	0	0.0	
F03002	22	16	15	93.8	+	13	5	7	12	0.42	1	86.7	80.0	92.3	5	7	0.42	100.0	0	0.0	
F03003	22	13	13	100.0	+	12	6	6	12	0.50	0	92.3	92.3	100.0	6	6	0.50	100.0	0	0.0	
F03004	22	16	15	93.8	+	15	7	8	15	0.47	0	100.0	100.0	100.0	7	8	0.47	100.0	0	0.0	
F03005	23	16	15	93.8	+	15	2	6	8	0.25	7	100.0	53.3	53.3	2	5	0.29	87.5	0	0.0	
F03006	23	18	18	100.0	+	16	8	8	16	0.50	0	88.9	88.9	100.0	8	8	0.50	100.0	0	0.0	
F03007	23	16	16	100.0	+	16	5	9	14	0.36	2	100.0	87.5	87.5	2	4	0.33	42.9	0	0.0	
F03008	22	18	15	83.3	+	14	4	10	14	0.29	0	93.3	93.3	100.0	4	10	0.29	100.0	0	0.0	
F03009	22	17	17	100.0	+	16	5	8	13	0.38	3	94.1	76.5	81.3	5	8	0.38	100.0	0	0.0	
F03010	23	18	17	94.4	+	15	8	7	15	0.53	0	88.2	88.2	100.0	8	7	0.53	100.0	0	0.0	
F03011		17	16	94.1	-	Dam died on the gestation day 23.															
F03012	22	16	15	93.8	+	14	8	6	14	0.57	0	93.3	93.3	100.0	8	6	0.57	100.0	0	0.0	
F03013	23	16	15	93.8	+	14	6	8	14	0.43	0	93.3	93.3	100.0	6	8	0.43	100.0	0	0.0	
Number of dams	12	13	13	13	12 <sup>a)</sup>	12			12	12	12	12	12	12			12	12	12	12	
Total		212	202			173	71	89	160		13				68	83			0		
Mean	22.5	16.3	15.5	95.4		14.4	5.9	7.4	13.3	0.44	1.1	93.1	86.1	92.9	5.7	6.9	0.44	94.2		0.0	
S.D.	0.5	1.4	1.3	4.7		1.3	1.8	1.3	2.1	0.10	2.1	4.9	12.1	13.9	2.1	1.6	0.10	16.6		0.0	
%					92.3																
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
Statistical method	AN	KW	KW	AN	KW	KW	AN	AN	KW	AN	KW	AN	DT	KW	AN	AN	KW	KW		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.

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

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 37-4. Observation of offspring (F<sub>1</sub>)

DMP 1000 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 <sup>b)</sup>			
						Number of offspring	Live		Sex ratio	Dead offspring				4 days	Sex ratio	Viability index (%)	(Number)	(%)		
							Male	Female											Total	
F04001	23	13	13	100.0	+	11	7	4	11	0.64	0	84.6	84.6	100.0	7	4	0.64	100.0	0	0.0
F04002	22	17	17	100.0	+	16	10	6	16	0.63	0	94.1	94.1	100.0	10	6	0.63	100.0	0	0.0
F04003	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
F04004	23	16	16	100.0	+	16	9	7	16	0.56	0	100.0	100.0	100.0	9	6	0.60	93.8	0	0.0
F04005	22	15	14	93.3	+	13	9	4	13	0.69	0	92.9	92.9	100.0	9	4	0.69	100.0	0	0.0
F04006	23	17	16	94.1	+	15	8	7	15	0.53	0	93.8	93.8	100.0	8	7	0.53	100.0	0	0.0
F04007	23	17	15	88.2	+	14	5	7	12	0.42	2	93.3	80.0	85.7	0	0	c)	0.0	0	0.0
F04008	22	16	13	81.3	+	12	5	7	12	0.42	0	92.3	92.3	100.0	5	7	0.42	100.0	0	0.0
F04009	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
F04010	22	16	16	100.0	+	16	9	7	16	0.56	0	100.0	100.0	100.0	9	7	0.56	100.0	0	0.0
F04011	22	15	15	100.0	+	14	10	4	14	0.71	0	93.3	93.3	100.0	10	4	0.71	100.0	0	0.0
F04012	23	17	17	100.0	+	17	8	9	17	0.47	0	100.0	100.0	100.0	8	8	0.50	94.1	0	0.0
F04013	22	17	17	100.0	+	17	6	11	17	0.35	0	100.0	100.0	100.0	6	11	0.35	100.0	0	0.0
Number of dams	13	13	13	13	13 <sup>a)</sup>	13			13	13	13	13	13	13			12	13	13	13
Total		207	200			191	98	91	189		2				93	82			0	
Mean	22.4	15.9	15.4	96.7		14.7	7.5	7.0	14.5	0.52	0.2	95.2	94.2	98.9	7.2	6.3	0.54	91.4		0.0
S.D.	0.5	1.2	1.4	6.0		1.8	1.9	2.2	2.0	0.12	0.6	4.6	6.2	4.0	2.7	2.9	0.13	27.5		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	KW	AN	KW	KW	AN	AN	KW	AN	KW	AN	DT	KW	AN	AN	KW	KW	KW	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.

c): Total litter loss on the lactation day 1.

NS: Not significantly different from the control group.

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

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 38-1. Body weights of offspring (F<sub>1</sub>) before weaning

Corn oil (control)

Dam No.	Days after birth					
	Male body weight				Female body weight	
	0		4		4	
F01001	7.7	(10)	12.5	(10)	6.6	(5) 11.3 (5)
F01002	6.5	(1)	12.7	(1)	6.4	(7) 12.1 (7)
F01003	6.3	(7)	10.3	(7)	5.8	(8) 9.8 (8)
F01004	6.4	(7)	11.4	(7)	6.0	(7) 10.6 (7)
F01005	6.6	(9)	10.8	(9)	6.3	(3) 10.5 (3)
F01006	6.8	(4)	10.2	(4)	6.6	(11) 9.9 (11)
F01007	6.6	(6)	11.3	(6)	6.1	(8) 11.1 (8)
F01008	6.7	(10)	12.0	(10)	6.5	(6) 10.7 (6)
F01009	6.7	(2)	10.8	(2)	5.7	(1) Female offspring deid.
F01010	6.3	(8)	9.6	(8)	6.3	(7) 9.7 (7)
F01011	6.7	(6)	11.4	(6)	6.5	(7) 10.9 (7)
F01012	6.8	(6)	10.2	(6)	6.1	(9) 10.0 (9)
F01013	6.6	(7)	10.5	(7)	6.2	(10) 9.9 (10)
Number of dams	13		13		13	12
Mean	6.7		11.1		6.2	10.5
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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 38-2. Body weights of offspring (F<sub>1</sub>) before weaning

DMIP 62.5 mg/kg

Dam No.	Days after birth			
	Male body weight		Female body weight	
	0	4	0	4
F02001	6.2 (10)	9.3 (10)	5.2 (5)	8.1 (5)
F02002	7.5 (7)	11.8 (7)	7.1 (8)	11.4 (8)
F02003	7.3 (8)	11.4 (8)	6.7 (7)	10.5 (7)
F02004	6.1 (10)	10.3 (10)	5.8 (6)	10.1 (6)
F02005	6.6 (5)	10.2 (5)	6.3 (10)	10.1 (10)
F02006	Total litter loss.			
F02007	6.9 (5)	10.4 (5)	7.2 (11)	11.0 (11)
F02008	6.5 (8)	10.2 (8)	6.3 (8)	9.6 (8)
F02009	6.9 (8)	11.4 (8)	6.3 (8)	10.8 (8)
F02010	6.1 (7)	11.2 (7)	5.7 (7)	10.5 (7)
F02011	6.2 (8)	9.5 (8)	5.7 (9)	8.4 (9)
F02012	7.2 (9)	10.9 (9)	6.3 (7)	9.7 (7)
F02013	6.3 (8)	11.6 (7)	5.8 (7)	10.5 (6)
Number of dams	12	12	12	12
Mean	6.7	10.7	6.2	10.1
S.D.	0.5	0.8	0.6	1.0
Significance	NS	NS	NS	NS
Statistical method	AN	KW	AN	KW

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.

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 38-3. Body weights of offspring (F<sub>1</sub>) before weaning

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F03001	7.4	(7)	12.0	(7)	7.2	(6)	11.5	(6)
F03002	6.7	(5)	10.7	(5)	6.3	(7)	9.9	(7)
F03003	7.3	(6)	12.0	(6)	6.4	(6)	11.2	(6)
F03004	6.8	(7)	10.2	(7)	6.4	(8)	9.8	(8)
F03005	5.6	(2)	11.2	(2)	5.2	(6)	10.0	(5)
F03006	7.1	(8)	10.8	(8)	6.7	(8)	10.8	(8)
F03007	5.9	(5)	5.3	(2)	5.6	(9)	5.1	(4)
F03008	6.5	(4)	9.3	(4)	5.9	(10)	9.0	(10)
F03009	7.1	(5)	12.2	(5)	6.8	(8)	11.5	(8)
F03010	7.0	(8)	11.5	(8)	6.9	(7)	11.0	(7)
F03011	Dam died on the gestation day 23.							
F03012	6.9	(8)	11.1	(8)	6.3	(6)	10.7	(6)
F03013	6.6	(6)	12.0	(6)	6.1	(8)	10.8	(8)
Number of dams	12		12		12		12	
Mean	6.7		10.7		6.3		10.1	
S.D.	0.5		1.9		0.6		1.7	
Significance	NS		NS		NS		NS	
Statistical method	AN		KW		AN		KW	

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.

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 38-4. Body weights of offspring (F<sub>1</sub>) before weaning

DMIP 1000 mg/kg

Dam No.	Days after birth			
	Male body weight		Female body weight	
	0	4	0	4
F04001	7.2 (7)	12.7 (7)	7.1 (4)	12.1 (4)
F04002	6.6 (10)	9.1 (10)	6.1 (6)	8.4 (6)
F04003	6.2 (5)	10.5 (5)	5.9 (10)	9.7 (10)
F04004	6.5 (9)	10.5 (9)	6.2 (7)	10.1 (6)
F04005	6.6 (9)	10.6 (9)	6.3 (4)	10.4 (4)
F04006	7.3 (8)	10.3 (8)	6.8 (7)	9.9 (7)
F04007	5.9 (5)	Total litter loss.	5.1 (7)	Total litter loss.
F04008	6.5 (5)	10.4 (5)	6.0 (7)	10.4 (7)
F04009	6.3 (7)	10.7 (7)	5.9 (8)	10.2 (8)
F04010	6.5 (9)	9.7 (9)	5.9 (7)	9.2 (7)
F04011	6.6 (10)	10.4 (10)	6.4 (4)	9.6 (4)
F04012	5.8 (8)	9.1 (8)	5.5 (9)	9.0 (8)
F04013	6.7 (6)	9.9 (6)	5.9 (11)	9.1 (11)
Number of dams	13	12	13	12
Mean	6.5	10.3	6.1	9.8
S.D.	0.4	0.9	0.5	0.9
Significance	NS	NS	NS	NS
Statistical method	AN	KW	AN	KW

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.

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 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 39-1. General conditions in offspring (F<sub>1</sub>) before weaning

Corn oil (control)		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
		F01001	Number of offspring	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01002	Number of offspring	8	8	8	8	8
	General appearance, No abnormality	8	8	8	8	8
F01003	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01004	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01005	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F01006	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01007	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01008	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01009	Number of offspring	3	3	2	2	2
	General appearance, No abnormality	3	2	2	2	2
	General appearance, Death	0	1	0	0	0
F01010	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01011	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01012	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01013	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
	Number of offspring	172	172	171	171	171
	General appearance, No abnormality	172	171	171	171	171
	General appearance, Death		1			
	Abnormal findings of offspring, Bent tail					

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 39-2. General conditions in offspring (F<sub>1</sub>) before weaning

DMIP 62.5 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
		F02001	Number of offspring	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02002	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02003	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02004	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02005	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02006	Total litter loss on the lactation day 0.					
F02007	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	15	15	15	15	15
	Abnormal findings of offspring, Bent tail	1	1	1	1	1
F02008	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02009	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02010	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02011	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F02012	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02013	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
	Number of offspring	186	186	185	184	184
	General appearance, No abnormality	185	184	183	183	183
	General appearance, Death		1	1		
	Abnormal findings of offspring, Bent tail	1	1	1	1	1

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 39-3. General conditions in offspring (F<sub>1</sub>) before weaning

DMIP 250 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
		F03001	Number of offspring	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03002	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F03003	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F03004	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03005	Number of offspring	8	8	7	7	7
	General appearance, No abnormality	8	7	7	7	7
	General appearance, Death	0	1	0	0	0
F03006	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F03007	Number of offspring	14	14	10	10	7
	General appearance, No abnormality	14	10	10	7	6
	General appearance, Death	0	4	0	3	1
F03008	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03009	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03010	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03011	Dam died on the gestation day 23.					
F03012	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03013	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
	Number of offspring	160	160	155	155	152
	General appearance, No abnormality	160	155	155	152	151
	General appearance, Death		5		3	1
	Abnormal findings of offspring, Bent tail					

Combined repeat dose and reproductive/developmental toxicity screening test of 1,3-Benzenedicarboxylic acid, dimethyl ester by oral administration in rats

Appendix 39-4. General conditions in offspring (F<sub>1</sub>) before weaning

DMIP 1000 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
		F04001	Number of offspring	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F04002	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F04003	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04004	Number of offspring	16	16	16	15	15
	General appearance, No abnormality	16	16	15	15	15
	General appearance, Death	0	0	1	0	0
F04005	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F04006	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04007	Number of offspring	12	12	0	0	0
	General appearance, No abnormality	12	0	0	0	0
	General appearance, Death	0	12	0	0	0
F04008	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F04009	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04010	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F04011	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04012	Number of offspring	17	17	16	16	16
	General appearance, No abnormality	17	16	16	16	16
	General appearance, Death	0	1	0	0	0
F04013	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
	Number of offspring	189	189	176	175	175
	General appearance, No abnormality	189	176	175	175	175
	General appearance, Death		13	1		
	Abnormal findings of offspring, Bent tail					