試験番号:R-13-004

最終報告書

Methyl 3-methoxypropanoate のラットを用いる
反復投与毒性・生殖発生毒性併合試験

厚生労働省医薬食品局審査管理課 化学物質安全対策室 委託

試験施設

一般財団法人食品薬品安全センター 秦[redacted]

〒257-8523 神奈川県秦野市落合 729 番地の 5

TEL 0463-82-4751

試験委託者	厚生労働省医薬食品局審査管理課 化学物質安全対策室 (東京都千代田区霞が関 1-2-2)
試験番号	R-13-004
被験物質	Methyl 3-methoxypropanoate
試験項目	反復投与毒性・生殖発生毒性併合試験
試験開始日	2013 年 9 月 5 日
実験開始日	2013 年 9 月 30 日
実験終了日	2014 年 1 月 9 日
試験終了日	試験責任者の捺印日
試資料保管場所	秦野研究所資料保存室
被験物質保管場所	秦野研究所被験物質保存庫
保管期間	試験終了後 10 年間 その後の保管については試験委託者と協議する。
運営管理者	財団法人食品薬品安全センター秦野研究所 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、環保企発第 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、環保企発第 110331010 号環境省総合環境政策局長通知)を遵守して実施した。

2014 年 3 月 26 日　　試験責任者 [redacted]

試験従事者

試験責任者	[redacted]
試験担当主任者	
試験担当者 投与観察	
動物飼育管理 (検疫を含む)	
血液学的検査 (採血を含む) 血液生化学的検査 尿検査 病理学検査	
被験物質管理 検体調製 化学分析	

目次

(最終ページ:318 ページ)

要約

Methyl 3-methoxypropanoate の反復投与毒性・生殖発生毒性併合試験を化審法ガイドラインに従って実施した。被験物質を注射用水(媒体)に溶解して、0、62.5、250ならびに1000 mg/kgの用量で、各群とも雌雄各12匹のCrl:CD(SD)ラットに強制経口投与した。雄は42日間投与した後に剖検し、雌は交配前14日間および交配期間、妊娠期間を通して哺育4日まで41～44日間投与し、出生児は哺育4日、母動物は哺育5日に剖検した。また、0および1000 mg/kgの用量に非交配(サテライト)群(10匹/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群の各5例、雌の非交配群の各5例は42日間投与した後、14日間飼育して剖検した。

1. 反復投与毒性学的所見および毒性の回復性

1000 mg/kg群の雄、非交配雌および交配雌に投与後の一過性の流涎が観察され、詳細な症状観察でも交配雌に流涎がみられた。投与開始直後の摂餌量減少が1000 mg/kg群の雄および非交配雌で認められ、交配雌も同様の傾向を示した。また、同群では哺育期間中の摂餌量も減少した。尿量の増加が1000 mg/kg群の雄で認められ、非交配雌は増加傾向を示した。また、雄および非交配雌に酸性尿、尿中電解質濃度の減少傾向および尿中電解質排泄量の増加傾向が認められた。さらに非交配雌は尿蛋白、ケトン体およびナトリウム排泄量が増加した。血小板数の減少、プロトロンビン時間の延長、活性化部分トロンボプラスチン時間の短縮が1000 mg/kg群の非交配雌で認められた。乳酸脱水素酵素(LDH)活性、グルコース濃度およびトリグリセライド濃度の増加傾向が1000 mg/kg群の雄に認められ、250 mg/kg群では有意差が認められた。また、LDH活性は250 mg/kg以上の分娩雌も増加傾向を示した。1000 mg/kg群の非交配雌で胆汁酸濃度が増加し、雄および分娩雌も増加傾向を示した。また、同群の雄および非交配雌は総ビリルビン濃度が増加した。肝臓重量の増加が1000 mg/kg群の非交配雌および交配雌で認められ、雄も増加傾向を示した。また、雄および非交配雌の腎臓重量が増加傾向を示した。

14日間の回復期間終了後、1000 mg/kg群の非交配雌で尿比重、尿中電解質濃度および尿中電解質排泄量の増加、腎臓重量の増加が認められた。その他、観察された全ての所見には回復性が認められた。

2. 生殖発生毒性学的所見および出生児所見

1000 mg/kg群では平均発情回帰日数および妊娠期間が延長し、産児数および出産生児数の減少が認められた。また、同群では分娩および哺育不良による全哺育児死亡例が1例認められた。

3. 無毒性量

親動物に対する一般毒性学的無毒性量は一般状態、血液学的検査、血液生化学的検査、器官重量結果から雌雄ともに62.5 mg/kg/day、生殖発生毒性および次世代児に対する無毒性量は平均発情回帰日数および妊娠期間の延長、産児数の減少が認められたことから250 mg/kg/dayと考えられた。

試験目的

本試験は、ラットに Methyl 3-methoxypropanoate を一定期間反復投与した時に現れ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を明らかにすることを目的とした。

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、環保企発第 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、環保企発第 110331010 号環境省総合環境政策局長通知)を遵守して実施した。

動物愛護

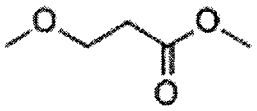
全ての実験操作は、「動物の愛護及び管理に関する法律」(昭和 48 年 10 月 1 日、法律第 105 号、平成 24 年 9 月 5 日 一部改正)、「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」(平成 18 年 4 月 28 日、環境省告示第 88 号)および「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」(平成 18 年 6 月 1 日、科発第 0601001 号)を遵守し、「一般財団法人食品薬品安全センター動物実験に関する指針(機関内規程)」(平成 2 年 10 月 1 日、平成 25 年 4 月 1 日改定)に基づいて実施した。本試験における動物実験計画は、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:1130206A)。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 Methyl 3-methoxypropanoate(別名:3-メトキシプロピオン酸メチル、CAS No.:3852-09-3、分子式:$C_5H_{10}O_3$、分子量:118.13、外観・性状:無色澄明の液体、特異臭、融点:購入元からのデータなし、沸点:145°C(初留点)、1-オクタノール/水分配係数:購入元からのデータなし、蒸気圧:購入元からのデータなし、溶解性:エタノール及びアセトンに溶け、水に溶けにくい、ロット番号:WEE5103、Annex A、以下、MMP)は和光純薬工業株式会社より購入し(被験物質入手:2013 年 6 月 14 日)、使用時まで室温、遮光、密閉下(実測値 15.9～24.6℃)で保管した。

MMP の構造式を次に示す。



被験物質の安定性は、実験開始前および実験終了後に秦野研究所にて性状の確認および赤外吸収スペクトルを測定し、色調や性状、スペクトルに変化がないことを他試験(試験番号 Q-13-010)で確認した。

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8.5週齢のSprague-Dawley(SD)系〔Crl:CD(SD)、SPF〕ラットの雄55匹、雌83匹を購入し、6号室に収容した。入荷日も含めて13日間、検疫と飼育環境への馴化のため飼育した。その間毎日、動物の一般状態を観察し、入荷日(検疫 1 日)および検疫終了日に体重を測定した。検疫・馴化期間中は動物の尾にフェルトペンで馴化番号を記し、飼育ケージに試験番号、性別および馴化番号を記入した動物カードを掛けて識別した。また、雌動物については、検疫 2 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	:2013年9月18日
入荷時体重	:雄282.1～307.3 g、雌185.7～219.1 g
検疫終了日	:2013年9月30日
検疫終了時体重	:雄365.7～431.2 g、雌214.3～289.5 g

検疫・馴化の結果、入荷した動物において雄 1 匹(馴化番号 9)では頚背部に脱毛がみられ、痂皮形成に移行した。その他、検疫期間中の一般状態および体重推移に異常は認められなかった。雄動物では一般状態に異常が観察された1匹、雌動物では規則的な4日の性周期の回帰が認められない8匹および詳細な症状観察で口腔粘膜に結節が確認された 1 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。群分けから除外した雄動物 7 匹、雌動物 15 匹は全て余剰動物とし、雄動物 1 例は深麻酔下で安楽死させ、それ以外の動物は他目的に転用した。

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)収容し、固型飼料(CE-2、日本クレア)と水道水(秦野市水道局給水)を自由に摂取させて飼育した(ただし、未分娩例および全哺育児死亡例を除いて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 匹ずつ収容し、床敷として紙パルプ製チップ(ペパークリーン、日本エスエルシー)を適宜供給した。飼育期間中の動物室の温度は 21.5～24.5℃、湿度は 48.0～68.5%であった。また、供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを確認した。

3. 投与検体

1)調製

被験物質を秤量し、媒体(注射用水、製造元:光製薬、製造番号:C2XCH1)を加え撹拌混和させ、200 mg/mL 液を調製した。さらに、200 mg/mL 液を媒体によって希釈し、50 ならびに 12.5 mg/mL 液を段階的に調製した。調製した検体は冷蔵、遮光、密閉下(実測値 1～6℃)で保管し、安定性の保証期間内に使用した。

2)安定性試験

本被験物質を用いて先立って実施された試験(試験番号 Q-13-010)において、本被験物質の調製検体(0.01 および 200 mg/mL)について、冷蔵、遮光条件下における 8 日間の安定性は確認されている。

3)含量の測定

本試験の初回調製検体(調製日:2013 年 9 月 30 日)について、12.5、50 および 200 mg/mL 濃度の調製検体の含量を測定した。その結果、平均含量は調製濃度の 97.9～100.7%であり、各測定値のばらつきは平均値の 98.2～101.6%で規定範囲内にあった(Annex B)。

調製検体中の被験物質濃度は以下の方法で測定した。12.5、50、200 mg/mL の投与検体 1 mL を正確にとり、水を加えて適宜希釈して試料溶液(約 10 μg/mL)を調製した。試料溶液の調製は投与検体の採取から n=3 とした。試料溶液および標準溶液を以下に示す測定条件で高速液体クロマトグラフィーにより測定し、標準溶液から作成した検量線を用いて調製検体中の MMP 濃度を算出した。

測定条件

検出器	紫外可視吸光光度計
分析カラム	CAPCELL PAK C18 UG120(内径 4.6 mm、長さ 250 mm、粒子径 5 μm、資生堂)
移動相	水/アセトニトリル(8:2 v/v)
流量	1 mL/min
カラム設定温度	40℃
試料設定温度	室温(設定なし)
注入量	10 μL
測定波長	210 nm
オートインジェクタ洗浄液	水/アセトニトリル(8:2 v/v)
システムの適合性	測定開始前に水を 1 回、測定開始前及び測定終了後に標準溶液(St 2)を 1 回ずつ測定した。水のクロマトグラム上に MMP のピーク保持時間付近に妨害ピークがないことを確認した。また、標準溶液(St 2)においてピーク保持時間とピーク面積の変動(測定開始前に対する測定終了後の偏差%)を確認した。変動の許容基準は保持時間が±3.0%以内、ピーク面積が±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、「Methyl 3-methoxypropanoate 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-13-003)の結果 [1)]をもとに設定した。すなわち、0(媒体、注射用水)、250、500 ならびに 1000 mg/kg の MMP を 10 週齢の雌雄各 3 匹の SD 系ラットに 14 日間、反復強制経口投与した。なお、この予備試験で用いた被験物質および媒体は本試験と同じロットを用いた。

雄の 1000 mg/kg 投与群において、投与 7 日以降の投与後に一過性の流涎が観察された。しかし、詳細な症状観察では神経毒性を示唆する変化は観察されなかった。また、血液生化学的検査および器官重量測定(肝臓、腎臓、脾臓、副腎、精巣、精巣上体)結果においても、被験物質の影響を示唆する変化は認められなかった。したがって、1000 mg/kg の MMP は急性期に重篤な変化をもたらす濃度ではなく、被験物質の雌雄動物に対する一般毒性学的変化、さらに生殖毒性への影響も評価ができると考えられた。以上の結果から、1000 mg/kg を本試験における高用量群の投与量に設定し、以下、公比 4 で減じて、250 mg/kg を中用量、62.5 mg/kg を低用量に設定することとした。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。

本試験では、雄動物は交配前 14 日間、交配期間(最長 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 14 日間、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非交配(サテライト)群では投与 42 日まで、経口的に 1 日 1 回、1 週 7 回、9 時 02 分～12 時 08 分に投与した。また、交尾は確認されたが分娩しなかった雌は剖検前日(妊娠 25 日相当日)まで投与した。投与容量は 5 mL/kg とし、雌雄ともに最新の測定日の体重を基準に投与液量を算出した。なお、対照群には媒体である注射用水を同様に投与した。

本試験開始時の群構成および動物番号を次に示した。

群	投与物質	投与量 (mg/kg)	濃度 (mg/mL)	投与容量 (mL/kg)	動物番号	
					雄	雌
対照群	注射用水 (媒体)	0	0	5	M01001～M01012*	F01001～F01012
低用量群	MMP	62.5	12.5	5	M02013～M02024	F02013～F02024
中用量群	MMP	250	50	5	M03025～M03036	F03025～F03036
高用量群	MMP	1000	200	5	M04037～M04048*	F04037～F04048
対照群〔非交配(サテライト)群〕	注射用水 (媒体)	0	0	5	-	F05049～F05058*
高用量群〔非交配(サテライト)群〕	MMP	1000	200	5	-	F06059～F06068*

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

5. 検査法

1)親動物(F0)

①一般状態の観察

全例について、飼育期間中は毎日 1 回以上、投与期間中は投与前後の毎日 2 回以上観察した。さらに、症状が発現した場合には、断続的に観察を継続した。

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、雌動物は非交配(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、前項に示した方法で、一般状態を観察した。

③詳細な症状観察

雌雄動物は検疫終了日、投与 7、14、23、30、36 および 42 日(分娩例は哺育 0 日から 4 日の間に 1 回)、1000 mg/kg 投与群の 1 例は投与 49 日、回復期間中は回復 7 および 14 日にも、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 05 分～14 時 38 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

握力測定および自発運動測定は、雄は投与 39 日に、雌は投与 41 日に検査した。対象動物は雄および非交配(サテライト)群は各群の動物番号の若い 5 例とし、分娩雌は投与期間が近接し、可能な限り分娩から日数が経過した各群 5 例とした。

投与 42 日の詳細な症状観察に引き続き、雌雄ともに刺激に対する感覚運動反応を検査した。対象動物は、雄の対照群は上切歯が一部欠損したことにより体重推移および摂餌量に影響が認められた 1 例(動物番号 M01002)を除く動物番号の若い 5 例、その他の群は各群の動物番号の若い 5 例とした。分娩雌は投与期間が近接し、可能な限り分娩から日数が経過した各群 5 例、非交配(サテライト)群は各群の動物番号の若い 5 例とした。

(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、室町機械)を用いて、20 分間の自発運動量(区画移動数および立ち上がり回数)を計測し、計測値は 5 分毎に集計した。試験対象動物は、検査直前に別室の装置設置場所(行動観察室 2)に運搬し、速やかに自発運動測定を開始した。

⑤体重測定

雄および雌動物の非交配(サテライト)群は、投与 1(投与開始日)、4、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、4、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。1000 mg/kg 投与群の 1 例はさらに投与 21、28 日、分娩が確認されなかった動物では妊娠 26 日相当日にも測定した。

⑥摂餌量測定

雄および雌動物の非交配(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、非交配(サテライト)群のみ投与 21～22 日にも測定した。雌動物は投与 1～2、7～8、14～15 日、妊娠 0～1、7～8、14～15、20～21 日および哺育 3～4 日に測定した。なお、上切歯の欠損がみられた対照群の雄 1 例の投与 41～42 日の測定値は評価対象から除外した。

⑦尿検査

雄動物および雌動物の非交配(サテライト)群を検査対象とし、投与 37 日の検査では各群動物番号の若い 5 例、また、回復 13 日における検査では回復例全例を検査した。

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

項目	測定法	使用機器
色調・濁度	視診	
pH・潜血・蛋白・糖・ケトン体	試験紙法	オーションイレブン AE-4020(アークレイ)
ウロビリノーゲン・ビリルビン	同上	同上
沈渣	鏡検	光学顕微鏡
尿量	計量	メスシリンダー等
比重	屈折法	デジタル臨床屈折計 SU-202(エルマ販売)
ナトリウムイオン濃度	イオン電極法	全自動分析装置 JCA-BM6010(日本電子)
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、動物入荷 2 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非交配(サテライト)群を除く全例の腟スメア標本を作製し、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、群毎の平均発情回帰日数(個体毎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 日の間隔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 15 時 14 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、腟栓を確認し、同居中の雌の腟垢標本を作製して鏡検した。腟内に腟栓あるいは腟垢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)×100, %〕、妊娠率〔(妊娠動物数/交尾した雌動物数)×100, %〕

を算出した。

⑩妊娠・分娩・哺育状態の観察

交尾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った。午前と午後に観察し、15 時までに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。分娩状態については直接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 1～4 日の間に哺育状態を毎日観察した。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、各群の出産率[(生児出産雌数/妊娠動物数)×100, %]を算出した。哺育 5 日の剖検時に卵巣については実体顕微鏡下で妊娠黄体数を、子宮については着床数を数え、着床率〔(着床数/妊娠黄体数)×100, %〕を算出した。

⑪採血

雄の投与終了時剖検では、対照群は 1 例(動物番号 M01002)を除く動物番号の若い 5 例、その他の群は各群の動物番号の若い 5 例、回復 15 日における剖検では回復例全例で採血を行った。また、雌の投与終了時剖検では、分娩例について投与期間が近接している各群 5 例、非交配(サテライト)群の投与終了時剖検では各群動物番号の若い 5 例、回復 15 日における剖検では回復例全例で採血を行った。いずれも解剖前 18～22 時間絶食させた後、腹部後大静脈から以下の 1)、2)、3)の順に注射筒を換えて採血した。

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

⑫血液学的検査

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

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

⑬血液生化学的検査

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)	ﾋﾞｳﾚｯﾄ法	自動分析装置 JCA-BM6010(日本電子)
ｱﾙﾌﾞﾐﾝ濃度(rALB)	BCG 法	同上
ｸﾞﾙｺｰｽ濃度(Glc)	ﾍｷｿｷﾅｰｾﾞ・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ﾀﾞｰｾﾞ・HMMPS 法	同上
ﾄﾘｸﾞﾘｾﾗｲﾄﾞ濃度(TG)	GPO・HMMPS 法、ｸﾞﾘｾﾘﾝ消去法	同上
ﾘﾝ脂質濃度(PL)	ｺﾘﾝｵｷｼﾀﾞｰｾﾞ・DAOS 法	同上
尿素窒素濃度(BUN)	ｳﾚｱｰｾﾞ・GℓDH 法,ｳﾚｱｰｾﾞ律速系	同上
ｸﾚｱﾁﾆﾝ濃度(cre)	Jaffé 法	同上
γ-ｸﾞﾙﾀﾐﾙﾄﾗﾝｽﾍﾟﾌﾟﾁﾀﾞｰｾﾞ活性(γ-GTP)	IFCC 法	同上
ｱﾙｶﾘﾌｫｽﾌｧﾀｰｾﾞ活性(ALP)	GSCC 法	同上
ｱｽﾊﾟﾗｷﾞﾝ酸ｱﾐﾉﾄﾗﾝｽﾌｪﾗｰｾﾞ活性(AST)	IFCC 法	同上
ｱﾗﾆﾝｱﾐﾉﾄﾗﾝｽﾌｪﾗｰｾﾞ活性(ALT)	IFCC 法	同上
乳酸脱水素酵素活性(LDH)	JSCC 標準化対応法	自動分析装置 JCA-BM6010(日本電子)
ｶﾙｼｳﾑ濃度(Ca)	OCPC 法	同上
総ﾋﾞﾘﾙﾋﾞﾝ濃度(tbil)	酵素法	同上
無機ﾘﾝ濃度(IP)	ﾓﾘﾌﾞﾃﾞﾝ酸直接法	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	同上
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

雄動物および雌動物の非交配(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、交尾はしたが分娩しなかった雌(250 mg/kg 投与群の 1 例:動物番号 F03030、1000 mg/kg 投与群の 2 例:動物番号 F04038 および F04044)は妊娠 26 日相当日に、雄動物および非交配(サテライト)群の回復観察例は回復 15 日に、それぞれ剖検した。

血液学的検査、血液生化学的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た。

なお、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(腹側葉)、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髄、骨格筋、坐骨神経および病変部(胸腺、腎臓、脾臓、胃、上顎骨、皮膚、胎児および胎盤)を採取し、保存した。肺および気管支は15 cm水柱以下の圧力で、気管内に10%中性緩衝ホルマリン溶液5 mL以下を注入し固定してから摘出して同固定液に保存した。精巣および精巣上体はブアン液に固定(長期保存は10%中性緩衝ホルマリン溶液)し、その他は10%中性緩衝ホルマリン溶液に固定した。なお、未分娩例および全哺育児死亡例の器官重量値は評価対象から除外した。

⑮病理組織学的検査

剖検した動物のうち、雄および非交配(サテライト)群の投与終了時剖検では対照群は1例(動物番号M01002)を除く動物番号の若い5例ならびに高用量群の動物番号が若い5例、雌の投与終了時剖検では分娩例について投与期間が近接している対照群ならびに高用量群の5例について、病理組織学的検査対象器官(保存した器官・組織)のヘマトキシリン・エオジン(HE)標本を作製し、病理組織学的検査を実施した。また、剖検時に病変がみられた器官のうち、被験物質の影響が示唆された器官(胸腺、腎臓、脾臓および胃)についても検査した。

回復群については、投与期間終了時の病理組織学検査の結果、被験物質投与によると考えられた変化が観察されなかったが、非交配群雌の回復期間終了時に腎臓重量の増加、尿中電解質濃度に変動が認められたために、同群雌の腎臓についても病変部と併せて病理組織学検査を実施した。

2)出生児(F_1)

①出生児の観察

哺育0日に生存児数および死亡児数を雌雄別に数えて、性別および外表奇形の有無を観察し、分娩率[(産児数/着床痕数)×100, %]、生児出産率[(出産生児数/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。なお、62.5 mg/kg投与群の1例(動物番号F02016の雄哺育児)の体重値はアーチファクトが混在する可能性が考えられたことから評価対象から除外した。

②剖検

死亡児は肉眼による異常(口蓋を含む)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日に肉眼による異常(口蓋を含む)の有無を観察してセボフルラン吸入麻酔下に放血致死させて剖検し、内部器官の異常の有無を観察した。

6. データの解析法

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%)。

MMP 各投与群の病理組織学検査所見のうち、グレード分けした病理組織所見は、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、MMP 各投与群と対照群との間の有意差検定を行った(有意水準:5%)。

その他のデータは、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、非交配(サテライト)群内あるいはその他の群内で比較した。その際、解析の対象が 2 群の場合には、まず F 検定を行い、有意差が認められなければ Student's - t 検定を行った。F 検定において有意差が認められた場合は、Aspin-Welch 検定を行った。解析の対象が 3 群以上の場合は、先ず、Bartlett の方法により各群の分散の一様性について検定を行った。分散が一様である場合には、一元配置型の分散分析を行い、群間に有意性が認められる場合は、Dunnett 法により多重比較を行った。一方、いずれかの群で分散が 0 となる場合および分散が一様でない場合には、Kruskal-Wallis の順位検定を行い、群間に有意性が認められる場合には、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

2013 年 11 月 12 日、哺育 4 日に全哺育児が死亡した母動物(動物番号 F04043)の搬出時体重を測定せずに飼育室から搬出した。当日は該当動物の哺育 4 日の体重を測定していたため、同日の体重値は存在し、測定した各器官の比体重値計算も実施できることから、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 1-1～Table 4, Appendix 1-1-1～Appendix 4-4)

試験期間を通して、死亡動物は観察されなかった。

投与 11 日以降に 1000 mg/kg 投与群において投与後の一過性の流涎が雄 11 例、交配雌 10 例、非交配雌 9 例に散見された。一過性の流涎は投与後 1 時間から 4 時間以内に消失した。

分娩雌の 1000 mg/kg 投与群の 1 例(全哺育児死亡例)では、哺育 0 日に赤色尿が観察された。

雄の対照群の 1 例では、投与 42 日および 43 日に上顎切歯の欠損が観察された。

その他、250 mg/kg 以下の投与群には雌雄ともに一般状態の変化は観察されなかった。

回復期間中の 1000 mg/kg 投与群において、雄の 1 例では回復 8 日以降に、雌の 1 例では回復 13 日以降に後頚部の痂皮が観察されたが、ごく軽度であり、被験物質の影響ではないと判断した。

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

雄では、上顎切歯の欠損が観察された対照群の 1 例で投与 42 日に立毛が観察された。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、排尿数も対照群と比較して差はなかった。

雌では、投与 30 日に 1000 mg/kg 投与群の 1 例に流涎が観察された。また、対照群の 1 例において投与 30 日に、非交配雌の対照群の 1 例において投与 23、30、36、42 日および回復 7、14 日に挙尾が観察された。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、排尿数も対照群と比較して差はなかった。

3)体重(Table 7-1～Table 10, Appendix 7-1-1～Appendix 10-4)

雄の MMP 各投与群の体重は投与期間を通して対照群と同様に推移し、対照群と MMP 各投与群との間に有意差は認められなかった。

反復投与毒性を評価した非交配雌においては、投与 14 日に 1000 mg/kg 投与群で有意(P<0.05)に増加した。生殖能を評価した雌の MMP 各投与群の体重は、交配前、妊娠期間中、哺育期間を通して対照群と同様に推移した。その他の測定日では対照群と同様に推移し、対照群と 1000 mg/kg 投与群との間に有意差は認められなかった。

回復期間中の体重推移は、雌雄ともに対照群と 1000 mg/kg 投与群との間に有意差は認められなかった。

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

雄および非交配雌では、1000 mg/kg 投与群において投与 1～2 日の摂餌量が対照群と比較して有意(P<0.01 あるいは P<0.05)に低下した。また、交配雌でも同様の傾向が認められた。

雄の 62.5 および 250 mg/kg 投与群において投与 41～42 日の摂餌量が対照群と比較して有意(P<0.01)に増加した。

交配雌では、1000 mg/kg 投与群において妊娠 20 日の摂餌量が対照群と比較して低下傾向を示し、哺育 3～4 日の摂餌量が有意(P<0.05)に低下した。その他、交配前、妊娠期間中を通して、対照群との間に有意差は認められなかった。

回復期間の雄では、回復 6～7 日の 1000 mg/kg 投与群の摂餌量が対照群と比較して有意(P<0.05)に増加した。雌では、対照群と 1000 mg/kg 投与群との間に有意差は認められなかった。

5)機能検査

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

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、眼瞼反射、正向反射の検査では、雄、交配雌および非交配雌いずれの群の検査対象動物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 17-1～Appendix 19-2)

雄、交配雌および非交配雌の前肢、後肢の握力には、対照群と MMP 各投与群との間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 20-1～Appendix 22-2)

雄、交配雌および非交配雌の区画移動数および立ち上がり回数には、対照群と MMP 各投与群との間に有意差は認められなかった。

6)尿検査(Table 23-1～Table 24-4, Appendix 23-1-1～Appendix 24-4-2)

①投与期間終了時

雄では 62.5 および 250 mg/kg 投与群の各 1 例において潜血が認められた。1000 mg/kg 投与群において尿量が対照群と比較して有意(P<0.01)に増加し、尿中電解質濃度の減少傾向および尿中電解質排泄量の増加傾向が認められた。尿は対照群と比較して酸性を示した。

雌では 1000 mg/kg 投与群において尿量が増加傾向を示した。ナトリウム排泄量が対照群と比較して有意(P<0.05)に増加し、尿中電解質濃度の減少傾向および尿中電解質排泄量の増加傾向が認められた。尿は対照群と比較して酸性を示し、尿蛋白およびケトン体が増加した。

②回復期間終了時

雄では対照群と 1000 mg/kg 投与群との間に有意差は認められなかった。

雌の 1000 mg/kg 投与群において、比重(P<0.05)、ナトリウムイオン濃度、カリウムイオン濃度および塩素イオン濃度が有意(P<0.01)な高値を示した。また、カリウムイオン排泄量および塩素イオン排泄量も有意(P<0.05)な高値を示した。

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

①投与期間終了時

雄では、1000 mg/kg 投与群の単球比率が有意(P<0.05)に増加した。

分娩雌では、250 mg/kg 投与群の単球比率が有意(P<0.05)に低下した。

1000 mg/kg 投与群の非交配雌では、血小板数が有意(P<0.01)に減少し、単球比率が有意(P<0.05)に増加した。また、プロトロンビン時間が有意(P<0.01)に延長、活性化部分トロンボプラスチン時間が有意(P<0.05)に短縮した。

②回復期間終了時

雄では、1000 mg/kg 投与群の赤血球数が有意(P<0.01)に減少し、平均赤血球容積および平均赤血球血色素量が有意(P<0.05)に増加した。また、好塩基球比率が有意(P<0.05)に低下した。

雌では、1000 mg/kg 投与群の単球比率が有意(P<0.05)に低下した。

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

①投与期間終了時

雄では、250 mg/kg 以上の投与群においてグルコース濃度、トリグリセライド濃度および乳酸脱水素酵素活性の高値が認められ、250 mg/kg 投与群においては有意差(P<0.01 あるいは P<0.05)が認められた。また、1000 mg/kg 投与群において胆汁酸濃度が増加傾向を示し、総ビリルビン濃度が有意(P<0.05)に増加した。

分娩雌では、乳酸脱水素酵素活性が 250 mg/kg 以上の投与群で増加傾向を示し、胆汁酸濃度が 1000 mg/kg 投与群で増加傾向を示した。

1000 mg/kg 投与群の非交配雌では、胆汁酸濃度および総ビリルビン濃度が有意(P<0.05)な高値を示し、アラニンアミノトランスフェラーゼ活性および尿素窒素濃度が有意(P<0.05)な低値を示した。

②回復期間終了時

雄では、1000 mg/kg 投与群においてカルシウム濃度が有意(P<0.05)な低値を示した。

雌では、1000 mg/kg 投与群においてカルシウム濃度が有意(P<0.05)な高値を示し、ナトリウムイオン濃度および塩素イオン濃度が有意(P<0.05)な低値を示した。

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

①投与期間終了時

雄では、62.5 mg/kg 投与群において左精巣の実重量が有意(P<0.05)に増加し、1000 mg/kg 投与群において腎臓の実重量が増加傾向を示し、左腎臓の実重量に有意差(P<0.05)が認められた。また、肝臓重量は実重量、相対重量ともに増加傾向を示した。

分娩雌では、250 mg/kg 投与群において左腎臓の実重量が有意(P<0.05)に減少し、1000 mg/kg 投与群において肝臓の実重量および相対重量が有意(P<0.01)に増加した。

1000 mg/kg 投与群の非交配雌では、腎臓の実重量が増加傾向を示し、右腎臓の実重量に有意差(P<0.05)が認められた。また、肝臓の実重量(P<0.05)および相対重量(P<0.01)が有意に増加した。

②回復期間終了時

雄では 1000 mg/kg 投与群において脾臓の実重量および相対重量が有意(P<0.05)に減少した。

雌では 1000 mg/kg 投与群において腎臓の実重量および相対重量、卵巣の実重量および相対重量が有意(P<0.01)に増加した。

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

①雄の投与期間終了時屠殺例

1000 mg/kg 投与群において、腎臓の大型化が 1 例、肝臓に白色斑が 1 例、それぞれ観察された。また、対照群では肝臓の横隔膜結節が 1 例観察された。左側上切歯が欠損していた対照群の 1 例では前胃粘膜が水腫様(一部暗色領域)を呈していた。

②雄の回復期間終了時屠殺例

1000 mg/kg 投与群において、前胃粘膜の肥厚および水腫様が 1 例、背側皮膚の痂皮が 1 例、それぞれ認められた。

③雌の投与期間終了時屠殺例

哺育 5 日剖検例では、1000 mg/kg 投与群の 1 例に胸腺の小型化が認められた。腺胃粘膜の暗色点(領域)が 62.5 mg/kg 投与群および対照群に各 1 例観察された。

生後 4 日に全出生児が死亡した 1000 mg/kg 投与群の 1 例では、腎臓および脾臓の大型化、胸腺の小型化が観察された。

未分娩であった 250 mg/kg 投与群の 1 例では脾臓の小型化が認められ、子宮内(左子宮角)に死亡胎児が 1 匹認められた。なお、未分娩(不妊)であった 1000 mg/kg 投与群の 2 例には、肉眼的観察に異常は認められなかった。

④非交配(サテライト)群の投与期間終了時屠殺例

1000 mg/kg 投与群において、下垂体に嚢胞が 1 例、腺胃粘膜に暗色点が 1 例、それぞれ認められた。

⑤非交配(サテライト)群の回復期間終了時屠殺例

脾臓の小型化および背側皮膚に痂皮が 1000 mg/kg 投与群に各 1 例、腺胃粘膜に白色の突出域が対照群の 1 例に、それぞれ認められた。

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

①雄の投与期間終了時屠殺例

肺では肺胞内に泡沫細胞の集簇が対照群の 1 例および 1000 mg/kg 投与群の 3 例に、小肉芽腫が両群の各 2 例に、動脈壁の鉱質沈着が 1000 mg/kg 投与群の 2 例に観察された。

肝臓では小肉芽腫が対照群の 3 例および 1000 mg/kg 投与群の 4 例に観察された。剖検時に肉眼的所見があった 1000 mg/kg 投与群の 1 例では被膜下に限局性の線維化が認められ、対照群の 1 例では横隔膜結節が観察された以外には著変はなかった。

脾臓では褐色色素の沈着および髄外造血像が、対照群および 1000 mg/kg 投与群の全例に観察された。

腎臓では皮質に塩基性尿細管が対照群の 2 例および 1000 mg/kg 投与群の 3 例に、間質へのリンパ球浸潤が対照群の 2 例および 1000 mg/kg 投与群の 1 例に、被膜下の限局性の線維化が 1000 mg/kg 投与群の 1 例に観察された。

胃では 1000 mg/kg 投与群の腺胃粘膜下織に水腫および炎症細胞浸潤が各 1 例、腺胃胃底腺の嚢胞状拡張が 1 例、それぞれ認められた。また、剖検時に肉眼的所見のあった対照群の 1 例では前胃粘膜下織に炎症細胞浸潤をともなった潰瘍が観察された。

精巣では、精細管の委縮が対照群の 2 例に観察された。

精巣上体では、間質にリンパ球浸潤が対照群および 1000 mg/kg 投与群の各 1 例に、対照群の 1 例では管腔内に細胞残屑が観察された。

前立腺では、間質にリンパ球浸潤が 1000 mg/kg 投与群の 2 例に観察された。

その他、1000 mg/kg 投与群では膵臓腺房細胞の限局性の委縮が 1 例、ハーダー腺の間質にリンパ球浸潤が 2 例に観察された。また、対照群では下垂体の嚢胞が 1 例、心臓では心筋(左心室)の線維化が 1 例に、それぞれ観察された。

なお、いずれの所見も両群間に程度および頻度に差は認められなかった。

その他の組織学検査対象器官・組織には、病理組織学的変化は認められなかった。

②雄の回復期間終了時屠殺例

剖検時に肉眼的所見が認められた 1000 mg/kg 投与群の胃では、前胃の扁平上皮過形成、粘膜下織の水腫が観察された。

③雌の投与期間終了時屠殺例(哺育 5 日剖検)

肺では肺胞内に泡沫細胞の集簇が対照群および 1000 mg/kg 投与群の各 3 例に、小肉芽腫が対照群の 1 例に観察された。

肝臓では門脈周囲性の肝細胞脂肪化が対照群の 2 例および 1000 mg/kg 投与群の 1 例に、小肉芽腫が対照群の 2 例および 1000 mg/kg 投与群の 3 例に、髄外造血が対照群および 1000 mg/kg 投与群の各 1 例に観察された。また、対照群の 1 例に限局性の壊死が観察された。

脾臓では褐色色素の沈着および髄外造血像が対照群および 1000 mg/kg 投与群の全例に観察された。剖検時に肉眼的所見があった 250 mg/kg 投与群の 1 例では、褐色色素の沈着および髄外造血像が認められたが、他動物と程度に違いはなかった。

腎臓では 1000 mg/kg 投与群に皮質に塩基性尿細管が 1 例、間質へのリンパ球浸潤が 1 例、皮髄境界部に鉱質沈着が 1 例、それぞれ観察された。

胃では腺胃胃底腺の嚢胞状拡張が 1000 mg/kg 投与群に 1 例、腺胃粘膜下織の水腫が対照群の 1 例に認められた。また、剖検時に肉眼的所見があった対照群および 62.5 mg/kg 投与群の各 1 例では、腺胃粘膜下織の水腫および腺胃胃底腺の嚢胞状拡張が観察されたがごく軽度の変化であった。

卵巣、子宮および膣には病理組織学的変化は観察されなかった。

その他、1000 mg/kg 投与群では甲状腺に鰓後体遺残が 2 例、心臓では心筋(左心室)の線維化が 1 例、観察された。また、対照群では下垂体に嚢胞が 1 例観察された。

なお、いずれの所見も両群間に程度および頻度に差は認められなかった。

その他の組織学検査対象器官・組織には、病理組織学的変化は認められなかった。

哺育 4 日に全哺育児が死亡した 1000 mg/kg 投与群の 1 例の病変部(胸腺、脾臓、腎臓)を観察した結果、胸腺の委縮、脾臓では褐色色素の沈着および髄外造血像が認められた。髄外造血の程度は他動物よりも強かった。腎臓では、皮質に好塩基尿細管、近位尿細管の変性/壊死および遠位尿細管の限局性の拡張、間質へのリンパ球浸潤が観察された。

④非交配(サテライト)群の投与期間終了時屠殺例

肺では肺胞内に泡沫細胞の集簇が対照群の 2 例、1000 mg/kg 投与群の 4 例に、小肉芽腫が 1000 mg/kg 投与群の 2 例に観察された。

肝臓では門脈周囲性の肝細胞脂肪化が 1000 mg/kg 投与群の 2 例に、小肉芽腫が対照群の 4 例および 1000 mg/kg 投与群の 5 例に、髄外造血が 1000 mg/kg 投与群の 1 例に観察された。

脾臓では褐色色素の沈着および髄外造血像が、対照群および 1000 mg/kg 投与群の全例に観察された。

腎臓では皮質に塩基性尿細管が対照群の 1 例および 1000 mg/kg 投与群の 4 例に、間質へのリンパ球浸潤が対照群の 1 例および 1000 mg/kg 投与群の 3 例に、皮髄境界部あるいは乳頭部に鉱質沈着が 1000 mg/kg 投与群の 3 例に、皮髄境界部あるいは乳頭部に嚢胞あるいは硝子円柱が 1000 mg/kg 投与群の 3 例に、それぞれ観察された。

胃では腺胃胃底腺の嚢胞状拡張が対照群および 1000 mg/kg 投与群に各 1 例、腺胃粘膜下織の水腫が対照群の 2 例に認められた。

卵巣、子宮および膣には病理組織学的変化は観察されなかった。

その他、下垂体に嚢胞が対照群および 1000 mg/kg 投与群の各 1 例に、ハーダー腺間質にリンパ腔浸潤が 1000 mg/kg 投与群の 1 例に、甲状腺に鰓後体遺残が対照群の 1 例に観察された。

なお、いずれの所見も両群間に程度および頻度に差は認められなかった。

また、1000 mg/kg 投与群の 1 例で上皮小体が組織切片上になく観察できなかった。

その他の組織学検査対象器官・組織には、病理組織学的変化は認められなかった。

⑤非交配(サテライト)群の回復期間終了時屠殺例

剖検時に肉眼的所見が認められた対照群の胃では、病理組織学的変化は認められなかった。

腎臓では間質にリンパ球浸潤が対照群および 1000 mg/kg 投与群に各 1 例観察されたが、程度に差は認められなかった。また、皮髄境界部に鉱質沈着が 1000 mg/kg 投与群に 1 例観察されたが、ごく軽度な変化であった。その他、対照群において、皮質に好塩基性尿細管が 1 例、皮髄境界部に嚢胞が 1 例観察された。

2. 生殖能力

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

1000 mg/kg 投与群では、投与開始後、性周期は 4 あるいは 5 日の間隔で正常に回帰したが、平均発情回帰日数が有意(P<0.05)に延長した。250 mg/kg 以下の投与群では平均発情回帰日数には変化はみられなかった。交配の結果、全ての動物において交尾が確認され、交尾までの日数およびその間に回帰した発情期の回数に、対照群と MMP 各投与群との間に有意差は認められなかった。

1000 mg/kg 投与群の 2 例(動物番号 F04038 および F04044)は、交尾は確認されたが妊娠していなかった(後述)。それ以外の動物は妊娠が確認された。

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

出産率には対照群と MMP 各投与群との間に差は認められなかった。

妊娠期間は 1000 mg/kg 投与群において対照群と比較して有意(P<0.01)に延長した。250 mg/kg 以下の投与群の妊娠期間には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 37-1～Appendix 37-4)

250 mg/kg 投与群の 1 例(動物番号 F03030)、1000 mg/kg 投与群の 2 例(動物番号 F04038 および F04044)は妊娠 25 日までに分娩が確認されなかった。剖検の結果、250 mg/kg 投与群の 1 例では妊娠黄体および着床痕(黄体数 6、着床数 1)が認められ、子宮内に 1 匹の死亡胎児が認められた。1000 mg/kg 投与群の 2 例では着床痕および妊娠黄体は認められず、不妊と判断した。これら以外の全ての妊娠動物は妊娠 22 あるいは 23 日に出産した。

1000 mg/kg 投与群の 1 例(動物番号 F04043)は、分娩終了後に児を集める行動がみられず、出生児の半数(12 匹のうち 6 匹)が死亡していたことから分娩状態不良と判断した。この腹では哺育 1 日には児 5 匹の死亡が認められ、哺育 4 日に全哺育児が死亡した。その他の動物の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 MMP 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 37-1～Appendix 37-4)

分娩率および性比には、対照群と MMP 各投与群との間に有意差は認められなかった。

1000 mg/kg 投与群では、対照群と比較して産児数(P<0.05)および出産生児数(P<0.01)が有意に減少した。

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

哺育 0 および 4 日における出生児の体重には、対照群と MMP 各投与群との間に顕著な差は認められなかった。

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

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、母動物の喰殺により存在が不明になったと推察される児(不明児)、あるいは死後の自己融解により内部器官が観察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ず、内部器官の観察が可能であった死亡児についても内部器官に異常は認められなかった。

哺育 4 日の出生児剖検の結果、対照群の児 3 匹(母動物番号 F01008)に削痩が観察された。この母動物は哺育 3～4 日の摂餌量が他動物より少なく、哺育期間中の体重増加量も他動物と比較して少なかった。その他の動物に異常は認められなかった。

考察

雌雄ラットの交配前および交配期間中、ならびに雄では交配期間終了後を通して計 42 日間、生殖能を評価した交配雌では妊娠期間を通して哺育 4 日まで 41～44 日間、非交配雌では雄と同様の期間、未分娩例は妊娠25日相当日まで42～54日間、Methyl 3-methoxypropanoateを強制経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

1. 反復投与毒性学的所見

1000 mg/kg 投与群では投与後の一過性の流涎が雌雄に観察され、詳細な症状観察においても雌 1 例で観察された。しかし、詳細な症状観察の他の項目では神経毒性を示唆する変化は観察されず、投与後一過性の変化であること、また、同量を投与した予備試験の雄においても観察されている[1]ことから、被験物質の刺激性に起因した変化であると考えられた。

同群では投与開始直後に 1000 mg/kg 投与群の雌雄および哺育期間中の分娩雌に摂餌量減少がみられ、被験物質投与による変化と考えられた。また、250 mg/kg 以下の投与群の摂餌量に有意差がみられた測定点が散見されたが、いずれも僅かな変化であることから被験物質投与による影響ではないと判断した。

また、酸性を示した尿量の増加、尿中電解質濃度の変動が雌雄ともに認められ、さらに雌では尿蛋白、ケトン体およびナトリウム排泄量が増加したことから MMP の 1000 mg/kg 投与は腎臓の排泄機能に影響を及ぼすと考えられた。しかし、腎臓および膀胱の病理組織学的な検査では被験物質投与によると考えられる変化は認められなかった。その他、雄の 62.5 および 250 mg/kg 投与群の各 1 例に潜血陽性尿が

認められたが、1000 mg/kg 投与群では認められなかったことから偶発的な変化であり被験物質投与による影響ではないと考えた。

さらに、血小板数の減少、プロトロンビン時間の延長、活性化部分トロンボプラスチン時間の短縮が非交配雌において認められたことから MMP の 1000 mg/kg 投与群は血液凝固系にも影響を及ぼす可能性が示唆された。しかし、同群の一般状態観察および剖検所見から出血および貧血傾向は認められず、脾臓の重量変化および造血系に関連する組織に病理組織学的な異常は認められなかった。その他、250 および 1000 mg/kg 投与群で白血球分類比の変動が認められたが、白血球数に変化がみられないこと、感染症を示唆する変化も認められていないことから、被験物質投与の影響ではないと判断した。

LDH 活性の上昇が 250 mg/kg 以上の投与群の雄および分娩雌に認められた。LDH は肝臓、腎臓および心臓に比較的多く存在し、細胞の障害時に血中に逸脱する酵素である。本試験の結果、器官重量および病理組織学的検査において心臓障害を示唆する変化は認められなかった。しかし、肝臓および腎臓障害の指標となる胆汁酸濃度および総ビリルビン濃度の高値が 1000 mg/kg 投与群の雌雄(分娩雌を除く)でみられ、さらにグルコース濃度およびトリグリセライド濃度の高値も 250 mg/kg 以上の投与群の雄で観察された。軽度ではあるが肝臓および腎臓重量が 1000 mg/kg 投与群の雌雄ともに増加し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関連した変化と考えられた。しかし、肝臓および腎臓の病理組織学的検査では被験物質投与の影響と考えられる変化は認められなかった。また、1000 mg/kg 投与群の非交配雌では ALT 活性および尿素窒素濃度が低値を示したが、雄には認められない変化であること、これらの値の低値は毒性学的に意義が乏しいことから被験物質投与の影響ではないと判断した。

その他、62.5 mg/kg 投与群の雄において精巣重量が増加し、250 mg/kg 投与群の分娩雌において左腎臓の重量が減少したが、これらは僅かな変化であり、被験物質投与に関連すると考えられる病理組織学的な変化が観察されていないこと、用量依存的ではないことから偶発的な変化であり被験物質投与による影響ではないと判断した。

2. 毒性の回復性

14 日間の回復期間終了後、腎臓障害に起因すると考えられる尿比重、尿中電解質濃度および尿中電解質排泄量の増加が 1000 mg/kg 投与群の雌で認められた。腎臓重量が増加していることからも 14 日間の回復期間終了後も腎臓への影響は継続していると推察された。しかし、被験物質の影響を示唆する病理組織学的な変化は認められず、投与期間終了時にみられた尿量の増加は認められていないことから回復性を示す変化であると考えられた。また、同群ではカルシウム濃度の高値、ナトリウムイオン濃度および塩素イオン濃度の低値がみられ、雄の 1000 mg/kg 投与群ではカルシウム濃度が低値を示したが、僅かな変化であることから、被験物質投与による影響ではないと判断した。

1000 mg/kg 投与群の雄において赤血球数が減少し、平均赤血球容積および平均赤血球血色素量が増加した。しかし、2012 年～2013 年に実施した同種試験の媒体対照群(媒体:注射用水、動物数 25 匹)の背景値(平均値±2SD:843±92×10^4/μL、最小値～最大値:728～952×10^4/μL)と比較すると背景値

の範囲内であった。さらに、血色素量、ヘマトクリット値および網状赤血球比率に変化がみられないこと、脾臓重量に変化はみられず、病理組織学検査の結果においても髄外造血の亢進は認められないことから被験物質投与による影響ではないと判断した。

その他、1000 mg/kg 投与群の雄では好塩基球数の減少、雌では単球数の減少がみられたが、僅かな変化であることから偶発的な変化であり被験物質投与による影響ではないと判断した。また、同群の雄では脾臓重量の減少、雌では卵巣重量の増加が認められた。血液学的検査および血液生化学的検査において貧血を示唆する変化は認められず、剖検においても異常は認められなかったこと、投与期間中に同様の変化がみられなかったことから、偶発的な変化であり被験物質投与による影響ではないと判断した。

3. 生殖発生毒性学的所見および出生児所見

平均発情回帰日数および妊娠期間の延長が 1000 mg/kg 投与群で認められたことから、MMP は発情周期および妊娠期間に影響を及ぼすと考えられた。

交尾率には影響はみられなかったが、1000 mg/kg 投与群では 2 例に不妊が認められた。1 例は 5 日の間隔で正常に回帰していたが、発情周期の 4 日目に交尾が確認された。別の 1 例は投与後に発情周期が 4 日から 5 日の間隔に延長し、雄動物との同居翌日から発情周期が回帰しなくなったが、14 日経過後に交尾が確認された。各動物の発情周期から推察すると、2 例とも予想される交尾日の前日に腟栓が確認されたことから、交尾適期ではなかったことが不妊の原因として考えられた。しかし、対照群と比較して差が認められないことから、MMP は妊娠率に影響を及ぼさないと考えられた。

産児数および出産生児数の減少が 1000 mg/kg 投与群で認められた。黄体数および着床数に顕著な変化は認められず、子宮内に吸収胚が観察されなかったことから、児数の減少は子宮内死亡の増加が原因ではなく、分娩時に死亡児数が増加したことに起因する変化であり、被験物質投与による影響と考えられた。また、同群では哺育 4 日に全哺育児が死亡した腹が 1 例認められた。この動物は妊娠後期から摂餌量減少が認められ、生後 1 日までにほとんどの児が死亡し、生児は 1 匹のみであった。しかし、同群の他動物は正常に分娩し、哺育状態も良好であった。哺育児が全例死亡した母動物には赤色尿も観察されたことから、母動物の一般状態が悪化した二次的な変化と考えられ、MMP は分娩および哺育状態に影響を及ぼさないと考えられた。また、生後 4 日までの生存率にも被験物質投与による影響は認められなかった。

250 mg/kg 投与群の 1 例は妊娠 26 日まで分娩が確認されず、子宮内に 1 匹の死亡胎児が認められた。しかし、着床数が少ない時に観察される事象であること、発現頻度が低いことから、この動物の着床数が少なかったことに起因する偶発的な変化であり被験物質投与による影響ではないと考えられた。

4. 無毒性量

以上の結果から、本試験条件下における Methyl 3-methoxypropanoate の親動物に対する一般毒性学的無毒性量は一般状態、血液学的検査、血液生化学的検査、器官重量結果から雌雄ともに

62.5 mg/kg/day、生殖発生毒性学的な無毒性量は平均発情回帰日数および妊娠期間の延長、産児数および出産生児数の減少が認められたことから 250 mg/kg/day、次世代児に対する無毒性量は産児数および出産生児数の減少が認められたことから 250 mg/kg/day と考えられた。また、腎臓障害は 14 日間の回復期間終了後も消失しなかったが、投与期間終了時にみられた尿量の増加は認められていないことから回復性を示す変化であると考えられた。

参考文献

1) Methyl 3-methoxypropanoate 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)

Annex A

検査成績書

2013年6月14日
和光純薬工業株式会社

財団法人食品薬品安全センター　御中

[redacted]

Code No.134-10885

3-メトキシプロピオン酸メチル

規格／等級	和光特級
Lot No.	WEE5103
数量	500ml × 4

検査項目	検査成績	規格値
外観	無色澄明の液体	無色澄明の液体
水分	0.00%	0.1%以下
酸(CH3CH2COOHとして)	0.03%以下	0.03%以下
含量(毛管カラムGC)	100.0%	99.0%以上
検査年月日	2012/12/18	

判　定	合格	検査責任者	[redacted]

(1/1)　　成績書発行番号　9031648

Annex B

試験番号	R－13－004

含　量　試　験　結　果

被験物質：Methyl 3-methoxypropanoate　　調製年月日：2013年9月30日
ロット番号：WEE5103　　測定年月日：2013年9月30日
媒　　体：注射用水

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 (%)
1	12.5	12.3	12.2	98.4	97.9	100.8
2		12.4		99.2		101.6
3		12.0		96.0		98.4
4	50.0	48.2	49.1	96.4	98.3	98.2
5		49.5		99.0		100.8
6		49.7		99.4		101.2
7	200	202	201	101.0	100.7	100.5
8		200		100.0		99.5
9		202		101.0		100.5

含量の許容基準(溶液検体)

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate 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
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
MMP 62.5 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
MMP 250 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
MMP 1000 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	12	7	12	10	12	9	12	9	12	8	12	7	12	6	12	7	12	7	12	8	12	4	12	6	12	6	12	5
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	5	0	2	0	3	0	3	0	4	0	5	0	6	0	5	0	5	0	4	0	8	0	6	0	6	0	7

Pre: Before administration, Post: after administration.

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
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	6
	Mouth, Loss of teeth	0	0	0	0	0	0	0	0	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	1
MMP 62.5 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
MMP 250 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
MMP 1000 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	General appearance, No abnormality	12	6	12	6	12	4	12	3	12	3	12	7	12	6	12	4	12	9	12	9	12	5	12	10	12	6	12	4	12	6	12	8	12	6	7
	Mouth, Salivation	0	6	0	6	0	8	0	9	0	9	0	5	0	6	0	8	0	3	0	3	0	7	0	2	0	6	0	8	0	6	0	4	0	6	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate 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	15
Control (vehicle: water for injection)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
MMP 1000 mg/kg	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	4	4	4	4	4	4	4	4
	Skin, Crust formation	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate 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
Control (vehicle: water for injection)	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	5	5	1	1
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	5	5	1	1
MMP 62.5 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	7	7	4	4
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	7	7	4	4
MMP 250 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	3	3	1	1
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	3	3	1	1
MMP 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	8	8	6	6	1	1
	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	7	10	8	10	8	10	9	10	8	8	7	6	5	1	1
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	2	0	2	0	1	0	2	0	1	0	1	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate 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
Control (vehicle: water for injection)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
MMP 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
	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	8	10	7	10	7	10	8	10	9	10	8	10	8	10	7	10	7	10	7	10	5	10	7	10	3	10	6	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	2	0	3	0	3	0	2	0	1	0	2	0	2	0	3	0	3	0	3	0	5	0	3	0	7	0	4	0	5

Pre: Before administration, Post: after administration.

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	Pré	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	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	10	10	10	10	10	10	10	10	10	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
MMP 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	7	10	7	10	5	10	6	7	10	10	6	10	8	10	4	10	9	10	9	10	7	10	8	10	6	10	6	10	3	10	9	10	4	5
	Mouth, Salivation	0	3	0	3	0	5	0	4	3	0	0	4	0	2	0	6	0	1	0	1	0	3	0	2	0	4	0	4	0	7	0	1	0	6	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate 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
Control (vehicle: water for injection)	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
MMP 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	4	4	4
	Skin, Crust formation	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate 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
Control (vehicle: water for injection)	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	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
MMP 62.5 mg/kg	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	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
MMP 250 mg/kg	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	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
MMP 1000 mg/kg	Number of dams	10	10	10	10	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	8	10	9	10	9	10	5	10	6	10	9	10	5	10	5	10	6	10	7	10	7	10	5	10	5	10	6
	Mouth, Salivation	0*	2	0	1	0	1	0	5	0	4	0	1	0	5	0	5	0	4	0	3	0	3	0	5	0	5	0	4

Pre: Before administration, Post: after administration.

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		24		25		26
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	0	0	0	0	0	0	0
MMP 62.5 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	0	0	0	0	0	0	0
MMP 250 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	1	1	1	1	1	1	1
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	1	1	1	1	1	1	1
MMP 1000 mg/kg	Number of dams	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	0	0	0	0	0	0	0
	General appearance, No abnormality	10	7	10	6	10	9	10	8	10	9	10	9	10	8	10	7	9	8	0	0	0	0	0	0	0
	Mouth, Salivation	0	3	0	4	0	1	0	2	0	1	0	1	0	2	0	3	0	1	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate 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
Control (vehicle: water for injection)	Number of dams	8	8	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	8	8	12	12	12	12	12	12	12	12	12
MMP 62.5 mg/kg	Number of dams	9	9	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	9	9	12	12	12	12	12	12	12	12	12
MMP 250 mg/kg	Number of dams	4	4	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	4	4	11	11	11	11	11	11	11	11	11
MMP 1000 mg/kg	Number of dams	6	6	10	10	10	10	10	10	10	9	9
	General appearance, No abnormality	5	5	10	8	10	8	10	8	10	7	9
	Mouth, Salivation	0	1	0	2	0	2	0	2	0	2	0
	Excretion, Reddish urine	1	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 Methyl 3-methoxypropanoate by oral administration in rats

Table 5. Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery [a]	
				7	14	23	30	36	42	7	14
[Piloerection]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	1	0	0
	MMP 62.5 mg/kg	12	0	0	0	0	0	0	0		
	MMP 250 mg/kg	12	0	0	0	0	0	0	0		
	MMP 1000 mg/kg	12	0	0	0	0	0	0	0	0	0
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	12	1 [c]	1	0	0	1	1	2	1	2
	MMP 62.5 mg/kg	12	2	2	1	2	2	2	0		
	MMP 250 mg/kg	12	0	1	0	1	0	1	0		
	MMP 1000 mg/kg	12	1	3	1	4	3	5	1	1	0

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

[b] Values represent number of animals with the findings.

[c] Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate 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	
				7	14	23	30	36	42		49			
[Salivation]	Control (vehicle: water for injection)	12	0 [a]	0	0	0	0	0					0	
	MMP 62.5 mg/kg	12	0	0	0	0	0	0					0	
	MMP 250 mg/kg	12	0	0	0	0	0	0	0	(1)			0	(11)
	MMP 1000 mg/kg	12	0	0	0	0	1	0	0	(2)	0	(1)	0	(10)
[Straub tail]	Control (vehicle: water for injection)	12	0 [a]	0	0	0	1	0					0	
	MMP 62.5 mg/kg	12	0	0	0	0	0	0					0	
	MMP 250 mg/kg	12	0	0	0	0	0	0	0	(1)			0	(11)
	MMP 1000 mg/kg	12	0	0	0	0	0	0	0	(2)	0	(1)	0	(10)
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0					0	
	MMP 62.5 mg/kg	12	0	0	0	0	0	0					0	
	MMP 250 mg/kg	12	0	0	0	0	0	0	0	(1)			0	(11)
	MMP 1000 mg/kg	12	1	0	0	1	0	0	0	(2)	0	(1)	0	(10)

[a] Values represent number of animals with the findings.

[b] Values represent total score of each group.

Figures in parentheses indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery [a]	
				7	14	23	30	36	42	7	14
[Straub tail]	Control (vehicle: water for injection)	10	0 [b]	0	0	1	1	1	1	1	1
	MMP 1000 mg/kg	10	0	0	0	0	0	0	0	0	0
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	10	1 [c]	0	0	0	0	0	0	0	0
	MMP 1000 mg/kg	10	1	0	0	0	0	0	0	0	0

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

[b] Values represent number of animals with the findings.

[c] Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 7-1. Body weights of male rats

Group		Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males		12	12	12	12
Days of administration					
	1	401.7 ± 14.4	400.6 ± 11.5	398.9 ± 14.0	397.4 ± 11.0
	4	414.0 ± 14.2	412.9 ± 11.8	409.4 ± 14.4	405.5 ± 14.5
	7	427.1 ± 15.8	422.6 ± 13.1	423.2 ± 17.4	421.8 ± 16.4
	14	448.5 ± 18.1	446.4 ± 14.0	444.2 ± 19.3	446.3 ± 18.1
	21	462.8 ± 17.1	462.1 ± 12.8	461.5 ± 23.7	466.4 ± 19.9
	28	481.7 ± 18.8	483.6 ± 15.6	478.3 ± 27.1	482.2 ± 21.6
	35	496.1 ± 18.1	501.0 ± 19.2	495.3 ± 29.9	498.5 ± 25.5
	42	496.5 ± 23.3	513.6 ± 19.5	507.6 ± 29.8	507.8 ± 30.3

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of males	5	5
Days of recovery		
1	505.2 ± 10.0	508.7 ± 37.0
7	524.6 ± 6.2	534.6 ± 39.3
14	531.9 ± 11.0	535.8 ± 47.9

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 8-1. Body weights of female rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of females	12	12	12	12
Days of administration				
1	247.7 ± 11.6	247.2 ± 10.7	242.9 ± 11.2	250.3 ± 9.7
4	251.9 ± 10.7	251.9 ± 12.2	252.3 ± 11.5	252.1 ± 12.3
7	256.9 ± 12.9	254.9 ± 17.3	257.0 ± 10.8	258.7 ± 10.8
14	264.7 ± 17.4	263.1 ± 19.1	268.5 ± 10.9	271.4 ± 13.5

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	10	10
Days of administration		
1	245.8 ± 10.9	252.6 ± 8.3
4	252.0 ± 12.4	256.3 ± 11.8
7	257.0 ± 11.4	264.3 ± 9.4
14	266.2 ± 13.1	279.0 ± 12.2 *
21	272.5 ± 16.8	283.9 ± 13.1
28	280.4 ± 21.6	291.6 ± 16.3
35	286.4 ± 23.0	296.3 ± 13.0
42	292.5 ± 20.1	304.8 ± 18.0

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	5	5
Days of recovery		
1	284.7 ± 30.9	304.6 ± 21.1
7	298.8 ± 31.2	307.1 ± 23.1
14	292.7 ± 31.0	312.3 ± 20.7

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 9. Body weights of dams during pregnancy

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of dams	12	12	12	10
Days of pregnancy				
0	273.0 ± 14.3	274.8 ± 20.0	273.6 ± 10.4	281.7 ± 10.6
7	311.6 ± 15.1	314.1 ± 22.1	312.9 ± 14.2	319.8 ± 9.9
14	351.4 ± 15.4	351.8 ± 27.2	347.2 ± 18.5	353.5 ± 13.0
20	442.3 ± 23.7	437.9 ± 33.7	426.7 ± 33.5	426.4 ± 17.9

Each value shows mean ± S.D. (g).

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 10. Body weights of dams during lactation

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of dams	12	12	11	10
Days of lactation				
0	331.1 ± 22.7	339.4 ± 27.3	330.0 ± 17.1	339.2 ± 21.6
4	347.1 ± 21.1	346.6 ± 24.3	342.9 ± 17.2	352.3 ± 21.0

Each value shows mean ± S.D. (g).

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 11-1. Food consumption of male rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males	12	12	12	12
Days of administration				
1	29.2 ± 3.5	29.4 ± 1.2	29.4 ± 2.1	23.4 ± 2.3 **
7	30.0 ± 2.5	29.2 ± 2.0	30.8 ± 2.4	28.3 ± 1.5
14	25.6 ± 2.3	27.0 ± 1.9	27.1 ± 2.4	25.5 ± 1.8
29	28.2 ± 2.4	29.8 ± 2.0	28.6 ± 2.1	27.2 ± 3.0
35	29.1 ± 2.1	30.5 ± 2.1	30.0 ± 2.6	28.5 ± 1.8
41	26.2 ± 1.9 (11)	29.2 ± 2.3 **	29.4 ± 2.0 **	27.9 ± 2.2

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of males	5	5
Days of recovery		
6	27.2 ± 3.4	31.1 ± 0.6 *
12	31.2 ± 2.7	32.8 ± 1.5

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 12-1. Food consumption of female rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of females	12	12	12	12
Days of administration				
1	20.1 ± 4.2	20.2 ± 1.7	19.3 ± 3.4	18.2 ± 3.5
7	19.5 ± 3.0	20.4 ± 3.5	22.1 ± 2.1	19.6 ± 2.3
14	19.8 ± 2.9	19.6 ± 3.6	20.6 ± 2.1	20.3 ± 2.5

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	10	10
Days of administration		
1	20.4 ± 2.5	18.3 ± 1.6 *
7	19.6 ± 2.9	20.5 ± 2.3
14	20.0 ± 3.3	20.1 ± 2.2
21	20.9 ± 2.4	21.9 ± 3.1
29	20.7 ± 2.3	22.7 ± 2.7
35	20.6 ± 3.7	20.7 ± 3.3
41	19.7 ± 3.0	20.0 ± 2.6

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	5	5
Days of recovery		
6	21.7 ± 3.4	20.4 ± 3.3
12	18.7 ± 1.7	20.8 ± 4.7

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 13. Food consumption in dams during pregnancy

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of dams	12	12	12	10
Days of pregnancy				
0	21.8 ± 1.8	22.1 ± 4.0	22.3 ± 2.5	21.9 ± 2.8
7	28.0 ± 3.6	27.9 ± 3.5	27.1 ± 3.9	26.1 ± 2.6
14	28.5 ± 2.8	28.2 ± 3.4	27.8 ± 4.7	27.7 ± 2.7
20	25.7 ± 4.0	26.8 ± 3.0	23.9 ± 2.7	21.3 ± 8.2

Each value shows mean ± S.D. (g).

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 14. Food consumption in dams during lactation

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of dams	12	12	11	10
Days of lactation				
3	42.3 ± 11.2	42.3 ± 4.2	40.5 ± 5.0	33.8 ± 9.6 *

Each value shows mean ± S.D. (g).

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 15. Functional findings of male rats at the end of the dosing period

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
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
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Female, dam				
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
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
Female, satellite groups				
Number of animals	5			5
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Preyer's reaction	100			100
Withdrawal reflex	100			100
Eyelid reflex	100			100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 17. Assessment of grip strength of male rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males	5	5	5	5
Administration period				
Forelimb	0.388 ± 0.083	0.531 ± 0.159	0.576 ± 0.208	0.498 ± 0.143
Hindlimb	0.294 ± 0.070	0.408 ± 0.108	0.316 ± 0.044	0.384 ± 0.035

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 Methyl 3-methoxypropanoate by oral administration in rats

Table 18. Assessment of grip strength of female rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of females	5	5	5	5
Administration period				
Forelimb	0.454 ± 0.179	0.496 ± 0.183	0.547 ± 0.171	0.632 ± 0.202
Hindlimb	0.291 ± 0.046	0.331 ± 0.054	0.238 ± 0.040	0.261 ± 0.038

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	5	5
Administration period		
Forelimb	0.542 ± 0.123	0.429 ± 0.178
Hindlimb	0.328 ± 0.075	0.274 ± 0.035

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 Methyl 3-methoxypropanoate by oral administration in rats

Table 20. Motor activity of male rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males	5	5	5	5
Administration period				
Ambulation (counts)				
5min	1045 ± 189	1286 ± 284	1152 ± 126	1194 ± 57
10min	906 ± 162	1219 ± 405	1067 ± 115	1034 ± 181
15min	764 ± 110	1049 ± 359	875 ± 201	910 ± 196
20min	550 ± 147	731 ± 638	852 ± 161	634 ± 132
Total	3265 ± 502	4284 ± 1606	3947 ± 456	3771 ± 515
Rearing (counts)				
5min	27 ± 12	24 ± 6	28 ± 8	30 ± 5
10min	19 ± 6	21 ± 8	23 ± 6	21 ± 9
15min	15 ± 9	16 ± 6	15 ± 8	15 ± 7
20min	9 ± 9	10 ± 10	10 ± 5	6 ± 5
Total	69 ± 32	71 ± 19	76 ± 14	73 ± 21

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 Methyl 3-methoxypropanoate by oral administration in rats

Table 21. Motor activity of female rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of females	5	5	5	5
Administration period				
Ambulation (counts)				
5min	1027 ± 203	1219 ± 117	1121 ± 216	1015 ± 178
10min	820 ± 235	932 ± 140	890 ± 353	817 ± 207
15min	840 ± 196	885 ± 147	907 ± 578	698 ± 180
20min	592 ± 333	585 ± 192	783 ± 213	412 ± 295
Total	3279 ± 740	3620 ± 407	3701 ± 1331	2943 ± 765
Rearing (counts)				
5min	21 ± 8	31 ± 8	22 ± 12	25 ± 8
10min	13 ± 8	14 ± 4	9 ± 6	13 ± 11
15min	13 ± 11	15 ± 9	11 ± 10	11 ± 9
20min	5 ± 6	4 ± 6	6 ± 10	2 ± 4
Total	52 ± 19	64 ± 14	47 ± 29	51 ± 23

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 Methyl 3-methoxypropanoate by oral administration in rats

Table 22. Motor activity of female rats, satellite group

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	5	5
Administration period		
Ambulation (counts)		
5min	1239 ± 77	1140 ± 243
10min	1183 ± 124	1091 ± 284
15min	1090 ± 75	1008 ± 220
20min	1026 ± 232	964 ± 142
Total	4539 ± 413	4202 ± 746
Rearing (counts)		
5min	37 ± 13	34 ± 7
10min	38 ± 17	32 ± 16
15min	30 ± 13	35 ± 15
20min	30 ± 21	27 ± 16
Total	134 ± 59	128 ± 34

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 Methyl 3-methoxypropanoate by oral administration in rats

Table 23-1. Urinalysis in male rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males	5	5	5	5
pH				
≦5.0	0	0	0	0
5.5	0	0	0	0
6.0	0	0	0	1
6.5	0	1	3	4
7.0	3	3	2	0
7.5	1	0	0	0
8.0	1	1	0	0
8.5	0	0	0	0
≧9.0	0	0	0	0
Protein				
- (negative)	0	0	0	0
± (10 ≦ and < 30 mg/dL)	0	1	1	0
+ (30 ≦ and < 100 mg/dL)	5	3	4	5
2+ (100 ≦ and < 300 mg/dL)	0	1	0	0
3+ (300 ≦ and < 600 mg/dL)	0	0	0	0
4+ (600 mg/dL ≦)	0	0	0	0
Glucose				
- (negative)	5	5	5	5
± (30 ≦ and < 70 mg/dL)	0	0	0	0
+ (70 ≦ and < 150 mg/dL)	0	0	0	0
2+ (150 ≦ and < 300 mg/dL)	0	0	0	0
3+ (300 ≦ and < 1,000 mg/dL)	0	0	0	0
4+ (1,000 mg/dL ≦)	0	0	0	0
Ketone				
- (negative)	1	0	2	1
± (5 ≦ and < 10 mg/dL)	4	4	3	4
+ (10 ≦ and < 40 mg/dL)	0	1	0	0
2+ (40 ≦ and < 80 mg/dL)	0	0	0	0
3+ (80 ≦ and < 150 mg/dL)	0	0	0	0
4+ (150 mg/dL ≦)	0	0	0	0
Bilirubin				
- (negative)	5	5	5	5
+ (0.5 ≦ and < 2.0 mg/dL)	0	0	0	0
2+ (2.0 ≦ and < 6.0 mg/dL)	0	0	0	0
3+ (6.0 ≦ and < 10.0 mg/dL)	0	0	0	0
4+ (10.0 mg/dL ≦)	0	0	0	0
Occult blood				
- (negative)	5	4	4	5
± (0.03 ≦ and <0.06 mg/dL)	0	0	0	0
+ (0.06 ≦ and <0.20 mg/dL)	0	0	1	0
2+ (0.20 ≦ and <1.00 mg/dL)	0	1	0	0
3+ (1.00 mg/dL ≦)	0	0	0	0
Urobilinogen				
± (normal)	3	3	5	5
+ (2.0 ≦ and < 4.0 mg/dL)	2	2	0	0
2+ (4.0 ≦ and < 8.0 mg/dL)	0	0	0	0
3+ (8.0 ≦ and < 12.0 mg/dL)	0	0	0	0
4+ (12.0 mg/dL ≦)	0	0	0	0
Color				
light yellow	5	5	5	5
yellow	0	0	0	0
yellowish brown	0	0	0	0
brown	0	0	0	0
bloody	0	0	0	0
Turbidity				
- (negative)	5	5	5	5
± (trace)	0	0	0	0
+ (slight)	0	0	0	0
2+ (moderate)	0	0	0	0
3+ (marked)	0	0	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 23-1 (continued). Urinalysis in male rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males	5	5	5	5
Red Blood cells				
- (not observed)	5	4	5	5
±(1-9/3 visual field)	0	0	0	0
+ (10-99/3 visual field)	0	1	0	0
2+ (100-299/3 visual field)	0	0	0	0
3+ (≧300/3 visual field)	0	0	0	0
White Blood cells				
- (not observed)	5	5	5	5
±(1-9/3 visual field)	0	0	0	0
+ (10-99/3 visual field)	0	0	0	0
2+ (100-299/3 visual field)	0	0	0	0
3+ (≧300/3 visual field)	0	0	0	0
Casts				
- (not observed)	5	5	5	5
±(1-9/3 visual field)	0	0	0	0
+ (10-99/3 visual field)	0	0	0	0
2+ (100-299/3 visual field)	0	0	0	0
3+ (≧300/3 visual field)	0	0	0	0
Cristals				
- (not observed)	0	0	0	2
±(a few)	5	5	5	3
+ (abundant)	0	0	0	0
Epithelial cells				
- (not observed)	5	5	5	5
±(a few)	0	0	0	0
+ (abundant)	0	0	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 23-2. Urinalysis in male rats

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males	5	5	5	5
Urine volume (mL/24hr)	14.0 ± 1.7	14.5 ± 3.4	16.8 ± 3.6	21.2 ± 3.6 **
Specific gravity	1.062 ± 0.016	1.061 ± 0.008	1.062 ± 0.009	1.057 ± 0.010
Electrolyte, density				
Na(mEq/L)	112.3 ± 39.7	100.1 ± 28.3	117.7 ± 20.9	95.6 ± 20.8
K(mEq/L)	266.0 ± 81.2	247.1 ± 57.9	269.0 ± 38.0	232.3 ± 50.4
Cl(mEq/L)	140.5 ± 58.3	108.3 ± 54.0	144.2 ± 23.1	123.9 ± 22.2
Electrolyte, gross volume				
Na(mEq/24hr)	1.56 ± 0.55	1.45 ± 0.47	1.95 ± 0.45	1.98 ± 0.27
K(mEq/24hr)	3.69 ± 1.11	3.59 ± 1.09	4.44 ± 0.72	4.80 ± 0.46
Cl(mEq/24hr)	1.95 ± 0.82	1.65 ± 0.90	2.40 ± 0.56	2.58 ± 0.30

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 Methyl 3-methoxypropanoate by oral administration in rats

Table 23-3. Urinalysis in male rats of the recovery period

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of males	5	5
pH		
≦5.0	0	0
5.5	0	0
6.0	0	0
6.5	0	0
7.0	1	1
7.5	2	2
8.0	1	1
8.5	1	1
≧9.0	0	0
Protein		
- (negative)	0	0
±(10 ≦ and < 30 mg/dL)	0	0
+ (30 ≦ and < 100 mg/dL)	5	5
2+ (100 ≦ and < 300 mg/dL)	0	0
3+ (300 ≦ and < 600 mg/dL)	0	0
4+ (600 mg/dL ≦)	0	0
Glucose		
- (negative)	5	5
±(30 ≦ and < 70 mg/dL)	0	0
+ (70 ≦ and < 150 mg/dL)	0	0
2+ (150 ≦ and < 300 mg/dL)	0	0
3+ (300 ≦ and < 1,000 mg/dL)	0	0
4+ (1,000 mg/dL ≦)	0	0
Ketone		
- (negative)	0	0
±(5 ≦ and < 10 mg/dL)	3	2
+ (10 ≦ and < 40 mg/dL)	2	3
2+ (40 ≦ and < 80 mg/dL)	0	0
3+ (80 ≦ and < 150 mg/dL)	0	0
4+ (150 mg/dL ≦)	0	0
Bilirubin		
- (negative)	5	5
+ (0.5 ≦ and < 2.0 mg/dL)	0	0
2+ (2.0 ≦ and < 6.0 mg/dL)	0	0
3+ (6.0 ≦ and < 10.0 mg/dL)	0	0
4+ (10.0 mg/dL ≦)	0	0
Occult blood		
- (negative)	5	5
±(0.03 ≦ and <0.06 mg/dL)	0	0
+ (0.06 ≦ and <0.20 mg/dL)	0	0
2+ (0.20 ≦ and <1.00 mg/dL)	0	0
3+ (1.00 mg/dL ≦)	0	0
Urobilinogen		
±(normal)	3	0
+ (2.0 ≦ and < 4.0 mg/dL)	2	5
2+ (4.0 ≦ and < 8.0 mg/dL)	0	0
3+ (8.0 ≦ and < 12.0 mg/dL)	0	0
4+ (12.0 mg/dL ≦)	0	0
Color		
light yellow	5	5
yellow	0	0
yellowish brown	0	0
brown	0	0
bloody	0	0
Turbidity		
- (negative)	5	5
±(trace)	0	0
+ (slight)	0	0
2+ (moderate)	0	0
3+ (marked)	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 23-3 (continued). Urinalysis in male rats of the recovery period

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of males	5	5
Red Blood cells		
- (not observed)	5	5
±(1-9/3 visual field)	0	0
+ (10-99/3 visual field)	0	0
2+ (100-299/3 visual field)	0	0
3+ (≧300/3 visual field)	0	0
White Blood cells		
- (not observed)	5	5
±(1-9/3 visual field)	0	0
2+ (100-299/3 visual field)	0	0
3+ (≧300/3 visual field)	0	0
Casts		
- (not observed)	5	5
±(1-9/3 visual field)	0	0
+ (10-99/3 visual field)	0	0
2+ (100-299/3 visual field)	0	0
3+ (≧300/3 visual field)	0	0
Cristals		
- (not observed)	0	0
±(a few)	5	4
+ (abundant)	0	1
Epithelial cells		
- (not observed)	5	5
±(a few)	0	0
+ (abundant)	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 23-4. Urinalysis in male rats of the recovery period

Group	Control (vehicle: water for injection)			MMP 1000 mg/kg		
Number of males	5			5		
Urine volume (mL/24hr)	19.2	±	6.3	14.4	±	5.0
Specific gravity	1.058	±	0.015	1.069	±	0.015
Electrolyte, density						
Na(mEq/L)	130.3	±	45.5	146.7	±	51.1
K(mEq/L)	265.2	±	72.3	315.3	±	88.2
Cl(mEq/L)	154.0	±	51.9	177.5	±	62.6
Electrolyte, gross volume						
Na(mEq/24hr)	2.30	±	0.19	2.05	±	0.68
K(mEq/24hr)	4.74	±	0.29	4.42	±	1.36
Cl(mEq/24hr)	2.71	±	0.19	2.51	±	0.93

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	5	5
pH		
≦5.0	0	0
5.5	0	0
6.0	0	0
6.5	2	5
7.0	3	0
7.5	0	0
8.0	0	0
8.5	0	0
≧9.0	0	0
Protein		
- (negative)	1	0
±(10 ≦ and < 30 mg/dL)	3	1
+ (30 ≦ and < 100 mg/dL)	1	4
2+ (100 ≦ and < 300 mg/dL)	0	0
3+ (300 ≦ and < 600 mg/dL)	0	0
4+ (600 mg/dL ≦)	0	0
Glucose		
- (negative)	5	5
±(30 ≦ and < 70 mg/dL)	0	0
+ (70 ≦ and < 150 mg/dL)	0	0
2+ (150 ≦ and < 300 mg/dL)	0	0
3+ (300 ≦ and < 1,000 mg/dL)	0	0
4+ (1,000 mg/dL ≦)	0	0
Ketone		
- (negative)	3	0
±(5 ≦ and < 10 mg/dL)	2	1
+ (10 ≦ and < 40 mg/dL)	0	4
2+ (40 ≦ and < 80 mg/dL)	0	0
3+ (80 ≦ and < 150 mg/dL)	0	0
4+ (150 mg/dL ≦)	0	0
Bilirubin		
- (negative)	5	5
+ (0.5 ≦ and < 2.0 mg/dL)	0	0
2+ (2.0 ≦ and < 6.0 mg/dL)	0	0
3+ (6.0 ≦ and < 10.0 mg/dL)	0	0
4+ (10.0 mg/dL ≦)	0	0
Occult blood		
- (negative)	5	5
±(0.03 ≦ and <0.06 mg/dL)	0	0
+ (0.06 ≦ and <0.20 mg/dL)	0	0
2+ (0.20 ≦ and <1.00 mg/dL)	0	0
3+ (1.00 mg/dL ≦)	0	0
Urobilinogen		
±(normal)	4	5
+ (2.0 ≦ and < 4.0 mg/dL)	1	0
2+ (4.0 ≦ and < 8.0 mg/dL)	0	0
3+ (8.0 ≦ and < 12.0 mg/dL)	0	0
4+ (12.0 mg/dL ≦)	0	0
Color		
light yellow	5	5
yellow	0	0
yellowish brown	0	0
brown	0	0
bloody	0	0
Turbidity		
- (negative)	5	5
±(trace)	0	0
+ (slight)	0	0
2+ (moderate)	0	0
3+ (marked)	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	5	5
Red Blood cells		
- (not observed)	5	5
±(1-9/3 visual field)	0	0
+ (10-99/3 visual field)	0	0
2+ (100-299/3 visual field)	0	0
3+ (≧300/3 visual field)	0	0
White Blood cells		
- (not observed)	5	5
±(1-9/3 visual field)	0	0
2+ (100-299/3 visual field)	0	0
3+ (≧300/3 visual field)	0	0
Casts		
- (not observed)	5	5
±(1-9/3 visual field)	0	0
+ (10-99/3 visual field)	0	0
2+ (100-299/3 visual field)	0	0
3+ (≧300/3 visual field)	0	0
Cristals		
- (not observed)	3	2
±(a few)	2	3
+ (abundant)	0	0
Epithelial cells		
- (not observed)	5	5
±(a few)	0	0
+ (abundant)	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 24-2. Urinalysis in female rats, satellite group

Group	Control (vehicle: water for injection)			MMP 1000 mg/kg		
Number of females	5			5		
Urine volume (mL/24hr)	12.9	±	6.8	18.6	±	8.7
Specific gravity	1.064	±	0.018	1.054	±	0.013
Electrolyte, density						
Na(mEq/L)	110.6	±	31.4	106.2	±	31.2
K(mEq/L)	282.6	±	77.8	198.7	±	62.9
Cl(mEq/L)	150.1	±	46.8	112.9	±	38.5
Electrolyte, gross volume						
Na(mEq/24hr)	1.28	±	0.21	1.79	±	0.42 *
K(mEq/24hr)	3.24	±	0.39	3.52	±	1.24
Cl(mEq/24hr)	1.69	±	0.22	1.97	±	0.67

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 Methyl 3-methoxypropanoate by oral administration in rats

Table 24-3. Urinalysis in female rats of the recovery period

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	5	5
pH		
≦5.0	0	0
5.5	0	0
6.0	0	1
6.5	2	1
7.0	2	3
7.5	1	0
8.0	0	0
8.5	0	0
≧9.0	0	0
Protein		
- (negative)	1	0
±(10 ≦ and < 30 mg/dL)	2	1
+ (30 ≦ and < 100 mg/dL)	2	4
2+ (100 ≦ and < 300 mg/dL)	0	0
3+ (300 ≦ and < 600 mg/dL)	0	0
4+ (600 mg/dL ≦)	0	0
Glucose		
- (negative)	5	5
±(30 ≦ and < 70 mg/dL)	0	0
+ (70 ≦ and < 150 mg/dL)	0	0
2+ (150 ≦ and < 300 mg/dL)	0	0
3+ (300 ≦ and < 1,000 mg/dL)	0	0
4+ (1,000 mg/dL ≦)	0	0
Ketone		
- (negative)	4	1
±(5 ≦ and < 10 mg/dL)	1	3
+ (10 ≦ and < 40 mg/dL)	0	1
2+ (40 ≦ and < 80 mg/dL)	0	0
3+ (80 ≦ and < 150 mg/dL)	0	0
4+ (150 mg/dL ≦)	0	0
Bilirubin		
- (negative)	5	5
+ (0.5 ≦ and < 2.0 mg/dL)	0	0
2+ (2.0 ≦ and < 6.0 mg/dL)	0	0
3+ (6.0 ≦ and < 10.0 mg/dL)	0	0
4+ (10.0 mg/dL ≦)	0	0
Occult blood		
- (negative)	5	5
±(0.03 ≦ and <0.06 mg/dL)	0	0
+ (0.06 ≦ and <0.20 mg/dL)	0	0
2+ (0.20 ≦ and <1.00 mg/dL)	0	0
3+ (1.00 mg/dL ≦)	0	0
Urobilinogen		
±(normal)	4	2
+ (2.0 ≦ and < 4.0 mg/dL)	1	3
2+ (4.0 ≦ and < 8.0 mg/dL)	0	0
3+ (8.0 ≦ and < 12.0 mg/dL)	0	0
4+ (12.0 mg/dL ≦)	0	0
Color		
light yellow	5	5
yellow	0	0
yellowish brown	0	0
brown	0	0
bloody	0	0
Turbidity		
- (negative)	5	5
±(trace)	0	0
+ (slight)	0	0
2+ (moderate)	0	0
3+ (marked)	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 24-3 (continued). Urinalysis in female rats of the recovery period

Group	Control (vehicle: water for injection)	MMP 1000 mg/kg
Number of females	5	5
Red Blood cells		
- (not observed)	5	5
±(1-9/3 visual field)	0	0
+ (10-99/3 visual field)	0	0
2+ (100-299/3 visual field)	0	0
3+ (≧300/3 visual field)	0	0
White Blood cells		
- (not observed)	5	5
±(1-9/3 visual field)	0	0
+ (10-99/3 visual field)	0	0
2+ (100-299/3 visual field)	0	0
3+ (≧300/3 visual field)	0	0
Casts		
- (not observed)	5	5
±(1-9/3 visual field)	0	0
+ (10-99/3 visual field)	0	0
2+ (100-299/3 visual field)	0	0
3+ (≧300/3 visual field)	0	0
Cristals		
- (not observed)	2	2
±(a few)	3	3
+ (abundant)	0	0
Epithelial cells		
- (not observed)	5	5
±(a few)	0	0
+ (abundant)	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 24-4. Urinalysis in female rats of the recovery period

Group	Control (vehicle: water for injection)			MMP 1000 mg/kg		
Number of females	5			5		
Urine volume (mL/24hr)	9.4	±	3.5	10.0	±	2.7
Specific gravity	1.054	±	0.015	1.076	±	0.009 *
Electrolyte, density						
Na(mEq/L)	93.8	±	26.5	145.5	±	15.4 **
K(mEq/L)	175.8	±	70.3	339.3	±	39.5 **
Cl(mEq/L)	102.5	±	41.6	198.2	±	20.4 **
Electrolyte, gross volume						
Na(mEq/24hr)	0.89	±	0.46	1.44	±	0.31
K(mEq/24hr)	1.74	±	1.16	3.34	±	0.59 *
Cl(mEq/24hr)	1.01	±	0.68	1.95	±	0.35 *

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males		5	5	5	5
RBC	10000/μL	884 ± 33	891 ± 25	901 ± 16	914 ± 39
HGB	g/dL	15.8 ± 0.4	15.7 ± 0.6	16.0 ± 0.6	15.7 ± 0.6
Hematocrit	%	43.8 ± 1.5	43.6 ± 1.9	44.7 ± 1.9	43.5 ± 1.0
MCV	fL	49.6 ± 0.5	49.0 ± 2.1	49.6 ± 1.9	47.6 ± 1.2
MCH	pg	17.9 ± 0.2	17.6 ± 0.6	17.7 ± 0.7	17.2 ± 0.3
MCHC	g/dL	36.2 ± 0.4	36.0 ± 0.4	35.8 ± 0.5	36.2 ± 0.5
Platelet	10000/μL	110.6 ± 11.3	115.6 ± 6.7	118.0 ± 19.1	100.9 ± 5.5
PT	sec.	23.9 ± 8.2	24.0 ± 6.5	23.2 ± 6.4	17.5 ± 4.2
APTT	sec.	26.9 ± 4.2	27.9 ± 2.2	25.7 ± 3.4	22.9 ± 2.6
WBC	100/μL	93.9 ± 23.0	93.1 ± 33.9	98.0 ± 20.9	87.5 ± 28.0
Neutrophil	%	22.1 ± 9.3	18.4 ± 9.3	16.2 ± 3.2	15.5 ± 5.5
Eosinophil	%	1.2 ± 0.3	1.9 ± 0.7	1.6 ± 0.6	1.5 ± 0.6
Basophil	%	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.1
Monocyte	%	4.2 ± 1.0	5.1 ± 1.1	5.1 ± 0.6	6.5 ± 1.7 *
Lymphocyte	%	72.4 ± 9.8	74.7 ± 10.4	77.0 ± 3.5	76.3 ± 6.2
Reticulocyte	%	2.83 ± 0.44	2.56 ± 0.40	3.62 ± 1.04	2.46 ± 0.51

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 1000 mg/kg	
Number of males		5	5	
RBC	10000/μL	882 ± 23	816 ± 32	**
HGB	g/dL	15.0 ± 0.3	14.5 ± 0.6	
Hematocrit	%	43.1 ± 0.9	42.0 ± 1.8	
MCV	fL	48.9 ± 1.4	51.5 ± 1.1	*
MCH	pg	17.0 ± 0.2	17.7 ± 0.5	*
MCHC	g/dL	34.8 ± 0.9	34.4 ± 0.5	
Platelet	10000/μL	115.0 ± 14.9	115.2 ± 2.3	
PT	sec.	18.8 ± 4.5	17.7 ± 1.9	
APTT	sec.	22.0 ± 1.7	22.6 ± 1.2	
WBC	100/μL	130.3 ± 45.0	106.7 ± 14.6	
Neutrophil	%	17.2 ± 4.1	14.4 ± 6.2	
Eosinophil	%	1.1 ± 0.2	1.2 ± 0.3	
Basophil	%	0.1 ± 0.1	0.0 ± 0.0	*
Monocyte	%	3.8 ± 0.6	3.3 ± 0.9	
Lymphocyte	%	77.8 ± 3.9	81.0 ± 7.1	
Reticulocyte	%	3.43 ± 0.42	3.27 ± 0.34	

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of females		5	5	5	5
RBC	10000/μL	698 ± 30	688 ± 36	680 ± 35	723 ± 16
HGB	g/dL	13.7 ± 0.9	13.3 ± 0.8	13.3 ± 0.3	13.9 ± 0.2
Hematocrit	%	40.4 ± 3.1	39.3 ± 2.7	39.2 ± 1.1	40.8 ± 1.0
MCV	fL	57.8 ± 2.8	57.2 ± 3.8	57.7 ± 2.7	56.4 ± 1.6
MCH	pg	19.6 ± 0.7	19.3 ± 1.0	19.6 ± 0.8	19.2 ± 0.4
MCHC	g/dL	33.9 ± 0.6	33.8 ± 0.7	33.9 ± 0.3	34.0 ± 0.9
Platelet	10000/μL	122.6 ± 17.9	117.0 ± 20.7	117.2 ± 18.4	101.2 ± 12.7
PT	sec.	13.5 ± 0.4	12.8 ± 0.4	13.5 ± 0.3	14.2 ± 0.6
APTT	sec.	21.2 ± 1.3	19.8 ± 0.8	20.7 ± 0.8	19.7 ± 0.8
WBC	100/μL	122.1 ± 23.9	118.6 ± 29.1	117.3 ± 26.8	117.7 ± 36.9
Neutrophil	%	39.3 ± 11.7	42.7 ± 8.7	38.7 ± 8.7	38.7 ± 9.3
Eosinophil	%	0.8 ± 0.4	0.8 ± 0.4	0.6 ± 0.1	0.5 ± 0.1
Basophil	%	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
Monocyte	%	4.7 ± 0.9	4.4 ± 1.2	3.2 ± 0.6 *	5.0 ± 0.5
Lymphocyte	%	55.2 ± 11.3	52.1 ± 9.8	57.4 ± 9.2	55.8 ± 9.3
Reticulocyte	%	8.03 ± 0.88	7.25 ± 1.75	8.85 ± 1.21	7.45 ± 1.84

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 1000 mg/kg	
Number of females		5	5	
RBC	10000/μL	769 ± 13	792 ± 27	
HGB	g/dL	14.1 ± 0.2	14.5 ± 0.4	
Hematocrit	%	39.4 ± 0.8	40.8 ± 1.2	
MCV	fL	51.2 ± 1.0	51.5 ± 1.5	
MCH	pg	18.4 ± 0.2	18.3 ± 0.4	
MCHC	g/dL	35.8 ± 0.5	35.6 ± 0.3	
Platelet	10000/μL	118.4 ± 5.2	97.4 ± 8.6	**
PT	sec.	12.6 ± 0.4	13.8 ± 0.3	**
APTT	sec.	21.3 ± 1.3	19.9 ± 0.4	*
WBC	100/μL	73.4 ± 24.2	99.5 ± 43.0	
Neutrophil	%	17.4 ± 5.7	13.0 ± 6.2	
Eosinophil	%	1.7 ± 0.7	1.4 ± 0.2	
Basophil	%	0.0 ± 0.0	0.0 ± 0.1	
Monocyte	%	2.8 ± 0.8	4.1 ± 0.9	*
Lymphocyte	%	78.1 ± 5.1	81.4 ± 5.6	
Reticulocyte	%	2.91 ± 0.29	2.90 ± 0.52	

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 1000 mg/kg	
Number of females		5	5	
RBC	10000/μL	795 ± 20	761 ± 59	
HGB	g/dL	14.7 ± 0.1	13.9 ± 0.9	
Hematocrit	%	42.1 ± 1.0	40.3 ± 2.5	
MCV	fL	53.0 ± 2.6	53.0 ± 1.2	
MCH	pg	18.5 ± 0.5	18.2 ± 0.3	
MCHC	g/dL	34.9 ± 0.8	34.4 ± 0.5	
Platelet	10000/μL	99.4 ± 16.8	101.8 ± 11.3	
PT	sec.	13.0 ± 0.4	12.8 ± 0.6	
APTT	sec.	18.2 ± 1.3	17.7 ± 0.7	
WBC	100/μL	44.6 ± 16.6	43.6 ± 10.4	
Neutrophil	%	17.7 ± 4.6	13.2 ± 5.4	
Eosinophil	%	2.6 ± 0.8	1.8 ± 0.6	
Basophil	%	0.0 ± 0.0	0.0 ± 0.0	
Monocyte	%	3.9 ± 0.7	2.8 ± 0.7	*
Lymphocyte	%	75.8 ± 4.6	82.2 ± 5.2	
Reticulocyte	%	2.82 ± 0.35	2.81 ± 0.60	

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males		5	5	5	5
Total protein	g/dL	5.6 ± 0.3	5.7 ± 0.3	5.4 ± 0.3	5.4 ± 0.1
Albumin	g/dL	3.5 ± 0.1	3.6 ± 0.2	3.5 ± 0.2	3.6 ± 0.1
A/G		1.73 ± 0.07	1.71 ± 0.05	1.85 ± 0.18	2.07 ± 0.27
Glucose	mg/dL	122 ± 5	124 ± 8	138 ± 7 **	131 ± 8
Total cholesterol	mg/dL	41 ± 5	47 ± 7	43 ± 4	41 ± 10
Triglyceride	mg/dL	28 ± 13	37 ± 23	61 ± 17 *	40 ± 14
Phospholipid	mg/dL	70 ± 8	78 ± 14	80 ± 8	76 ± 10
AST	U/L	61 ± 4	62 ± 7	59 ± 4	62 ± 7
ALT	U/L	29 ± 3	34 ± 7	25 ± 2	32 ± 5
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0
LDH	U/L	65 ± 15	117 ± 93	139 ± 54 *	129 ± 66
Bile acid	μmol/L	6.3 ± 2.0	8.4 ± 3.9	10.1 ± 9.1	15.9 ± 8.7
BUN	mg/dL	14 ± 1	13 ± 1	13 ± 2	14 ± 3
Creatinine	mg/dL	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.0	0.4 ± 0.0
Total bilirubin	mg/dL	0.10 ± 0.03	0.11 ± 0.02	0.12 ± 0.03	0.14 ± 0.01 *
ALP	U/L	354 ± 61	303 ± 19	332 ± 37	312 ± 102
Inorganic phosphorus	mg/dL	5.8 ± 0.4	5.8 ± 0.2	5.7 ± 0.5	6.0 ± 0.5
Ca	mg/dL	8.8 ± 0.3	8.9 ± 0.3	8.9 ± 0.2	8.9 ± 0.2
Na	mEq/L	145.8 ± 0.9	146.2 ± 0.7	146.3 ± 1.1	145.9 ± 1.0
K	mEq/L	3.96 ± 0.20	3.93 ± 0.08	3.98 ± 0.11	4.08 ± 0.17
Cl	mEq/L	105.2 ± 0.7	105.4 ± 1.1	105.3 ± 1.9	105.5 ± 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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 1000 mg/kg	
Number of males		5	5	
Total protein	g/dL	5.5 ± 0.3	5.2 ± 0.2	
Albumin	g/dL	3.5 ± 0.2	3.5 ± 0.1	
A/G		1.78 ± 0.18	2.04 ± 0.20	
Glucose	mg/dL	145 ± 30	137 ± 15	
Total cholesterol	mg/dL	44 ± 6	42 ± 7	
Triglyceride	mg/dL	27 ± 13	23 ± 5	
Phospholipid	mg/dL	72 ± 8	66 ± 8	
AST	U/L	68 ± 5	68 ± 13	
ALT	U/L	28 ± 4	27 ± 3	
γ-GTP	U/L	0 ± 0	0 ± 0	
LDH	U/L	274 ± 154	234 ± 129	
Bile acid	μmol/L	7.4 ± 1.2	7.2 ± 3.2	
BUN	mg/dL	15 ± 1	14 ± 2	
Creatinine	mg/dL	0.5 ± 0.0	0.5 ± 0.1	
Total bilirubin	mg/dL	0.07 ± 0.02	0.07 ± 0.01	
ALP	U/L	452 ± 96	449 ± 68	
Inorganic phosphorus	mg/dL	6.2 ± 0.5	6.2 ± 0.4	
Ca	mg/dL	9.0 ± 0.2	8.7 ± 0.2	*
Na	mEq/L	145.3 ± 0.8	145.3 ± 0.4	
K	mEq/L	3.81 ± 0.23	3.79 ± 0.07	
Cl	mEq/L	106.3 ± 1.6	107.9 ± 1.1	

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of females		5	5	5	5
Total protein	g/dL	5.7 ± 0.4	5.8 ± 0.3	5.7 ± 0.1	5.6 ± 0.2
Albumin	g/dL	4.0 ± 0.4	3.9 ± 0.2	3.8 ± 0.1	3.9 ± 0.1
A/G		2.24 ± 0.27	2.08 ± 0.16	2.06 ± 0.15	2.24 ± 0.14
Glucose	mg/dL	123 ± 11	123 ± 9	128 ± 7	132 ± 7
Total cholesterol	mg/dL	53 ± 8	53 ± 7	47 ± 8	40 ± 7
Triglyceride	mg/dL	46 ± 20	43 ± 19	36 ± 18	44 ± 29
Phospholipid	mg/dL	107 ± 18	106 ± 8	95 ± 18	92 ± 9
AST	U/L	73 ± 15	81 ± 16	79 ± 8	74 ± 9
ALT	U/L	43 ± 13	50 ± 12	47 ± 4	38 ± 3
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0
LDH	U/L	88 ± 50	83 ± 56	124 ± 71	139 ± 118
Bile acid	μmol/L	10.6 ± 2.3	10.2 ± 4.0	8.2 ± 1.4	13.1 ± 7.8
BUN	mg/dL	14 ± 2	15 ± 3	14 ± 2	12 ± 2
Creatinine	mg/dL	0.5 ± 0.0	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
Total bilirubin	mg/dL	0.11 ± 0.03	0.10 ± 0.02	0.09 ± 0.04	0.10 ± 0.04
ALP	U/L	242 ± 40	323 ± 130	255 ± 45	194 ± 27
Inorganic phosphorus	mg/dL	6.1 ± 0.4	5.7 ± 0.4	5.7 ± 0.2	5.9 ± 1.0
Ca	mg/dL	8.9 ± 0.2	9.1 ± 0.4	8.9 ± 0.1	8.8 ± 0.2
Na	mEq/L	142.8 ± 2.0	141.8 ± 2.1	141.8 ± 2.5	142.4 ± 1.6
K	mEq/L	3.61 ± 0.15	3.68 ± 0.52	3.67 ± 0.30	3.68 ± 0.45
Cl	mEq/L	104.8 ± 2.0	105.0 ± 1.6	105.8 ± 2.4	105.3 ± 2.5

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 1000 mg/kg	
Number of females		5	5	
Total protein	g/dL	5.7 ± 0.3	5.6 ± 0.3	
Albumin	g/dL	3.9 ± 0.3	3.8 ± 0.3	
A/G		2.05 ± 0.07	2.07 ± 0.20	
Glucose	mg/dL	102 ± 13	113 ± 17	
Total cholesterol	mg/dL	49 ± 8	55 ± 6	
Triglyceride	mg/dL	15 ± 8	17 ± 4	
Phospholipid	mg/dL	93 ± 11	107 ± 13	
AST	U/L	67 ± 11	54 ± 5	
ALT	U/L	34 ± 13	20 ± 1	*
γ-GTP	U/L	0 ± 0	0 ± 0	
LDH	U/L	100 ± 37	114 ± 85	
Bile acid	μmol/L	11.4 ± 3.9	28.0 ± 15.9	*
BUN	mg/dL	20 ± 4	14 ± 3	*
Creatinine	mg/dL	0.5 ± 0.0	0.5 ± 0.0	
Total bilirubin	mg/dL	0.18 ± 0.02	0.25 ± 0.06	*
ALP	U/L	170 ± 68	176 ± 54	
Inorganic phosphorus	mg/dL	4.5 ± 0.5	5.7 ± 1.2	
Ca	mg/dL	8.5 ± 0.3	8.7 ± 0.5	
Na	mEq/L	145.6 ± 0.7	145.6 ± 0.5	
K	mEq/L	3.57 ± 0.11	3.60 ± 0.31	
Cl	mEq/L	106.1 ± 0.4	104.1 ± 2.3	

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 1000 mg/kg	
Number of females		5	5	
Total protein	g/dL	5.4 ± 0.3	5.4 ± 0.4	
Albumin	g/dL	3.8 ± 0.3	3.7 ± 0.2	
A/G		2.32 ± 0.16	2.26 ± 0.30	
Glucose	mg/dL	106 ± 8	121 ± 12	
Total cholesterol	mg/dL	52 ± 7	47 ± 8	
Triglyceride	mg/dL	15 ± 4	11 ± 3	
Phospholipid	mg/dL	94 ± 7	90 ± 11	
AST	U/L	56 ± 9	62 ± 8	
ALT	U/L	19 ± 4	25 ± 5	
γ-GTP	U/L	0 ± 0	0 ± 0	
LDH	U/L	75 ± 16	107 ± 76	
Bile acid	μmol/L	16.4 ± 15.2	12.7 ± 3.9	
BUN	mg/dL	17 ± 3	19 ± 3	
Creatinine	mg/dL	0.6 ± 0.1	0.6 ± 0.1	
Total bilirubin	mg/dL	0.10 ± 0.02	0.12 ± 0.05	
ALP	U/L	231 ± 50	227 ± 43	
Inorganic phosphorus	mg/dL	3.9 ± 0.7	4.5 ± 0.6	
Ca	mg/dL	8.2 ± 0.2	8.6 ± 0.3	*
Na	mEq/L	146.1 ± 1.2	144.0 ± 1.4	*
K	mEq/L	3.38 ± 0.19	4.01 ± 0.71	
Cl	mEq/L	110.2 ± 1.8	108.0 ± 1.0	*

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males		7	12	12	7
Body weight	(g)	463.9 ± 25.8	482.8 ± 18.0	476.4 ± 29.3	470.3 ± 24.1
Brain	(mg)	1984.2 ± 56.3	2059.9 ± 126.9	1992.6 ± 83.3	2013.1 ± 46.2
	(mg/g)	4.287 ± 0.236	4.270 ± 0.273	4.200 ± 0.355	4.290 ± 0.244
Thymus	(mg)	297.7 ± 49.5	323.2 ± 88.6	296.3 ± 105.4	253.6 ± 74.0
	(mg/g)	0.644 ± 0.112	0.667 ± 0.168	0.616 ± 0.197	0.538 ± 0.148
Heart	(mg)	1359.2 ± 106.8	1435.2 ± 118.3	1383.7 ± 99.1	1426.0 ± 82.6
	(mg/g)	2.931 ± 0.187	2.972 ± 0.209	2.906 ± 0.154	3.033 ± 0.129
Liver	(mg)	11945.7 ± 934.5	12996.5 ± 1222.0	12663.6 ± 1164.3	13237.7 ± 1152.5
	(mg/g)	25.770 ± 1.779	26.897 ± 1.960	26.550 ± 1.359	28.119 ± 1.453
Kidney (R)	(mg)	1558.7 ± 83.7	1634.7 ± 80.0	1694.2 ± 149.4	1718.0 ± 211.1
	(mg/g)	3.370 ± 0.284	3.390 ± 0.204	3.566 ± 0.355	3.651 ± 0.369
Kidney (L)	(mg)	1561.9 ± 62.8	1607.8 ± 82.6	1686.1 ± 165.8	1710.4 ± 140.0 *
	(mg/g)	3.374 ± 0.199	3.335 ± 0.215	3.551 ± 0.405	3.640 ± 0.280
Kidneys	(mg)	3120.6 ± 129.6	3242.6 ± 158.6	3380.3 ± 311.3	3428.4 ± 348.2
	(mg/g)	6.745 ± 0.465	6.725 ± 0.413	7.118 ± 0.754	7.291 ± 0.631
Spleen	(mg)	808.1 ± 56.0	868.7 ± 134.5	859.1 ± 159.3	755.6 ± 86.8
	(mg/g)	1.750 ± 0.196	1.798 ± 0.252	1.798 ± 0.289	1.608 ± 0.178
Testis (R)	(mg)	1613.8 ± 120.7	1731.1 ± 104.4	1712.5 ± 144.9	1631.9 ± 94.1
	(mg/g)	3.479 ± 0.167	3.587 ± 0.188	3.601 ± 0.309	3.479 ± 0.296
Testis (L)	(mg)	1597.9 ± 126.4	1765.4 ± 120.4 *	1713.5 ± 153.5	1620.2 ± 82.4
	(mg/g)	3.445 ± 0.194	3.655 ± 0.180	3.602 ± 0.313	3.457 ± 0.312
Testes	(mg)	3211.7 ± 245.0	3496.5 ± 217.8	3426.0 ± 294.8	3252.1 ± 172.0
	(mg/g)	6.923 ± 0.355	7.242 ± 0.349	7.203 ± 0.615	6.936 ± 0.603
Epididymis (R)	(mg)	629.6 ± 56.1	653.6 ± 57.1	641.4 ± 54.7	588.9 ± 55.7
	(mg/g)	1.362 ± 0.152	1.354 ± 0.105	1.352 ± 0.151	1.256 ± 0.146
Epididymis (L)	(mg)	613.1 ± 43.2	644.8 ± 48.4	630.3 ± 59.0	590.7 ± 44.0
	(mg/g)	1.328 ± 0.149	1.336 ± 0.092	1.329 ± 0.164	1.261 ± 0.140
Epididymides	(mg)	1242.7 ± 95.8	1298.4 ± 103.3	1271.8 ± 112.0	1179.6 ± 92.1
	(mg/g)	2.690 ± 0.295	2.690 ± 0.191	2.680 ± 0.313	2.517 ± 0.273

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of males		7	12	12	7
Prostate, ventral	(mg)	660.0 ± 183.8	617.0 ± 132.2	539.3 ± 82.9	500.7 ± 96.6
	(mg/g)	1.430 ± 0.411	1.278 ± 0.268	1.133 ± 0.171	1.069 ± 0.221
Seminal vesicles	(mg)	1636.0 ± 189.5	1767.2 ± 179.3	1620.1 ± 344.2	1631.8 ± 210.7
	(mg/g)	3.540 ± 0.482	3.661 ± 0.350	3.417 ± 0.759	3.466 ± 0.365
Thyroid gland	(mg)	22.4 ± 3.9	21.7 ± 3.5	20.3 ± 4.3	20.0 ± 3.3
	(mg/g)	0.048 ± 0.007	0.045 ± 0.007	0.043 ± 0.010	0.043 ± 0.008
Adrenal gland (R)	(mg)	24.1 ± 1.6	24.4 ± 1.6	25.9 ± 3.4	22.4 ± 2.4
	(mg/g)	0.052 ± 0.005	0.051 ± 0.004	0.055 ± 0.007	0.047 ± 0.004
Adrenal gland (L)	(mg)	26.1 ± 1.9	26.1 ± 2.2	26.8 ± 3.8	24.0 ± 2.9
	(mg/g)	0.057 ± 0.005	0.054 ± 0.004	0.056 ± 0.008	0.051 ± 0.006
Adrenal glands	(mg)	50.2 ± 2.5	50.5 ± 3.6	52.8 ± 6.9	46.4 ± 5.1
	(mg/g)	0.109 ± 0.009	0.105 ± 0.008	0.111 ± 0.014	0.099 ± 0.010

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)			MMP 1000 mg/kg			
Number of males		5			5			
Body weight	(g)	507.8	±	5.9	516.3	±	35.8	
Brain	(mg)	1987.7	±	70.5	2076.8	±	62.8	
	(mg/g)	3.914	±	0.139	4.035	±	0.248	
Thymus	(mg)	252.8	±	59.1	248.3	±	44.2	
	(mg/g)	0.497	±	0.112	0.486	±	0.108	
Heart	(mg)	1443.0	±	115.1	1505.1	±	196.4	
	(mg/g)	2.840	±	0.201	2.908	±	0.221	
Liver	(mg)	13174.6	±	458.9	12620.2	±	522.5	
	(mg/g)	25.942	±	0.798	24.496	±	1.220	
Kidney (R)	(mg)	1597.6	±	152.3	1701.2	±	91.6	
	(mg/g)	3.146	±	0.292	3.298	±	0.106	
Kidney (L)	(mg)	1632.6	±	147.6	1692.8	±	90.0	
	(mg/g)	3.214	±	0.270	3.283	±	0.115	
Kidneys	(mg)	3230.2	±	293.6	3394.0	±	174.8	
	(mg/g)	6.359	±	0.550	6.581	±	0.201	
Spleen	(mg)	884.4	±	83.3	730.6	±	93.4	*
	(mg/g)	1.741	±	0.153	1.416	±	0.173	*
Testis (R)	(mg)	1709.2	±	148.3	1708.2	±	144.3	
	(mg/g)	3.366	±	0.287	3.311	±	0.214	
Testis (L)	(mg)	1704.3	±	69.1	1693.0	±	173.9	
	(mg/g)	3.356	±	0.131	3.280	±	0.268	
Testes	(mg)	3413.5	±	217.1	3401.2	±	310.9	
	(mg/g)	6.722	±	0.416	6.591	±	0.464	
Epididymis (R)	(mg)	652.4	±	70.1	640.2	±	57.1	
	(mg/g)	1.284	±	0.132	1.240	±	0.069	
Epididymis (L)	(mg)	648.2	±	54.7	619.2	±	64.7	
	(mg/g)	1.277	±	0.110	1.198	±	0.078	
Epididymides	(mg)	1300.5	±	118.8	1259.4	±	121.6	
	(mg/g)	2.560	±	0.228	2.439	±	0.145	

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)			MMP 1000 mg/kg		
Number of males		5			5		
Prostate, ventral	(mg)	523.3	±	179.4	634.3	±	111.6
	(mg/g)	1.029	±	0.346	1.224	±	0.178
Seminal vesicles	(mg)	1546.6	±	184.8	1874.3	±	298.6
	(mg/g)	3.046	±	0.366	3.639	±	0.585
Thyroid gland	(mg)	22.9	±	5.9	23.0	±	6.3
	(mg/g)	0.045	±	0.012	0.044	±	0.009
Adrenal gland (R)	(mg)	28.1	±	4.0	24.9	±	3.3
	(mg/g)	0.055	±	0.008	0.048	±	0.008
Adrenal gland (L)	(mg)	30.7	±	3.7	26.4	±	2.6
	(mg/g)	0.060	±	0.007	0.052	±	0.006
Adrenal glands	(mg)	58.8	±	7.6	51.3	±	5.9
	(mg/g)	0.116	±	0.015	0.100	±	0.014

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of females		12	12	11	9
Body weight	(g)	314.8 ± 21.0	315.1 ± 23.3	312.1 ± 13.9	321.6 ± 11.8
Brain	(mg)	1909.9 ± 86.2	1941.9 ± 81.5	1888.6 ± 59.3	1916.1 ± 77.5
	(mg/g)	6.085 ± 0.396	6.194 ± 0.526	6.062 ± 0.316	5.965 ± 0.330
Thymus	(mg)	201.8 ± 55.9	224.3 ± 53.5	195.3 ± 55.2	202.5 ± 48.7
	(mg/g)	0.640 ± 0.164	0.707 ± 0.141	0.627 ± 0.178	0.628 ± 0.149
Heart	(mg)	1030.3 ± 77.9	1042.1 ± 102.7	1004.0 ± 46.8	1087.5 ± 55.8
	(mg/g)	3.276 ± 0.183	3.304 ± 0.152	3.221 ± 0.156	3.384 ± 0.180
Liver	(mg)	10141.7 ± 972.4	10508.3 ± 800.0	10055.9 ± 672.0	11219.7 ± 576.5 **
	(mg/g)	32.206 ± 2.188	33.386 ± 1.672	32.249 ± 2.128	34.899 ± 1.555 **
Kidney (R)	(mg)	1070.9 ± 45.0	1099.3 ± 81.4	1018.1 ± 64.3	1083.2 ± 76.8
	(mg/g)	3.415 ± 0.258	3.496 ± 0.227	3.266 ± 0.223	3.369 ± 0.216
Kidney (L)	(mg)	1067.0 ± 73.6	1086.7 ± 66.7	988.6 ± 82.2 *	1079.3 ± 84.0
	(mg/g)	3.402 ± 0.320	3.460 ± 0.239	3.170 ± 0.252	3.358 ± 0.249
Kidneys	(mg)	2137.8 ± 114.5	2186.0 ± 141.7	2006.7 ± 143.1	2162.6 ± 155.2
	(mg/g)	6.817 ± 0.565	6.956 ± 0.445	6.436 ± 0.462	6.727 ± 0.447
Spleen	(mg)	706.0 ± 94.5	725.1 ± 112.3	722.9 ± 99.3	759.9 ± 105.1
	(mg/g)	2.243 ± 0.267	2.303 ± 0.317	2.318 ± 0.309	2.366 ± 0.346
Ovary (R)	(mg)	56.1 ± 9.4	53.6 ± 11.2	48.9 ± 8.3	48.2 ± 8.6
	(mg/g)	0.178 ± 0.025	0.170 ± 0.029	0.157 ± 0.025	0.150 ± 0.027
Ovary (L)	(mg)	52.7 ± 8.9	52.2 ± 8.3	48.9 ± 7.4	51.5 ± 8.4
	(mg/g)	0.168 ± 0.031	0.166 ± 0.028	0.157 ± 0.026	0.160 ± 0.026
Ovaries	(mg)	108.9 ± 13.9	105.8 ± 16.2	97.8 ± 13.6	99.7 ± 10.3
	(mg/g)	0.346 ± 0.043	0.336 ± 0.044	0.313 ± 0.043	0.310 ± 0.032
Uterus	(mg)	592.6 ± 62.6	607.0 ± 87.7	615.7 ± 67.3	583.6 ± 62.9
	(mg/g)	1.888 ± 0.225	1.935 ± 0.317	1.976 ± 0.223	1.816 ± 0.200
Thyroid gland	(mg)	17.0 ± 3.2	17.3 ± 3.4	16.6 ± 4.3	16.8 ± 5.0
	(mg/g)	0.054 ± 0.008	0.055 ± 0.008	0.053 ± 0.013	0.052 ± 0.015
Adrenal gland (R)	(mg)	38.4 ± 6.5	41.3 ± 3.5	36.5 ± 5.7	37.6 ± 3.6
	(mg/g)	0.122 ± 0.020	0.132 ± 0.014	0.117 ± 0.020	0.117 ± 0.011
Adrenal gland (L)	(mg)	41.1 ± 6.8	43.7 ± 4.0	38.3 ± 7.3	39.5 ± 4.8
	(mg/g)	0.131 ± 0.021	0.139 ± 0.017	0.123 ± 0.026	0.123 ± 0.014
Adrenal glands	(mg)	79.5 ± 13.0	85.0 ± 7.1	74.8 ± 12.5	77.1 ± 8.3
	(mg/g)	0.253 ± 0.040	0.271 ± 0.030	0.241 ± 0.044	0.240 ± 0.024

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)			MMP 1000 mg/kg			
Number of females		5			5			
Body weight	(g)	283.2	±	5.6	285.8	±	8.4	
Brain	(mg)	1977.8	±	125.0	1882.7	±	73.0	
	(mg/g)	6.986	±	0.451	6.594	±	0.376	
Thymus	(mg)	333.0	±	66.4	344.2	±	135.3	
	(mg/g)	1.173	±	0.213	1.204	±	0.461	
Heart	(mg)	891.5	±	50.6	954.5	±	57.3	
	(mg/g)	3.147	±	0.136	3.341	±	0.212	
Liver	(mg)	7048.0	±	364.4	8293.7	±	746.3	*
	(mg/g)	24.884	±	1.072	29.004	±	2.283	**
Kidney (R)	(mg)	917.3	±	104.5	1024.7	±	17.1	*
	(mg/g)	3.236	±	0.326	3.588	±	0.145	
Kidney (L)	(mg)	917.0	±	131.4	992.0	±	69.7	
	(mg/g)	3.234	±	0.420	3.477	±	0.320	
Kidneys	(mg)	1834.4	±	234.7	2016.7	±	85.6	
	(mg/g)	6.470	±	0.741	7.066	±	0.462	
Spleen	(mg)	594.1	±	84.0	661.2	±	122.9	
	(mg/g)	2.096	±	0.276	2.324	±	0.488	
Ovary (R)	(mg)	53.6	±	13.4	43.3	±	4.7	
	(mg/g)	0.190	±	0.051	0.152	±	0.017	
Ovary (L)	(mg)	50.8	±	12.7	45.7	±	7.0	
	(mg/g)	0.180	±	0.047	0.160	±	0.027	
Ovaries	(mg)	104.3	±	24.2	89.0	±	7.2	
	(mg/g)	0.369	±	0.091	0.312	±	0.030	
Uterus	(mg)	570.6	±	208.1	687.9	±	201.6	
	(mg/g)	2.014	±	0.740	2.404	±	0.696	
Thyroid gland	(mg)	15.9	±	6.1	16.6	±	2.4	
	(mg/g)	0.056	±	0.022	0.058	±	0.009	
Adrenal gland (R)	(mg)	31.2	±	3.8	34.6	±	1.4	
	(mg/g)	0.110	±	0.014	0.121	±	0.007	
Adrenal gland (L)	(mg)	32.8	±	2.4	34.4	±	0.8	
	(mg/g)	0.116	±	0.010	0.120	±	0.004	
Adrenal glands	(mg)	64.0	±	6.1	69.0	±	1.9	
	(mg/g)	0.226	±	0.024	0.242	±	0.010	

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group		Control (vehicle: water for injection)			MMP 1000 mg/kg			
Number of females		5			5			
Body weight	(g)	282.7	±	29.7	294.1	±	20.5	
Brain	(mg)	1908.7	±	54.0	1945.2	±	53.7	
	(mg/g)	6.800	±	0.576	6.632	±	0.326	
Thymus	(mg)	299.9	±	104.3	239.8	±	61.9	
	(mg/g)	1.055	±	0.316	0.816	±	0.200	
Heart	(mg)	886.4	±	107.5	973.3	±	70.2	
	(mg/g)	3.141	±	0.273	3.311	±	0.120	
Liver	(mg)	6643.1	±	515.9	7296.7	±	543.9	
	(mg/g)	23.598	±	1.671	24.811	±	0.470	
Kidney (R)	(mg)	872.3	±	42.6	1054.5	±	91.4	**
	(mg/g)	3.105	±	0.253	3.591	±	0.280	*
Kidney (L)	(mg)	868.6	±	77.4	1015.4	±	98.6	*
	(mg/g)	3.086	±	0.259	3.456	±	0.264	
Kidneys	(mg)	1740.8	±	119.7	2069.9	±	186.3	*
	(mg/g)	6.190	±	0.498	7.047	±	0.528	*
Spleen	(mg)	516.6	±	47.5	558.8	±	156.1	
	(mg/g)	1.832	±	0.120	1.883	±	0.454	
Ovary (R)	(mg)	38.0	±	4.7	44.4	±	4.2	
	(mg/g)	0.135	±	0.016	0.151	±	0.013	
Ovary (L)	(mg)	37.7	±	3.8	48.4	±	4.8	**
	(mg/g)	0.134	±	0.013	0.165	±	0.012	**
Ovaries	(mg)	75.6	±	5.8	92.9	±	8.1	**
	(mg/g)	0.269	±	0.018	0.316	±	0.021	**
Uterus	(mg)	536.4	±	160.6	583.5	±	250.1	
	(mg/g)	1.877	±	0.384	1.974	±	0.778	
Thyroid gland	(mg)	14.1	±	1.8	16.0	±	5.3	
	(mg/g)	0.050	±	0.005	0.055	±	0.019	
Adrenal gland (R)	(mg)	30.4	±	2.4	31.8	±	3.1	
	(mg/g)	0.108	±	0.011	0.108	±	0.010	
Adrenal gland (L)	(mg)	31.5	±	2.6	32.2	±	3.4	
	(mg/g)	0.112	±	0.010	0.109	±	0.007	
Adrenal glands	(mg)	61.9	±	5.0	64.0	±	5.9	
	(mg/g)	0.220	±	0.022	0.218	±	0.015	

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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)		MMP 62.5 mg/kg		MMP 250 mg/kg		MMP 1000 mg/kg	
Findings / Grade	-	P	-	P	-	P	-	P
Kidney								
Enlargement, bilateral	7	0	12	0	12	0	6	1
Liver								
Diaphragmatic nodule	6	1	12	0	12	0	7	0
Whitish spot	7	0	12	0	12	0	6	1
Stomach								
Edematous, mucosa, dark colored area, forestomach	6	1	12	0	12	0	7	0
Tooth								
Defect, upper central incisor, left	6	1	12	0	12	0	7	0

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)		MMP 1000 mg/kg	
Findings / Grade	-	P	-	P
Skin				
Crust, dorsal neck	5	0	4	1
Stomach				
Edematous, mucosa, forestomach	5	0	4	1
Thickening, mucosa, forestomach	5	0	4	1

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)		MMP 62.5 mg/kg		MMP 250 mg/kg		MMP 1000 mg/kg	
Findings / Grade	-	P	-	P	-	P	-	P
Stomach								
Dark colored spot/area, mucosa glandular stomach	11	1	11	1	11	0	9	0
Thymus								
Small	12	0	12	0	11	0	8	1

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)		MMP 1000 mg/kg	
Findings / Grade	-	P	-	P
Pituitary gland				
Cyst	5	0	4	1
Stomach				
Dark colored spot, mucosa glandular stomach	5	0	4	1

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)		MMP 1000 mg/kg	
Findings / Grade	-	P	-	P
Skin				
Crust, dorsal neck	5	0	4	1
Spleen				
Small	5	0	4	1
Stomach				
Elevated area, whitish, mucosa, glandular stomach	4	1	5	0

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 33-1. Histopathological findings of male rats at the end of the dosing period [H.E. staining]

Group	Control (vehicle: water for injection)							MMP 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5							5						
Spinal cord	5							5						
Pituitary gland														
Cyst	4					1		5					0	
Submandibular gland	5							5						
Sublingual gland	5							5						
Lymph node, submandibular	5							5						
Thyroid gland	5							5						
Parathyroid gland	5							5						
Thymus	5							5						
Heart														
Fibrosis, myocardial, left ventricle	4	1	0	0	0			5	0	0	0	0		
Trachea	5							5						
Lung														
Cellular infiltration, foam cell, alveolus	4	1	0	0	0			2	3	0	0	0		
Microgranuloma	3	2	0	0	0			3	2	0	0	0		
Mineralization, arterial wall	5	0	0	0	0			3	2	0	0	0		
Bronchus	5							5						
Liver														
Fibrosis, focal, subcapsule	5	0	0	0	0			4	1	0	0	0		
Microgranuloma	2	3	0	0	0			1	4	0	0	0		
Nodule, hepatodiaphragmatic	4					1		5					0	
Pancreas														
Atrophy, acinar cell, focal	5	0	0	0	0			4	1	0	0	0		
Stomach														
Cellular infiltration, inflammatory, submucosa, glandular stomach	5	0	0	0	0			4	1	0	0	0		
Dilatation, cystic, fundic gland, glandular stomach	5	0	0	0	0			4	1	0	0	0		
Edema, submucosa, glandular stomach	5	0	0	0	0			4	1	0	0	0		
Duodenum	5							5						
Jejunum	5							5						
Ileum	5							5						

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Table 33-1 (continued). Histopathological findings of male rats at the end of the dosing period [H.E. staining]

Group	Control (vehicle: water for injection)							MMP 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Cecum	5							5						
Colon	5							5						
Rectum	5							5						
Lymph node, mesenteric	5							5						
Spleen														
Deposit, pigment, brown	0	2	3	0	0			0	1	4	0	0		
Hematopoiesis, extramedullary	0	0	4	1	0			0	0	4	1	0		
Kidney														
Basophilic tubule, cortex	3	2	0	0	0			2	2	1	0	0		
Cellular infiltration, lymphocyte, interstitial	3	2	0	0	0			4	1	0	0	0		
Fibrosis, focal, subcapsule	5	0	0	0	0			4	1	0	0	0		
Urinary bladder	5							5						
Adrenal gland	5							5						
Testis														
Atrophy, seminiferous tubule	3	2	0	0	0			5	0	0	0	0		
Epididymis														
Cell debris, lumen	4	1	0	0	0			5	0	0	0	0		
Cellular infiltration, lymphocyte, interstitial	4	1	0	0	0			4	1	0	0	0		
Prostate														
Cellular infiltration, lymphocyte, interstitial	5	0	0	0	0			3	2	0	0	0		
Seminal vesicle	5							5						
Coagulating gland	5							5						
Eyeball	5							5						
Harderian gland														
Cellular infiltration, lymphocyte, interstitial	5	0	0	0	0			3	2	0	0	0		
Sciatic nerve	5							5						
Skeletal muscle	5							5						
Femur	5							5						
Marrow, femur	5							5						

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Table 34-1. Histopathological findings of female rats at the end of the dosing period [H.E. staining]

Group	Control (vehicle: water for injection)							MMP 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5							5						
Spinal cord	5							5						
Pituitary gland														
Cyst	4					1		5					0	
Submandibular gland	5							5						
Sublingual gland	5							5						
Lymph node, submandibular	5							5						
Thyroid gland														
Ultimobranchial body	5					0		3					2	
Parathyroid gland	5							5						
Thymus	5							5						
Heart														
Fibrosis, myocardial, left ventricle	5	0	0	0	0			4	1	0	0	0		
Trachea	5							5						
Lung														
Cellular infiltration, foam cell, alveolus	2	3	0	0	0			2	3	0	0	0		
Microgranuloma	4	1	0	0	0			5	0	0	0	0		
Bronchus	5							5						
Liver														
Fatty change, hepatocyte, periportal	3	1	1	0	0			4	1	0	0	0		
Hematopoiesis, extramedullary	4	1	0	0	0			4	1	0	0	0		
Microgranuloma	3	2	0	0	0			2	3	0	0	0		
Necrosis, focal	4	1	0	0	0			5	0	0	0	0		
Pancreas														
Atrophy, acinar cell, focal	4	1	0	0	0			5	0	0	0	0		
Stomach														
Dilatation, cystic, fundic gland, glandular stomach	5	0	0	0	0			4	1	0	0	0		
Edema, submucosa, glandular stomach	4	1	0	0	0			5	0	0	0	0		
Duodenum	5							5						
Jejunum	5							5						

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Table 34-1 (continued). Histopathological findings of female rats at the end of the dosing period [H.E. staining]

Group	Control (vehicle: water for injection)							MMP 1000 mg/kg						
Findings / Grade	-	±	+	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	2	3	0	0			0	2	3	0	0		
Hematopoiesis, extramedullary	0	0	2	3	0			0	0	1	4	0		
Kidney														
Basophilic tubule, cortex	5	0	0	0	0			4	1	0	0	0		
Cellular infiltration, lymphocyte, interstitial	5	0	0	0	0			4	1	0	0	0		
Mineralization, cortico-medullary junction	5	0	0	0	0			4	1	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						

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Table 34-2. Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Group	Control (vehicle: water for injection)							MMP 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5							5						
Spinal cord	5							5						
Pituitary gland														
Cyst	4					1		4					1	
Submandibular gland	5							5						
Sublingual gland	5							5						
Lymph node, submandibular	5							5						
Thyroid gland														
Ultimobranchial body	4					1		5					0	
Parathyroid gland	5							4						1
Thymus	5							5						
Heart	5							5						
Trachea	5							5						
Lung														
Cellular infiltration, foam cell, alveolus	3	2	0	0	0			1	4	0	0	0		
Microglanuloma	5							3	2	0	0	0		
Bronchus	5							5						
Liver														
Fatty change, hepatocyte, periportal	5	0	0	0	0			3	2	0	0	0		
Hematopoiesis, extramedullary	5	0	0	0	0			4	1	0	0	0		
Microgranuloma	1	4	0	0	0			0	5	0	0	0		
Pancreas	5							5						
Stomach														
Dilatation, cystic, fundic gland, glandular stomach	4	1	0	0	0			4	1	0	0	0		
Edema, submucosa, glandular stomach	3	2	0	0	0			5	0	0	0	0		
Duodenum	5							5						
Jejunum	5							5						
Ileum	5							5						

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)							MMP 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Cecum	5							5						
Colon	5							5						
Rectum	5							5						
Lymph node, mesenteric	5							5						
Spleen														
Deposit, pigment, brown	0	0	5	0	0			0	1	4	0	0		
Hematopoiesis, extramedullary	0	0	3	2	0			0	0	3	2	0		
Kidney														
Basophilic tubule, cortex	4	1	0	0	0			1	4	0	0	0		
Cellular infiltration, lymphocyte, interstitial	4	1	0	0	0			2	3	0	0	0		
Cyst/ hyalin, cast, papilla/ cortico-medullary junction	5					0		2					3	
Mineralization, papilla/ cortico-medually junction	5	0	0	0	0			2	2	1	0	0		
Urinary bladder	5							5						
Adrenal gland	5							5						
Ovary	5							5						
Uterus	5							5						
Vagina	5							5						
Eyeball	5							5						
Harderian gland														
Cellular infiltration, lymphocyte, interstitial	5	0	0	0	0			4	1	0	0	0		
Sciatic nerve	5							5						
Skeletal muscle	5							5						
Femur	5							5						
Marrow, femur	5							5						

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Table 34-3. Histopathological findings of female rats at the end of the recovery period [H.E. staining]

Group	Control (vehicle: water for injection)							MMP 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Stomach	1						4	0						5
Kidney														
Basophilic tubule, cortex	4	1	0	0	0			5	0	0	0	0		
Cellular infiltration, lymphocyte, interstitial	4	1	0	0	0			4	1	0	0	0		
Cyst, cortico-medullary junction	4					1		5					0	
Mineralization, cortco-medullary junction	5	0	0	0	0			4	1	0	0	0		

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Table 35. Results of observations about estrous cycle

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of animals examined	12	12	12	12
Pre-treatment period				
Number of animals showing type of cycle				
4-day cycle	11	10	10	9
4/5-day cycle	0	0	1	0
5-day cycle	1	2	1	3
Mean length of estrous cycle in days; Mean±S.D. (N)	4.1 ± 0.3 (12)	4.2 ± 0.4 (12)	4.1 ± 0.2 (12)	4.3 ± 0.5 (12)
Treatment period				
Number of animals showing each type of cycle				
4-day cycle	11	9	11	5
4/5-day cycle	1	2	0	1
5-day cycle	0	1	1	6
Mean length of estrous cycle in days; Mean±S.D. (N)	4.0 ± 0.1 (12)	4.2 ± 0.3 (12)	4.1 ± 0.3 (12)	4.5 ± 0.5 ** (12)
Frequency of animals that show abnormal estrous cycles after the treatment	0 / 12	0 / 12	0 / 12	0 / 12
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 36. Results of observations about reproductive performance

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of mated pairs [A]	12	12	12	12
Number of copulated pairs [B]	12	12	12	12
Copulation index [(B/A)×100,%]	100.0	100.0	100.0	100.0
Number of fertile males [C]	12	12	12	10
Fertility index [(C/B)×100,%]	100.0	100.0	100.0	83.3
Pairing days until copulation ;Mean±S.D.(N)	2.0 ± 1.1 (12)	2.6 ± 1.3 (12)	2.3 ± 0.8 (12)	3.4 ± 3.4 (12)

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

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

Table 37. Observation of offspring (F_1)

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of dams	12	12	11	10
Gestation length (days)				
Mean ± S.D. per dam	22.1 ± 0.3	22.0 ± 0.0	22.0 ± 0.0	22.5 ± 0.5 **
Number of corpora lutea				
Total	198	196	183	155
Mean ± S.D. per dam	16.5 ± 1.8	16.3 ± 1.9	15.3 ± 3.1 (12)	15.5 ± 1.4
Number of implantation scars				
Total	198	193	177	149
Mean ± S.D. per dam	16.5 ± 1.8	16.1 ± 1.7	14.8 ± 4.5 (12)	14.9 ± 1.1
Implantation index (%) [a)]	100.0 ± 0.0	98.6 ± 2.6	92.6 ± 24.0 (12)	96.4 ± 5.2
Delivery index (dams,%) [b)]	100.0	100.0	91.7	100.0
Number of offspring at birth				
Total	190	178	166	135
Mean ± S.D. per dam	15.8 ± 1.7	14.8 ± 2.3	15.1 ± 1.4	13.5 ± 1.6 *
Number of live offspring at birth				
Male	93	86	80	57
Female	93	88	82	69
Total	186	174	162	126
Mean ± S.D. per dam	15.5 ± 1.7	14.5 ± 2.4	14.7 ± 1.6	12.6 ± 2.9 **
Sex ratio [c)]				
Mean ± S.D. per dam	0.50 ± 0.13	0.49 ± 0.16	0.49 ± 0.12	0.45 ± 0.13
Number of dead offspring				
Total	4	4	4	9
Mean ± S.D. per dam	0.3 ± 0.5	0.3 ± 0.8	0.4 ± 0.7	0.9 ± 1.9
Delivery index (offspring) [d)]				
Mean% ± S.D. per dam	96.1 ± 5.7	92.2 ± 9.6	94.3 ± 5.3	90.6 ± 9.0
Birth index [e)]				
Mean% ± S.D. per dam	94.2 ± 6.8	90.2 ± 10.9	91.9 ± 5.9	84.3 ± 17.3
Live birth index [f)]				
Mean% ± S.D. per dam	97.9 ± 3.1	97.8 ± 5.2	97.6 ± 4.4	92.7 ± 15.4
Number of offspring on day 4				
Male	84	86	79	50
Female	89	88	79	61
Sex ratio [c)]				
Mean ± S.D. per dam	0.48 ± 0.14	0.49 ± 0.16	0.50 ± 0.13	0.45 ± 0.12 (9)
Viability index [g)]				
Mean% ± S.D. per dam	92.5 ± 22.5	100.0 ± 0.0	97.9 ± 3.9	82.8 ± 32.4
Number of external abnormalities [h)]	0	0	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

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

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

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

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

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

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

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

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

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

Figures in parentheses indicate number of dams.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 38. Body weights of offspring (F_1) before weaning

Group		Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Number of dams		12	12	11	10
Male					
Days after birth					
	0	6.6 ± 0.4	6.7 ± 0.6	6.9 ± 0.3	6.2 ± 0.4
	4	9.9 ± 1.5	10.5 ± 1.1	10.4 ± 0.7	9.5 ± 0.7 (9)
Female					
Days after birth					
	0	6.3 ± 0.3	6.3 ± 0.4	6.5 ± 0.3	5.9 ± 0.4
	4	9.3 ± 1.5	10.0 ± 1.1	10.0 ± 0.8	8.7 ± 0.6 (9)

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 Methyl 3-methoxypropanoate by oral administration in rats

Table 39. General conditions in offspring (F_1) before weaning

Group	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
Control (vehicle: water for injection)	Number of offspring	186	186	184	183	182
	General appearance, No abnormality	186	184	183	182	175
	General appearance, Death		2	1	1	7
MMP 62.5 mg/kg	Number of offspring	174	174	174	174	174
	General appearance, No abnormality	174	174	174	174	174
MMP 250 mg/kg	Number of offspring	162	162	161	159	158
	General appearance, No abnormality	162	161	159	158	158
	General appearance, Death		1	2	1	
MMP 1000 mg/kg	Number of offspring	126	126	113	112	112
	General appearance, No abnormality	126	113	112	112	111
	General appearance, Death		13	1		1

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Table 40. Morphological observations of offspring (F_1)

Group	Control (vehicle: water for injection)	MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg
Dead offspring				
Number of dead offspring [a]	17	4	8	24
Number of missing offspring	9	0	3	14
Number of dead offspring examined [b]	8 (2)	4 (1)	5 (0)	10 (2)
Number of dead offspring with external changes	0	0	0	0
Number of dead offspring with visceral changes	0	0	0	0
Live offspring				
Number of live offspring examined (postnatal day 0)	190	178	166	135
Number of live offsping with external changes	0	0	0	0
Number of live offspring examined (postnatal day 4)	173	174	158	111
Number of live offspring with external changes				
Emaciation	3	0	0	0
Number of live offspring with visceral changes	0	0	0	0

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

a) including missing offspring

b) Parenthesis indicates the number of offspring not examined bacause of their autolysis.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

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

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

Control (vehicle: water for injection)

Male No.	Days of administration																																																	
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43															
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre															
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b	b	b															
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-															
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7															
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	6															
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	1	1	1															

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
b: Mouth, Loss of teeth.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

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

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

MMP 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
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

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

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

MMP 250 mg/kg

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	a	-	a	-	a	-	a
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	-	-	-	-	a	-	a	-	-	-	-	-	a	-	-	-	a	-	a	-	a	-	a
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	a	-	-	-	-	-	a	-	a	-	a	-	a	-	-	-	-	-	a	-	-	-	a
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	a	-	a	-	a	-	a	-	a
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	a	-	-	-	-	-	-	-	a	-	-	-	a	-	-
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	a	-	a	-	-	-	-	-	a
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	12	7	12	10	12	9	12	9	12	8	12	7	12	6	12	7	12	7	12	8	12	4	12	6	12	6	12	5
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	5	0	2	0	3	0	3	0	4	0	5	0	6	0	5	0	5	0	4	0	8	0	6	0	6	0	7

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

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

MMP 1000 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	
M04037	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	
M04038	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	-	-	a	-	a	-	-	-	a	-	a	-	a	-	a	-	-	-	
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	
M04041	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	a	-	-	-	-	-	a	-	a	-	a	-	a	-	
M04042	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04043	-	a	-	a	-	-	-	a	-	a	-	-	-	a	-	-	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	
M04044	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	a	-	-	-	a	-	a	-	a	-	-	-	a		
M04045	-	-	-	-	-	a	-	a	-	a	-	-	-	-	-	a	-	-	-	-	-	a	-	-	-	a	-	-	-	-	-	-	-	a		
M04046	-	-	-	-	-	a	-	a	-	a	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	a		
M04047	-	-	-	-	-	a	-	-	-	a	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04048	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a		
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
-	12	6	12	6	12	4	12	3	12	3	12	7	12	6	12	4	12	9	12	9	12	5	12	10	12	6	12	4	12	6	12	8	12	6	7	
a	0	6	0	6	0	8	0	9	0	9	0	5	0	6	0	8	0	3	0	3	0	7	0	2	0	6	0	8	0	6	0	4	0	6	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04045	-	-	-	-	-	-	-	a	a	a	a	a	a	a	a
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	4	4	4	4	4	4	4	4
a	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1

-: General appearance, No abnormality.

a: Skin, Crust formation.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	5	5	1	1
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	5	5	1	1

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Female No.	Days of administration																																			
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	7	7	4	4
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	7	7	4	4

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Female No.	Days of administration																																			
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	3	3	1	1
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	3	3	1	1

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Days of administration																																							
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04038	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> a	> -	> a	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	a	-	a	-	-	-	a	-	a	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	a	-	-	-	a						
F04044	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> a	> -	> -	> -	> -	> -	> -	> -	> a	> -	> -	> -	> -
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	a						
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	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	8	8	6	6	1	1
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	7	10	8	10	8	10	9	10	8	8	7	6	5	1	1
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	2	0	2	0	1	0	2	0	1	0	1	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Appendix 2-1-4 (continued). General conditions of female rats

MMP 1000 mg/kg

Female No.	Days of administration																																							
	19		20		21		22		23		24		25		26		27		28																					
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post																				
F04044	> a	> a	> a	> a	> a	> a	> a	> -	> a	> -	> a	> a	> a	> -	> a	> -	> a	> -	> a	> -																		

Pre: Before administration, Post: after administration.

-: Mouth, Salivation.

a: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

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

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

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

Control (vehicle: water for injection)

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
F05049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	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

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Female No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F06059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06060	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a
F06061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-
F06062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	a	-	-	-	-	-	-	-	a
F06063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	a	-	-	-	-
F06064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	a
F06068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	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	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	8	10	7	10	7	10	8	10	9	10	8	10	8	10	7	10	7	10	7	10	5	10	7	10	3	10	6	10	5
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	3	0	3	0	2	0	1	0	2	0	2	0	3	0	3	0	3	0	5	0	3	0	7	0	4	0	5

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

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

MMP 1000 mg/kg

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	
F06059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06060	-	-	-	a	-	a	-	a	a	-	-	-	-	a	-	a	-	-	-	-	-	a	-	-	-	a	-	a	-	a	-	-	-	a	-	
F06061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	
F06062	-	a	-	-	-	a	-	a	-	-	-	a	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	a	-	
F06063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	a		
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-		
F06066	-	-	-	-	-	a	-	a	a	-	-	a	-	-	-	a	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	-	-	a		
F06067	-	a	-	a	-	a	-	-	-	-	-	a	-	-	-	a	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	a		
F06068	-	a	-	a	-	a	-	a	a	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	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	5	
-	10	7	10	7	10	5	10	6	7	10	10	6	10	8	10	4	10	9	10	9	10	7	10	8	10	6	10	6	10	3	10	9	10	4	5	
a	0	3	0	3	0	5	0	4	3	0	0	4	0	2	0	6	0	1	0	1	0	3	0	2	0	4	0	4	0	7	0	1	0	6	0	

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F06064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06068	-	-	-	-	-	-	-	-	-	-	-	-	a	a	a
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, Crust formation.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 3-1. General conditions in dams during pregnancy

Control (vehicle: water for injection)

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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

Control (vehicle: water for injection)

Dam No.	Days of pregnancy																	
	14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 3-2. General conditions in dams during pregnancy

MMP 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
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

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

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

MMP 62.5 mg/kg

Dam No.	Days of pregnancy																	
	14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 3-3. General conditions in dams during pregnancy

MMP 250 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
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

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

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

MMP 250 mg/kg

Dam No.	Days of pregnancy																								
	14		15		16		17		18		19		20		21		22		23		24		25		26
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	1	1	1	1	1	1	1
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	1	1	1	1	1	1	1

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 3-4. General conditions in dams during pregnancy

MMP 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
F04037	-	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a
F04038	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-
F04039	-	-	-	-	-	-	-	a	-	a	-	-	-	a	-	-	-	-	-	-	-	a	-	a	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	a	-	-	-	-	-	a	-	a	-	-	-	-	-	-	-	a	-	a	-	-
F04043	-	-	-	-	-	a	-	a	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a
F04044	>	-	>	a	>	-	>	a	>	-	>	-	>	-	>	a	>	-	>	-	>	-	>	-	>	-	>	-
F04045	-	a	-	a	-	-	-	a	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	a	-	a
F04048	-	a	-	-	-	-	-	a	-	a	-	-	-	a	-	a	-	a	-	a	-	-	-	a	-	a	-	a
Number of dams	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
-	10	8	10	9	10	9	10	5	10	6	10	9	10	5	10	5	10	6	10	7	10	7	10	5	10	5	10	6
a	0	2	0	1	0	1	0	5	0	4	0	1	0	5	0	5	0	4	0	3	0	3	0	5	0	5	0	4

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Mouth, Salivation.

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

MMP 1000 mg/kg

Dam No.	Days of pregnancy																								
	14		15		16		17		18		19		20		21		22		23		24		25		26
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F04037	-	a	-	a	-	a	-	a	-	-	-	a	-	a	-	a	-	a							
F04038	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>
F04039	-	a	-	-	-	-	-	a	-	-	-	-	-	-	-	a	-	-							
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F04042	-	-	-	a	-	-	-	-	-	a	-	-	-	-	-	-	-	-							
F04043	-	-	-	a	-	-	-	-	-	-	-	-	-	a	-	-	-	-							
F04044	>	-	>	-	>	-	>	-	>	a	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>
F04045	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F04048	-	-	-	a	-	-	-	-	-	-	-	-	-	a	-	a	-	-							
Number of dams	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	0	0	0	0	0	0	0
-	10	7	10	6	10	9	10	8	10	9	10	9	10	8	10	7	9	8	0	0	0	0	0	0	0
a	0	3	0	4	0	1	0	2	0	1	0	1	0	2	0	3	0	1	0	0	0	0	0	0	0

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 4-1. General conditions in dams during lactation

Control (vehicle: water for injection)

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	-	-	-	-	-	-	-	-	-	-	-
Number of dams	8	8	12	12	12	12	12	12	12	12	12
-	8	8	12	12	12	12	12	12	12	12	12

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 4-2. General conditions in dams during lactation

MMP 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
F02013	-	-	-	-	-	-	-	-	-	-	-
F02014	-	-	-	-	-	-	-	-	-	-	-
F02015	#	#	-	-	-	-	-	-	-	-	-
F02016	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-
F02020	#	#	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-
F02024	#	#	-	-	-	-	-	-	-	-	-
Number of dams	9	9	12	12	12	12	12	12	12	12	12
-	9	9	12	12	12	12	12	12	12	12	12

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 4-3. General conditions in dams during lactation

MMP 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
F03025	#	#	-	-	-	-	-	-	-	-	-
F03026	#	#	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-
F03028	#	#	-	-	-	-	-	-	-	-	-
F03029	#	#	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-
F03032	#	#	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-
F03034	#	#	-	-	-	-	-	-	-	-	-
F03035	#	#	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-
Number of dams	4	4	11	11	11	11	11	11	11	11	11
-	4	4	11	11	11	11	11	11	11	11	11

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 4-4. General conditions in dams during lactation

MMP 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
F04037	-	a	-	a	-	a	-	a	-	a	-
F04039	#	#	-	-	-	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	a	-	-	-	-	-	-	-
F04042	#	#	-	-	-	-	-	-	-	-	-
F04043	b	-	-	-	-	-	-	-	-	Total litter loss	
F04045	-	-	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-
F04047	#	#	-	-	-	-	-	a	-	a	-
F04048	#	#	-	-	-	a	-	-	-	-	-
Number of dams	6	6	10	10	10	10	10	10	10	9	9
-	5	5	10	8	10	8	10	8	10	7	9
a	0	1	0	2	0	2	0	2	0	2	0
b	1	0	0	0	0	0	0	0	0	0	0

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

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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 5-1-1. Detailed clinical observations of male rats

Control (vehicle: water for injection)

Male No.	Open-field observations c)																	
	Piloerection									Urination								
	Pre [a]	T7 [b]	T14	T23	T30	T36	T42	R7 [c]	R14	Pre	T7	T14	T23	T30	T36	T42	R7	R14
M01001	2	2	2	2	2	2	2			0	0	0	0	1	1	1		
M01002	2	2	2	2	2	2	3			0	1	0	0	0	0	0		
M01003	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
M01004	2	2	2	2	2	2	2			1	0	0	0	0	0	1		
M01005	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
M01006	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
M01007	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
M01008	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	1
M01009	2	2	2	2	2	2	2	2	2	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
M01011	2	2	2	2	2	2	2	2	2	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	1	1
Total score	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 1	3: 0	3: 0	1	1	0	0	1	1	2	1	2
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

[a] pre-treatment; [b] day 7 of treatment; [c] day 7 of recovery

Piloerection [2, not observed; 3, slight]

Urination [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 behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 5-1-2. Detailed clinical observations of male rats

MMP 62.5 mg/kg

Male No.	Open-field observations [c]														
	Piloerection							Urination							
	Pre [a]	T7 [b]	T14	T23	T30	T36	T42	Pre	T7	T14	T23	T30	T36	T42
M02013	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M02014	2	2	2	2	2	2	2	0	0	0	0	1	0	0
M02015	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M02016	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M02017	2	2	2	2	2	2	2	0	1	0	0	0	0	0
M02018	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M02019	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M02020	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M02021	2	2	2	2	2	2	2	0	1	0	0	0	0	0
M02022	2	2	2	2	2	2	2	1	0	0	1	0	1	0
M02023	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M02024	2	2	2	2	2	2	2	1	0	1	1	1	1	0
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	2	2	1	2	2	2	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 7 of treatment

Piloerection [2, not observed; 3, slight]

Urination [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 behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 5-1-3. Detailed clinical observations of male rats

MMP 250 mg/kg

Male No.	Open-field observations [c]														
	Piloerection							Urination							
	Pre [a]	T7 [b]	T14	T23	T30	T36	T42	Pre	T7	T14	T23	T30	T36	T42
M03025	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M03026	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M03027	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M03028	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M03029	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M03030	2	2	2	2	2	2	2	0	1	0	0	0	0	0
M03031	2	2	2	2	2	2	2	0	0	0	1	0	0	0
M03032	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M03033	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M03034	2	2	2	2	2	2	2	0	0	0	0	0	0	0
M03035	2	2	2	2	2	2	2	0	0	0	0	0	1	0
M03036	2	2	2	2	2	2	2	0	0	0	0	0	0	0
Total score	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	0	1	0	1	0	1	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 7 of treatment

Piloerection [2, not observed; 3, slight]

Urination [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 behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 5-1-4. Detailed clinical observations of male rats

MMP 1000 mg/kg

Male No.	Open-field observations [c]																		
	Piloerection									Urination									
	Pre [a]	T7 [b]	T14	T23	T30	T36	T42	R7 [c]	R14	Pre	T7	T14	T23	T30	T36	T42	R7	R14
M04037	2	2	2	2	2	2	2			0	0	0	0	0	1	1		
M04038	2	2	2	2	2	2	2			1	0	0	1	1	1	0		
M04039	2	2	2	2	2	2	2			0	1	0	0	0	1	0		
M04040	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
M04041	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
M04042	2	2	2	2	2	2	2			0	0	0	1	1	1	0		
M04043	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
M04044	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0
M04045	2	2	2	2	2	2	2	2	2	0	1	0	1	0	0	0	0	0
M04046	2	2	2	2	2	2	2	2	2	0	1	0	0	0	0	0	0	0
M04047	2	2	2	2	2	2	2	2	2	0	0	1	1	1	1	0	1	0
M04048	2	2	2	2	2	2	2	2	2	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	3	1	4	3	5	1	1	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

[a] pre-treatment; [b] day 7 of treatment; [c] day 7 of recovery

Piloerection [2, not observed; 3, slight]

Urination [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 behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Observations made while handling [b]							Open-field observations [c]														
	Salivation							Straub tail							Urination							
	Pre [a]	T7 [b]	T14	T23	T30	T36	L [c]	Pre	T7	T14	T23	T30	T36	L	Pre	T7	T14	T23	T30	T36	L
F01001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01005	2	2	2	2	2	2	2	2	2	2	2	3	2	2	0	0	0	0	0	0	0
F01006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	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	3: 0	3: 0	3: 1	3: 0	3: 0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 7 of treatment; [c] lactation period

Salivation [2, not observed; 3, slight]

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

Urination [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 behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size), 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, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Female No.	Observations made while handling [b]							Open-field observations [c]													
	Salivation							Straub tail							Urination						
	Pre [a]	T7 [b]	T14	T23	T30	T36	L [c]	Pre	T7	T14	T23	T30	T36	L	Pre	T7	T14	T23	T30	T36	L
F02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02014	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02015	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02016	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02017	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02018	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02019	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02020	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02021	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02022	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02023	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
F02024	2	2	2	2	2	2	2	2	2	2	2	2	2	2	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	3: 0	3: 0	3: 0	3: 0	3: 0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 7 of treatment; [c] lactation period

Salivation [2, not observed; 3, slight]

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

Urination [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 behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size), 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, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Female No.	Observations made while handling [b]								Open-field observations [c]															
	Salivation								Straub tail								Urination							
	Pre [a]	T7 [b]	T14	T23	T30	T36	T42	L [c]	Pre	T7	T14	T23	T30	T36	T42	L	Pre	T7	T14	T23	T30	T36	T42	L
F03025	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03026	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03027	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03028	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03029	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03030	2	2	2	2	2	2	2		2	2	2	2	2	2	2		0	0	0	0	0	0	0	
F03031	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03032	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03033	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03034	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03035	2	2	2	2	2	2		2	2	2	2	2	2	2		2	0	0	0	0	0	0		0
F03036	2	2	2	2	2	2		2	2	2	2	2	2	2		2	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	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(11)

[a] pre-treatment; [b] day 7 of treatment; [c] lactation period

Salivation [2, not observed; 3, slight]

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

Urination [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 behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size), 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, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Observations made while handling [b]									Open-field observations [c]																		
	Salivation									Straub tail									Urination									
	Pre [a]	T7 [b]	T14	T23	T30	T36	T42	T49	L [c]	Pre	T7	T14	T23	T30	T36	T42	T49	L	Pre	T7	T14	T23	T30	T36	T42	T49	L
F04037	2	2	2	2	3	2			2	2	2	2	2	2	2			2	0	0	0	0	0	0			0
F04038	2	2	2	2	2	2	2			2	2	2	2	2	2	2			0	0	0	0	0	0	0		
F04039	2	2	2	2	2	2			2	2	2	2	2	2	2			2	0	0	0	0	0	0			0
F04040	2	2	2	2	2	2			2	2	2	2	2	2	2			2	0	0	0	0	0	0			0
F04041	2	2	2	2	2	2			2	2	2	2	2	2	2			2	0	0	0	0	0	0			0
F04042	2	2	2	2	2	2			2	2	2	2	2	2	2			2	1	0	0	0	0	0			0
F04043	2	2	2	2	2	2			2	2	2	2	2	2	2			2	0	0	0	0	0	0			0
F04044	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		0	0	0	0	0	0	0	0	
F04045	2	2	2	2	2	2			2	2	2	2	2	2	2			2	0	0	0	0	0	0			0
F04046	2	2	2	2	2	2			2	2	2	2	2	2	2			2	0	0	0	0	0	0			0
F04047	2	2	2	2	2	2			2	2	2	2	2	2	2			2	0	0	0	0	0	0			0
F04048	2	2	2	2	2	2			2	2	2	2	2	2	2			2	0	0	0	1	0	0			0
Total	3: 0	3: 0	3: 0	3: 0	3: 1	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	1	0	0	1	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)

[a] pre-treatment; [b] day 7 of treatment; [c] lactation period

Salivation [2, not observed; 3, slight]

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

Urination [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 behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size), 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, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Open-field observations c) Straub tail									Urination								
	Pre [a]	T7 [b]	T14	T23	T30	T36	T42	R7 [c]	R14	Pre	T7	T14	T23	T30	T36	T42	R7	R14
F05049	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
F05050	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
F05051	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
F05052	2	2	2	2	2	2	2			1	0	0	0	0	0	0		
F05053	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
F05054	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0
F05055	2	2	2	3	3	3	3	3	3	0	0	0	0	0	0	0	0	0
F05056	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0
F05057	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0
F05058	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0
Total	3: 0	3: 0	3: 0	3: 1	3: 1	3: 1	3: 1	3: 1	3: 1	1	0	0	0	0	0	0	0	0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

[a] pre-treatment; [b] day 7 of treatment; [c] day 7 of recovery

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

Urination [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 behavir, 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, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Open-field observations [c] Straub tail									Urination								
	Pre [a]	T7 [b]	T14	T23	T30	T36	T42	R7 [c]	R14	Pre	T7	T14	T23	T30	T36	T42	R7	R14
F06059	2	2	2	2	2	2	2			1	0	0	0	0	0	0		
F06060	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
F06061	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
F06062	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
F06063	2	2	2	2	2	2	2			0	0	0	0	0	0	0		
F06064	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0
F06065	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0
F06066	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0
F06067	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0
F06068	2	2	2	2	2	2	2	2	2	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	0	0	0	0	0	0	0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

[a] pre-treatment; [b] day 7 of treatment; [c] day 7 of recovery

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

Urination [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 behavir, 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, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M01001	414.0	424.0	439.4	458.0	473.8	488.1	505.8	521.6
M01002	414.5	426.4	441.0	467.4	483.9	512.4	522.9	455.9
M01003	381.6	396.1	406.1	420.2	432.1	442.7	459.5	459.3
M01004	387.1	393.3	404.1	417.3	431.8	455.5	464.4	464.8
M01005	400.4	410.0	416.6	436.8	456.3	474.0	493.4	494.8
M01006	396.9	407.8	421.4	448.7	464.0	483.6	497.3	507.4
M01007	403.0	415.3	428.6	449.9	459.2	481.4	495.8	506.9
M01008	388.1	406.8	423.4	451.7	466.5	480.3	500.5	510.5
M01009	408.5	428.4	442.6	469.2	478.8	489.2	496.0	501.6
M01010	384.8	400.3	413.9	433.6	455.3	476.3	496.6	505.2
M01011	426.3	439.8	455.9	469.4	480.2	501.6	513.0	521.5
M01012	415.6	420.1	431.9	459.9	471.6	494.7	508.3	508.3
Number of males	12	12	12	12	12	12	12	12
Mean	401.7	414.0	427.1	448.5	462.8	481.7	496.1	496.5
S.D.	14.4	14.2	15.8	18.1	17.1	18.8	18.1	23.3

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M02013	415.8	427.0	444.2	463.2	475.5	505.6	530.2	533.4
M02014	397.9	408.2	414.9	447.0	464.4	494.1	507.8	505.3
M02015	412.7	423.0	427.6	459.2	463.0	478.9	495.6	513.5
M02016	406.3	415.5	424.9	442.7	452.9	467.1	480.5	492.7
M02017	386.6	400.1	401.9	419.2	449.4	482.1	490.6	484.4
M02018	406.4	413.7	429.9	443.1	454.3	468.0	478.7	505.4
M02019	383.6	398.8	413.5	445.3	461.6	482.5	508.1	521.7
M02020	396.8	415.9	428.6	452.4	481.0	503.8	528.2	541.7
M02021	399.2	408.6	416.9	452.0	470.2	493.8	517.0	531.1
M02022	387.4	396.7	405.6	429.0	441.6	458.2	474.3	486.9
M02023	395.9	411.2	419.8	435.7	450.9	470.6	487.1	512.0
M02024	418.4	436.5	442.9	467.6	480.3	498.3	513.8	535.3
Number of males	12	12	12	12	12	12	12	12
Mean	400.6	412.9	422.6	446.4	462.1	483.6	501.0	513.6
S.D.	11.5	11.8	13.1	14.0	12.8	15.6	19.2	19.5
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M03025	431.0	437.4	461.3	486.4	513.0	539.2	551.7	559.6
M03026	388.7	399.2	406.0	418.7	432.1	447.7	466.4	473.0
M03027	392.2	396.8	413.7	433.0	448.6	477.7	487.2	503.2
M03028	379.0	387.8	400.9	425.2	452.4	464.6	483.5	486.5
M03029	400.5	413.1	423.2	454.1	481.6	496.7	519.2	529.3
M03030	384.1	394.7	405.8	435.9	450.2	467.2	488.3	510.3
M03031	393.8	410.4	415.7	432.9	443.6	455.8	469.6	490.3
M03032	393.5	400.0	415.4	428.3	431.2	440.7	441.4	451.7
M03033	411.0	425.3	437.5	465.1	483.6	505.7	529.6	543.5
M03034	398.8	409.6	426.4	443.4	462.5	474.5	504.8	520.7
M03035	410.7	420.5	438.1	452.7	471.1	486.9	506.8	515.5
M03036	403.4	418.3	434.7	454.5	467.7	482.6	495.3	507.8
Number of males	12	12	12	12	12	12	12	12
Mean	398.9	409.4	423.2	444.2	461.5	478.3	495.3	507.6
S.D.	14.0	14.4	17.4	19.3	23.7	27.1	29.9	29.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M04037	400.4	409.6	427.6	460.1	470.5	491.5	501.0	491.5
M04038	388.4	397.0	410.8	449.2	458.9	473.1	489.9	497.1
M04039	382.3	382.7	401.6	424.5	441.7	460.1	472.6	480.0
M04040	399.6	406.4	421.4	432.5	456.7	475.1	494.6	514.2
M04041	393.3	400.3	410.2	418.1	439.9	448.5	460.0	468.4
M04042	399.1	417.9	433.9	453.3	479.7	490.1	513.5	533.4
M04043	398.1	411.5	432.7	459.1	477.7	502.6	519.5	528.2
M04044	406.1	408.7	423.8	442.0	460.1	474.7	489.2	498.7
M04045	381.7	388.3	407.5	439.2	457.6	470.2	482.0	486.7
M04046	390.5	390.9	400.4	431.3	454.5	469.6	481.9	483.2
M04047	414.4	433.3	455.2	474.5	506.0	526.7	552.2	570.7
M04048	415.4	419.3	437.0	471.3	493.3	504.1	525.5	541.9
Number of males	12	12	12	12	12	12	12	12
Mean	397.4	405.5	421.8	446.3	466.4	482.2	498.5	507.8
S.D.	11.0	14.5	16.4	18.1	19.9	21.6	25.5	30.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of recovery		
	1	7	14
M01008	504.4	523.5	514.1
M01009	496.0	515.9	528.5
M01010	497.5	523.6	538.0
M01011	521.2	532.9	538.3
M01012	506.7	527.2	540.6
Number of males	5	5	5
Mean	505.2	524.6	531.9
S.D.	10.0	6.2	11.0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Days of recovery		
	1	7	14
M04044	495.6	516.5	518.5
M04045	480.5	504.0	481.4
M04046	471.8	498.6	507.3
M04047	554.6	582.4	592.4
M04048	540.9	571.3	579.6
Number of males	5	5	5
Mean	508.7	534.6	535.8
S.D.	37.0	39.3	47.9
Significance	NS	NS	NS
Statistical method	AW	AW	AW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Female No.	Days of administration			
	1	4	7	14
F01001	263.4	271.3	270.4	285.6
F01002	232.5	242.4	248.5	257.5
F01003	243.8	257.7	260.8	263.9
F01004	263.1	263.1	272.5	282.7
F01005	239.1	238.5	243.0	246.0
F01006	247.5	252.8	255.3	259.9
F01007	253.2	256.1	265.4	276.7
F01008	253.1	250.0	257.6	269.4
F01009	232.3	242.3	239.5	242.9
F01010	254.9	250.2	260.7	273.7
F01011	232.3	236.6	235.5	233.1
F01012	256.6	261.5	273.3	285.5
Number of females	12	12	12	12
Mean	247.7	251.9	256.9	264.7
S.D.	11.6	10.7	12.9	17.4

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Female No.	Days of administration			
	1	4	7	14
F02013	238.7	249.0	249.0	250.1
F02014	246.2	248.9	260.2	268.5
F02015	254.4	262.2	262.2	268.1
F02016	227.9	237.9	245.4	251.6
F02017	237.1	239.3	242.5	252.4
F02018	263.7	272.1	275.2	282.9
F02019	237.1	229.6	214.3	214.9
F02020	260.9	262.6	272.2	282.2
F02021	252.1	257.3	254.3	268.1
F02022	244.5	260.3	267.5	281.8
F02023	256.0	256.8	272.1	272.5
F02024	247.8	247.3	243.8	263.5
Number of females	12	12	12	12
Mean	247.2	251.9	254.9	263.1
S.D.	10.7	12.2	17.3	19.1
Significance	NS	NS	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Female No.	Days of administration			
	1	4	7	14
F03025	251.2	254.4	250.7	259.7
F03026	238.9	252.6	260.9	270.6
F03027	235.3	246.1	254.1	263.0
F03028	228.3	238.9	245.9	257.6
F03029	251.9	262.9	267.8	277.2
F03030	256.0	263.9	261.0	284.1
F03031	235.4	248.3	253.5	258.3
F03032	262.8	270.0	272.1	278.2
F03033	241.7	252.6	259.3	267.0
F03034	240.5	244.8	252.5	276.4
F03035	247.2	262.6	271.3	280.6
F03036	225.6	230.3	234.9	249.8
Number of females	12	12	12	12
Mean	242.9	252.3	257.0	268.5
S.D.	11.2	11.5	10.8	10.9
Significance	NS	NS	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Days of administration					
	1	4	7	14	21	28
F04037	253.0	254.6	262.1	279.1		
F04038	256.3	249.3	250.5	266.0		
F04039	251.8	259.1	257.8	281.2		
F04040	257.2	265.0	268.1	270.5		
F04041	237.8	229.9	244.4	254.1		
F04042	239.1	243.0	248.1	250.1		
F04043	238.5	236.6	251.2	268.1		
F04044	268.4	271.1	279.4	285.7	318.5	346.1
F04045	260.9	262.0	272.0	295.7		
F04046	241.1	241.0	252.2	256.6		
F04047	247.9	257.7	252.3	277.2		
F04048	251.4	256.0	266.4	272.0		
Number of females	12	12	12	12		
Mean	250.3	252.1	258.7	271.4		
S.D.	9.7	12.3	10.8	13.5		
Significance	NS	NS	NS	NS	---	---
Statistical method	AN	AN	AN	AN	NA	NA

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F05049	240.6	258.1	255.1	275.2	276.0	281.5	294.4	301.8
F05050	251.0	251.0	261.3	268.8	275.4	276.8	287.4	299.7
F05051	246.8	245.9	256.4	263.5	258.0	278.6	288.3	290.1
F05052	257.8	270.7	274.3	281.1	294.1	309.9	311.9	307.2
F05053	239.9	245.5	254.7	258.7	277.0	278.8	290.0	288.8
F05054	235.5	237.4	245.0	249.7	250.7	250.0	257.5	263.5
F05055	242.6	241.9	241.0	251.1	260.1	270.0	270.6	282.0
F05056	254.4	256.7	265.7	273.1	273.3	288.6	290.1	300.9
F05057	226.6	240.1	244.8	252.9	256.8	252.2	248.5	262.3
F05058	262.4	272.9	272.0	287.6	303.2	317.9	325.1	328.7
Number of females	10	10	10	10	10	10	10	10
Mean	245.8	252.0	257.0	266.2	272.5	280.4	286.4	292.5
S.D.	10.9	12.4	11.4	13.1	16.8	21.6	23.0	20.1

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F06059	255.6	255.4	262.5	285.0	295.2	305.6	304.4	314.2
F06060	253.0	248.6	265.4	264.1	276.9	275.6	295.6	300.1
F06061	248.3	246.8	263.2	280.5	282.0	278.5	290.8	293.1
F06062	259.5	269.8	268.1	280.3	299.0	302.3	308.2	321.8
F06063	253.8	256.3	257.5	278.0	286.4	290.6	293.3	302.4
F06064	243.0	241.7	257.2	265.1	274.1	271.1	274.6	287.1
F06065	266.5	274.4	278.9	291.8	299.3	309.7	310.5	315.9
F06066	237.3	242.8	253.5	268.5	259.2	280.8	281.5	279.1
F06067	252.7	257.0	255.6	273.4	273.8	283.1	289.5	294.6
F06068	256.7	270.5	281.0	303.0	293.2	318.3	314.8	339.2
Number of females	10	10	10	10	10	10	10	10
Mean	252.6	256.3	264.3	279.0	283.9	291.6	296.3	304.8
S.D.	8.3	11.8	9.4	12.2	13.1	16.3	13.0	18.0
Significance	NS	NS	NS	*	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of recovery		
	1	7	14
F05054	262.2	266.5	270.8
F05055	279.5	302.3	292.2
F05056	293.4	310.0	315.2
F05057	255.4	272.0	254.8
F05058	333.1	343.4	330.4
Number of females	5	5	5
Mean	284.7	298.8	292.7
S.D.	30.9	31.2	31.0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Days of recovery		
	1	7	14
F06064	289.9	290.7	300.3
F06065	318.6	320.6	326.9
F06066	286.1	288.8	287.8
F06067	293.6	294.1	307.1
F06068	334.8	341.4	339.4
Number of females	5	5	5
Mean	304.6	307.1	312.3
S.D.	21.1	23.1	20.7
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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 9-1. Body weights of dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	299.8	335.7	377.6	475.0
F01002	261.5	287.9	319.1	393.9
F01003	275.9	310.4	353.8	449.1
F01004	279.6	327.1	359.9	463.1
F01005	250.5	296.5	353.1	458.9
F01006	271.0	304.0	343.0	451.4
F01007	282.5	318.4	358.1	439.2
F01008	268.7	317.9	354.0	435.9
F01009	261.7	299.9	343.9	430.0
F01010	278.4	317.1	354.5	440.4
F01011	256.1	295.2	332.7	406.6
F01012	289.7	329.4	367.1	463.9
Number of dams	12	12	12	12
Mean	273.0	311.6	351.4	442.3
S.D.	14.3	15.1	15.4	23.7

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 9-2. Body weights of dams during pregnancy

MMP 62.5 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	263.9	293.2	322.8	406.3
F02014	261.4	304.5	337.6	421.9
F02015	289.0	323.6	359.5	452.7
F02016	255.9	286.7	326.0	407.4
F02017	267.6	305.7	354.6	448.6
F02018	299.4	348.8	395.8	493.1
F02019	242.3	294.9	323.1	407.0
F02020	289.2	340.4	383.1	462.0
F02021	278.0	300.9	334.1	419.5
F02022	310.3	348.9	393.0	498.4
F02023	283.1	321.9	362.8	437.8
F02024	258.0	299.4	329.2	400.1
Number of dams	12	12	12	12
Mean	274.8	314.1	351.8	437.9
S.D.	20.0	22.1	27.2	33.7
Significance	NS	NS	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 9-3. Body weights of dams during pregnancy

MMP 250 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F03025	274.6	326.9	368.5	453.9	
F03026	270.0	305.3	339.1	428.2	
F03027	267.2	297.1	322.5	398.0	
F03028	264.9	311.5	356.7	436.5	
F03029	276.9	325.6	357.6	438.1	
F03030	283.8	312.6	334.4	349.1	349.6
F03031	262.4	303.5	332.4	420.6	
F03032	283.7	317.7	353.7	435.5	
F03033	281.1	313.5	349.1	449.1	
F03034	283.6	335.4	380.6	479.7	
F03035	283.4	322.2	353.7	436.8	
F03036	251.9	283.6	318.1	395.4	
Number of dams	12	12	12	12	
Mean	273.6	312.9	347.2	426.7	
S.D.	10.4	14.2	18.5	33.5	
Significance	NS	NS	NS	NS	---
Statistical method	AN	AN	AN	AN	NA

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 9-4. Body weights of dams during pregnancy

MMP 1000 mg/kg

Dam No.		Days of pregnancy				
		0	7	14	20	26
F04037		285.2	320.3	347.5	397.6	
F04038	>	266.4 >	305.3 >	306.4 >	300.1 >	297.0
F04039		295.4	331.7	363.9	426.6	
F04040		286.5	317.6	354.8	442.2	
F04041		268.8	310.7	343.1	419.0	
F04042		273.3	315.8	360.6	442.5	
F04043		274.2	305.9	344.1	416.7	
F04044	>	338.7 >	361.2 >	373.0 >	357.7 >	351.0
F04045		292.9	328.6	357.2	427.6	
F04046		267.7	309.3	331.7	401.6	
F04047		279.1	335.7	379.0	451.5	
F04048		294.3	322.3	353.2	438.9	
Number of dams		10	10	10	10	
Mean		281.7	319.8	353.5	426.4	
S.D.		10.6	9.9	13.0	17.9	
Significance		NS	NS	NS	NS	---
Statistical method		AN	AN	AN	AN	NA

>: Excluded from analysis (not pregnant)
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 10-1. Body weights of dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation	
	0	4
F01001	371.3	381.6
F01002	297.6	312.3
F01003	331.3	349.3
F01004	318.1	369.7
F01005	350.6	337.4
F01006	320.4	345.5
F01007	341.8	339.5
F01008	327.6	328.2
F01009	327.8	330.7
F01010	346.1	365.7
F01011	291.5	332.8
F01012	349.1	372.2
Number of dams	12	12
Mean	331.1	347.1
S.D.	22.7	21.1

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 10-2. Body weights of dams during lactation

MMP 62.5 mg/kg

Dam No.	Days of lactation	
	0	4
F02013	285.2	315.8
F02014	327.1	341.6
F02015	352.5	356.8
F02016	306.5	307.5
F02017	334.3	345.9
F02018	371.6	373.8
F02019	335.2	328.3
F02020	373.8	386.1
F02021	319.3	334.4
F02022	357.8	376.8
F02023	368.5	356.0
F02024	340.5	335.8
Number of dams	12	12
Mean	339.4	346.6
S.D.	27.3	24.3
Significance	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 10-3. Body weights of dams during lactation

MMP 250 mg/kg

Dam No.	Days of lactation	
	0	4
F03025	356.9	361.9
F03026	314.9	347.7
F03027	308.5	323.4
F03028	333.7	347.7
F03029	322.6	334.7
F03031	302.7	334.3
F03032	341.3	336.3
F03033	349.9	368.8
F03034	331.3	330.2
F03035	341.9	367.3
F03036	325.9	319.3
Number of dams	11	11
Mean	330.0	342.9
S.D.	17.1	17.2
Significance	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 10-4. Body weights of dams during lactation

MMP 1000 mg/kg

Dam No.	Days of lactation		
	0	4	
F04037	325.0	348.2	
F04039	336.3	356.1	
F04040	338.2	367.0	
F04041	341.9	350.3	
F04042	349.4	362.3	
F04043	293.1	301.3	Total litter loss on the lactational day 4.
F04045	346.2	368.4	
F04046	330.2	335.4	
F04047	376.2	370.8	
F04048	355.5	363.0	
Number of dams	10	10	
Mean	339.2	352.3	
S.D.	21.6	21.0	
Significance	NS	NS	
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of administration					
	1	7	14	29	35	41
M01001	28.2	25.7	25.8	25.4	30.6	29.0
M01002	29.4	30.9	28.5	30.2	31.0	(0.7) a)
M01003	24.5	26.5	19.9	24.0	24.9	21.2
M01004	27.9	30.4	25.1	27.1	27.8	27.0
M01005	31.0	28.9	24.8	29.6	27.6	26.6
M01006	25.6	28.4	25.2	29.5	31.9	25.5
M01007	30.3	28.3	26.6	28.1	31.1	27.3
M01008	33.8	31.9	26.5	29.0	26.8	26.2
M01009	26.6	30.6	23.6	26.6	30.1	26.2
M01010	31.3	33.9	27.7	32.7	28.7	26.7
M01011	36.3	33.7	26.2	26.3	28.8	25.9
M01012	25.9	30.4	27.8	29.3	29.9	26.2
Number of males	12	12	12	12	12	11
Mean	29.2	30.0	25.6	28.2	29.1	26.2
S.D.	3.5	2.5	2.3	2.4	2.1	1.9

a) Excluded from data analysis (loss of teeth).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02013	30.3	28.2	25.6	28.1	28.5	28.4
M02014	27.5	31.3	25.0	31.2	29.0	28.3
M02015	29.3	29.8	29.7	33.0	33.0	32.1
M02016	29.6	29.2	24.8	28.9	28.2	28.8
M02017	29.0	26.4	27.4	30.3	30.7	28.2
M02018	29.8	30.3	24.8	27.3	27.5	29.9
M02019	29.7	29.5	28.9	28.3	34.2	26.5
M02020	29.3	32.5	29.7	33.2	31.7	34.3
M02021	26.7	25.8	28.5	30.6	32.6	27.3
M02022	30.2	29.6	27.1	30.1	31.2	31.5
M02023	30.1	27.3	26.3	27.6	29.1	27.4
M02024	30.7	30.4	25.9	28.8	30.4	28.1
Number of males	12	12	12	12	12	12
Mean	29.4	29.2	27.0	29.8	30.5	29.2
S.D.	1.2	2.0	1.9	2.0	2.1	2.3
Significance	NS	NS	NS	NS	NS	**
Statistical method	DT	DU	AN	AN	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.
DU: Analysis by Dunnett's test.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03025	31.2	32.1	28.4	28.5	29.2	27.7
M03026	30.4	29.0	25.2	26.0	34.6	29.3
M03027	29.9	27.0	23.2	28.7	29.1	28.9
M03028	28.8	30.0	29.8	29.4	28.1	29.4
M03029	28.4	32.5	30.7	27.4	30.1	31.4
M03030	25.5	29.4	25.5	26.7	31.8	31.1
M03031	27.5	27.8	23.9	26.7	28.3	29.8
M03032	29.6	31.6	25.0	27.1	26.9	24.8
M03033	28.6	33.4	28.7	30.6	29.2	30.2
M03034	33.2	35.2	27.6	33.4	34.6	32.2
M03035	31.8	29.8	28.1	29.8	31.3	29.7
M03036	27.5	31.8	28.5	28.3	27.1	28.0
Number of males	12	12	12	12	12	12
Mean	29.4	30.8	27.1	28.6	30.0	29.4
S.D.	2.1	2.4	2.4	2.1	2.6	2.0
Significance	NS	NS	NS	NS	NS	**
Statistical method	DT	DU	AN	AN	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.
DU: Analysis by Dunnett's test.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04037	23.0	28.8	25.9	26.6	27.7	26.0
M04038	22.0	25.4	23.8	25.1	27.3	25.0
M04039	22.0	30.0	24.8	30.1	29.5	27.6
M04040	22.9	27.4	24.0	29.0	29.3	24.5
M04041	23.9	26.5	26.3	29.4	27.4	30.0
M04042	24.4	29.9	26.4	24.0	26.3	30.2
M04043	26.7	28.6	26.4	26.7	28.4	28.0
M04044	24.2	29.2	26.9	32.6	30.5	28.5
M04045	20.5	28.2	21.0	21.4	27.9	27.6
M04046	21.3	26.7	26.8	26.4	26.3	29.5
M04047	28.4	29.9	26.3	26.7	32.7	31.8
M04048	21.7	29.0	26.9	28.7	29.1	25.9
Number of males	12	12	12	12	12	12
Mean	23.4	28.3	25.5	27.2	28.5	27.9
S.D.	2.3	1.5	1.8	3.0	1.8	2.2
Significance	**	NS	NS	NS	NS	NS
Statistical method	DT	DU	AN	AN	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.
DU: Analysis by Dunnett's test.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of recovery	
	6	12
M01008	25.7	27.6
M01009	25.6	34.4
M01010	33.2	29.4
M01011	25.2	31.7
M01012	26.5	32.7
Number of males	5	5
Mean	27.2	31.2
S.D.	3.4	2.7

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Days of recovery	
	6	12
M04044	31.3	33.8
M04045	30.8	31.1
M04046	30.4	31.9
M04047	32.0	34.8
M04048	31.1	32.5
Number of males	5	5
Mean	31.1	32.8
S.D.	0.6	1.5
Significance	*	NS
Statistical method	AW	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AW: Analysis by Aspin-Welch t-test.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of administration		
	1	7	14
F01001	22.9	22.3	14.8
F01002	18.8	19.8	22.9
F01003	24.1	17.4	21.6
F01004	20.6	19.4	20.7
F01005	19.1	13.9	17.6
F01006	15.0	22.4	17.5
F01007	23.3	18.4	20.9
F01008	22.5	18.7	23.8
F01009	11.5	24.1	17.1
F01010	22.1	17.5	22.8
F01011	15.8	23.4	17.4
F01012	25.8	16.7	21.0
Number of females	12	12	12
Mean	20.1	19.5	19.8
S.D.	4.2	3.0	2.9

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Female No.	Days of administration		
	1	7	14
F02013	18.3	20.3	17.4
F02014	18.9	15.3	17.9
F02015	20.6	23.8	22.9
F02016	20.6	20.3	21.1
F02017	21.1	18.4	23.0
F02018	17.8	25.0	24.6
F02019	17.7	15.1	12.4
F02020	21.9	16.1	21.0
F02021	21.8	20.4	15.7
F02022	21.1	24.9	19.1
F02023	22.8	22.5	22.8
F02024	20.3	22.2	17.6
Number of females	12	12	12
Mean	20.2	20.4	19.6
S.D.	1.7	3.5	3.6
Significance	NS	NS	NS
Statistical method	KW	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Female No.	Days of administration		
	1	7	14
F03025	12.4	23.1	18.9
F03026	23.4	22.1	22.0
F03027	21.8	21.7	22.9
F03028	20.0	21.0	22.0
F03029	24.3	26.2	23.3
F03030	17.9	21.6	20.7
F03031	18.8	22.1	18.8
F03032	19.4	21.5	21.0
F03033	15.6	24.1	22.3
F03034	20.7	23.3	18.7
F03035	21.4	21.4	19.8
F03036	15.9	17.5	16.5
Number of females	12	12	12
Mean	19.3	22.1	20.6
S.D.	3.4	2.1	2.1
Significance	NS	NS	NS
Statistical method	KW	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Days of administration		
	1	7	14
F04037	19.2	16.4	24.3
F04038	19.2	16.0	21.8
F04039	22.9	22.6	17.8
F04040	13.2	22.7	19.1
F04041	18.5	17.3	22.2
F04042	12.1	20.2	18.0
F04043	17.9	18.6	20.3
F04044	18.1	22.9	15.1
F04045	20.1	18.9	21.6
F04046	21.2	20.5	21.4
F04047	13.7	19.7	19.7
F04048	22.3	19.4	21.7
Number of females	12	12	12
Mean	18.2	19.6	20.3
S.D.	3.5	2.3	2.5
Significance	NS	NS	NS
Statistical method	KW	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of administration						
	1	7	14	21	29	35	41
F05049	21.6	22.0	17.2	23.8	22.0	16.2	21.6
F05050	24.8	16.3	24.4	25.9	25.4	17.5	23.9
F05051	21.0	15.9	20.8	18.9	20.8	24.7	18.1
F05052	18.1	21.5	22.9	19.9	18.6	23.7	18.1
F05053	22.2	19.8	19.1	22.4	21.2	20.8	15.5
F05054	21.1	16.7	18.0	19.9	20.1	16.7	19.2
F05055	19.0	19.7	16.3	20.4	22.5	20.8	21.5
F05056	21.3	18.0	23.6	18.3	17.1	22.9	20.9
F05057	19.2	21.6	15.2	19.3	20.3	16.4	22.6
F05058	15.8	24.8	22.8	19.9	19.3	26.0	15.1
Number of females	10	10	10	10	10	10	10
Mean	20.4	19.6	20.0	20.9	20.7	20.6	19.7
S.D.	2.5	2.9	3.3	2.4	2.3	3.7	3.0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06059	19.8	23.0	18.2	21.8	24.4	23.2	19.5
F06060	19.9	18.5	21.1	20.2	22.9	19.6	19.6
F06061	19.9	18.8	21.1	28.4	22.5	14.1	18.7
F06062	16.2	20.1	25.2	22.5	26.7	21.5	22.2
F06063	18.6	23.0	17.2	24.3	22.6	21.0	18.4
F06064	18.7	16.0	18.9	20.4	18.8	21.7	20.1
F06065	19.4	21.2	19.7	19.2	22.0	21.3	15.5
F06066	18.7	20.8	19.6	19.6	17.8	17.4	19.6
F06067	16.7	20.5	20.7	18.0	23.8	20.9	20.3
F06068	15.5	23.4	18.8	24.6	25.3	26.6	25.7
Number of females	10	10	10	10	10	10	10
Mean	18.3	20.5	20.1	21.9	22.7	20.7	20.0
S.D.	1.6	2.3	2.2	3.1	2.7	3.3	2.6
Significance	*	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of recovery	
	6	12
F05054	16.0	19.9
F05055	24.0	20.1
F05056	22.7	17.7
F05057	21.4	16.3
F05058	24.6	19.6
Number of females	5	5
Mean	21.7	18.7
S.D.	3.4	1.7

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Days of recovery	
	6	12
F06064	18.0	15.4
F06065	19.0	22.7
F06066	22.2	16.6
F06067	17.3	22.4
F06068	25.3	26.8
Number of females	5	5
Mean	20.4	20.8
S.D.	3.3	4.7
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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 13-1. Food consumption in dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	24.6	31.7	31.1	29.4
F01002	23.5	20.3	23.3	18.6
F01003	21.6	30.6	27.1	27.7
F01004	19.4	30.3	27.8	23.6
F01005	21.9	33.0	32.9	30.6
F01006	19.3	24.4	26.3	27.6
F01007	19.9	25.0	27.3	23.4
F01008	21.4	26.7	31.5	19.3
F01009	23.6	28.2	30.7	25.6
F01010	23.4	29.6	30.6	24.5
F01011	23.0	29.8	26.7	27.5
F01012	20.4	26.7	26.8	31.0
Number of dams	12	12	12	12
Mean	21.8	28.0	28.5	25.7
S.D.	1.8	3.6	2.8	4.0

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 13-2. Food consumption in dams during pregnancy

MMP 62.5 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	19.8	22.4	23.2	22.3
F02014	17.4	24.8	28.3	23.9
F02015	25.8	28.4	28.9	28.5
F02016	19.2	24.0	24.1	24.4
F02017	23.4	31.2	33.0	32.5
F02018	26.2	31.9	34.2	25.8
F02019	25.8	27.0	26.3	23.8
F02020	20.7	30.3	26.2	26.1
F02021	21.7	26.3	26.0	28.1
F02022	29.7	32.8	31.5	29.0
F02023	18.2	31.2	28.3	30.3
F02024	17.6	25.0	28.9	27.0
Number of dams	12	12	12	12
Mean	22.1	27.9	28.2	26.8
S.D.	4.0	3.5	3.4	3.0
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW

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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 13-3. Food consumption in dams during pregnancy

MMP 250 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03025	22.9	30.3	30.3	26.1
F03026	23.2	29.7	29.5	26.7
F03027	20.8	22.9	23.1	24.8
F03028	24.8	25.5	28.8	25.8
F03029	22.2	30.7	31.5	21.8
F03030	18.5	27.5	25.3	21.2
F03031	23.3	25.3	23.0	26.0
F03032	23.1	23.7	21.3	23.4
F03033	18.3	26.2	29.6	28.0
F03034	27.5	35.9	37.1	19.5
F03035	21.0	24.7	30.9	22.6
F03036	22.0	23.0	22.6	20.8
Number of dams	12	12	12	12
Mean	22.3	27.1	27.8	23.9
S.D.	2.5	3.9	4.7	2.7
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW

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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 13-4. Food consumption in dams during pregnancy

MMP 1000 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	19.3	25.3	24.0	21.4
F04038	> 23.6	> 26.6	> 17.3	> 17.4
F04039	20.3	26.8	27.4	24.5
F04040	19.1	28.0	28.7	28.9
F04041	26.0	27.3	29.5	24.4
F04042	21.9	27.2	25.3	27.9
F04043	24.0	28.8	27.6	0.5
F04044	> 19.3	> 29.2	> 22.2	> 20.0
F04045	18.5	21.4	25.4	20.3
F04046	25.7	22.2	25.6	21.5
F04047	24.0	28.6	33.1	17.3
F04048	19.9	25.5	29.9	26.6
Number of dams	10	10	10	10
Mean	21.9	26.1	27.7	21.3
S.D.	2.8	2.6	2.7	8.2
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW

>: Excluded from analysis (not pregnant)
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 14-1. Food consumption in dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation
	3
F01001	49.1
F01002	40.1
F01003	48.6
F01004	59.7
F01005	35.9
F01006	39.6
F01007	39.6
F01008	13.1
F01009	40.3
F01010	46.3
F01011	47.8
F01012	48.0
Number of dams	12
Mean	42.3
S.D.	11.2

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 14-2. Food consumption in dams during lactation

MMP 62.5 mg/kg

Dam No.	Days of lactation
	3
F02013	40.3
F02014	45.0
F02015	44.9
F02016	42.6
F02017	39.8
F02018	35.9
F02019	39.2
F02020	47.2
F02021	43.3
F02022	50.4
F02023	37.2
F02024	41.2
Number of dams	12
Mean	42.3
S.D.	4.2
Significance	NS
Statistical method	DT

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.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 14-3. Food consumption in dams during lactation

MMP 250 mg/kg

Dam No.	Days of lactation
	3
F03025	34.0
F03026	47.6
F03027	42.5
F03028	43.9
F03029	38.1
F03031	46.9
F03032	39.6
F03033	39.9
F03034	31.6
F03035	43.8
F03036	37.7
Number of dams	11
Mean	40.5
S.D.	5.0
Significance	NS
Statistical method	DT

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.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 14-4. Food consumption in dams during lactation

MMP 1000 mg/kg

Dam No.	Days of lactation	
	3	
F04037	32.6	
F04039	41.6	
F04040	44.8	
F04041	36.9	
F04042	39.7	
F04043	12.2	Total litter loss on the lactational day 4.
F04045	38.1	
F04046	23.9	
F04047	30.8	
F04048	37.7	
Number of dams	10	
Mean	33.8	
S.D.	9.6	
Significance	*	
Statistical method	DT	

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.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M01001	2	2	2	2	+	+	+
M01003	2	2	2	2	+	+	+
M01004	2	2	2	2	+	+	+
M01005	2	2	2	2	+	+	+
M01006	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 Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M02013	2	2	2	2	+	+	+
M02014	2	2	2	2	+	+	+
M02015	2	2	2	2	+	+	+
M02016	2	2	2	2	+	+	+
M02017	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M03025	2	2	2	2	+	+	+
M03026	2	2	2	2	+	+	+
M03027	2	2	2	2	+	+	+
M03028	2	2	2	2	+	+	+
M03029	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M04037	2	2	2	2	+	+	+
M04038	2	2	2	2	+	+	+
M04039	2	2	2	2	+	+	+
M04040	2	2	2	2	+	+	+
M04041	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F01005	2	2	2	2	+	+	+
F01007	2	2	2	2	+	+	+
F01008	2	2	2	2	+	+	+
F01010	2	2	2	2	+	+	+
F01012	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 16-1-2. Functional findings of female rats at the end of the dosing period

MMP 62.5 mg/kg

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F02014	2	2	2	2	+	+	+
F02016	2	2	2	2	+	+	+
F02017	2	2	2	2	+	+	+
F02020	2	2	2	2	+	+	+
F02024	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 16-1-3. Functional findings of female rats at the end of the dosing period

MMP 250 mg/kg

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F03026	2	2	2	2	+	+	+
F03027	2	2	2	2	+	+	+
F03028	2	2	2	2	+	+	+
F03029	2	2	2	2	+	+	+
F03031	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 16-1-4. Functional findings of female rats at the end of the dosing period

MMP 1000 mg/kg

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F04041	2	2	2	2	+	+	+
F04042	2	2	2	2	+	+	+
F04045	2	2	2	2	+	+	+
F04047	2	2	2	2	+	+	+
F04048	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 16-2-1. Functional findings of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)
Female, satellite groups

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F05049	2	2	2	2	+	+	+
F05050	2	2	2	2	+	+	+
F05051	2	2	2	2	+	+	+
F05052	2	2	2	2	+	+	+
F05053	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female, satellite groups

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F06059	2	2	2	2	+	+	+
F06060	2	2	2	2	+	+	+
F06061	2	2	2	2	+	+	+
F06062	2	2	2	2	+	+	+
F06063	2	2	2	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 17-1. Assessment of grip strength of male rats

Control (vehicle: water for injection)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M01001	0.287	0.178
M01002	0.409	0.280
M01003	0.461	0.349
M01004	0.466	0.337
M01005	0.316	0.325
Number of males	5	5
Mean	0.388	0.294
S.D.	0.083	0.070

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 17-2. Assessment of grip strength of male rats

MMP 62.5 mg/kg

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M02013	0.574	0.490
M02014	0.460	0.239
M02015	0.296	0.460
M02016	0.706	0.489
M02017	0.621	0.361
Number of males	5	5
Mean	0.531	0.408
S.D.	0.159	0.108

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 17-3. Assessment of grip strength of male rats

MMP 250 mg/kg

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M03025	0.247	0.338
M03026	0.662	0.314
M03027	0.539	0.369
M03028	0.809	0.251
M03029	0.624	0.308
Number of males	5	5
Mean	0.576	0.316
S.D.	0.208	0.044

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 17-4. Assessment of grip strength of male rats

MMP 1000 mg/kg

Male No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
M04037	0.506	0.402
M04038	0.672	0.360
M04039	0.599	0.362
M04040	0.330	0.358
M04041	0.384	0.437
Number of males	5	5
Mean	0.498	0.384
S.D.	0.143	0.035

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 18-1. Assessment of grip strength of female rats

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F01005	0.346	0.296
F01007	0.349	0.279
F01008	0.304	0.251
F01010	0.729	0.367
F01012	0.541	0.262
Number of females	5	5
Mean	0.454	0.291
S.D.	0.179	0.046

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 18-2. Assessment of grip strength of female rats

MMP 62.5 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F02014	0.234	0.287
F02016	0.526	0.300
F02017	0.401	0.380
F02020	0.689	0.290
F02024	0.628	0.399
Number of females	5	5
Mean	0.496	0.331
S.D.	0.183	0.054

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 18-3. Assessment of grip strength of female rats

MMP 250 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F03026	0.568	0.172
F03027	0.581	0.252
F03028	0.641	0.257
F03029	0.691	0.277
F03031	0.255	0.232
Number of females	5	5
Mean	0.547	0.238
S.D.	0.171	0.040

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 18-4. Assessment of grip strength of female rats

MMP 1000 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F04041	0.420	0.257
F04042	0.472	0.212
F04045	0.819	0.266
F04047	0.584	0.253
F04048	0.866	0.318
Number of females	5	5
Mean	0.632	0.261
S.D.	0.202	0.038

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 19-1. Assessment of grip strength of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F05049	0.454	0.262
F05050	0.479	0.338
F05051	0.431	0.414
F05052	0.705	0.242
F05053	0.640	0.384
Number of females	5	5
Mean	0.542	0.328
S.D.	0.123	0.075

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 19-2. Assessment of grip strength of female rats, satellite group

MMP 1000 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F06059	0.238	0.238
F06060	0.635	0.323
F06061	0.326	0.283
F06062	0.603	0.283
F06063	0.344	0.242
Number of females	5	5
Mean	0.429	0.274
S.D.	0.178	0.035

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 20-1. Motor activity of male rats

Control (vehicle: water for injection)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1312	1125	913	763	4113	40	26	15	10	91
M01002	1162	946	610	583	3301	18	12	7	5	42
M01003	949	962	808	382	3101	17	21	15	1	54
M01004	962	785	737	444	2928	19	12	8	5	44
M01005	839	711	752	580	2882	41	22	29	23	115
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1045	906	764	550	3265	27	19	15	9	69
S.D.	189	162	110	147	502	12	6	9	9	32

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 20-2. Motor activity of male rats

MMP 62.5 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02013	1108	973	778	185	3044	28	17	14	0	59
M02014	1396	1423	1065	1081	4965	32	31	14	15	92
M02015	1053	817	1094	725	3689	20	10	20	13	63
M02016	1735	1823	1611	1602	6771	17	27	23	23	90
M02017	1137	1057	698	61	2953	22	19	8	0	49
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1286	1219	1049	731	4284	24	21	16	10	71
S.D.	284	405	359	638	1606	6	8	6	10	19

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 20-3. Motor activity of male rats

MMP 250 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03025	1171	1026	575	901	3673	38	27	4	12	81
M03026	1343	1195	1065	1097	4700	24	27	25	15	91
M03027	1000	1088	857	834	3779	33	20	17	13	83
M03028	1089	1134	1056	750	4029	27	27	14	3	71
M03029	1158	894	824	676	3552	18	14	13	9	54
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1152	1067	875	852	3947	28	23	15	10	76
S.D.	126	115	201	161	456	8	6	8	5	14

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 20-4. Motor activity of male rats

MMP 1000 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04037	1104	797	686	540	3127	29	11	13	7	60
M04038	1220	1052	1041	625	3938	26	20	12	4	62
M04039	1182	1016	1048	597	3843	35	28	24	3	90
M04040	1255	1304	1068	862	4489	35	32	20	14	101
M04041	1208	1000	705	546	3459	26	14	7	4	51
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1194	1034	910	634	3771	30	21	15	6	73
S.D.	57	181	196	132	515	5	9	7	5	21

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 21-1. Motor activity of female rats

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01005	792	443	653	440	2328	11	3	4	0	18
F01007	1259	998	974	817	4048	28	9	12	5	54
F01008	1126	1020	867	994	4007	18	24	6	13	61
F01010	1123	761	630	571	3085	30	16	10	9	65
F01012	836	877	1076	136	2925	17	13	31	0	61
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1027	820	840	592	3279	21	13	13	5	52
S.D.	203	235	196	333	740	8	8	11	6	19

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 21-2. Motor activity of female rats

MMP 62.5 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02014	1120	795	803	284	3002	22	11	18	1	52
F02016	1098	1099	1024	542	3763	30	19	24	0	73
F02017	1275	780	975	703	3733	39	9	20	2	70
F02020	1385	975	955	787	4102	39	13	12	15	79
F02024	1215	1011	668	608	3502	27	17	1	3	48
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1219	932	885	585	3620	31	14	15	4	64
S.D.	117	140	147	192	407	8	4	9	6	14

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 21-3. Motor activity of female rats

MMP 250 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03026	1162	1115	830	765	3872	39	18	14	23	94
F03027	956	589	491	675	2711	19	6	3	2	30
F03028	910	518	311	521	2260	16	4	0	1	21
F03029	1117	872	1128	865	3982	27	10	14	2	53
F03031	1458	1358	1775	1090	5681	8	6	25	0	39
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1121	890	907	783	3701	22	9	11	6	47
S.D.	216	353	578	213	1331	12	6	10	10	29

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 21-4. Motor activity of female rats

MMP 1000 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04041	1244	1049	830	831	3954	32	13	15	9	69
F04042	747	529	432	258	1966	32	1	0	0	33
F04045	1013	717	698	47	2475	21	13	11	0	45
F04047	1064	973	892	389	3318	27	30	24	0	81
F04048	1009	818	639	537	3003	14	6	6	2	28
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1015	817	698	412	2943	25	13	11	2	51
S.D.	178	207	180	295	765	8	11	9	4	23

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05049	1225	1238	1012	1274	4749	56	64	50	65	235
F05050	1293	1253	1161	1172	4879	22	24	15	33	94
F05051	1341	1318	1164	1008	4831	40	44	31	24	139
F05052	1157	1080	1013	664	3914	33	32	32	10	107
F05053	1181	1027	1101	1012	4321	32	24	22	18	96
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1239	1183	1090	1026	4539	37	38	30	30	134
S.D.	77	124	75	232	413	13	17	13	21	59

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 22-2. Motor activity of female rats, satellite group

MMP 1000 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06059	1053	1094	1105	1080	4332	25	21	26	26	98
F06060	1401	1165	793	782	4141	41	21	16	12	90
F06061	1363	1476	1305	1080	5224	41	57	43	17	158
F06062	1067	1036	1047	1038	4188	30	37	32	28	127
F06063	814	683	789	839	3125	33	23	56	54	166
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1140	1091	1008	964	4202	34	32	35	27	128
S.D.	243	284	220	142	746	7	16	15	16	34

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-1-1. Urinalysis in male rats

Control (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	7.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01002	7.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01003	8.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M01004	7.0	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
M01005	7.5	+	-	±	-	-	+	light yellow	-	-	-	-	±	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field, 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-1-2. Urinalysis in male rats

MMP 62.5 mg/kg

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02013	8.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M02014	7.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M02015	7.0	2+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M02016	7.0	±	-	±	-	2+	±	light yellow	-	+	-	-	±	-
M02017	6.5	+	-	±	-	-	+	light yellow	-	-	-	-	±	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field, 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-1-3. Urinalysis in male rats

MMP 250 mg/kg

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03025	7.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M03026	7.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
M03027	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M03028	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M03029	6.5	+	-	±	-	+	±	light yellow	-	-	-	-	±	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field, 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-1-4. Urinalysis in male rats

MMP 1000 mg/kg

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04037	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	-	-
M04038	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	-	-
M04039	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M04040	6.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M04041	6.5	+	-	-	-	-	±	light yellow	-	-	-	-	±	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field, 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-2-1. Urinalysis in male rats

Control (vehicle: water for injection)

Male No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
M01001	12.0	1.074	147.6	295.1	161.8	1.77	3.54	1.94
M01002	14.2	1.035	43.8	128.4	38.0	0.62	1.82	0.54
M01003	16.3	1.061	121.0	271.0	151.1	1.97	4.42	2.46
M01004	14.9	1.066	125.4	293.4	171.0	1.87	4.37	2.55
M01005	12.6	1.075	123.7	342.3 §	180.4	1.56	4.31	2.27
Number of males	5	5	5	5	5	5	5	5
Mean	14.0	1.062	112.3	266.0	140.5	1.56	3.69	1.95
S.D.	1.7	0.016	39.7	81.2	58.3	0.55	1.11	0.82

S.G.: Specific gravity

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-2-2. Urinalysis in male rats

MMP 62.5 mg/kg

Male No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
M02013	14.0	1.071	148.8	349.2 §	182.7	2.08	4.89	2.56
M02014	9.9	1.067	91.5	219.6	36.1	0.91	2.17	0.36
M02015	14.7	1.059	96.2	234.4	116.1	1.41	3.45	1.71
M02016	19.5	1.052	88.7	226.1	123.5	1.73	4.41	2.41
M02017	14.6	1.054	75.2	206.4	82.9	1.10	3.01	1.21
Number of males	5	5	5	5	5	5	5	5
Mean	14.5	1.061	100.1	247.1	108.3	1.45	3.59	1.65
S.D.	3.4	0.008	28.3	57.9	54.0	0.47	1.09	0.90
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN	AN	AN

S.G.: Specific gravity

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.

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-2-3. Urinalysis in male rats

MMP 250 mg/kg

Male No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
M03025	18.0	1.062	131.6	283.4	157.3	2.37	5.10	2.83
M03026	20.6	1.047	83.2	203.3	105.2	1.71	4.19	2.17
M03027	12.3	1.069	113.3	292.2	141.2	1.39	3.59	1.74
M03028	13.7	1.069	134.6	295.9	156.7	1.84	4.05	2.15
M03029	19.5	1.064	125.8	270.3	160.7	2.45	5.27	3.13
Number of males	5	5	5	5	5	5	5	5
Mean	16.8	1.062	117.7	269.0	144.2	1.95	4.44	2.40
S.D.	3.6	0.009	20.9	38.0	23.1	0.45	0.72	0.56
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN	AN	AN

S.G.: Specific gravity

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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-2-4. Urinalysis in male rats

MMP 1000 mg/kg

Male No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
M04037	19.1	1.058	94.3	240.5	121.6	1.80	4.59	2.32
M04038	22.0	1.054	80.6	221.9	123.4	1.77	4.88	2.71
M04039	16.8	1.074	131.6	314.6 §	160.6	2.21	5.28	2.70
M04040	26.3	1.050	88.9	195.2	111.6	2.34	5.13	2.94
M04041	21.8	1.049	82.7	189.3	102.4	1.80	4.13	2.23
Number of males	5	5	5	5	5	5	5	5
Mean	21.2	1.057	95.6	232.3	123.9	1.98	4.80	2.58
S.D.	3.6	0.010	20.8	50.4	22.2	0.27	0.46	0.30
Significance	**	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN	AN	AN

S.G.: Specific gravity

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.

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-3-1. Urinalysis in male rats of the recovery period

Control (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01008	8.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01009	8.0	+	-	+	-	-	±	light yellow	-	-	-	-	±	-
M01010	7.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01011	7.0	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
M01012	7.5	+	-	+	-	-	+	light yellow	-	-	-	-	±	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field, 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-3-2. Urinalysis in male rats of the recovery period

MMP 1000 mg/kg

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04044	8.0	+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M04045	7.5	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
M04046	8.5	+	-	+	-	-	+	light yellow	-	-	-	-	+	-
M04047	7.0	+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M04048	7.5	+	-	±	-	-	+	light yellow	-	-	-	-	±	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field, 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-4-1. Urinalysis in male rats of the recovery period

Control (vehicle: water for injection)

Male No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
M01008	12.7	1.071	200.8	337.6 §	228.5	2.55	4.29	2.90
M01009	21.3	1.049	104.9	222.7	120.8	2.23	4.74	2.57
M01010	20.1	1.056	113.8	251.6	144.3	2.29	5.06	2.90
M01011	28.2	1.038	84.7	174.8	96.2	2.39	4.93	2.71
M01012	13.8	1.075	147.5	339.2 §	180.4	2.04	4.68	2.49
Number of males	5	5	5	5	5	5	5	5
Mean	19.2	1.058	130.3	265.2	154.0	2.30	4.74	2.71
S.D.	6.3	0.015	45.5	72.3	51.9	0.19	0.29	0.19

S.G.: Specific gravity

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 23-4-2. Urinalysis in male rats of the recovery period

MMP 1000 mg/kg

Male No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
M04044	11.4	1.086	205.4	411.6 §	238.6	2.34	4.69	2.72
M04045	10.3	1.058	84.1	212.0	90.7	0.87	2.18	0.93
M04046	11.2	1.082	187.9	385.3 §	227.6	2.10	4.32	2.55
M04047	17.4	1.071	146.7	329.9 §	193.4	2.55	5.74	3.37
M04048	21.7	1.050	109.4	237.7	137.0	2.37	5.16	2.97
Number of males	5	5	5	5	5	5	5	5
Mean	14.4	1.069	146.7	315.3	177.5	2.05	4.42	2.51
S.D.	5.0	0.015	51.1	88.2	62.6	0.68	1.36	0.93
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	AW	AW	AW

S.G.: Specific gravity

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.

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05049	7.0	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
F05050	7.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
F05051	7.0	±	-	-	-	-	±	light yellow	-	-	-	-	-	-
F05052	6.5	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F05053	6.5	±	-	±	-	-	±	light yellow	-	-	-	-	-	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06059	6.5	±	-	±	-	-	±	light yellow	-	-	-	-	-	-
F06060	6.5	+	-	+	-	-	±	light yellow	-	-	-	-	±	-
F06061	6.5	+	-	+	-	-	±	light yellow	-	-	-	-	±	-
F06062	6.5	+	-	+	-	-	±	light yellow	-	-	-	-	±	-
F06063	6.5	+	-	+	-	-	±	light yellow	-	-	-	-	-	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field, 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
F05049	8.6	1.079	117.1	340.2 §	175.1	1.01	2.93	1.51
F05050	10.9	1.072	109.3	322.6 §	176.2	1.19	3.52	1.92
F05051	11.5	1.062	111.1	289.7	166.2	1.28	3.33	1.91
F05052	24.9	1.033	63.7	147.2	66.8	1.59	3.67	1.66
F05053	8.8	1.072	151.8	313.0 §	166.0	1.34	2.75	1.46
Number of females	5	5	5	5	5	5	5	5
Mean	12.9	1.064	110.6	282.6	150.1	1.28	3.24	1.69
S.D.	6.8	0.018	31.4	77.8	46.8	0.21	0.39	0.22

S.G.: Specific gravity

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
F06059	33.2	1.033	57.1	135.9	70.1	1.90	4.51	2.33
F06060	12.9	1.069	127.7	264.7	153.0	1.65	3.42	1.97
F06061	11.0	1.056	111.7	133.0	80.1	1.23	1.46	0.88
F06062	17.5	1.060	136.5	254.9	150.6	2.39	4.46	2.64
F06063	18.3	1.051	97.9	205.1	110.8	1.79	3.75	2.03
Number of females	5	5	5	5	5	5	5	5
Mean	18.6	1.054	106.2	198.7	112.9	1.79	3.52	1.97
S.D.	8.7	0.013	31.2	62.9	38.5	0.42	1.24	0.67
Significance	NS	NS	NS	NS	NS	*	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	AW	TT

S.G.: Specific gravity

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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 24-3-1. Urinalysis in female rats of the recovery period

Control (vehicle: water for injection)

Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05054	7.5	-	-	-	-	-	±	light yellow	-	-	-	-	±	-
F05055	7.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
F05056	6.5	±	-	±	-	-	±	light yellow	-	-	-	-	-	-
F05057	6.5	±	-	-	-	-	±	light yellow	-	-	-	-	-	-
F05058	7.0	+	-	-	-	-	+	light yellow	-	-	-	-	±	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field, 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 24-3-2. Urinalysis in female rats of the recovery period

MMP 1000 mg/kg

Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06064	6.0	+	-	±	-	-	±	light yellow	-	-	-	-	-	-
F06065	7.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
F06066	6.5	+	-	+	-	-	+	light yellow	-	-	-	-	-	-
F06067	7.0	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
F06068	7.0	+	-	±	-	-	+	light yellow	-	-	-	-	±	-

Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL; 3+: 300≦and<600 mg/dL; 4+: 600 mg/dL≦
Glucose, -: negative; ±: 30≦and<70 mg/dL; +: 70≦and<150 mg/dL; 2+: 150≦and<300 mg/dL; 3+: 300≦and<1,000 mg/dL; 4+: 1,000 mg/dL≦
Ketone, -: negative; ±(5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL; 3+: 80≦and<150 mg/dL; 4+: 150 mg/dL≦
Bilirubin, -: negative; +: 0.5≦and<2.0 mg/dL; 2+: 2.0≦and<6.0 mg/dL; 3+: 6.0≦and<10.0 mg/dL; 4+: 10.0 mg/dL≦
Occult blood, -: negative; ±: 0.03≦and<0.06 mg/dL; +: 0.06≦and<0.20 mg/dL; 2+: 0.20≦and<1.00 mg/dL; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL; 3+: 8.0≦and<12.0 mg/dL; 4+: 12.0 mg/dL≦
Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field, 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≧300/3 visual field
Cristals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few; +: abundant

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 24-4-1. Urinalysis in female rats of the recovery period

Control (vehicle: water for injection)

Female No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
F05054	11.5	1.054	129.7	254.5	143.5	1.49	2.93	1.65
F05055	7.6	1.048	67.1	136.2	74.3	0.51	1.04	0.56
F05056	12.8	1.053	98.0	240.8	144.5	1.25	3.08	1.85
F05057	4.3	1.077	105.7	158.2	99.1	0.45	0.68	0.43
F05058	11.0	1.037	68.4	89.4	50.9	0.75	0.98	0.56
Number of females	5	5	5	5	5	5	5	5
Mean	9.4	1.054	93.8	175.8	102.5	0.89	1.74	1.01
S.D.	3.5	0.015	26.5	70.3	41.6	0.46	1.16	0.68

S.G.: Specific gravity

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 24-4-2. Urinalysis in female rats of the recovery period

MMP 1000 mg/kg

Female No.	Urine volume	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
	mL/24hr		mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
F06064	8.7	1.075	129.5	362.5 §	214.2	1.13	3.15	1.86
F06065	14.6	1.061	128.8	275.9	166.2	1.88	4.03	2.43
F06066	8.1	1.078	154.6	341.1 §	203.9	1.25	2.76	1.65
F06067	10.2	1.082	162.4	380.2 §	215.7	1.66	3.88	2.20
F06068	8.5	1.084	152.3	336.7	190.9	1.29	2.86	1.62
Number of females	5	5	5	5	5	5	5	5
Mean	10.0	1.076	145.5	339.3	198.2	1.44	3.34	1.95
S.D.	2.7	0.009	15.4	39.5	20.4	0.31	0.59	0.35
Significance	NS	*	**	**	**	NS	*	*
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

S.G.: Specific gravity

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.

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	RBC 10000/μL	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/μL	PT sec.	APTT sec.	WBC 100/μL	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M01001	846	15.4	41.9	49.5	18.2	36.8	125.5	15.2	23.1	97.6	13.3	0.9	0.1	3.4	82.3	3.11
M01003	913	16.3	45.5	49.8	17.9	35.8	100.9	19.2	24.4	82.1	32.7	1.2	0.0	3.5	62.6	2.63
M01004	855	15.5	42.7	49.9	18.1	36.3	97.9	35.5	33.7	61.3	18.1	1.0	0.0	4.6	76.3	2.52
M01005	918	16.2	44.8	48.8	17.6	36.2	115.4	20.6	25.2	120.3	14.9	1.7	0.0	3.8	79.6	2.43
M01006	886	15.8	44.2	49.9	17.8	35.7	113.3	29.0	28.2	108.3	31.6	1.2	0.1	5.7	61.4	3.45
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	884	15.8	43.8	49.6	17.9	36.2	110.6	23.9	26.9	93.9	22.1	1.2	0.0	4.2	72.4	2.83
S.D.	33	0.4	1.5	0.5	0.2	0.4	11.3	8.2	4.2	23.0	9.3	0.3	0.1	1.0	9.8	0.44

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Male No.	RBC 10000/μL	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/μL	PT sec.	APTT sec.	WBC 100/μL	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M02013	889	15.6	42.9	48.3	17.5	36.4	122.1	21.8	26.1	147.5	10.2	0.9	0.1	4.3	84.5	2.89
M02014	908	15.5	43.3	47.7	17.1	35.8	106.4	35.4	31.6	86.3	12.3	2.1	0.0	3.8	81.8	2.40
M02015	901	15.4	42.2	46.8	17.1	36.5	121.3	20.1	26.2	98.8	20.6	1.5	0.1	6.5	71.3	2.89
M02016	849	15.2	42.8	50.4	17.9	35.5	117.0	22.8	28.3	58.3	33.5	2.4	0.0	5.8	58.3	2.67
M02017	907	16.8	47.0	51.8	18.5	35.7	111.2	20.1	27.4	74.7	15.2	2.4	0.0	5.0	77.4	1.95
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	891	15.7	43.6	49.0	17.6	36.0	115.6	24.0	27.9	93.1	18.4	1.9	0.0	5.1	74.7	2.56
S.D.	25	0.6	1.9	2.1	0.6	0.4	6.7	6.5	2.2	33.9	9.3	0.7	0.1	1.1	10.4	0.40
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 25-1-3. Hematological findings of male rats at the end of the dosing period

MMP 250 mg/kg

Male No.	RBC	HGB	Hematocrit	MCV	MCH	MCHC	Platelet	PT	APTT	WBC	Neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte	Reticulocyte
	10000/μL	g/dL	%	fL	pg	g/dL	10000/μL	sec.	sec.	100/μL	%	%	%	%	%	%
M03025	903	16.8	47.0	52.0	18.6	35.7	102.5	23.2	24.8	85.2	14.0	1.1	0.0	4.7	80.2	3.16
M03026	907	15.8	43.3	47.7	17.4	36.5	119.6	29.2	26.5	94.9	18.3	1.1	0.0	6.0	74.6	5.30
M03027	905	16.5	46.3	51.2	18.2	35.6	102.5	19.5	27.4	79.6	17.4	2.6	0.0	5.5	74.5	3.40
M03028	917	15.5	44.1	48.1	16.9	35.1	116.3	29.4	29.3	96.9	11.7	1.9	0.0	4.9	81.5	2.52
M03029	874	15.4	42.8	49.0	17.6	36.0	149.3	14.5	20.3	133.2	19.5	1.4	0.1	4.6	74.4	3.70
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	901	16.0	44.7	49.6	17.7	35.8	118.0	23.2	25.7	98.0	16.2	1.6	0.0	5.1	77.0	3.62
S.D.	16	0.6	1.9	1.9	0.7	0.5	19.1	6.4	3.4	20.9	3.2	0.6	0.0	0.6	3.5	1.04
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	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 lay out).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	RBC	HGB	Hematocrit	MCV	MCH	MCHC	Platelet	PT	APTT	WBC	Neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte	Reticulocyte
	10000/μL	g/dL	%	fL	pg	g/dL	10000/μL	sec.	sec.	100/μL	%	%	%	%	%	%
M04037	934	15.7	43.1	46.1	16.8	36.4	99.1	24.3	27.2	61.9	14.8	1.0	0.0	6.0	78.2	1.60
M04038	855	14.9	42.0	49.1	17.4	35.5	97.9	15.0	21.6	83.2	10.3	1.0	0.0	4.2	84.5	2.51
M04039	902	15.7	43.7	48.4	17.4	35.9	94.6	16.2	21.1	106.6	11.8	2.2	0.1	7.9	78.0	2.68
M04040	958	16.4	44.7	46.7	17.1	36.7	108.2	13.7	21.0	124.9	24.4	1.4	0.1	6.2	67.9	2.96
M04041	920	16.0	44.0	47.8	17.4	36.4	104.7	18.4	23.6	61.0	16.4	2.1	0.0	8.4	73.1	2.53
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	914	15.7	43.5	47.6	17.2	36.2	100.9	17.5	22.9	87.5	15.5	1.5	0.0	6.5	76.3	2.46
S.D.	39	0.6	1.0	1.2	0.3	0.5	5.5	4.2	2.6	28.0	5.5	0.6	0.1	1.7	6.2	0.51
Significance	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	DU	AN	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	RBC 10000/μL	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/μL	PT sec.	APTT sec.	WBC 100/μL	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M01008	892	15.3	42.6	47.8	17.2	35.9	110.6	14.3	19.7	158.6	13.0	0.9	0.1	4.2	81.8	2.95
M01009	890	15.1	44.4	49.9	17.0	34.0	114.3	23.1	23.7	123.4	18.9	1.1	0.0	3.7	76.3	3.71
M01010	909	15.2	42.7	47.0	16.7	35.6	140.4	14.5	20.8	188.8 §	23.4	1.0	0.1	3.7	71.8	3.40
M01011	865	14.8	43.5	50.3	17.1	34.0	102.8	18.5	23.0	72.5	14.9	1.4	0.1	4.6	79.0	3.12
M01012	852	14.6	42.1	49.4	17.1	34.7	106.7	23.7	23.0	108.0	15.6	1.3	0.0	2.9	80.2	3.99
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	882	15.0	43.1	48.9	17.0	34.8	115.0	18.8	22.0	130.3	17.2	1.1	0.1	3.8	77.8	3.43
S.D.	23	0.3	0.9	1.4	0.2	0.9	14.9	4.5	1.7	45.0	4.1	0.2	0.1	0.6	3.9	0.42

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	RBC 10000/μL	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/μL	PT sec.	APTT sec.	WBC 100/μL	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M04044	842	15.3	43.9	52.1	18.2	34.9	117.5	18.7	24.3	102.8	13.8	0.8	0.0	3.5	81.9	3.07
M04045	840	14.7	43.5	51.8	17.5	33.8	114.9	15.3	21.3	115.9	11.9	1.3	0.0	2.5	84.3	2.96
M04046	769	14.1	40.7	52.9	18.3	34.6	112.3	18.9	23.2	97.8	12.2	1.1	0.0	3.8	82.9	3.03
M04047	833	14.4	42.2	50.7	17.3	34.1	117.4	16.1	22.4	126.9	9.0	1.3	0.0	2.4	87.3	3.61
M04048	795	13.8	39.8	50.1	17.4	34.7	113.9	19.7	22.0	90.3	25.0	1.7	0.0	4.5	68.8	3.66
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	816	14.5	42.0	51.5	17.7	34.4	115.2	17.7	22.6	106.7	14.4	1.2	0.0	3.3	81.0	3.27
S.D.	32	0.6	1.8	1.1	0.5	0.5	2.3	1.9	1.2	14.6	6.2	0.3	0.0	0.9	7.1	0.34
Significance	**	NS	NS	*	*	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	RBC 10000/μL	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/μL	PT sec.	APTT sec.	WBC 100/μL	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F01005	645	12.5	36.4	56.4	19.4	34.3	120.8	13.5	20.6	135.5	40.7	0.4	0.0	3.8	55.1	6.92
F01007	709	13.2	38.5	54.3	18.6	34.3	120.1	13.0	22.1	154.0	49.5	0.5	0.1	4.7	45.2	7.79
F01008	702	13.7	40.2	57.3	19.5	34.1	152.0	14.0	22.7	122.3	20.5	0.7	0.0	6.0	72.8	8.82
F01010	722	14.9	44.0	60.9	20.6	33.9	116.6	13.7	19.4	94.9	37.3	1.3	0.0	3.9	57.5	7.61
F01012	710	14.1	42.8	60.3	19.9	32.9	103.5	13.3	21.4	103.7	48.4	1.2	0.0	5.1	45.3	9.02
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	698	13.7	40.4	57.8	19.6	33.9	122.6	13.5	21.2	122.1	39.3	0.8	0.0	4.7	55.2	8.03
S.D.	30	0.9	3.1	2.8	0.7	0.6	17.9	0.4	1.3	23.9	11.7	0.4	0.0	0.9	11.3	0.88

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Female No.	RBC 10000/μL	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/μL	PT sec.	APTT sec.	WBC 100/μL	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F02014	672	13.3	40.6	60.4	19.8	32.8	86.1	12.9	19.0	112.1	31.8	0.4	0.1	3.7	64.0	7.32
F02016	651	11.9	34.6	53.1	18.3	34.4	136.7	12.9	20.0	169.9 §	38.5	0.4	0.0	3.4	57.7	10.22
F02017	680	13.9	41.0	60.3	20.4	33.9	106.5	12.3	19.3	104.9	40.3	1.4	0.1	3.6	54.6	6.65
F02020	747	13.7	39.7	53.1	18.3	34.5	130.5	12.7	21.1	99.1	53.4	0.9	0.0	5.2	40.5	5.84
F02024	689	13.6	40.6	58.9	19.7	33.5	125.4	13.3	19.8	107.0	49.7	0.7	0.0	6.1	43.5	6.23
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	688	13.3	39.3	57.2	19.3	33.8	117.0	12.8	19.8	118.6	42.7	0.8	0.0	4.4	52.1	7.25
S.D.	36	0.8	2.7	3.8	1.0	0.7	20.7	0.4	0.8	29.1	8.7	0.4	0.1	1.2	9.8	1.75
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	AN	AN	AN	AN	AN	DU	AN	AN	AN	KW	AN	DU	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DU: Analysis by Dunnett's test.
§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Female No.	RBC	HGB	Hematocrit	MCV	MCH	MCHC	Platelet	PT	APTT	WBC	Neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte	Reticulocyte
	10000/μL	g/dL	%	fL	pg	g/dL	10000/μL	sec.	sec.	100/μL	%	%	%	%	%	%
F03026	690	13.2	39.0	56.5	19.1	33.8	120.8	13.2	20.8	80.5	36.4	0.4	0.0	3.2	60.0	8.40
F03027	632	12.8	37.6	59.5	20.3	34.0	111.0	13.9	20.5	143.2	31.8	0.6	0.0	2.7	64.9	9.26
F03028	728	13.5	39.6	54.4	18.5	34.1	116.1	13.5	20.3	107.5	35.8	0.7	0.0	4.0	59.5	6.99
F03029	686	13.3	39.1	57.0	19.4	34.0	144.4	13.1	19.9	111.3	35.6	0.6	0.0	2.5	61.3	9.42
F03031	664	13.6	40.7	61.3	20.5	33.4	93.6	13.7	22.0	144.0	54.0	0.7	0.1	3.7	41.5	10.16
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	680	13.3	39.2	57.7	19.6	33.9	117.2	13.5	20.7	117.3	38.7	0.6	0.0	3.2	57.4	8.85
S.D.	35	0.3	1.1	2.7	0.8	0.3	18.4	0.3	0.8	26.8	8.7	0.1	0.0	0.6	9.2	1.21
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS
Statistical method	AN	KW	AN	AN	AN	AN	AN	DU	AN	AN	AN	KW	AN	DU	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 26-1-4. Hematological findings of female rats at the end of the dosing period

MMP 1000 mg/kg

Female No.	RBC	HGB	Hematocrit	MCV	MCH	MCHC	Platelet	PT	APTT	WBC	Neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte	Reticulocyte
	10000/μL	g/dL	%	fL	pg	g/dL	10000/μL	sec.	sec.	100/μL	%	%	%	%	%	%
F04041	742	13.8	42.1	56.7	18.6	32.8	89.0	14.7	20.8	68.8	22.5	0.6	0.0	5.2	71.7	9.84
F04042	700	13.8	41.3	59.0	19.7	33.4	87.8	14.8	18.8	169.2 §	43.1	0.6	0.1	4.7	51.5	8.98
F04045	714	13.7	40.0	56.0	19.2	34.3	106.7	13.6	19.1	131.0	44.2	0.4	0.0	5.2	50.2	5.79
F04047	733	14.1	40.7	55.5	19.2	34.6	104.4	13.9	19.6	102.5	44.7	0.4	0.0	5.7	49.2	5.95
F04048	725	13.9	39.7	54.8	19.2	35.0	117.9	13.8	20.2	116.8	38.8	0.7	0.0	4.3	56.2	6.71
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	723	13.9	40.8	56.4	19.2	34.0	101.2	14.2	19.7	117.7	38.7	0.5	0.0	5.0	55.8	7.45
S.D.	16	0.2	1.0	1.6	0.4	0.9	12.7	0.6	0.8	36.9	9.3	0.1	0.0	0.5	9.3	1.84
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	AN	AN	AN	AN	AN	DU	AN	AN	AN	KW	AN	DU	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DU: Analysis by Dunnett's test.
§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	RBC 10000/μL	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/μL	PT sec.	APTT sec.	WBC 100/μL	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F05049	773	14.2	38.8	50.2	18.4	36.6	123.3	12.8	19.9	112.4	25.1	1.2	0.1	2.9	70.7	3.04
F05050	778	14.0	38.9	50.0	18.0	36.0	112.0	12.0	20.2	74.4	21.8	0.9	0.0	1.9	75.4	3.34
F05051	784	14.5	40.7	51.9	18.5	35.6	117.4	12.8	23.1	64.0	13.6	2.3	0.0	3.0	81.1	2.82
F05052	753	14.0	39.3	52.2	18.6	35.6	124.0	13.1	22.0	69.6	12.7	1.6	0.0	2.2	83.5	2.67
F05053	758	13.9	39.3	51.8	18.3	35.4	115.3	12.4	21.2	46.7	13.8	2.4	0.0	3.9	79.9	2.67
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	769	14.1	39.4	51.2	18.4	35.8	118.4	12.6	21.3	73.4	17.4	1.7	0.0	2.8	78.1	2.91
S.D.	13	0.2	0.8	1.0	0.2	0.5	5.2	0.4	1.3	24.2	5.7	0.7	0.0	0.8	5.1	0.29

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	RBC 10000/μL	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/μL	PT sec.	APTT sec.	WBC 100/μL	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F06059	817	15.1	42.1	51.5	18.5	35.9	108.2	13.2	19.9	143.6	10.6	1.7	0.1	4.2	83.4	2.27
F06060	813	14.7	41.1	50.6	18.1	35.8	99.2	14.0	20.6	114.6	8.6	1.5	0.0	4.9	85.0	2.41
F06061	753	13.9	39.2	52.1	18.5	35.5	95.5	13.9	19.6	52.2	9.7	1.5	0.0	3.4	85.4	3.36
F06062	803	14.3	39.8	49.6	17.8	35.9	99.8	14.0	19.7	55.4	12.0	1.3	0.0	5.1	81.6	3.22
F06063	776	14.6	41.6	53.6	18.8	35.1	84.5	13.8	19.6	131.9	23.9	1.2	0.1	3.1	71.7	3.24
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	792	14.5	40.8	51.5	18.3	35.6	97.4	13.8	19.9	99.5	13.0	1.4	0.0	4.1	81.4	2.90
S.D.	27	0.4	1.2	1.5	0.4	0.3	8.6	0.3	0.4	43.0	6.2	0.2	0.1	0.9	5.6	0.52
Significance	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	AW	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	RBC 10000/μL	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/μL	PT sec.	APTT sec.	WBC 100/μL	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F05054	811	14.8	41.6	51.3	18.2	35.6	120.9	12.5	18.3	55.2	15.0	2.0	0.0	3.1	79.9	2.47
F05055	788	14.7	42.8	54.3	18.7	34.3	87.8	12.7	17.6	54.7	22.0	2.0	0.0	3.8	72.2	2.88
F05056	811	14.7	41.1	50.7	18.1	35.8	94.5	13.5	16.3	59.0	16.2	2.0	0.0	4.7	77.1	2.49
F05057	764	14.7	43.5	56.9	19.2	33.8	112.8	12.8	19.2	21.8	12.4	3.2	0.0	4.6	79.8	2.98
F05058	800	14.5	41.5	51.9	18.1	34.9	81.1	13.4	19.4	32.1	23.1	3.7	0.0	3.4	69.8	3.30
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	795	14.7	42.1	53.0	18.5	34.9	99.4	13.0	18.2	44.6	17.7	2.6	0.0	3.9	75.8	2.82
S.D.	20	0.1	1.0	2.6	0.5	0.8	16.8	0.4	1.3	16.6	4.6	0.8	0.0	0.7	4.6	0.35

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	RBC	HGB	Hematocrit	MCV	MCH	MCHC	Platelet	PT	APTT	WBC	Neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte	Reticulocyte
	10000/μL	g/dL	%	fL	pg	g/dL	10000/μL	sec.	sec.	100/μL	%	%	%	%	%	%
F06064	750	13.9	40.1	53.5	18.5	34.7	98.1	13.4	17.2	53.2	10.1	1.7	0.0	2.1	86.1	2.25
F06065	795	14.3	42.4	53.3	18.0	33.7	96.0	13.3	18.2	29.7	14.4	1.7	0.0	2.4	81.5	3.67
F06066	663	12.3	36.0	54.3	18.6	34.2	88.7	12.4	17.4	47.9	6.9	2.7	0.0	3.3	87.1	2.45
F06067	811	14.5	41.5	51.2	17.9	34.9	117.5	13.0	18.6	35.5	13.2	2.0	0.0	2.3	82.5	3.18
F06068	787	14.3	41.5	52.7	18.2	34.5	108.5	12.1	17.1	51.7	21.4	1.0	0.0	3.7	73.9	2.48
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	761	13.9	40.3	53.0	18.2	34.4	101.8	12.8	17.7	43.6	13.2	1.8	0.0	2.8	82.2	2.81
S.D.	59	0.9	2.5	1.2	0.3	0.5	11.3	0.6	0.7	10.4	5.4	0.6	0.0	0.7	5.2	0.60
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS
Statistical method	TT	AW	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01001	5.3	3.4	1.79	120	43	36	75	62	28	0	86	8.4	14	0.5	0.11	369
M01003	5.8	3.7	1.76	128	38	21	65	56	24	0	51	7.8	14	0.5	0.14	348
M01004	5.3	3.4	1.79	114	34	16	58	59	30	0	51	4.3	14	0.4	0.07	419
M01005	5.6	3.5	1.67	125	47	18	71	66	30	0	73	6.8	15	0.4	0.09	378
M01006	5.8	3.6	1.64	124	45	47	79	64	31	0	65	4.2	13	0.5	0.09	256
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.5	1.73	122	41	28	70	61	29	0	65	6.3	14	0.5	0.10	354
S.D.	0.3	0.1	0.07	5	5	13	8	4	3	0	15	2.0	1	0.1	0.03	61

Control (vehicle: water for injection)

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01001	5.4	8.6	144.3	3.83	104.5
M01003	6.0	9.1	146.3	3.90	104.3
M01004	5.8	8.4	146.6	3.75	105.4
M01005	5.3	8.8	145.6	4.15	105.8
M01006	6.3	9.2	146.4	4.19	105.8
Number of males	5	5	5	5	5
Mean	5.8	8.8	145.8	3.96	105.2
S.D.	0.4	0.3	0.9	0.20	0.7

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M02013	5.6	3.5	1.67	133	54	39	86	62	31	0	58	11.9	15	0.5	0.11	302
M02014	5.4	3.4	1.70	115	38	27	59	58	31	0	79	4.6	14	0.4	0.10	278
M02015	6.2	3.9	1.70	118	55	76	95	58	31	0	282	5.9	13	0.5	0.09	292
M02016	5.6	3.5	1.67	121	42	21	72	57	30	0	91	13.3	11	0.4	0.10	325
M02017	5.6	3.6	1.80	132	47	23	78	73	47	0	74	6.5	13	0.4	0.13	318
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.6	1.71	124	47	37	78	62	34	0	117	8.4	13	0.4	0.11	303
S.D.	0.3	0.2	0.05	8	7	23	14	7	7	0	93	3.9	1	0.1	0.02	19
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DT	DU	AN	DU	AN	AN	DU	AN	DT	KW	AN	AN	DU	KW

MMP 62.5 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M02013	6.1	9.1	146.1	3.87	105.3
M02014	6.0	8.5	146.9	4.04	106.2
M02015	5.5	8.9	145.1	3.98	103.8
M02016	5.7	8.9	146.4	3.87	106.6
M02017	5.9	9.2	146.5	3.88	104.9
Number of males	5	5	5	5	5
Mean	5.8	8.9	146.2	3.93	105.4
S.D.	0.2	0.3	0.7	0.08	1.1
Significance	NS	NS	NS	NS	NS
Statistical method	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).
DT: Analysis by Dunnett type mean rank test.
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 Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 250 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M03025	5.4	3.5	1.84	136	43	67	85	57	23	0	88	5.2	15	0.5	0.13	336
M03026	5.8	3.8	1.90	148	48	83	89	65	28	0	103	6.8	10	0.5	0.15	389
M03027	5.3	3.5	1.94	130	41	37	71	59	27	0	202	6.4	15	0.5	0.09	299
M03028	5.1	3.4	2.00	136	38	56	73	60	24	0	192	5.8	14	0.4	0.14	337
M03029	5.6	3.4	1.55	142	45	63	83	55	25	0	109	26.3	13	0.5	0.10	297
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.5	1.85	138	43	61	80	59	25	0	139	10.1	13	0.5	0.12	332
S.D.	0.3	0.2	0.18	7	4	17	8	4	2	0	54	9.1	2	0.0	0.03	37
Significance	NS	NS	NS	**	NS	*	NS	NS	NS	NS	*	NS	NS	NS	NS	NS
Statistical method	AN	AN	DT	DU	AN	DU	AN	AN	DU	AN	DT	KW	AN	AN	DU	KW

MMP 250 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M03025	6.1	8.7	146.9	3.99	106.8
M03026	5.8	9.1	146.3	3.83	104.9
M03027	4.9	8.8	144.9	4.13	102.6 §
M03028	5.9	8.8	147.8	3.94	107.3
M03029	6.0	9.1	145.7	4.01	104.7
Number of males	5	5	5	5	5
Mean	5.7	8.9	146.3	3.98	105.3
S.D.	0.5	0.2	1.1	0.11	1.9
Significance	NS	NS	NS	NS	NS
Statistical method	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).
DT: Analysis by Dunnett type mean rank test.
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
NA: Not analyzed.
§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 27-1-4. Biochemical findings of male rats at the end of the dosing period

MMP 1000 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04037	5.5	3.5	1.75	146	31	58	74	65	40	0	141	6.7	11	0.4	0.15	215
M04038	5.2	3.7	2.47	127	41	32	78	60	31	0	76	6.1	15	0.5	0.16	240
M04039	5.3	3.6	2.12	126	48	39	83	71	27	0	79	21.5	14	0.4	0.14	365
M04040	5.5	3.6	1.89	128	53	49	86	53	30	0	112	21.8	18	0.4	0.13	463
M04041	5.3	3.6	2.12	130	30	23	61	62	32	0	236	23.3	13	0.4	0.14	276
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.6	2.07	131	41	40	76	62	32	0	129	15.9	14	0.4	0.14	312
S.D.	0.1	0.1	0.27	8	10	14	10	7	5	0	66	8.7	3	0.0	0.01	102
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS
Statistical method	AN	AN	DT	DU	AN	DU	AN	AN	DU	AN	DT	KW	AN	AN	DU	KW

MMP 1000 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04037	5.7	8.9	147.2	3.91	107.5
M04038	5.4	8.7	146.1	3.90	104.8
M04039	6.4	9.0	145.4	4.27	105.7
M04040	5.9	8.9	144.5	4.12	102.4
M04041	6.5	9.2	146.4	4.22	107.2
Number of males	5	5	5	5	5
Mean	6.0	8.9	145.9	4.08	105.5
S.D.	0.5	0.2	1.0	0.17	2.1
Significance	NS	NS	NS	NS	NS
Statistical method	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).
DT: Analysis by Dunnett type mean rank test.
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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01008	5.5	3.4	1.62	130	47	22	74	66	26	0	292	7.9	16	0.5	0.06	368
M01009	5.6	3.7	1.95	194	46	48	83	73	32	0	293	5.8	15	0.5	0.10	580
M01010	5.9	3.6	1.57	126	50	19	74	72	27	0	500	9.1	15	0.5	0.07	520
M01011	5.3	3.5	1.94	154	40	32	71	67	32	0	76	7.2	14	0.5	0.06	427
M01012	5.1	3.3	1.83	121	35	16	60	61	23	0	210	6.8	15	0.5	0.06	363
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.5	1.78	145	44	27	72	68	28	0	274	7.4	15	0.5	0.07	452
S.D.	0.3	0.2	0.18	30	6	13	8	5	4	0	154	1.2	1	0.0	0.02	96

Control (vehicle: water for injection)

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01008	6.2	8.9	144.2	3.93	105.8
M01009	6.9	9.4	145.4	4.08	104.3
M01010	6.4	9.0	145.1	3.90	105.5
M01011	5.6	9.0	146.4	3.56	108.2
M01012	5.7	8.8	145.6	3.59	107.5
Number of males	5	5	5	5	5
Mean	6.2	9.0	145.3	3.81	106.3
S.D.	0.5	0.2	0.8	0.23	1.6

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04044	5.4	3.5	1.84	139	34	19	57	67	31	0	231	6.3	14	0.5	0.06	478
M04045	5.0	3.4	2.13	162	40	31	65	61	24	0	242	5.6	13	0.5	0.08	373
M04046	5.1	3.4	2.00	125	41	20	63	53	27	0	88	5.2	14	0.4	0.06	524
M04047	5.0	3.5	2.33	133	54	27	77	72	25	0	172	12.9	17	0.5	0.08	379
M04048	5.5	3.6	1.89	124	40	20	70	87	28	0	437	6.0	12	0.6	0.06	489
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.2	3.5	2.04	137	42	23	66	68	27	0	234	7.2	14	0.5	0.07	449
S.D.	0.2	0.1	0.20	15	7	5	8	13	3	0	129	3.2	2	0.1	0.01	68
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

MMP 1000 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04044	5.9	8.8	145.1	3.72	106.4
M04045	6.2	8.8	145.9	3.75	108.0
M04046	6.4	8.4	144.9	3.81	108.7
M04047	6.8	8.6	145.1	3.90	107.5
M04048	5.7	8.8	145.3	3.77	109.1
Number of males	5	5	5	5	5
Mean	6.2	8.7	145.3	3.79	107.9
S.D.	0.4	0.2	0.4	0.07	1.1
Significance	NS	*	NS	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F01005	5.2	3.5	2.06	135	51	50	100	66	46	0	37	7.1	11	0.5	0.08	255
F01007	5.7	4.0	2.35	109	61	71	126	99	62	0	84	12.0	13	0.5	0.13	215
F01008	6.0	3.9	1.86	113	46	19	85	70	28	0	64	12.9	16	0.5	0.08	187
F01010	5.5	3.9	2.44	129	44	55	99	60	35	0	82	11.4	15	0.5	0.15	271
F01012	6.3	4.5	2.50	127	61	33	126	71	45	0	171	9.6	17	0.6	0.09	283
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	4.0	2.24	123	53	46	107	73	43	0	88	10.6	14	0.5	0.11	242
S.D.	0.4	0.4	0.27	11	8	20	18	15	13	0	50	2.3	2	0.0	0.03	40

Control (vehicle: water for injection)

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F01005	5.7	8.7	139.5	3.58	102.2
F01007	6.2	8.9	143.1	3.39 §	103.7 §
F01008	6.3	9.1	142.9	3.79	106.7
F01010	5.8	8.8	143.9	3.71	106.7
F01012	6.7	9.1	144.6	3.57	104.5
Number of females	5	5	5	5	5
Mean	6.1	8.9	142.8	3.61	104.8
S.D.	0.4	0.2	2.0	0.15	2.0

§. Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F02014	5.6	3.9	2.29	124	47	58	99	67	46	0	39	8.9	11	0.4	0.13	362
F02016	5.6	3.7	1.95	121	50	63	100	107	72	0	61	15.5	18	0.5	0.07	336
F02017	5.9	4.0	2.11	113	50	31	103	83	48	0	45	9.6	13	0.5	0.10	512
F02020	6.3	4.3	2.15	118	52	47	113	69	44	0	94	12.3	15	0.6	0.10	220
F02024	5.8	3.8	1.90	137	66	16	116	77	41	0	175	4.7	16	0.6	0.09	184
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.9	2.08	123	53	43	106	81	50	0	83	10.2	15	0.5	0.10	323
S.D.	0.3	0.2	0.16	9	7	19	8	16	12	0	56	4.0	3	0.1	0.02	130
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	AN	AN	AN	KW

MMP 62.5 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F02014	5.4	8.9	140.8	3.74	105.7
F02016	6.4	8.8	138.6	4.52	102.3
F02017	5.5	9.0	143.5 §	3.53 §	106.4
F02020	6.0	9.7	142.2	3.51	104.9
F02024	5.4	9.2	143.7	3.12	105.6
Number of females	5	5	5	5	5
Mean	5.7	9.1	141.8	3.68	105.0
S.D.	0.4	0.4	2.1	0.52	1.6
Significance	NS	NS	NS	NS	NS
Statistical method	KW	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).
§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 28-1-3. Biochemical findings of female rats at the end of the dosing period

MMP 250 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F03026	5.5	3.8	2.24	133	48	37	104	73	41	0	64	8.4	12	0.5	0.07	217
F03027	5.8	3.9	2.05	121	59	61	122	76	49	0	65	8.9	14	0.5	0.15	288
F03028	5.7	3.7	1.85	124	43	27	87	92	51	0	210	9.3	15	0.5	0.07	278
F03029	5.7	3.9	2.17	125	48	12	83	72	44	0	90	5.8	11	0.6	0.11	297
F03031	5.7	3.8	2.00	138	36	43	80	82	48	0	193	8.6	17	0.6	0.07	197
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.8	2.06	128	47	36	95	79	47	0	124	8.2	14	0.5	0.09	255
S.D.	0.1	0.1	0.15	7	8	18	18	8	4	0	71	1.4	2	0.1	0.04	45
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	AN	AN	AN	KW

MMP 250 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F03026	5.9	8.9	142.4	3.79	105.4
F03027	6.0	9.0	138.0	4.13	104.9
F03028	5.6	9.1	142.1	3.47	104.6
F03029	5.5	8.9	145.1	3.35	110.0
F03031	5.7	8.8	141.4	3.61 §	103.9
Number of females	5	5	5	5	5
Mean	5.7	8.9	141.8	3.67	105.8
S.D.	0.2	0.1	2.5	0.30	2.4
Significance	NS	NS	NS	NS	NS
Statistical method	KW	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).
§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F04041	5.3	3.7	2.31	130	36	79	90	62	34	0	44	8.6	11	0.5	0.14	189
F04042	5.9	4.0	2.11	144	37	67	88	74	40	0	193	26.5	14	0.5	0.07	237
F04045	5.5	3.9	2.44	130	35	10	81	88	43	0	60	12.9	13	0.6	0.08	181
F04047	5.6	3.8	2.11	124	51	25	101	72	38	0	75	7.5	12	0.5	0.05	198
F04048	5.8	4.0	2.22	133	42	41	101	74	36	0	323	10.0	10	0.4	0.14	163
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.9	2.24	132	40	44	92	74	38	0	139	13.1	12	0.5	0.10	194
S.D.	0.2	0.1	0.14	7	7	29	9	9	3	0	118	7.8	2	0.1	0.04	27
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	AN	AN	AN	KW

MMP 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F04041	6.5	8.9	142.0	4.36	106.1
F04042	7.4	9.0	140.8	3.60	102.0
F04045	5.0	8.4	141.5	3.63	104.3
F04047	5.0	8.8	144.9	3.72	108.7
F04048	5.7	9.0	143.0	3.09	105.4
Number of females	5	5	5	5	5
Mean	5.9	8.8	142.4	3.68	105.3
S.D.	1.0	0.2	1.6	0.45	2.5
Significance	NS	NS	NS	NS	NS
Statistical method	KW	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05049	5.3	3.5	1.94	91	50	7	93	72	39	0	161	14.8	18	0.5	0.18	280
F05050	6.1	4.1	2.05	124	52	15	100	57	26	0	103	13.5	14	0.5	0.20	149
F05051	5.5	3.7	2.06	94	43	14	85	58	25	0	83	6.2	20	0.5	0.15	144
F05052	5.9	4.0	2.11	99	59	28	106	62	27	0	65	14.1	21	0.5	0.20	99
F05053	5.9	4.0	2.11	101	39	11	80	84	55	0	86	8.2	26	0.6	0.17	176
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.9	2.05	102	49	15	93	67	34	0	100	11.4	20	0.5	0.18	170
S.D.	0.3	0.3	0.07	13	8	8	11	11	13	0	37	3.9	4	0.0	0.02	68

Control (vehicle: water for injection)

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05049	5.3	8.3	145.2	3.74	106.8
F05050	4.7	8.6	144.9	3.44	105.8
F05051	4.3	8.3	146.0	3.53	106.0
F05052	4.0	9.0	146.6	3.55	106.1
F05053	4.3	8.5	145.1	3.57	105.8
Number of females	5	5	5	5	5
Mean	4.5	8.5	145.6	3.57	106.1
S.D.	0.5	0.3	0.7	0.11	0.4

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06059	6.1	4.3	2.39	131	63	17	122	50	21	0	247	39.0	11	0.6	0.30	123
F06060	5.3	3.5	1.94	95	54	12	98	57	20	0	140	48.6	15	0.5	0.25	126
F06061	5.3	3.6	2.12	94	50	17	95	52	21	0	36	26.4	12	0.5	0.31	221
F06062	5.7	3.8	2.00	117	58	22	119	50	19	0	46	14.4	19	0.5	0.19	168
F06063	5.5	3.6	1.89	126	48	17	100	62	19	0	102	11.4	14	0.5	0.18	242
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.8	2.07	113	55	17	107	54	20	0	114	28.0	14	0.5	0.25	176
S.D.	0.3	0.3	0.20	17	6	4	13	5	1	0	85	15.9	3	0.0	0.06	54
Significance	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	AW	TT	TT	TT	TT

MMP 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06059	7.5	9.4	145.6	4.09	101.2
F06060	6.1	8.1	145.0	3.71	104.5
F06061	5.1	8.4	145.9	3.50	104.9
F06062	4.5	8.8	145.3	3.34	102.7
F06063	5.3	8.6	146.4	3.35	107.4
Number of females	5	5	5	5	5
Mean	5.7	8.7	145.6	3.60	104.1
S.D.	1.2	0.5	0.5	0.31	2.3
Significance	NS	NS	NS	NS	NS
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 28-3-1. Biochemical findings of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05054	5.1	3.5	2.19	105	55	21	100	49	18	0	58	10.9	14	0.5	0.07	204
F05055	5.1	3.6	2.40	105	51	16	94	48	15	0	59	9.9	16	0.6	0.11	205
F05056	5.3	3.6	2.12	96	44	13	85	60	24	0	78	43.5	19	0.6	0.12	312
F05057	5.6	4.0	2.50	118	47	12	89	69	22	0	94	8.4	15	0.5	0.12	245
F05058	5.8	4.1	2.41	108	63	11	101	56	17	0	87	9.4	20	0.7	0.08	189
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.8	2.32	106	52	15	94	56	19	0	75	16.4	17	0.6	0.10	231
S.D.	0.3	0.3	0.16	8	7	4	7	9	4	0	16	15.2	3	0.1	0.02	50

Control (vehicle: water for injection)

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05054	4.1	8.0	145.5	3.65	109.1
F05055	4.2	8.0	146.5	3.16	111.1
F05056	4.9	8.0	144.4	3.43	108.5
F05057	3.4	8.4	147.6	3.39	112.9
F05058	3.0	8.4	146.4	3.25 §	109.6
Number of females	5	5	5	5	5
Mean	3.9	8.2	146.1	3.38	110.2
S.D.	0.7	0.2	1.2	0.19	1.8

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06064	5.2	3.6	2.25	105	46	13	87	61	23	0	86	17.6	18	0.7	0.14	270
F06065	5.4	3.6	2.00	119	50	15	93	49	20	0	43	14.2	15	0.6	0.07	201
F06066	4.9	3.6	2.77	134	34	8	74	71	33	0	70	11.9	20	0.8	0.18	169
F06067	6.0	4.1	2.16	114	52	11	105	62	22	0	98	12.7	18	0.6	0.07	231
F06068	5.3	3.6	2.12	132	54	10	91	67	28	0	237	7.0	22	0.5	0.14	264
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.7	2.26	121	47	11	90	62	25	0	107	12.7	19	0.6	0.12	227
S.D.	0.4	0.2	0.30	12	8	3	11	8	5	0	76	3.9	3	0.1	0.05	43
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	AW	TT	TT	TT	TT

MMP 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06064	4.7	8.6	144.6	3.89	106.3
F06065	3.4	8.1	146.1	3.53	108.5
F06066	5.1	8.9	142.6	5.21	108.1
F06067	4.4	8.8	143.0	3.97	108.3
F06068	4.7	8.7	143.7	3.44	108.8
Number of females	5	5	5	5	5
Mean	4.5	8.6	144.0	4.01	108.0
S.D.	0.6	0.3	1.4	0.71	1.0
Significance	NS	*	*	NS	*
Statistical method	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M01001	497.1	1993.4	4.010	271.5	0.546	1380.0	2.776	12022.9	24.186	1696.8	3.413	1670.1	3.360	3366.9	6.773	726.7	1.462
M01002	458.3	1985.7	4.333	260.3	0.568	1194.8	2.607	10455.0	22.813	1499.0	3.271	1605.6	3.503	3104.6	6.774	835.8	1.824
M01003	433.4	1945.9	4.490	288.5	0.666	1350.1	3.115	12085.2	27.885	1600.1	3.692	1515.3	3.496	3115.4	7.188	905.5	2.089
M01004	427.2	1979.4	4.633	302.8	0.709	1246.8	2.919	10942.8	25.615	1628.8	3.813	1563.3	3.659	3192.1	7.472	778.6	1.823
M01005	470.8	1949.8	4.141	397.5	0.844	1415.9	3.007	12546.8	26.650	1500.0	3.186	1578.8	3.353	3078.8	6.540	828.7	1.760
M01006	479.8	1933.8	4.030	313.1	0.653	1422.5	2.965	13115.7	27.336	1511.8	3.151	1499.2	3.125	3011.0	6.276	787.6	1.642
M01007	480.7	2101.2	4.371	249.9	0.520	1504.3	3.129	12451.4	25.903	1474.3	3.067	1501.3	3.123	2975.6	6.190	793.7	1.651
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	463.9	1984.2	4.287	297.7	0.644	1359.2	2.931	11945.7	25.770	1558.7	3.370	1561.9	3.374	3120.6	6.745	808.1	1.750
S.D.	25.8	56.3	0.236	49.5	0.112	106.8	0.187	934.5	1.779	83.7	0.284	62.8	0.199	129.6	0.465	56.0	0.196

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	1832.8	3.687	1839.9	3.701	3672.7	7.388	657.0	1.322	594.6	1.196	1251.6	2.518
M01002	1624.3	3.544	1599.3	3.490	3223.6	7.034	663.2	1.447	621.2	1.355	1284.4	2.803
M01003	1598.6	3.689	1591.8	3.673	3190.4	7.361	619.6	1.430	621.3	1.434	1240.9	2.863
M01004	1427.6	3.342	1441.6	3.375	2869.2	6.716	656.1	1.536	664.5	1.555	1320.6	3.091
M01005	1584.6	3.366	1499.6	3.185	3084.2	6.551	640.3	1.360	624.0	1.325	1264.3	2.685
M01006	1656.6	3.453	1645.5	3.430	3302.1	6.882	663.7	1.383	638.6	1.331	1302.3	2.714
M01007	1571.9	3.270	1567.6	3.261	3139.5	6.531	507.3	1.055	527.6	1.098	1034.9	2.153
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1613.8	3.479	1597.9	3.445	3211.7	6.923	629.6	1.362	613.1	1.328	1242.7	2.690
S.D.	120.7	0.167	126.4	0.194	245.0	0.355	56.1	0.152	43.2	0.149	95.8	0.295

Control (vehicle: water for injection)

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	930.9	1.873	1858.4	3.738	30.5	0.061	24.2	0.049	27.1	0.055	51.3	0.103
M01002	601.5	1.312	1623.4	3.542	21.8	0.048	26.7	0.058	27.5	0.060	54.2	0.118
M01003	782.0	1.804	1602.6	3.698	22.3	0.051	23.7	0.055	26.1	0.060	49.8	0.115
M01004	769.3	1.801	1832.1	4.289	21.2	0.050	25.6	0.060	24.6	0.058	50.2	0.118
M01005	500.4	1.063	1521.5	3.232	20.7	0.044	22.3	0.047	29.1	0.062	51.4	0.109
M01006	646.4	1.347	1706.9	3.558	17.7	0.037	23.6	0.049	23.8	0.050	47.4	0.099
M01007	389.2	0.810	1307.3	2.720	22.8	0.047	22.5	0.047	24.6	0.051	47.1	0.098
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	660.0	1.430	1636.0	3.540	22.4	0.048	24.1	0.052	26.1	0.057	50.2	0.109
S.D.	183.8	0.411	189.5	0.482	3.9	0.007	1.6	0.005	1.9	0.005	2.5	0.009

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M02013	500.0	1906.0	3.812	295.2	0.590	1472.6	2.945	13842.6	27.685	1679.8	3.360	1592.3	3.185	3272.1	6.544	893.5	1.787
M02014	475.0	2276.1	4.792	307.6	0.648	1429.6	3.010	12065.6	25.401	1694.4	3.567	1709.3	3.599	3403.7	7.166	810.5	1.706
M02015	483.9	2209.4	4.566	210.5	0.435	1704.0	3.521	14079.4	29.096	1776.7	3.672	1738.7	3.593	3515.4	7.265	692.7	1.431
M02016	465.7	2086.9	4.481	229.1	0.492	1332.1	2.860	11402.5	24.485	1684.0	3.616	1652.3	3.548	3336.3	7.164	726.9	1.561
M02017	460.8	1997.9	4.336	349.1	0.758	1353.3	2.937	11520.2	25.000	1515.3	3.288	1515.7	3.289	3031.0	6.578	794.2	1.724
M02018	471.3	1888.7	4.007	271.9	0.577	1385.6	2.940	13332.5	28.289	1501.3	3.185	1442.9	3.062	2944.2	6.247	872.3	1.851
M02019	492.0	2157.0	4.384	286.6	0.583	1487.3	3.023	12288.9	24.977	1604.2	3.261	1614.5	3.282	3218.7	6.542	762.6	1.550
M02020	506.7	2136.4	4.216	452.9	0.894	1601.5	3.161	15561.0	30.710	1591.9	3.142	1608.7	3.175	3200.6	6.317	1016.3	2.006
M02021	498.6	2145.9	4.304	358.3	0.719	1350.4	2.708	14046.8	28.172	1672.4	3.354	1635.3	3.280	3307.7	6.634	1185.6	2.378
M02022	455.1	1916.7	4.212	335.5	0.737	1332.8	2.929	12251.0	26.919	1694.7	3.724	1658.1	3.643	3352.8	7.367	919.1	2.020
M02023	477.1	1998.8	4.189	264.4	0.554	1324.6	2.776	12863.1	26.961	1595.9	3.345	1598.0	3.349	3193.9	6.694	841.9	1.765
M02024	506.9	1999.2	3.944	516.9	1.020	1448.5	2.858	12704.9	25.064	1606.3	3.169	1528.0	3.014	3134.3	6.183	909.3	1.794
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	482.8	2059.9	4.270	323.2	0.667	1435.2	2.972	12996.5	26.897	1634.7	3.390	1607.8	3.335	3242.6	6.725	868.7	1.798
S.D.	18.0	126.9	0.273	88.6	0.168	118.3	0.209	1222.0	1.960	80.0	0.204	82.6	0.215	158.6	0.413	134.5	0.252
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	AN	AN	AN	AN	AN	AN	AN	KW	AN	DT	AN	KW	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).
DT: Analysis by Dunnett type mean rank test.
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	1871.0	3.742	1994.1	3.988	3865.1	7.730	749.9	1.500	745.5	1.491	1495.4	2.991
M02014	1680.9	3.539	1736.4	3.656	3417.3	7.194	642.5	1.353	637.1	1.341	1279.6	2.694
M02015	1632.5	3.374	1676.4	3.464	3308.9	6.838	598.5	1.237	606.7	1.254	1205.2	2.491
M02016	1647.1	3.537	1690.9	3.631	3338.0	7.168	593.5	1.274	617.8	1.327	1211.3	2.601
M02017	1611.0	3.496	1624.8	3.526	3235.8	7.022	604.3	1.311	587.9	1.276	1192.2	2.587
M02018	1848.1	3.921	1854.1	3.934	3702.2	7.855	700.4	1.486	690.3	1.465	1390.7	2.951
M02019	1872.5	3.806	1833.7	3.727	3706.2	7.533	745.9	1.516	718.0	1.459	1463.9	2.975
M02020	1668.5	3.293	1724.2	3.403	3392.7	6.696	648.0	1.279	640.2	1.263	1288.2	2.542
M02021	1848.1	3.707	1874.2	3.759	3722.3	7.466	700.7	1.405	631.6	1.267	1332.3	2.672
M02022	1610.4	3.539	1582.0	3.476	3192.4	7.015	634.4	1.394	629.8	1.384	1264.2	2.778
M02023	1756.6	3.682	1721.2	3.608	3477.8	7.289	594.5	1.246	598.6	1.255	1193.1	2.501
M02024	1726.7	3.406	1872.2	3.693	3598.9	7.100	630.2	1.243	634.1	1.251	1264.3	2.494
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1731.1	3.587	1765.4	3.655	3496.5	7.242	653.6	1.354	644.8	1.336	1298.4	2.690
S.D.	104.4	0.188	120.4	0.180	217.8	0.349	57.1	0.105	48.4	0.092	103.3	0.191
Significance	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	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).
DT: Analysis by Dunnett type mean rank test.
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 62.5 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	802.5	1.605	1977.0	3.954	23.6	0.047	26.3	0.053	29.4	0.059	55.7	0.111
M02014	799.5	1.683	1597.0	3.362	17.2	0.036	24.1	0.051	24.9	0.052	49.0	0.103
M02015	415.3	0.858	1541.9	3.186	25.6	0.053	22.5	0.046	23.7	0.049	46.2	0.095
M02016	632.1	1.357	1693.8	3.637	18.6	0.040	25.0	0.054	24.3	0.052	49.3	0.106
M02017	476.7	1.035	1868.4	4.055	22.2	0.048	27.2	0.059	27.0	0.059	54.2	0.118
M02018	636.7	1.351	1907.4	4.047	18.3	0.039	25.4	0.054	28.8	0.061	54.2	0.115
M02019	669.1	1.360	1524.9	3.099	26.6	0.054	26.5	0.054	28.6	0.058	55.1	0.112
M02020	475.1	0.938	1764.3	3.482	21.6	0.043	23.1	0.046	25.8	0.051	48.9	0.097
M02021	794.4	1.593	1843.7	3.698	23.5	0.047	23.1	0.046	24.7	0.050	47.8	0.096
M02022	600.5	1.319	1718.9	3.777	26.2	0.058	22.9	0.050	23.4	0.051	46.3	0.102
M02023	539.2	1.130	1660.7	3.481	18.7	0.039	22.8	0.048	24.5	0.051	47.3	0.099
M02024	563.0	1.111	2108.1	4.159	17.7	0.035	24.4	0.048	28.1	0.055	52.5	0.104
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	617.0	1.278	1767.2	3.661	21.7	0.045	24.4	0.051	26.1	0.054	50.5	0.105
S.D.	132.2	0.268	179.3	0.350	3.5	0.007	1.6	0.004	2.2	0.004	3.6	0.008
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	DU	AN	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).
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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 29-1-3. Organ weights of male rats at the end of the dosing period

MMP 250 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M03025	518.9	2062.4	3.975	287.9	0.555	1548.9	2.985	13770.5	26.538	1615.7	3.114	1617.5	3.117	3233.2	6.231	860.0	1.657
M03026	438.7	1999.5	4.558	247.6	0.564	1393.2	3.176	12000.5	27.355	1633.1	3.723	1635.0	3.727	3268.1	7.450	743.1	1.694
M03027	475.1	1882.2	3.962	311.7	0.656	1415.9	2.980	11773.7	24.782	1493.3	3.143	1489.0	3.134	2982.3	6.277	764.8	1.610
M03028	457.1	2107.4	4.610	307.2	0.672	1274.6	2.788	12323.7	26.961	1511.2	3.306	1436.0	3.142	2947.2	6.448	1066.4	2.333
M03029	486.2	1946.9	4.004	409.4	0.842	1459.6	3.002	13363.9	27.486	1788.9	3.679	1675.7	3.447	3464.6	7.126	1017.5	2.093
M03030	483.2	2002.8	4.145	212.3	0.439	1487.7	3.079	12787.5	26.464	1777.4	3.678	1842.7	3.814	3620.1	7.492	969.2	2.006
M03031	454.3	1935.2	4.260	304.9	0.671	1272.2	2.800	11396.3	25.085	1724.0	3.795	1702.4	3.747	3426.4	7.542	624.8	1.375
M03032	420.7	2060.3	4.897	128.0	0.304	1232.2	2.929	10189.1	24.219	1682.8	4.000	1758.4	4.180	3441.2	8.180	644.7	1.532
M03033	516.5	1850.1	3.582	553.5	1.072	1410.2	2.730	13406.2	25.956	1547.4	2.996	1517.9	2.939	3065.3	5.935	1121.6	2.172
M03034	492.1	2065.4	4.197	293.7	0.597	1454.9	2.957	14202.0	28.860	2022.5	4.110	2019.6	4.104	4042.1	8.214	879.4	1.787
M03035	488.3	1928.3	3.949	266.2	0.545	1369.1	2.804	13670.5	27.996	1817.2	3.721	1840.0	3.768	3657.2	7.490	784.1	1.606
M03036	486.2	2071.0	4.260	232.6	0.478	1285.3	2.644	13079.1	26.901	1716.6	3.531	1699.5	3.495	3416.1	7.026	833.7	1.715
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	476.4	1992.6	4.200	296.3	0.616	1383.7	2.906	12663.6	26.550	1694.2	3.566	1686.1	3.551	3380.3	7.118	859.1	1.798
S.D.	29.3	83.3	0.355	105.4	0.197	99.1	0.154	1164.3	1.359	149.4	0.355	165.8	0.405	311.3	0.754	159.3	0.289
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	AN	AN	AN	AN	AN	AN	AN	KW	AN	DT	AN	KW	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).
DT: Analysis by Dunnett type mean rank test.
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

MMP 250 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	1881.1	3.625	1833.1	3.533	3714.2	7.158	693.6	1.337	674.3	1.299	1367.9	2.636
M03026	1547.1	3.527	1560.7	3.558	3107.8	7.084	560.4	1.277	565.9	1.290	1126.3	2.567
M03027	1471.7	3.098	1471.7	3.098	2943.4	6.195	588.2	1.238	574.1	1.208	1162.3	2.446
M03028	1765.1	3.862	1681.6	3.679	3446.7	7.540	667.4	1.460	644.5	1.410	1311.9	2.870
M03029	1602.6	3.296	1633.6	3.360	3236.2	6.656	656.3	1.350	602.6	1.239	1258.9	2.589
M03030	1728.2	3.577	1691.4	3.500	3419.6	7.077	605.4	1.253	592.3	1.226	1197.7	2.479
M03031	1764.3	3.884	1787.0	3.934	3551.3	7.817	606.9	1.336	612.2	1.348	1219.1	2.683
M03032	1686.0	4.008	1681.0	3.996	3367.0	8.003	729.8	1.735	730.3	1.736	1460.1	3.471
M03033	1729.9	3.349	1822.3	3.528	3552.2	6.877	582.6	1.128	571.4	1.106	1154.0	2.234
M03034	1986.9	4.038	2030.8	4.127	4017.7	8.164	718.8	1.461	736.7	1.497	1455.5	2.958
M03035	1587.8	3.252	1552.9	3.180	3140.7	6.432	636.7	1.304	602.5	1.234	1239.2	2.538
M03036	1799.0	3.700	1815.9	3.735	3614.9	7.435	651.1	1.339	657.3	1.352	1308.4	2.691
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1712.5	3.601	1713.5	3.602	3426.0	7.203	641.4	1.352	630.3	1.329	1271.8	2.680
S.D.	144.9	0.309	153.5	0.313	294.8	0.615	54.7	0.151	59.0	0.164	112.0	0.313
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	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).
DT: Analysis by Dunnett type mean rank test.
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

MMP 250 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	546.4	1.053	1386.8	2.673	17.4	0.034	27.5	0.053	29.6	0.057	57.1	0.110
M03026	501.6	1.143	1450.6	3.307	22.7	0.052	21.6	0.049	22.7	0.052	44.3	0.101
M03027	558.0	1.174	1547.4	3.257	20.8	0.044	24.5	0.052	22.1	0.047	46.6	0.098
M03028	594.5	1.301	1472.3	3.221	29.4	0.064	28.1	0.061	25.7	0.056	53.8	0.118
M03029	443.6	0.912	1101.1	2.265	18.1	0.037	30.1	0.062	30.7	0.063	60.8	0.125
M03030	466.4	0.965	2467.6	5.107	18.9	0.039	28.7	0.059	30.0	0.062	58.7	0.121
M03031	644.7	1.419	1731.4	3.811	15.9	0.035	24.7	0.054	26.5	0.058	51.2	0.113
M03032	380.8	0.905	1695.7	4.031	20.4	0.048	25.9	0.062	27.7	0.066	53.6	0.127
M03033	558.8	1.082	1323.9	2.563	24.1	0.047	25.1	0.049	26.2	0.051	51.3	0.099
M03034	509.4	1.035	1807.3	3.673	25.3	0.051	30.4	0.062	33.6	0.068	64.0	0.130
M03035	613.4	1.256	1871.9	3.834	15.7	0.032	18.9	0.039	21.0	0.043	39.9	0.082
M03036	654.5	1.346	1585.2	3.260	15.4	0.032	25.5	0.052	26.2	0.054	51.7	0.106
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	539.3	1.133	1620.1	3.417	20.3	0.043	25.9	0.055	26.8	0.056	52.8	0.111
S.D.	82.9	0.171	344.2	0.759	4.3	0.010	3.4	0.007	3.8	0.008	6.9	0.014
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	DU	AN	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).
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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 29-1-4. Organ weights of male rats at the end of the dosing period

MMP 1000 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M04037	461.3	2061.6	4.469	144.1	0.312	1391.6	3.017	11644.9	25.244	1710.3	3.708	1740.7	3.773	3451.0	7.481	744.3	1.613
M04038	473.2	2023.5	4.276	249.7	0.528	1558.2	3.293	13036.6	27.550	1485.9	3.140	1520.6	3.213	3006.5	6.354	627.8	1.327
M04039	448.0	1921.9	4.290	282.8	0.631	1384.6	3.091	12967.9	28.946	1628.9	3.636	1700.9	3.797	3329.8	7.433	860.7	1.921
M04040	487.3	2022.0	4.149	367.7	0.755	1407.8	2.889	14269.5	29.283	1654.8	3.396	1675.7	3.439	3330.5	6.835	787.3	1.616
M04041	432.8	2046.8	4.729	221.5	0.512	1298.5	3.000	11974.3	27.667	1599.2	3.695	1638.5	3.786	3237.7	7.481	654.3	1.512
M04042	496.9	1988.4	4.002	309.0	0.622	1475.9	2.970	14494.3	29.169	1804.5	3.632	1713.5	3.448	3518.0	7.080	829.9	1.670
M04043	492.7	2027.7	4.115	200.2	0.406	1465.1	2.974	14276.4	28.976	2142.2	4.348	1982.8	4.024	4125.0	8.372	785.2	1.594
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	470.3	2013.1	4.290	253.6	0.538	1426.0	3.033	13237.7	28.119	1718.0	3.651	1710.4	3.640	3428.4	7.291	755.6	1.608
S.D.	24.1	46.2	0.244	74.0	0.148	82.6	0.129	1152.5	1.453	211.1	0.369	140.0	0.280	348.2	0.631	86.8	0.178
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS
Statistical method	AN	KW	AN	AN	AN	AN	AN	AN	AN	KW	AN	DT	AN	KW	AN	AN	AN

Appendix 29-1-4 (continued). Organ weights of male rats at the end of the dosing period

MMP 1000 mg/kg

Male No.	Testis (R) (mg)	Testis (R) (mg/g)	Testis (L) (mg)	Testis (L) (mg/g)	Testes (mg)	Testes (mg/g)	Epididymis (R) (mg)	Epididymis (R) (mg/g)	Epididymis (L) (mg)	Epididymis (L) (mg/g)	Epididymides (mg)	Epididymides (mg/g)
M04037	1516.3	3.287	1541.5	3.342	3057.8	6.629	534.1	1.158	619.4	1.343	1153.5	2.501
M04038	1597.6	3.376	1578.4	3.336	3176.0	6.712	557.7	1.179	546.9	1.156	1104.6	2.334
M04039	1619.0	3.614	1617.8	3.611	3236.8	7.225	568.1	1.268	576.9	1.288	1145.0	2.556
M04040	1618.7	3.322	1561.1	3.204	3179.8	6.525	596.5	1.224	581.4	1.193	1177.9	2.417
M04041	1742.3	4.026	1766.4	4.081	3508.7	8.107	656.9	1.518	649.0	1.500	1305.9	3.017
M04042	1555.1	3.130	1577.9	3.175	3133.0	6.305	537.4	1.082	530.6	1.068	1068.0	2.149
M04043	1774.0	3.601	1698.3	3.447	3472.3	7.047	671.6	1.363	630.4	1.279	1302.0	2.643
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1631.9	3.479	1620.2	3.457	3252.1	6.936	588.9	1.256	590.7	1.261	1179.6	2.517
S.D.	94.1	0.296	82.4	0.312	172.0	0.603	55.7	0.146	44.0	0.140	92.1	0.273
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	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).
DT: Analysis by Dunnett type mean rank test.
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 29-1-4 (continued). Organ weights of male rats at the end of the dosing period

MMP 1000 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	548.4	1.189	1756.0	3.807	15.3	0.033	25.5	0.055	28.5	0.062	54.0	0.117
M04038	345.0	0.729	1336.6	2.825	18.6	0.039	22.1	0.047	21.8	0.046	43.9	0.093
M04039	574.6	1.283	1550.2	3.460	22.8	0.051	20.9	0.047	22.8	0.051	43.7	0.098
M04040	519.5	1.066	1599.3	3.282	25.0	0.051	21.5	0.044	23.8	0.049	45.3	0.093
M04041	519.6	1.201	1444.4	3.337	21.5	0.050	18.7	0.043	21.3	0.049	40.0	0.092
M04042	606.8	1.221	1936.7	3.898	19.1	0.038	22.6	0.045	22.4	0.045	45.0	0.091
M04043	391.1	0.794	1799.1	3.652	17.5	0.036	25.2	0.051	27.7	0.056	52.9	0.107
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	500.7	1.069	1631.8	3.466	20.0	0.043	22.4	0.047	24.0	0.051	46.4	0.099
S.D.	96.6	0.221	210.7	0.365	3.3	0.008	2.4	0.004	2.9	0.006	5.1	0.010
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	DU	AN	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).
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 Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		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)
M01008	507.2	2025.8	3.994	215.4	0.425	1452.6	2.864	12481.6	24.609	1575.8	3.107	1667.8	3.288	3243.6	6.395	812.5	1.602
M01009	499.5	2014.3	4.033	213.6	0.428	1387.3	2.777	12931.5	25.889	1668.0	3.339	1600.8	3.205	3268.8	6.544	784.4	1.570
M01010	508.2	1972.6	3.882	299.6	0.590	1380.3	2.716	13551.0	26.665	1608.0	3.164	1635.0	3.217	3243.0	6.381	984.1	1.936
M01011	508.0	1872.7	3.686	202.8	0.399	1356.2	2.670	13405.1	26.388	1361.4	2.680	1423.7	2.803	2785.1	5.482	923.3	1.818
M01012	516.2	2053.0	3.977	332.5	0.644	1638.8	3.175	13503.6	26.160	1775.0	3.439	1835.7	3.556	3610.7	6.995	917.8	1.778
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	507.8	1987.7	3.914	252.8	0.497	1443.0	2.840	13174.6	25.942	1597.6	3.146	1632.6	3.214	3230.2	6.359	884.4	1.741
S.D.	5.9	70.5	0.139	59.1	0.112	115.1	0.201	458.9	0.798	152.3	0.292	147.6	0.270	293.6	0.550	83.3	0.153

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

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	1957.2	3.859	1817.1	3.583	3774.3	7.441	753.5	1.486	744.4	1.468	1497.9	2.953
M01009	1624.4	3.252	1655.4	3.314	3279.8	6.566	578.1	1.157	624.2	1.250	1202.3	2.407
M01010	1618.1	3.184	1673.4	3.293	3291.5	6.477	630.2	1.240	639.0	1.257	1269.2	2.497
M01011	1608.4	3.166	1652.4	3.253	3260.8	6.419	608.7	1.198	610.2	1.201	1218.9	2.399
M01012	1737.9	3.367	1723.0	3.338	3460.9	6.705	691.3	1.339	623.1	1.207	1314.4	2.546
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1709.2	3.366	1704.3	3.356	3413.5	6.722	652.4	1.284	648.2	1.277	1300.5	2.560
S.D.	148.3	0.287	69.1	0.131	217.1	0.416	70.1	0.132	54.7	0.110	118.8	0.228

Control (vehicle: water for injection)

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	595.2	1.174	1524.3	3.005	22.3	0.044	30.2	0.060	31.3	0.062	61.5	0.121
M01009	538.2	1.077	1470.9	2.945	26.2	0.052	21.6	0.043	25.1	0.050	46.7	0.093
M01010	465.5	0.916	1870.3	3.680	28.3	0.056	31.2	0.061	35.3	0.069	66.5	0.131
M01011	264.2	0.520	1426.6	2.808	24.7	0.049	30.4	0.060	31.9	0.063	62.3	0.123
M01012	753.2	1.459	1441.1	2.792	13.1	0.025	27.1	0.052	30.0	0.058	57.1	0.111
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	523.3	1.029	1546.6	3.046	22.9	0.045	28.1	0.055	30.7	0.060	58.8	0.116
S.D.	179.4	0.346	184.8	0.366	5.9	0.012	4.0	0.008	3.7	0.007	7.6	0.015

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M04044	502.7	2018.6	4.016	311.1	0.619	1464.3	2.913	12548.8	24.963	1723.8	3.429	1713.4	3.408	3437.2	6.837	794.9	1.581
M04045	476.9	2050.3	4.299	257.7	0.540	1246.5	2.614	11867.4	24.884	1556.0	3.263	1588.7	3.331	3144.7	6.594	572.3	1.200
M04046	493.8	2088.0	4.228	251.6	0.510	1473.7	2.984	12762.8	25.846	1674.2	3.390	1632.3	3.306	3306.5	6.696	789.1	1.598
M04047	557.9	2047.2	3.669	232.1	0.416	1793.1	3.214	12595.1	22.576	1777.4	3.186	1824.4	3.270	3601.8	6.456	777.4	1.393
M04048	550.4	2180.1	3.961	189.0	0.343	1548.0	2.813	13326.8	24.213	1774.7	3.224	1705.2	3.098	3479.9	6.322	719.4	1.307
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	516.3	2076.8	4.035	248.3	0.486	1505.1	2.908	12620.2	24.496	1701.2	3.298	1692.8	3.283	3394.0	6.581	730.6	1.416
S.D.	35.8	62.8	0.248	44.2	0.108	196.4	0.221	522.5	1.220	91.6	0.106	90.0	0.115	174.8	0.201	93.4	0.173
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	*
Statistical method	AW	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.
AW: Analysis by Aspin-Welch t-test.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	1502.9	2.990	1424.1	2.833	2927.0	5.823	588.3	1.170	574.3	1.142	1162.6	2.313
M04045	1668.4	3.498	1693.5	3.551	3361.9	7.049	613.3	1.286	587.5	1.232	1200.8	2.518
M04046	1709.4	3.462	1654.9	3.351	3364.3	6.813	609.7	1.235	574.4	1.163	1184.1	2.398
M04047	1900.1	3.406	1836.8	3.292	3736.9	6.698	657.6	1.179	633.4	1.135	1291.0	2.314
M04048	1760.3	3.198	1855.8	3.372	3616.1	6.570	731.9	1.330	726.6	1.320	1458.5	2.650
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1708.2	3.311	1693.0	3.280	3401.2	6.591	640.2	1.240	619.2	1.198	1259.4	2.439
S.D.	144.3	0.214	173.9	0.268	310.9	0.464	57.1	0.069	64.7	0.078	121.6	0.145
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

MMP 1000 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	730.3	1.453	2141.4	4.260	21.8	0.043	28.5	0.057	29.7	0.059	58.2	0.116
M04045	458.9	0.962	1841.7	3.862	17.0	0.036	26.5	0.056	26.5	0.056	53.0	0.111
M04046	596.2	1.207	1550.1	3.139	20.3	0.041	20.7	0.042	23.5	0.048	44.2	0.090
M04047	720.3	1.291	1623.2	2.909	33.6	0.060	22.0	0.039	24.3	0.044	46.3	0.083
M04048	665.6	1.209	2215.1	4.025	22.4	0.041	26.6	0.048	28.2	0.051	54.8	0.100
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	634.3	1.224	1874.3	3.639	23.0	0.044	24.9	0.048	26.4	0.052	51.3	0.100
S.D.	111.6	0.178	298.6	0.585	6.3	0.009	3.3	0.008	2.6	0.006	5.9	0.014
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AW: Analysis by Aspin-Welch t-test.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	347.5	2034.3	5.854	168.0	0.483	1045.2	3.008	11097.4	31.935	1096.4	3.155	1084.0	3.119	2180.4	6.275	664.9	1.913
F01002	285.0	1874.9	6.579	183.8	0.645	895.2	3.141	8603.0	30.186	1112.8	3.905	1191.1	4.179	2303.9	8.084	628.5	2.205
F01003	313.5	1719.7	5.485	234.1	0.747	1030.3	3.286	10395.6	33.160	1044.6	3.332	1040.4	3.319	2085.0	6.651	707.7	2.257
F01004	334.8	1970.7	5.886	186.4	0.557	1159.2	3.462	10793.4	32.238	1140.5	3.407	1210.6	3.616	2351.1	7.022	822.8	2.458
F01005	322.0	1960.3	6.088	206.0	0.640	1014.4	3.150	10102.8	31.375	1034.4	3.212	1013.2	3.147	2047.6	6.359	668.7	2.077
F01006	314.1	1945.4	6.194	127.4	0.406	1079.2	3.436	10157.5	32.338	1073.1	3.416	1100.0	3.502	2173.1	6.918	793.5	2.526
F01007	304.3	1900.1	6.244	130.5	0.429	1030.8	3.387	9841.0	32.340	1063.5	3.495	1006.9	3.309	2070.4	6.804	560.4	1.842
F01008	296.4	1976.0	6.667	217.2	0.733	955.6	3.224	8033.0	27.102	997.0	3.364	979.1	3.303	1976.1	6.667	550.0	1.856
F01009	300.7	1798.3	5.980	176.9	0.588	1076.1	3.579	10439.6	34.718	1144.3	3.805	1097.2	3.649	2241.5	7.454	766.6	2.549
F01010	329.8	1868.2	5.665	323.5	0.981	982.5	2.979	10478.5	31.772	1036.8	3.144	1008.2	3.057	2045.0	6.201	750.8	2.277
F01011	286.7	1909.8	6.661	193.5	0.675	951.6	3.319	10246.6	35.740	1041.4	3.632	1014.0	3.537	2055.4	7.169	724.6	2.527
F01012	343.0	1961.3	5.718	274.3	0.800	1143.8	3.335	11512.3	33.564	1065.7	3.107	1058.9	3.087	2124.6	6.194	833.5	2.430
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	314.8	1909.9	6.085	201.8	0.640	1030.3	3.276	10141.7	32.206	1070.9	3.415	1067.0	3.402	2137.8	6.817	706.0	2.243
S.D.	21.0	86.2	0.396	55.9	0.164	77.9	0.183	972.4	2.188	45.0	0.258	73.6	0.320	114.5	0.565	94.5	0.267

Appendix 30-1-1 (continued). Organ weights of female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(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	70.8	0.204	50.7	0.146	121.5	0.350	639.3	1.840	25.5	0.073	44.3	0.127	43.7	0.126	88.0	0.253
F01002	36.7	0.129	40.8	0.143	77.5	0.272	567.6	1.992	16.1	0.056	31.0	0.109	32.4	0.114	63.4	0.222
F01003	60.6	0.193	45.6	0.145	106.2	0.339	613.0	1.955	15.5	0.049	37.5	0.120	37.3	0.119	74.8	0.239
F01004	61.9	0.185	55.3	0.165	117.2	0.350	550.1	1.643	17.7	0.053	42.9	0.128	51.3	0.153	94.2	0.281
F01005	59.7	0.185	49.9	0.155	109.6	0.340	648.3	2.013	14.8	0.046	36.1	0.112	40.2	0.125	76.3	0.237
F01006	70.3	0.224	58.9	0.188	129.2	0.411	547.1	1.742	14.1	0.045	33.2	0.106	35.2	0.112	68.4	0.218
F01007	49.4	0.162	73.9	0.243	123.3	0.405	513.9	1.689	13.7	0.045	40.7	0.134	38.7	0.127	79.4	0.261
F01008	50.9	0.172	54.6	0.184	105.5	0.356	684.1	2.308	18.5	0.062	24.1	0.081	30.0	0.101	54.1	0.183
F01009	55.7	0.185	48.5	0.161	104.2	0.347	682.4	2.269	16.9	0.056	43.1	0.143	46.8	0.156	89.9	0.299
F01010	51.3	0.156	41.9	0.127	93.2	0.283	598.4	1.814	15.3	0.046	37.5	0.114	41.1	0.125	78.6	0.238
F01011	54.3	0.189	56.4	0.197	110.7	0.386	493.2	1.720	15.7	0.055	46.1	0.161	50.0	0.174	96.1	0.335
F01012	52.0	0.152	56.1	0.164	108.1	0.315	574.3	1.674	19.8	0.058	44.2	0.129	46.4	0.135	90.6	0.264
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	56.1	0.178	52.7	0.168	108.9	0.346	592.6	1.888	17.0	0.054	38.4	0.122	41.1	0.131	79.5	0.253
S.D.	9.4	0.025	8.9	0.031	13.9	0.043	62.6	0.225	3.2	0.008	6.5	0.020	6.8	0.021	13.0	0.040

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 30-1-2. Organ weights of female rats at the end of the dosing period

MMP 62.5 mg/kg

Female No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
F02013	284.8	1852.7	6.505	130.5	0.458	882.8	3.100	9224.7	32.390	1026.6	3.605	1038.0	3.645	2064.6	7.249	625.8	2.197
F02014	312.1	1985.7	6.362	192.0	0.615	1011.1	3.240	10087.6	32.322	1179.2	3.778	1183.3	3.791	2362.5	7.570	791.1	2.535
F02015	324.5	1856.9	5.722	199.6	0.615	1038.6	3.201	9899.1	30.506	1103.5	3.401	1124.7	3.466	2228.2	6.867	682.0	2.102
F02016	297.4	1900.0	6.389	177.9	0.598	913.0	3.070	10192.4	34.272	1068.1	3.591	1026.3	3.451	2094.4	7.042	707.6	2.379
F02017	299.4	1999.6	6.679	229.7	0.767	1017.4	3.398	10256.8	34.258	1080.2	3.608	1047.3	3.498	2127.5	7.106	735.5	2.457
F02018	345.7	1959.3	5.668	285.3	0.825	1151.4	3.331	10805.1	31.256	1225.6	3.545	1223.5	3.539	2449.1	7.084	900.9	2.606
F02019	284.3	1926.6	6.777	207.4	0.730	993.5	3.495	10046.4	35.337	1032.2	3.631	1056.7	3.717	2088.9	7.348	743.4	2.615
F02020	349.1	2023.2	5.795	251.9	0.722	1132.4	3.244	11941.0	34.205	1093.8	3.133	1054.1	3.019	2147.9	6.153	659.3	1.889
F02021	315.8	2008.5	6.360	303.2	0.960	1055.3	3.342	11267.7	35.680	1214.7	3.846	1145.8	3.628	2360.5	7.475	807.8	2.558
F02022	346.3	1876.3	5.418	270.9	0.782	1243.7	3.591	11795.3	34.061	1167.2	3.370	1061.6	3.066	2228.8	6.436	905.1	2.614
F02023	324.4	1825.8	5.628	274.8	0.847	1100.2	3.391	10305.2	31.767	1030.5	3.177	1065.4	3.284	2095.9	6.461	563.4	1.737
F02024	297.2	2088.7	7.028	168.1	0.566	965.7	3.249	10277.8	34.582	970.3	3.265	1013.7	3.411	1984.0	6.676	579.4	1.950
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	315.1	1941.9	6.194	224.3	0.707	1042.1	3.304	10508.3	33.386	1099.3	3.496	1086.7	3.460	2186.0	6.956	725.1	2.303
S.D.	23.3	81.5	0.526	53.5	0.141	102.7	0.152	800.0	1.672	81.4	0.227	66.7	0.239	141.7	0.445	112.3	0.317
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	DU	DU	DU	AN	DU	AN	DU	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 30-1-2 (continued). Organ weights of female rats at the end of the dosing period

MMP 62.5 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	40.9	0.144	65.2	0.229	106.1	0.373	583.4	2.048	13.7	0.048	41.9	0.147	41.5	0.146	83.4	0.293
F02014	45.3	0.145	43.7	0.140	89.0	0.285	578.7	1.854	17.7	0.057	36.1	0.116	42.7	0.137	78.8	0.252
F02015	52.4	0.161	45.2	0.139	97.6	0.301	673.4	2.075	11.6	0.036	44.0	0.136	46.8	0.144	90.8	0.280
F02016	40.2	0.135	51.0	0.171	91.2	0.307	592.8	1.993	15.6	0.052	36.8	0.124	38.3	0.129	75.1	0.253
F02017	48.1	0.161	41.3	0.138	89.4	0.299	477.3	1.594	17.4	0.058	41.9	0.140	42.5	0.142	84.4	0.282
F02018	54.2	0.157	56.0	0.162	110.2	0.319	737.0	2.132	24.6	0.071	37.0	0.107	39.5	0.114	76.5	0.221
F02019	54.3	0.191	53.2	0.187	107.5	0.378	776.6	2.732	15.1	0.053	45.6	0.160	50.5	0.178	96.1	0.338
F02020	74.4	0.213	66.6	0.191	141.0	0.404	633.7	1.815	17.8	0.051	47.0	0.135	49.9	0.143	96.9	0.278
F02021	41.5	0.131	45.2	0.143	86.7	0.275	515.3	1.632	17.0	0.054	41.4	0.131	45.7	0.145	87.1	0.276
F02022	64.6	0.187	58.3	0.168	122.9	0.355	529.0	1.528	21.2	0.061	40.4	0.117	39.3	0.113	79.7	0.230
F02023	67.7	0.209	46.5	0.143	114.2	0.352	608.9	1.877	18.8	0.058	44.1	0.136	43.8	0.135	87.9	0.271
F02024	59.9	0.202	54.4	0.183	114.3	0.385	577.6	1.943	16.9	0.057	39.7	0.134	43.3	0.146	83.0	0.279
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	53.6	0.170	52.2	0.166	105.8	0.336	607.0	1.935	17.3	0.055	41.3	0.132	43.7	0.139	85.0	0.271
S.D.	11.2	0.029	8.3	0.028	16.2	0.044	87.7	0.317	3.4	0.008	3.5	0.014	4.0	0.017	7.1	0.030
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 30-1-3. Organ weights of female rats at the end of the dosing period

MMP 250 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		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)
F03025	326.6	1852.7	5.673	225.4	0.690	1039.1	3.182	9860.0	30.190	1049.2	3.212	1064.0	3.258	2113.2	6.470	624.2	1.911
F03026	303.2	1789.8	5.903	214.5	0.707	1006.2	3.319	10284.3	33.919	997.8	3.291	978.7	3.228	1976.5	6.519	674.8	2.226
F03027	306.2	1843.8	6.022	139.1	0.454	903.8	2.952	10457.1	34.151	991.7	3.239	920.0	3.005	1911.7	6.243	734.5	2.399
F03028	302.6	1975.5	6.528	272.0	0.899	1018.1	3.365	10517.2	34.756	1086.6	3.591	1041.7	3.442	2128.3	7.033	787.4	2.602
F03029	300.9	1903.1	6.325	119.5	0.397	994.6	3.305	9434.7	31.355	877.3	2.916	845.0	2.808	1722.3	5.724	595.7	1.980
F03030	349.6 a)	2052.9 a)	5.872 a)	376.2 a)	1.076 a)	1032.6 a)	2.954 a)	11813.3 a)	33.791 a)	1161.0 a)	3.321 a)	1104.5 a)	3.159 a)	2265.5 a)	6.480 a)	586.4 a)	1.677 a)
F03031	305.4	1882.7	6.165	219.3	0.718	1012.9	3.317	10164.8	33.284	1008.8	3.303	1019.6	3.339	2028.4	6.642	746.4	2.444
F03032	321.9	1864.0	5.791	128.7	0.400	970.8	3.016	10839.8	33.674	984.7	3.059	942.2	2.927	1926.9	5.986	642.6	1.996
F03033	339.9	1899.3	5.588	267.8	0.788	1021.2	3.004	10499.1	30.889	999.3	2.940	962.6	2.832	1961.9	5.772	919.4	2.705
F03034	313.7	2001.5	6.380	156.2	0.498	1034.5	3.298	10659.3	33.979	1070.3	3.412	1004.3	3.201	2074.6	6.613	828.1	2.640
F03035	320.6	1899.5	5.925	167.6	0.523	1082.1	3.375	9072.8	28.299	1120.5	3.495	1154.3	3.600	2274.8	7.095	634.7	1.980
F03036	291.8	1862.4	6.382	238.6	0.818	961.2	3.294	8825.9	30.246	1012.8	3.471	942.6	3.230	1955.4	6.701	763.8	2.618
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	312.1	1888.6	6.062	195.3	0.627	1004.0	3.221	10055.9	32.249	1018.1	3.266	988.6	3.170	2006.7	6.436	722.9	2.318
S.D.	13.9	59.3	0.316	55.2	0.178	46.8	0.156	672.0	2.128	64.3	0.223	82.2	0.252	143.1	0.462	99.3	0.309
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	DU	DU	DU	AN	DU	AN	DU	AN	AN	AN

a) Excluded from data analysis (not delivery, dead fetal remnant).
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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 30-1-3 (continued). Organ weights of female rats at the end of the dosing period

MMP 250 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03025	52.9	0.162	50.7	0.155	103.6	0.317	534.3	1.636	14.2	0.043	37.8	0.116	41.2	0.126	79.0	0.242
F03026	43.6	0.144	45.9	0.151	89.5	0.295	684.2	2.257	16.4	0.054	35.4	0.117	39.7	0.131	75.1	0.248
F03027	36.5	0.119	41.6	0.136	78.1	0.255	560.2	1.830	10.5	0.034	31.0	0.101	32.1	0.105	63.1	0.206
F03028	54.4	0.180	66.0	0.218	120.4	0.398	625.8	2.068	17.5	0.058	46.2	0.153	49.2	0.163	95.4	0.315
F03029	53.3	0.177	41.2	0.137	94.5	0.314	646.0	2.147	20.4	0.068	35.4	0.118	28.4	0.094	63.8	0.212
F03030	55.0 a)	0.157 a)	41.5 a)	0.119 a)	96.5 a)	0.276 a)	1075.9 a)	3.078 a)	21.5 a)	0.061 a)	25.5 a)	0.073 a)	26.8 a)	0.077 a)	52.3 a)	0.150 a)
F03031	47.9	0.157	46.3	0.152	94.2	0.308	555.5	1.819	18.0	0.059	42.7	0.140	47.5	0.156	90.2	0.295
F03032	42.4	0.132	47.3	0.147	89.7	0.279	551.1	1.712	9.5	0.030	40.9	0.127	38.6	0.120	79.5	0.247
F03033	57.3	0.169	46.7	0.137	104.0	0.306	739.9	2.177	24.0	0.071	32.4	0.095	34.8	0.102	67.2	0.198
F03034	63.3	0.202	58.5	0.186	121.8	0.388	681.2	2.172	21.0	0.067	38.1	0.121	40.8	0.130	78.9	0.252
F03035	48.6	0.152	43.8	0.137	92.4	0.288	568.8	1.774	15.3	0.048	25.7	0.080	26.3	0.082	52.0	0.162
F03036	37.6	0.129	49.5	0.170	87.1	0.298	625.5	2.144	15.9	0.054	35.6	0.122	42.9	0.147	78.5	0.269
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	48.9	0.157	48.9	0.157	97.8	0.313	615.7	1.976	16.6	0.053	36.5	0.117	38.3	0.123	74.8	0.241
S.D.	8.3	0.025	7.4	0.026	13.6	0.043	67.3	0.223	4.3	0.013	5.7	0.020	7.3	0.026	12.5	0.044
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

a) Excluded from data analysis (not delivery, dead fetal remnant).
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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 30-1-4. Organ weights of female rats at the end of the dosing period

MMP 1000 mg/kg

Female No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
F04037	311.9	1776.1	5.694	251.2	0.805	1009.6	3.237	10422.2	33.415	1038.4	3.329	981.3	3.146	2019.7	6.475	827.3	2.652
F04038	297.0 b)	1802.7 b)	6.070 b)	217.3 b)	0.732 b)	868.6 b)	2.925 b)	11398.4 b)	38.378 b)	1111.6 b)	3.743 b)	1003.6 b)	3.379 b)	2115.2 b)	7.122 b)	479.7 b)	1.615 b)
F04039	312.9	2017.0	6.446	195.7	0.625	1139.6	3.642	11082.5	35.419	1031.9	3.298	1097.0	3.506	2128.9	6.804	872.1	2.787
F04040	339.4	1814.1	5.345	210.2	0.619	1091.1	3.215	11843.5	34.895	1192.0	3.512	1181.4	3.481	2373.4	6.993	805.2	2.372
F04041	306.1	1905.5	6.225	93.1	0.304	997.7	3.259	10850.4	35.447	1026.1	3.352	1026.2	3.352	2052.3	6.705	642.9	2.100
F04042	330.8	1977.0	5.976	256.9	0.777	1099.5	3.324	12195.1	36.865	1187.2	3.589	1147.8	3.470	2335.0	7.059	863.1	2.609
F04043	301.3 c)	1869.9 c)	6.206 c)	78.0 c)	0.259 c)	925.7 c)	3.072 c)	13490.1 c)	44.773 c)	1269.5 c)	4.213 c)	1270.0 c)	4.215 c)	2539.5 c)	8.428 c)	1368.0 c)	4.540 c)
F04044	351.0 b)	1943.3 b)	5.536 b)	268.7 b)	0.766 b)	1183.3 b)	3.371 b)	13442.8 b)	38.299 b)	1082.6 b)	3.084 b)	1013.8 b)	2.888 b)	2096.4 b)	5.973 b)	740.9 b)	2.111 b)
F04045	323.7	1906.0	5.888	178.6	0.552	1154.7	3.567	11460.9	35.406	1062.7	3.283	1021.8	3.157	2084.5	6.440	655.0	2.023
F04046	311.3	1936.5	6.221	211.1	0.678	1097.5	3.526	11135.7	35.772	1112.8	3.575	1098.4	3.528	2211.2	7.103	863.9	2.775
F04047	335.4	1944.6	5.798	194.2	0.579	1060.4	3.162	10569.5	31.513	968.2	2.887	968.4	2.887	1936.6	5.774	676.8	2.018
F04048	322.9	1967.8	6.094	231.4	0.717	1137.8	3.524	11417.7	35.360	1129.8	3.499	1191.8	3.691	2321.6	7.190	632.8	1.960
Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	321.6	1916.1	5.965	202.5	0.628	1087.5	3.384	11219.7	34.899	1083.2	3.369	1079.3	3.358	2162.6	6.727	759.9	2.366
S.D.	11.8	77.5	0.330	48.7	0.149	55.8	0.180	576.5	1.555	76.8	0.216	84.0	0.249	155.2	0.447	105.1	0.346
Significance	NS	NS	NS	NS	NS	NS	NS	**	**	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	DU	DU	DU	AN	DU	AN	DU	AN	AN	AN

b) Excluded from data analysis (not pregnant).
c) 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.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 30-1-4 (continued). Organ weights of female rats at the end of the dosing period

MMP 1000 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04037	50.1	0.161	41.7	0.134	91.8	0.294	456.8	1.465	18.7	0.060	35.1	0.113	36.8	0.118	71.9	0.231
F04038	32.3 b)	0.109 b)	36.2 b)	0.122 b)	68.5 b)	0.231 b)	507.1 b)	1.707 b)	17.7 b)	0.060 b)	27.1 b)	0.091 b)	31.8 b)	0.107 b)	58.9 b)	0.198 b)
F04039	63.8	0.204	53.5	0.171	117.3	0.375	642.3	2.053	20.3	0.065	42.3	0.135	46.7	0.149	89.0	0.284
F04040	49.7	0.146	43.7	0.129	93.4	0.275	559.0	1.647	21.3	0.063	34.8	0.103	36.7	0.108	71.5	0.211
F04041	34.5	0.113	52.4	0.171	86.9	0.284	633.5	2.070	11.2	0.037	35.8	0.117	33.8	0.110	69.6	0.227
F04042	45.4	0.137	52.1	0.157	97.5	0.295	618.7	1.870	15.9	0.048	38.3	0.116	41.6	0.126	79.9	0.242
F04043	58.6 c)	0.194 c)	44.8 c)	0.149 c)	103.4 c)	0.343 c)	629.1 c)	2.088 c)	18.2 c)	0.060 c)	31.4 c)	0.104 c)	33.8 c)	0.112 c)	65.2 c)	0.216 c)
F04044	46.8 b)	0.133 b)	55.8 b)	0.159 b)	102.6 b)	0.292 b)	364.6 b)	1.039 b)	20.1 b)	0.057 b)	59.0 b)	0.168 b)	44.1 b)	0.126 b)	103.1 b)	0.294 b)
F04045	55.7	0.172	39.4	0.122	95.1	0.294	556.4	1.719	6.5	0.020	42.3	0.131	43.6	0.135	85.9	0.265
F04046	40.1	0.129	57.1	0.183	97.2	0.312	528.5	1.698	18.5	0.059	33.0	0.106	34.8	0.112	67.8	0.218
F04047	50.8	0.151	64.2	0.191	115.0	0.343	629.6	1.877	16.9	0.050	41.8	0.125	45.0	0.134	86.8	0.259
F04048	43.6	0.135	59.6	0.185	103.2	0.320	627.6	1.944	21.5	0.067	35.4	0.110	36.5	0.113	71.9	0.223
Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	48.2	0.150	51.5	0.160	99.7	0.310	583.6	1.816	16.8	0.052	37.6	0.117	39.5	0.123	77.1	0.240
S.D.	8.6	0.027	8.4	0.026	10.3	0.032	62.9	0.200	5.0	0.015	3.6	0.011	4.8	0.014	8.3	0.024
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

b) Excluded from data analysis (not pregnant).
c) 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.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 30-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	287.5	1971.1	6.856	402.8	1.401	933.1	3.246	6986.3	24.300	1052.3	3.660	1112.6	3.870	2164.9	7.530	587.3	2.043
F05050	280.0	2173.6	7.763	333.6	1.191	917.1	3.275	7299.7	26.070	950.9	3.396	931.9	3.328	1882.8	6.724	678.5	2.423
F05051	279.7	1840.3	6.580	276.3	0.988	832.2	2.975	6561.4	23.459	798.0	2.853	795.7	2.845	1593.7	5.698	521.5	1.864
F05052	290.8	1995.7	6.863	394.9	1.358	933.9	3.211	7498.9	25.787	959.2	3.298	949.7	3.266	1908.9	6.564	680.5	2.340
F05053	277.9	1908.1	6.866	257.4	0.926	841.1	3.027	6893.5	24.806	826.2	2.973	795.3	2.862	1621.5	5.835	502.9	1.810
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	283.2	1977.8	6.986	333.0	1.173	891.5	3.147	7048.0	24.884	917.3	3.236	917.0	3.234	1834.4	6.470	594.1	2.096
S.D.	5.6	125.0	0.451	66.4	0.213	50.6	0.136	364.4	1.072	104.5	0.326	131.4	0.420	234.7	0.741	84.0	0.276

Appendix 30-2-1 (continued). Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	41.9	0.146	40.3	0.140	82.2	0.286	654.8	2.278	12.9	0.045	34.9	0.121	34.3	0.119	69.2	0.241
F05050	50.4	0.180	38.5	0.138	88.9	0.318	888.5	3.173	15.2	0.054	30.5	0.109	33.7	0.120	64.2	0.229
F05051	53.0	0.189	64.6	0.231	117.6	0.420	423.7	1.515	25.6	0.092	28.0	0.100	31.7	0.113	59.7	0.213
F05052	46.1	0.159	46.5	0.160	92.6	0.318	517.3	1.779	9.3	0.032	27.2	0.094	29.2	0.100	56.4	0.194
F05053	76.4	0.275	63.9	0.230	140.3	0.505	368.8	1.327	16.3	0.059	35.5	0.128	35.1	0.126	70.6	0.254
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	53.6	0.190	50.8	0.180	104.3	0.369	570.6	2.014	15.9	0.056	31.2	0.110	32.8	0.116	64.0	0.226
S.D.	13.4	0.051	12.7	0.047	24.2	0.091	208.1	0.740	6.1	0.022	3.8	0.014	2.4	0.010	6.1	0.024

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

MMP 1000 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	292.2	1806.3	6.182	549.7	1.881	1010.4	3.458	9213.8	31.533	1020.1	3.491	986.8	3.377	2006.9	6.868	639.2	2.188
F06060	280.6	1808.5	6.445	267.8	0.954	928.7	3.310	8350.1	29.758	1048.1	3.735	1061.2	3.782	2109.3	7.517	792.3	2.824
F06061	275.7	1966.8	7.134	317.6	1.152	917.3	3.327	7210.7	26.154	1016.4	3.687	998.7	3.622	2015.1	7.309	757.5	2.748
F06062	296.3	1897.5	6.404	195.0	0.658	895.0	3.021	8031.3	27.105	1003.9	3.388	879.0	2.967	1882.9	6.355	479.7	1.619
F06063	284.3	1934.6	6.805	390.8	1.375	1020.9	3.591	8662.7	30.470	1035.0	3.641	1034.3	3.638	2069.3	7.279	637.3	2.242
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	285.8	1882.7	6.594	344.2	1.204	954.5	3.341	8293.7	29.004	1024.7	3.588	992.0	3.477	2016.7	7.066	661.2	2.324
S.D.	8.4	73.0	0.376	135.3	0.461	57.3	0.212	746.3	2.283	17.1	0.145	69.7	0.320	85.6	0.462	122.9	0.488
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	TT	AW	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.

Appendix 30-2-2 (continued). Organ weights of female rats at the end of the dosing period, satellite group

MMP 1000 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	38.8	0.133	37.6	0.129	76.4	0.261	689.8	2.361	16.8	0.057	33.4	0.114	34.7	0.119	68.1	0.233
F06060	39.4	0.140	54.5	0.194	93.9	0.335	458.5	1.634	14.7	0.052	37.0	0.132	34.9	0.124	71.9	0.256
F06061	42.8	0.155	48.8	0.177	91.6	0.332	872.3	3.164	15.4	0.056	34.2	0.124	34.4	0.125	68.6	0.249
F06062	45.3	0.153	48.0	0.162	93.3	0.315	903.1	3.048	15.3	0.052	34.5	0.116	35.1	0.118	69.6	0.235
F06063	50.3	0.177	39.6	0.139	89.9	0.316	515.8	1.814	20.7	0.073	33.9	0.119	33.1	0.116	67.0	0.236
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	43.3	0.152	45.7	0.160	89.0	0.312	687.9	2.404	16.6	0.058	34.6	0.121	34.4	0.120	69.0	0.242
S.D.	4.7	0.017	7.0	0.027	7.2	0.030	201.6	0.696	2.4	0.009	1.4	0.007	0.8	0.004	1.9	0.010
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 30-3-1. Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		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)
F05054	257.1	1902.5	7.400	222.2	0.864	776.9	3.022	6283.0	24.438	860.3	3.346	834.5	3.246	1694.8	6.592	512.1	1.992
F05055	282.3	1877.5	6.651	234.2	0.830	1005.4	3.561	7045.0	24.956	833.4	2.952	793.2	2.810	1626.6	5.762	542.1	1.920
F05056	299.4	1897.9	6.339	478.6	1.599	845.8	2.825	6303.6	21.054	863.6	2.884	855.2	2.856	1718.8	5.741	538.1	1.797
F05057	251.6	1864.4	7.410	265.2	1.054	807.3	3.209	6237.8	24.793	858.7	3.413	861.3	3.423	1720.0	6.836	436.2	1.734
F05058	322.9	2001.4	6.198	299.4	0.927	996.6	3.086	7346.0	22.750	945.3	2.928	998.6	3.093	1943.9	6.020	554.5	1.717
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	282.7	1908.7	6.800	299.9	1.055	886.4	3.141	6643.1	23.598	872.3	3.105	868.6	3.086	1740.8	6.190	516.6	1.832
S.D.	29.7	54.0	0.576	104.3	0.316	107.5	0.273	515.9	1.671	42.6	0.253	77.4	0.259	119.7	0.498	47.5	0.120

Appendix 30-3-1 (continued). Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	37.0	0.144	32.0	0.124	69.0	0.268	413.2	1.607	12.5	0.049	29.1	0.113	30.3	0.118	59.4	0.231
F05055	42.1	0.149	35.8	0.127	77.9	0.276	544.9	1.930	14.1	0.050	29.8	0.106	29.9	0.106	59.7	0.211
F05056	43.2	0.144	40.4	0.135	83.6	0.279	464.9	1.553	12.7	0.042	27.9	0.093	29.6	0.099	57.5	0.192
F05057	31.9	0.127	39.1	0.155	71.0	0.282	448.6	1.783	14.4	0.057	31.2	0.124	31.7	0.126	62.9	0.250
F05058	35.6	0.110	41.1	0.127	76.7	0.238	810.4	2.510	16.9	0.052	34.2	0.106	35.9	0.111	70.1	0.217
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	38.0	0.135	37.7	0.134	75.6	0.269	536.4	1.877	14.1	0.050	30.4	0.108	31.5	0.112	61.9	0.220
S.D.	4.7	0.016	3.8	0.013	5.8	0.018	160.6	0.384	1.8	0.005	2.4	0.011	2.6	0.010	5.0	0.022

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 30-3-2. Organ weights of female rats at the end of the recovery period

MMP 1000 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		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)
F06064	282.2	1957.0	6.935	224.6	0.796	935.4	3.315	6829.6	24.201	986.2	3.495	995.9	3.529	1982.1	7.024	603.7	2.139
F06065	309.1	1943.7	6.288	224.4	0.726	1046.5	3.386	7693.9	24.891	1026.8	3.322	961.6	3.111	1988.4	6.433	707.8	2.290
F06066	268.5	1874.7	6.982	269.3	1.003	870.2	3.241	6809.4	25.361	1070.8	3.988	985.4	3.670	2056.2	7.658	301.4	1.123
F06067	290.8	1927.2	6.627	156.7	0.539	1006.1	3.460	7119.8	24.483	983.5	3.382	946.0	3.253	1929.5	6.635	540.6	1.859
F06068	319.7	2023.4	6.329	324.1	1.014	1008.2	3.154	8030.6	25.119	1205.0	3.769	1188.2	3.717	2393.2	7.486	640.6	2.004
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	294.1	1945.2	6.632	239.8	0.816	973.3	3.311	7296.7	24.811	1054.5	3.591	1015.4	3.456	2069.9	7.047	558.8	1.883
S.D.	20.5	53.7	0.326	61.9	0.200	70.2	0.120	543.9	0.470	91.4	0.280	98.6	0.264	186.3	0.528	156.1	0.454
Significance	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	AW	AW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Appendix 30-3-2 (continued). Organ weights of female rats at the end of the recovery period

MMP 1000 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06064	42.7	0.151	43.5	0.154	86.2	0.305	414.4	1.468	24.8	0.088	29.6	0.105	32.7	0.116	62.3	0.221
F06065	51.8	0.168	54.5	0.176	106.3	0.344	1022.6	3.308	12.9	0.042	29.7	0.096	31.8	0.103	61.5	0.199
F06066	42.8	0.159	44.0	0.164	86.8	0.323	543.0	2.022	12.8	0.048	33.0	0.123	29.1	0.108	62.1	0.231
F06067	41.1	0.141	51.8	0.178	92.9	0.319	448.2	1.541	12.4	0.043	29.9	0.103	29.8	0.102	59.7	0.205
F06068	43.7	0.137	48.4	0.151	92.1	0.288	489.4	1.531	17.2	0.054	36.6	0.114	37.7	0.118	74.3	0.232
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	44.4	0.151	48.4	0.165	92.9	0.316	583.5	1.974	16.0	0.055	31.8	0.108	32.2	0.109	64.0	0.218
S.D.	4.2	0.013	4.8	0.012	8.1	0.021	250.1	0.778	5.3	0.019	3.1	0.010	3.4	0.007	5.9	0.015
Significance	NS	NS	**	**	**	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	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 Methyl 3-methoxypropanoate by oral administration in rats

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

Findings	Group	Control (vehicle: water for injection)							MMP 62.5 mg/kg												MMP 250 mg/kg												MMP 1000 mg/kg						
	Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043
Kidney																																							
Enlargement, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-
Liver																																							
Diaphragmatic nodule		-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Whitish spot		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-
Stomach																																							
Edematous, mucosa, dark colored area, forestomach		-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tooth																																							
Defect, upper central incisor, left		-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal changes P: Non-graded change

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)					MMP 1000 mg/kg				
Findings / Animal No.	M01008	M01009	M01010	M01011	M01012	M04044	M04045	M04046	M04047	M04048
Skin										
Crust, dorsal neck	-	-	-	-	-	-	P	-	-	-
Stomach										
Edematous, mucosa, forestomach	-	-	-	-	-	-	-	-	P	-
Thickening, mucosa, forestomach	-	-	-	-	-	-	-	-	P	-

- : No abnormal changes P : Non-graded change

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Findings	Group	Control (vehicle: water for injection)											
	Animal No.	F01 001	F01 002	F01 003	F01 004	F01 005	F01 006	F01 007	F01 008	F01 009	F01 010	F01 011	F01 012
	Fate												
Kidney													
Discoloration, pale colored, bilateral		-	-	-	-	-	-	-	-	-	-	-	-
Spleen													
Enlargement		-	-	-	-	-	-	-	-	-	-	-	-
Small		-	-	-	-	-	-	-	-	-	-	-	-
Stomach													
Dark colored spot/area, mucosa, glandular stomach		-	-	-	-	-	-	-	-	P	-	-	-
Thymus													
Small		-	-	-	-	-	-	-	-	-	-	-	-
Uterus													
Remnant, dead fetus, right horn		-	-	-	-	-	-	-	-	-	-	-	-

Findings	Group	MMP 62.5 mg/kg											
	Animal No.	F02 013	F02 014	F02 015	F02 016	F02 017	F02 018	F02 019	F02 020	F02 021	F02 022	F02 023	F02 024
	Fate												
Kidney													
Discoloration, pale colored, bilateral		-	-	-	-	-	-	-	-	-	-	-	-
Spleen													
Enlargement		-	-	-	-	-	-	-	-	-	-	-	-
Small		-	-	-	-	-	-	-	-	-	-	-	-
Stomach													
Dark colored spot/area, mucosa, glandular stomach		-	-	-	-	-	-	-	-	P	-	-	-
Thymus													
Small		-	-	-	-	-	-	-	-	-	-	-	-
Uterus													
Remnant, dead fetus, right horn		-	-	-	-	-	-	-	-	-	-	-	-

Findings	Group	MMP 250 mg/kg											
	Animal No.	F03 025	F03 026	F03 027	F03 028	F03 029	F03 030	F03 031	F03 032	F03 033	F03 034	F03 035	F03 036
	Fate						ND						
Kidney													
Discoloration, pale colored, bilateral		-	-	-	-	-	-	-	-	-	-	-	-
Spleen													
Enlargement		-	-	-	-	-	-	-	-	-	-	-	-
Small		-	-	-	-	-	P	-	-	-	-	-	-
Stomach													
Dark colored spot/area, mucosa, glandular stomach		-	-	-	-	-	-	-	-	-	-	-	-
Thymus													
Small		-	-	-	-	-	-	-	-	-	-	-	-
Uterus													
Remnant, dead fetus, right horn		-	-	-	-	-	P	-	-	-	-	-	-

Findings	Group	MMP 1000 mg/kg											
	Animal No.	F04 037	F04 038	F04 039	F04 040	F04 041	F04 042	F04 043	F04 044	F04 045	F04 046	F04 047	F04 048
	Fate	NP						TL	NP				
Kidney													
Discoloration, pale colored, bilateral		-	-	-	-	-	-	P	-	-	-	-	-
Spleen													
Enlargement		-	-	-	-	-	-	P	-	-	-	-	-
Small		-	-	-	-	-	-	-	-	-	-	-	-
Stomach													
Dark colored spot/area, mucosa, glandular stomach		-	-	-	-	-	-	-	-	-	-	-	-
Thymus													
Small		-	-	-	-	P	-	P	-	-	-	-	-
Uterus													
Remnant, dead fetus, right horn		-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

Fate : blanks, Subjected to autopsy on day 5 of lactation; ND, Not delivery; NP, Not pregnant; TL, Total litter loss

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)					MMP 1000 mg/kg				
Findings / Animal No.	F05049	F05050	F05051	F05052	F05053	F06059	F06060	F06061	F06062	F06063
Pituitary gland										
Cyst	-	-	-	-	-	P	-	-	-	-
Stomach										
Dark colored spot, mucosa glandular stomach	-	-	-	-	-	-	-	-	P	-

- : No abnormal changes P : Non-graded change

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

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

Group	Control (vehicle: water for injection)					MMP 1000 mg/kg				
Findings / Animal No.	F05054	F05055	F05056	F05057	F05058	F06064	F06065	F06066	F06067	F06068
Skin										
Crust, dorsal neck	-	-	-	-	-	-	-	-	-	P
Spleen										
Small	-	-	-	-	-	-	-	P	-	-
Stomach										
Elevated area, whitish, mucosa, glandular stomach	-	-	-	P	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 33-1. Histopathological findings of male rats at the end of the dosing period [H.E. staining]

Group	Control (vehicle: water for injection)						MMP 1000 mg/kg				
Findings / Animal No.	M01001	M01002	M01003	M01004	M01005	M01006	M04037	M04038	M04039	M04040	M04041
Brain		NE									
	-		-	-	-	-	-	-	-	-	-
Spinal cord		NE									
	-		-	-	-	-	-	-	-	-	-
Pituitary gland		NE									
Cyst	-		-	-	-	P	-	-	-	-	-
Submandibular gland		NE									
	-		-	-	-	-	-	-	-	-	-
Sublingual gland		NE									
	-		-	-	-	-	-	-	-	-	-
Lymph node, submandibular		NE									
	-		-	-	-	-	-	-	-	-	-
Thyroid gland		NE									
	-		-	-	-	-	-	-	-	-	-
Parathyroid gland		NE									
	-		-	-	-	-	-	-	-	-	-
Thymus		NE									
	-		-	-	-	-	-	-	-	-	-
Heart		NE									
Fibrosis, myocardial, left ventlicle	-		-	-	±	-	-	-	-	-	-
Trachea		NE									
	-		-	-	-	-	-	-	-	-	-
Lung		NE									
Cellular infiltration, foam cell, alveolus	-		-	-	±	-	-	-	±	±	±
Microgranuloma	-		-	±	±	-	±	±	-	-	-
Mineralization, arterial wall	-		-	-	-	-	-	-	±	-	±
Bronchus		NE									
	-		-	-	-	-	-	-	-	-	-
Liver		NE									
Fibrosis, focal, subcapsule	-		-	-	-	-	-	-	±	-	-
Microgranuloma	±		-	±	-	±	±	±	±	±	-
Nodule, hepatodiaphragmatic	-		P	-	-	-	-	-	-	-	-
Pancreas		NE									
Atrophy, acinar cell, focal	-		-	-	-	-	-	-	-	-	±
Stomach											
Cellular infiltration, inflammatory, submucosa, fore/ glandular stomach	-	±[a)]	-	-	-	-	-	-	±[b)]	-	-
Dilatation, cystic, fundic gland, glandular stomach	-	-	-	-	-	-	±	-	-	-	-
Edema, submucosa, glandular stomach	-	-	-	-	-	-	-	-	±	-	-
Ulcer, submucosa, forestomach	-	±	-	-	-	-	-	-	-	-	-
Duodenum		NE									
	-		-	-	-	-	-	-	-	-	-
Jejunum		NE									
	-		-	-	-	-	-	-	-	-	-

-: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P: Non-graded change NE: Not examined M: Missing A: Autolysis
a): forestomach; b): glandular stomach

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 33-1 (continued). Histopathological findings of male rats at the end of the dosing period [H.E. staining]

Group	Control (vehicle: water for injection)						MMP 1000 mg/kg				
Findings / Animal No.	M01001	M01002	M01003	M01004	M01005	M01006	M04037	M04038	M04039	M04040	M04041
Ileum		NE									
	-		-	-	-	-	-	-	-	-	-
Cecum		NE									
	-		-	-	-	-	-	-	-	-	-
Colon		NE									
	-		-	-	-	-	-	-	-	-	-
Rectum		NE									
	-		-	-	-	-	-	-	-	-	-
Lymph node, mesenteric		NE									
	-		-	-	-	-	-	-	-	-	-
Spleen		NE									
Deposit, pigment, brown	+		+	±	+	±	±	+	+	+	+
Hematopoiesis, extramedullary	+		+	+	2+	+	+	+	2+	+	+
Kidney		NE									
Basophilic tubule, cortex	-		-	-	±	±	±	+	±	-	-
Cellular infiltration, lymphocyte, interstitial	-		-	-	±	±	-	-	±	-	-
Fibrosis, focal, subcapsule	-		-	-	-	-	-	-	-	±	-
Urinary bladder		NE									
	-		-	-	-	-	-	-	-	-	-
Adrenal gland		NE									
	-		-	-	-	-	-	-	-	-	-
Testis		NE									
Atrophy, seminiferous tubule	-		-	±	-	±	-	-	-	-	-
Epididymis		NE									
Cell debris, lumen	-		-	±	-	-	-	-	-	-	-
Cellular infiltration, lymphocyte, interstitial	±		-	-	-	-	±	-	-	-	-
Prostate		NE									
Cellular infiltration, lymphocyte, interstitial	-		-	-	-	-	±	-	±	-	-
Seminal vesicle		NE									
	-		-	-	-	-	-	-	-	-	-
Coagulating gland		NE									
	-		-	-	-	-	-	-	-	-	-
Eyeball		NE									
	-		-	-	-	-	-	-	-	-	-
Harderian gland		NE									
Cellular infiltration, lymphocyte, interstitial	-		-	-	-	-	-	±	±	-	-
Sciatic nerve		NE									
	-		-	-	-	-	-	-	-	-	-
Skeletal muscle		NE									
	-		-	-	-	-	-	-	-	-	-
Femur		NE									
	-		-	-	-	-	-	-	-	-	-
Marrow, femur		NE									
	-		-	-	-	-	-	-	-	-	-

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 33-2. Histopathological findings of male rats at the end of the recovery period [H.E. staining]

Findings	Group	Control (vehicle: water for injection)					MMP 1000 mg/kg				
	Animal No.	M01008	M01009	M01010	M01011	M01012	M04044	M04045	M04046	M04047	M04048
Stomach		NE	NE	NE	NE	NE	NE	NE	NE		NE
Edema, submucosa, forestomach										±	
Hyperplasia, squamous cell, forestomach										±	

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 34-1. Histopathological findings of female rats at the end of the dosing period [H.E. staining]

Group	Control (vehicle: water for injection)						MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg					
Findings / Animal No.	F01005	F01007	F01008	F01009	F01010	F01012	F02021	F03030	F04041	F04042	F04043	F04045	F04047	F04048
Brain	-	-	-	NE	-	-			-	-	NE	-	-	-
Spinal cord	-	-	-	NE	-	-			-	-	NE	-	-	-
Pituitary gland				NE							NE			
Cyst	-	-	-		P	-			-	-		-	-	-
Submandibular gland	-	-	-	NE	-	-			-	-	NE	-	-	-
Sublingual gland	-	-	-	NE	-	-			-	-	NE	-	-	-
Lymph node, submandibular	-	-	-	NE	-	-			-	-	NE	-	-	-
Thyroid gland				NE							NE			
Ultimobranchial body	-	-	-		-	-			-	-		P	P	-
Parathyroid gland	-	-	-	NE	-	-			-	-	NE	-	-	-
Thymus				NE										
Atrophy	-	-	-		-	-			-	-	2+	-	-	-
Heart				NE							NE			
Fibrosis, myocardial, left ventricle	-	-	-		-	-			-	-		±	-	-
Trachea	-	-	-	NE	-	-			-	-	NE	-	-	-
Lung				NE							NE			
Cellular infiltration, foam cell, alveolus	±	±	-		-	±			-	±		±	±	-
Microgranuloma	-	-	-		±	-			-	-		-	-	-
Bronchus	-	-	-	NE	-	-			-	-	NE	-	-	-
Liver				NE							NE			
Fatty change, hepatocyte, periportal	-	±	+		-	-			-	-		±	-	-
Hematopoiesis, extramedullary	-	-	-		±	-			-	-		-	-	±
Microgranuloma	-	-	±		-	±			±	±		-	±	-
Necrosis, focal	-	±	-		-	-			-	-		-	-	-
Pancreas				NE							NE			
Atrophy, acinar cell, focal	-	-	-		-	±			-	-		-	-	-
Stomach											NE			
Dilatation, cystic, fundic gland, glandular stomach	-	-	-	±	-	-	±		-	±		-	-	-
Edema, submucosa, glandular stomach	-	-	-	±	-	±	±		-	-		-	-	-
Duodenum	-	-	-	NE	-	-			-	-	NE	-	-	-
Jejunum	-	-	-	NE	-	-			-	-	NE	-	-	-

-: 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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 34-1 (continued). Histopathological findings of female rats at the end of the dosing period [H.E. staining]

Group	Control (vehicle: water for injection)						MMP 62.5 mg/kg	MMP 250 mg/kg	MMP 1000 mg/kg					
Findings / Animal No.	F01005	F01007	F01008	F01009	F01010	F01012	F02021	F03030	F04041	F04042	F04043	F04045	F04047	F04048
Ileum				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Cecum				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Colon				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Rectum				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Lymph node, mesenteric				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Spleen				NE										
Deposit, pigment, brown	±	+	+		±	+		+	+	+	+	±	+	±
Hematopoiesis, extramedullary	+	+	2+		2+	2+		2+	2+	2+	3+	+	2+	2+
Kidney				NE										
Basophilic tubule, cortex	-	-	-		-	-			±	-	±	-	-	-
Cellular infiltration, lymphocyte, interstitial	-	-	-		-	-			-	±	±	-	-	-
Degeneration/necrosis, cortex, proximal tubule	-	-	-		-	-			-	-	+	-	-	-
Dilatation, lumen, focal, distal tubule	-	-	-		-	-			-	-	+	-	-	-
Mineralization, cortico-medullary junction	-	-	-		-	-			-	-	-	±	-	-
Urinary bladder				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Adrenal gland				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Ovary				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Uterus				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Vagina				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Eyeball				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Harderian gland				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Sciatic nerve				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Skeletal muscle				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Femur				NE							NE			
	-	-	-		-	-			-	-		-	-	-
Marrow, femur				NE							NE			
	-	-	-		-	-			-	-		-	-	-

-: 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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 34-2. Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Group	Control (vehicle: water for injection)					MMP 1000 mg/kg				
Findings / Animal No.	F05049	F05050	F05051	F05052	F05053	F06059	F06060	F06061	F06062	F06063
Brain	-	-	-	-	-	-	-	-	-	-
Spinal cord	-	-	-	-	-	-	-	-	-	-
Pituitary gland										
Cyst	-	P	-	-	-	P	-	-	-	-
Submandibular gland	-	-	-	-	-	-	-	-	-	-
Sublingual gland	-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular	-	-	-	-	-	-	-	-	-	-
Thyroid gland										
Ultimobranchial body	-	-	P	-	-	-	-	-	-	-
Parathyroid gland	-	-	-	-	-	-	M	-	-	-
Thymus	-	-	-	-	-	-	-	-	-	-
Heart	-	-	-	-	-	-	-	-	-	-
Trachea	-	-	-	-	-	-	-	-	-	-
Lung										
Cellular infiltration, foam cell, alveolus	±	±	-	-	-	±	±	±	±	-
Micorgranuloma	-	-	-	-	-	±	-	±	-	-
Bronchus	-	-	-	-	-	-	-	-	-	-
Liver										
Fatty change, hepatocyte, periportal	-	-	-	-	-	-	±	-	-	±
Hematopoiesis, extramedullary	-	-	-	-	-	-	-	-	-	±
Microgranuloma	±	-	±	±	±	±	±	±	±	±
Pancreas	-	-	-	-	-	-	-	-	-	-
Stomach										
Dilatation, cystic, fundic gland, glandular stomach	-	-	-	±	-	-	-	-	±	-
Edema, submucosa, glandular stomach	±	±	-	-	-	-	-	-	-	-
Duodenum	-	-	-	-	-	-	-	-	-	-
Jejunum	-	-	-	-	-	-	-	-	-	-

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 34-2 (continued). Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Group	Control (vehicle: water for injection)					MMP 1000 mg/kg				
Findings / Animal No.	F05049	F05050	F05051	F05052	F05053	F06059	F06060	F06061	F06062	F06063
Ileum	-	-	-	-	-	-	-	-	-	-
Cecum	-	-	-	-	-	-	-	-	-	-
Colon	-	-	-	-	-	-	-	-	-	-
Rectum	-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric	-	-	-	-	-	-	-	-	-	-
Spleen										
Deposit, pigment, brown	+	+	+	+	+	+	±	+	+	+
Hematopoiesis, extramedullary	+	+	2+	+	2+	2+	+	+	+	2+
Kidney										
Basophilic tubule, cortex	-	-	-	-	±	-	±	±	±	±
Cellular infiltration, lymphocyte, interstitial	-	±	-	-	-	±	-	±	±	-
Cyst/ hyalin, cast, papilla/ cortico-medullary junction	-	-	-	-	-	P a),b)	P b)	P c)	-	-
Mineralization, papilla/ cortico-medually junction	-	-	-	-	-	-	± b)	± c)	-	+ b)
Urinary bladder	-	-	-	-	-	-	-	-	-	-
Adrenal gland	-	-	-	-	-	-	-	-	-	-
Ovary	-	-	-	-	-	-	-	-	-	-
Uterus	-	-	-	-	-	-	-	-	-	-
Vagina	-	-	-	-	-	-	-	-	-	-
Eyeball	-	-	-	-	-	-	-	-	-	-
Harderian gland										
Cellular infiltration, lymphocyte, interstitial	-	-	-	-	-	±	-	-	-	-
Sciatic nerve	-	-	-	-	-	-	-	-	-	-
Skeletal muscle	-	-	-	-	-	-	-	-	-	-
Femur	-	-	-	-	-	-	-	-	-	-
Marrow, femur	-	-	-	-	-	-	-	-	-	-

-: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P: Non-graded change NE: Not examined M: Missing A: Autolysis
a): hyalin, cast; b): cortico-medullary junction; c): papilla

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 34-3. Histopathological findings of female rats at the end of the recovery period [H.E. staining]

Group	Control (vehicle: water for injection)					MMP 1000 mg/kg				
Findings / Animal No.	F05054	F05055	F05056	F05057	F05058	F06064	F06065	F06066	F06067	F06068
Stomach	NE	NE	NE		NE	NE	NE	NE	NE	NE
				-						
Kidney										
Basophilic tubule, cortex	-	-	±	-	-	-	-	-	-	-
Cellular infiltration, lymphocyte, interstitial	-	-	-	-	±	±	-	-	-	-
Cyst, cortico-medullary junction	-	-	P	-	-	-	-	-	-	-
Mineralization, cortico-medullary junction	-	-	-	-	-	-	-	-	-	±

- : 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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 35-1. Results of observations about estrous cycle

Control (vehicle: water for injection)

Animal No.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F01001	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 P E D D D E	4-day	4.0	D D P PL	1
F01002	E D D P E D D P E D D D E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F01003	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 D P E D	4/5-day	4.5	D P PL	1
F01004	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F01005	D D D E D D D E D D D E D	4-day	4.0	D D E D D D E D D D E D D D	4-day	4.0	PL	1
F01006	D D D E E D D D P E D D D	5-day	5.0	E D D D E D D P E D D P E D	4-day	4.0	D P PL	1
F01007	D D D E D D D E D D D E D	4-day	4.0	D P E D D P E D D D E D D D	4-day	4.0	PL	1
F01008	D D D E D D D E D D D E D	4-day	4.0	D P E D D P E D D P E D D D	4-day	4.0	PL	1
F01009	D E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F01010	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F01011	P E D D P 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	4-day	4.0	D P PL	1
F01012	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
Mean			4.1			4.0		1.0
S.D.			0.3			0.1		0.0
(N)			(12)			(12)		(12)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 35-2. Results of observations about estrous cycle

MMP 62.5 mg/kg

Animal No.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F02013	D E D D P E D D D E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F02014	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 D E D D P	4-day	4.0	PL	1
F02015	D E D D D E D D P E D D P	4-day	4.0	E D D P E D D D E D D D E D	4-day	4.0	D P PL	1
F02016	E D D D E D D P E D D D E	4-day	4.0	D D P E D D P E D D D E D D	4-day	4.0	P PL	1
F02017	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 P	4-day	4.0	PL	1
F02018	P E D D D E D D P E D D P	4-day	4.0	E D D D E D D P E D D P E D	4-day	4.0	D P PL	1
F02019	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 P P E D D P	4/5-day	4.5	D D P PL	1
F02020	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F02021	D D E D D D E D D D E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1
F02022	D P E D D D P E D D D P E	5-day	5.0	D D D E E D D P E E D D P E	4/5-day	4.5	D D D PL	1
F02023	E D D D P E D D D P E D D	5-day	5.0	P E E D D P P E D D D P E D	5-day	5.0	D P P PL	1
F02024	D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	PL	1
Mean			4.2			4.2		1.0
S.D.			0.4			0.3		0.0
(N)			(12)			(12)		(12)

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 35-3. Results of observations about estrous cycle

MMP 250 mg/kg

Animal No.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F03025	E D D D E D D D D E D D P	4/5-day	4.5	E D D P E D D P E D D D E D	4-day	4.0	D P PL	1
F03026	E D D D E D D P E D D D E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03027	E D D P E D D P E D D D E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03028	E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03029	E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03030	P E D D D E D D D E D D P	4-day	4.0	E D D P E E D D P E E D D D	5-day	5.0	PL	1
F03031	E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03032	D D P E D D D E E D D D E	4/5-day	4.5	D D D E D D P E D D P E D D	4-day	4.0	P PL	1
F03033	P E D D P E D D D E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F03034	D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F03035	D D D P E D D D E D D D E	4-day	4.0	D D D E D D D E D D D E D D	4-day	4.0	D PL	1
F03036	E D D D E D D D E D D D E	4-day	4.0	D D D E D D D E D D D E D D	4-day	4.0	D PL	1
Mean			4.1			4.1		1.0
S.D.			0.2			0.3		0.0
(N)			(12)			(12)		(12)

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 35-4. Results of observations about estrous cycle

MMP 1000 mg/kg

Animal No.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F04037	D D E D D D E D D P E D D	4-day	4.0	P E D D D P E D D D P E D D	5-day	5.0	D P PL	1
F04038	D D D P E D D D E E D D D	5-day	5.0	P E D D P P E D D P E E D D	5-day	5.0	D PL	1
F04039	D D E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1
F04040	P E D D P E D D D E D D P	4-day	4.0	E D D D E D D P E D D D E D	4-day	4.0	D P PL	1
F04041	D D P E D D D E D D D E D	4-day	4.0	D D E D D D E D D D P E D D	4/5-day	4.5	P PL	1
F04042	D E D D P E D D D E D D D	4-day	4.0	E D D D E D D P E D D D E D	4-day	4.0	D D PL	1
F04043	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 D E D D D	4-day	4.0	PL	1
F04044	D D P E D D P E D D P E D	4-day	4.0	D P E E D D D E E D D D E E	5-day	5.0	D D D D D D D D D D D D D PL	1
F04045	D D P E D D P E D D D E D	4-day	4.0	D D E D D P E D D D E D D D	4-day	4.0	PL	1
F04046	E D D D P E D D D P E D D	5-day	5.0	D P E D D D P E D D D P E D	5-day	5.0	D D PL	1
F04047	D D D E D D D E E D D D P	5-day	5.0	E D D D P E D D D P E D D D	5-day	5.0	P PL	1
F04048	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E E D D D E E D	5-day	5.0	D P PL	1
Mean			4.3			4.5 **		1.0
S.D.			0.5			0.5		0.0
(N)			(12)			(12)		(12)

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 36-1. Results of observations about reproductive performance

Control (vehicle: water for injection)

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M01001	F01001	+	+	4
M01002	F01002	+	+	2
M01003	F01003	+	+	3
M01004	F01004	+	+	1
M01005	F01005	+	+	1
M01006	F01006	+	+	3
M01007	F01007	+	+	1
M01008	F01008	+	+	1
M01009	F01009	+	+	3
M01010	F01010	+	+	1
M01011	F01011	+	+	3
M01012	F01012	+	+	1
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.0
S.D.				1.1
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 36-2. Results of observations about reproductive performance

MMP 62.5 mg/kg

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M02013	F02013	+	+	3
M02014	F02014	+	+	1
M02015	F02015	+	+	3
M02016	F02016	+	+	2
M02017	F02017	+	+	1
M02018	F02018	+	+	3
M02019	F02019	+	+	4
M02020	F02020	+	+	1
M02021	F02021	+	+	4
M02022	F02022	+	+	4
M02023	F02023	+	+	4
M02024	F02024	+	+	1
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.6
S.D.				1.3
(N)				(12)

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

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 36-3. Results of observations about reproductive performance

MMP 250 mg/kg

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M03025	F03025	+	+	3
M03026	F03026	+	+	2
M03027	F03027	+	+	2
M03028	F03028	+	+	2
M03029	F03029	+	+	2
M03030	F03030	+	+	1
M03031	F03031	+	+	2
M03032	F03032	+	+	2
M03033	F03033	+	+	3
M03034	F03034	+	+	4
M03035	F03035	+	+	2
M03036	F03036	+	+	2
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.3
S.D.				0.8
(N)				(12)

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

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 36-4. Results of observations about reproductive performance

MMP 1000 mg/kg

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M04037	F04037	+	+	3
M04038	F04038	+	-	2
M04039	F04039	+	+	4
M04040	F04040	+	+	3
M04041	F04041	+	+	2
M04042	F04042	+	+	3
M04043	F04043	+	+	1
M04044	F04044	+	-	14
M04045	F04045	+	+	1
M04046	F04046	+	+	3
M04047	F04047	+	+	2
M04048	F04048	+	+	3
Total		+: 12, -: 0	+: 10, -: 2	
Mean				3.4
S.D.				3.4
(N)				(12)

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

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 37-1. Observation of offspring (F_1)

Control (vehicle: water for injection)

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities [b] (Number)	(%)
F01001	22	18	18	100.0	+	18	8	10	18	0.44	0	100.0	100.0	100.0	7	10	0.41	94.4	0	0.0
F01002	22	14	14	100.0	+	14	5	9	14	0.36	0	100.0	100.0	100.0	5	9	0.36	100.0	0	0.0
F01003	22	19	19	100.0	+	17	9	7	16	0.56	1	89.5	84.2	94.1	9	6	0.60	93.8	0	0.0
F01004	23	19	19	100.0	+	18	8	9	17	0.47	1	94.7	89.5	94.4	8	9	0.47	100.0	0	0.0
F01005	22	16	16	100.0	+	16	5	11	16	0.31	0	100.0	100.0	100.0	5	11	0.31	100.0	0	0.0
F01006	22	18	18	100.0	+	18	11	7	18	0.61	0	100.0	100.0	100.0	11	7	0.61	100.0	0	0.0
F01007	22	17	17	100.0	+	17	7	10	17	0.41	0	100.0	100.0	100.0	7	10	0.41	100.0	0	0.0
F01008	22	15	15	100.0	+	15	9	5	14	0.64	1	100.0	93.3	93.3	1	2	0.33	21.4	0	0.0
F01009	22	16	16	100.0	+	15	7	7	14	0.50	1	93.8	87.5	93.3	7	7	0.50	100.0	0	0.0
F01010	22	14	14	100.0	+	13	10	3	13	0.77	0	92.9	92.9	100.0	10	3	0.77	100.0	0	0.0
F01011	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
F01012	22	17	17	100.0	+	14	8	6	14	0.57	0	82.4	82.4	100.0	8	6	0.57	100.0	0	0.0
Number of dams	12	12	12	12	12 [a]	12			12	12	12	12	12	12			12	12	12	12
Total		198	198			190	93	93	186		4				84	89			0	
Mean	22.1	16.5	16.5	100.0		15.8	7.8	7.8	15.5	0.50	0.3	96.1	94.2	97.9	7.0	7.4	0.48	92.5		0.0
S.D.	0.3	1.8	1.8	0.0		1.7	1.9	2.3	1.7	0.13	0.5	5.7	6.8	3.1	2.6	2.8	0.14	22.5		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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 37-2. Observation of offspring (F_1)

MMP 62.5 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan-tation scars	Implan-tation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities b) (Number)	(%)
F02013	22	15	15	100.0	+	14	6	8	14	0.43	0	93.3	93.3	100.0	6	8	0.43	100.0	0	0.0
F02014	22	15	15	100.0	+	14	4	10	14	0.29	0	93.3	93.3	100.0	4	10	0.29	100.0	0	0.0
F02015	22	17	17	100.0	+	14	9	3	12	0.75	2	82.4	70.6	85.7	9	3	0.75	100.0	0	0.0
F02016	22	15	15	100.0	+	15	2	13	15	0.13	0	100.0	100.0	100.0	2	13	0.13	100.0	0	0.0
F02017	22	16	16	100.0	+	16	7	7	14	0.50	2	100.0	87.5	87.5	7	7	0.50	100.0	0	0.0
F02018	22	19	18	94.7	+	18	10	8	18	0.56	0	100.0	100.0	100.0	10	8	0.56	100.0	0	0.0
F02019	22	15	15	100.0	+	14	8	6	14	0.57	0	93.3	93.3	100.0	8	6	0.57	100.0	0	0.0
F02020	22	16	16	100.0	+	15	7	8	15	0.47	0	93.8	93.8	100.0	7	8	0.47	100.0	0	0.0
F02021	22	15	14	93.3	+	14	8	6	14	0.57	0	100.0	100.0	100.0	8	6	0.57	100.0	0	0.0
F02022	22	21	20	95.2	+	20	13	7	20	0.65	0	100.0	100.0	100.0	13	7	0.65	100.0	0	0.0
F02023	22	17	17	100.0	+	12	7	5	12	0.58	0	70.6	70.6	100.0	7	5	0.58	100.0	0	0.0
F02024	22	15	15	100.0	+	12	5	7	12	0.42	0	80.0	80.0	100.0	5	7	0.42	100.0	0	0.0
Number of dams	12	12	12	12	12 a)	12			12	12	12	12	12	12			12	12	12	12
Total		196	193			178	86	88	174		4				86	88			0	
Mean	22.0	16.3	16.1	98.6		14.8	7.2	7.3	14.5	0.49	0.3	92.2	90.2	97.8	7.2	7.3	0.49	100.0		0.0
S.D.	0.0	1.9	1.7	2.6		2.3	2.9	2.5	2.4	0.16	0.8	9.6	10.9	5.2	2.9	2.5	0.16	0.0		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	DU	AN	KW	KW	KW	DU	AN	AN	DU	AN	KW	AN	KW	KW	AN	AN	AN	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.

DU: Analysis by Dunnett's test.

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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 37-3. Observation of offspring (F_1)

MMP 250 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan-tation scars	Implan-tation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities b) (Number)	(%)
F03025	22	16	16	100.0	+	15	6	9	15	0.40	0	93.8	93.8	100.0	6	9	0.40	100.0	0	0.0
F03026	22	16	16	100.0	+	16	11	5	16	0.69	0	100.0	100.0	100.0	11	4	0.73	93.8	0	0.0
F03027	22	16	16	100.0	+	14	10	4	14	0.71	0	87.5	87.5	100.0	10	4	0.71	100.0	0	0.0
F03028	22	16	16	100.0	+	16	7	7	14	0.50	2	100.0	87.5	87.5	7	7	0.50	100.0	0	0.0
F03029	22	16	16	100.0	+	16	6	10	16	0.38	0	100.0	100.0	100.0	5	10	0.33	93.8	0	0.0
F03030	-	6	1	16.7	-	Not delivery, dead fetal remnant														
F03031	22	16	16	100.0	+	14	6	8	14	0.43	0	87.5	87.5	100.0	6	8	0.43	100.0	0	0.0
F03032	22	17	16	94.1	+	15	7	8	15	0.47	0	93.8	93.8	100.0	7	8	0.47	100.0	0	0.0
F03033	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
F03034	22	19	19	100.0	+	18	9	9	18	0.50	0	94.7	94.7	100.0	9	7	0.56	88.9	0	0.0
F03035	22	15	15	100.0	+	15	7	7	14	0.50	1	100.0	93.3	93.3	7	7	0.50	100.0	0	0.0
F03036	22	15	15	100.0	+	13	4	8	12	0.33	1	86.7	80.0	92.3	4	8	0.33	100.0	0	0.0
Number of dams	11	12	12	12	11 a)	11			11	11	11	11	11	11			11	11	11	11
Total		183	177			166	80	82	162		4				79	79			0	
Mean	22.0	15.3	14.8	92.6		15.1	7.3	7.5	14.7	0.49	0.4	94.3	91.9	97.6	7.2	7.2	0.50	97.9		0.0
S.D.	0.0	3.1	4.5	24.0		1.4	2.0	1.8	1.6	0.12	0.7	5.3	5.9	4.4	2.1	1.8	0.13	3.9		0.0
%					91.7															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	DU	AN	KW	KW	KW	DU	AN	AN	DU	AN	KW	AN	KW	KW	AN	AN	AN	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.

DU: Analysis by Dunnett's test.

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 Methyl 3-methoxypropanoate by oral administration in rats

Appendix 37-4. Observation of offspring (F_1)

MMP 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: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities b) (Number)	(%)
F04037	23	15	15	100.0	+	11	5	6	11	0.45	0	73.3	73.3	100.0	5	6	0.45	100.0	0	0.0
F04038	Not pregnant																			
F04039	22	16	15	93.8	+	14	10	4	14	0.71	0	93.3	93.3	100.0	10	4	0.71	100.0	0	0.0
F04040	23	18	16	88.9	+	14	5	9	14	0.36	0	87.5	87.5	100.0	5	9	0.36	100.0	0	0.0
F04041	22	14	14	100.0	+	14	4	10	14	0.29	0	100.0	100.0	100.0	4	10	0.29	100.0	0	0.0
F04042	22	18	17	94.4	+	17	8	9	17	0.47	0	100.0	100.0	100.0	7	8	0.47	88.2	0	0.0
F04043	23	14	14	100.0	+	12	2	4	6	0.33	6	85.7	42.9	50.0	0	0 c)		0.0	0	0.0
F04044	Not pregnant																			
F04045	23	15	13	86.7	+	13	4	8	12	0.33	1	100.0	92.3	92.3	4	8	0.33	100.0	0	0.0
F04046	23	15	15	100.0	+	12	6	5	11	0.55	1	80.0	73.3	91.7	3	3	0.50	54.5	0	0.0
F04047	22	15	15	100.0	+	14	7	7	14	0.50	0	93.3	93.3	100.0	6	6	0.50	85.7	0	0.0
F04048	22	15	15	100.0	+	14	6	7	13	0.46	1	93.3	86.7	92.9	6	7	0.46	100.0	0	0.0
Number of dams	10	10	10	10	10 a)	10			10	10	10	10	10	10			9	10	10	10
Total		155	149			135	57	69	126		9				50	61			0	
Mean	22.5	15.5	14.9	96.4		13.5	5.7	6.9	12.6	0.45	0.9	90.6	84.3	92.7	5.0	6.1	0.45	82.8		0.0
S.D.	0.5	1.4	1.1	5.2		1.6	2.3	2.1	2.9	0.13	1.9	9.0	17.3	15.4	2.6	3.0	0.12	32.4		0.0
%					100.0															
Significance	**	NS	NS	NS	NS	*	NS	NS	**	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	DU	AN	KW	KW	KW	DU	AN	AN	DU	AN	KW	AN	KW	KW	AN	AN	AN	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 lactational day 4.

Significantly different from control (vehicle: water for injection) (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 38-1. Body weights of offspring (F_1) before weaning

Control (vehicle: water for injection)

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F01001	6.0	(8)	9.7	(7)	6.2	(10)	9.3	(10)
F01002	6.5	(5)	10.0	(5)	6.0	(9)	9.6	(9)
F01003	6.4	(9)	10.1	(9)	6.0	(7)	9.2	(6)
F01004	6.9	(8)	9.9	(8)	6.8	(9)	10.0	(9)
F01005	6.7	(5)	8.9	(5)	6.5	(11)	9.1	(11)
F01006	5.9	(11)	9.0	(11)	5.6	(7)	8.1	(7)
F01007	6.4	(7)	9.0	(7)	6.4	(10)	8.5	(10)
F01008	6.8	(9)	6.3	(2)	6.5	(5)	5.9	(3)
F01009	6.8	(7)	11.5	(7)	6.4	(7)	10.4	(7)
F01010	7.1	(10)	11.9	(10)	6.5	(3)	11.2	(3)
F01011	6.4	(6)	10.1	(6)	6.3	(9)	9.3	(9)
F01012	6.7	(8)	11.8	(8)	6.4	(6)	11.4	(6)
Number of dams	12		12		12		12	
Mean	6.6		9.9		6.3		9.3	
S.D.	0.4		1.5		0.3		1.5	

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 38-2. Body weights of offspring (F_1) before weaning

MMP 62.5 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F02013	6.4	(6)	10.5	(6)	5.9	(8)	9.7	(8)
F02014	6.3	(4)	10.9	(4)	6.4	(10)	10.4	(10)
F02015	7.7	(9)	12.0	(9)	7.1	(3)	12.2	(3)
F02016	6.8	(1) a)	9.1	(2)	6.3	(13)	9.8	(13)
F02017	6.3	(7)	10.3	(7)	6.0	(7)	9.6	(7)
F02018	5.6	(10)	8.8	(10)	5.5	(8)	8.7	(8)
F02019	6.7	(8)	9.7	(8)	6.2	(6)	9.6	(6)
F02020	7.2	(7)	11.0	(7)	6.7	(8)	10.3	(8)
F02021	6.6	(8)	10.4	(8)	6.0	(6)	9.8	(6)
F02022	6.0	(13)	9.2	(13)	5.9	(7)	8.3	(7)
F02023	7.0	(7)	12.1	(7)	6.6	(5)	11.8	(5)
F02024	7.4	(5)	11.7	(5)	6.6	(7)	10.3	(7)
Number of dams	12		12		12		12	
Mean	6.7		10.5		6.3		10.0	
S.D.	0.6		1.1		0.4		1.1	
Significance	NS		NS		NS		NS	
Statistical method	DU		AN		DU		DU	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
DU: Analysis by Dunnett's test.
AN: Analysis by variance (one-way layout).
a) Data of one male body weight was excluded because of artifactitious value.

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 38-3. Body weights of offspring (F_1) before weaning

MMP 250 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F03025	6.9	(6)	10.4	(6)	6.6	(9)	10.4	(9)
F03026	7.0	(11)	9.9	(11)	6.3	(5)	9.3	(4)
F03027	6.9	(10)	10.6	(10)	6.5	(4)	10.1	(4)
F03028	6.5	(7)	10.1	(7)	6.4	(7)	9.5	(7)
F03029	6.6	(6)	9.3	(5)	6.1	(10)	8.9	(10)
F03030	Not delivery, dead fetal remnant							
F03031	6.8	(6)	10.7	(6)	6.7	(8)	11.0	(8)
F03032	7.1	(7)	9.9	(7)	6.7	(8)	9.6	(8)
F03033	7.2	(7)	11.3	(7)	6.9	(7)	10.1	(7)
F03034	6.4	(9)	9.3	(9)	6.1	(9)	9.3	(7)
F03035	7.1	(7)	10.8	(7)	6.5	(7)	10.1	(7)
F03036	7.2	(4)	11.6	(4)	6.9	(8)	11.6	(8)
Number of dams	11		11		11		11	
Mean	6.9		10.4		6.5		10.0	
S.D.	0.3		0.7		0.3		0.8	
Significance	NS		NS		NS		NS	
Statistical method	DU		AN		DU		DU	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
DU: Analysis by Dunnett's test.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 38-4. Body weights of offspring (F_1) before weaning

MMP 1000 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F04037	6.3	(5)	9.9	(5)	5.9	(6)	9.2	(6)
F04038	Not pregnant							
F04039	6.2	(10)	9.7	(10)	5.9	(4)	8.7	(4)
F04040	6.9	(5)	10.6	(5)	6.2	(9)	9.9	(9)
F04041	6.5	(4)	8.5	(4)	6.5	(10)	7.8	(10)
F04042	5.9	(8)	8.3	(7)	6.3	(9)	8.3	(8)
F04043	5.8	(2)	Total litter loss		5.2	(4)	Total litter loss	
F04044	Not pregnant							
F04045	6.3	(4)	9.4	(4)	5.8	(8)	8.8	(8)
F04046	5.6	(6)	10.2	(3)	5.2	(5)	8.5	(3)
F04047	6.2	(7)	9.3	(6)	5.9	(7)	8.2	(6)
F04048	6.7	(6)	9.3	(6)	6.3	(7)	9.1	(7)
Number of dams	10		9		10		9	
Mean	6.2		9.5		5.9		8.7	
S.D.	0.4		0.7		0.4		0.6	
Significance	NS		NS		NS		NS	
Statistical method	DU		AN		DU		DU	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
DU: Analysis by Dunnett's test.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 39-1. General conditions in offspring (F_1) before weaning

Control (vehicle: water for injection)

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F01001	Number of offspring	18	18	18	17	17
	General appearance, No abnormality	18	18	17	17	17
	General appearance, Death	0	0	1	0	0
F01002	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01003	Number of offspring	16	16	15	15	15
	General appearance, No abnormality	16	15	15	15	15
	General appearance, Death	0	1	0	0	0
F01004	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F01005	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01006	Number of offspring	18	18	18	18	18
	General appearance, No abnormality	18	18	18	18	18
F01007	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F01008	Number of offspring	14	14	13	13	12
	General appearance, No abnormality	14	13	13	12	5
	General appearance, Death	0	1	0	1	7
F01009	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01010	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01011	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01012	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
	Number of offspring	186	186	184	183	182
	General appearance, No abnormality	186	184	183	182	175
	General appearance, Death		2	1	1	7

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 39-2. General conditions in offspring (F_1) before weaning

MMP 62.5 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F02013	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02014	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02015	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02016	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02017	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02018	Number of offspring	18	18	18	18	18
	General appearance, No abnormality	18	18	18	18	18
F02019	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02020	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02021	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02022	Number of offspring	20	20	20	20	20
	General appearance, No abnormality	20	20	20	20	20
F02023	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02024	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
	Number of offspring	174	174	174	174	174
	General appearance, No abnormality	174	174	174	174	174

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 39-3. General conditions in offspring (F_1) before weaning

MMP 250 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth 0	1	2	3	4
F03025	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03026	Number of offspring	16	16	16	16	15
	General appearance, No abnormality	16	16	16	15	15
	General appearance, Death	0	0	0	1	0
F03027	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03028	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03029	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
F03030	Not delivery, dead fetal remnant					
F03031	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03032	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03033	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03034	Number of offspring	18	18	17	16	16
	General appearance, No abnormality	18	17	16	16	16
	General appearance, Death	0	1	1	0	0
F03035	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03036	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
	Number of offspring	162	162	161	159	158
	General appearance, No abnormality	162	161	159	158	158
	General appearance, Death		1	2	1	

Combined repeat dose and reproductive/developmental toxicity screening test of Methyl 3-methoxypropanoate by oral administration in rats

Appendix 39-4. General conditions in offspring (F_1) before weaning

MMP 1000 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F04037	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F04038	Not pregnant					
F04039	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04040	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04041	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04042	Number of offspring	17	17	15	15	15
	General appearance, No abnormality	17	15	15	15	15
	General appearance, Death	0	2	0	0	0
F04043	Number of offspring	6	6	1	1	1
	General appearance, No abnormality	6	1	1	1	0
	General appearance, Death	0	5	0	0	1
F04044	Not pregnant					
F04045	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F04046	Number of offspring	11	11	6	6	6
	General appearance, No abnormality	11	6	6	6	6
	General appearance, Death	0	5	0	0	0
F04047	Number of offspring	14	14	13	12	12
	General appearance, No abnormality	14	13	12	12	12
	General appearance, Death	0	1	1	0	0
F04048	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
	Number of offspring	126	126	113	112	112
	General appearance, No abnormality	126	113	112	112	111
	General appearance, Death		13	1		1

信頼性保証書

表題　　Methyl 3-methoxypropanoate のラットを用いる反復投与毒性・生殖発生毒性併合試験

試験番号　　R-13-004

この試験に関する信頼性保証部門による査察および監査状況等は下記のとおりであった。

査察・監査項目	査察・監査年月日	運営管理者および試験責任者への報告年月日
試験計画書	2013年 9月 5日	2013年 9月 5日
試験計画書変更書 R-13-004-No.1	2013年11月11日	2013年11月11日
動物の受入れおよび検疫	2013年 9月18日	2013年 9月18日
群分け、検体調製および含量試験	2013年 9月30日	2013年10月 1日
体重測定、給餌量測定、投与および一般状態の観察	2013年10月 1日	2013年10月 1日
性周期観察	2013年10月 2日	2013年10月 2日
詳細な症状観察	2013年10月 7日	2013年10月 7日
交尾確認	2013年10月16日	2013年10月16日
尿検査	2013年11月6、7日	2013年11月7日
分娩状態および出生児の観察	2013年11月 7日	2013年11月 7日
機能検査	2013年11月8、11日	2013年11月11日
出生児剖検、雄動物剖検、血液学的検査、血液生化学的検査、器官重量測定および固定	2013年11月12、13日	2013年11月13日
病理組織学検査(標本作製:切り出し)	2013年11月21日	2013年11月21日
報告書草案および生データ	2014年 2月3～6日	2014年 2月 6日
最終報告書	2014年 3月26日	2014年 3月26日

試験は、「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成 23 年 3 月 31 日、薬食発 0331 第 8 号、平成 23・03・29 製局第 6 号、環保企発第 110331010 号)を遵守して実施され、また、この報告書は試験に使用された方法および手順を正確に記載し、記載された結果は試験の生データを正確に反映していることを保証する。

2014年3月26日

一般財団法人食品薬品安全センター 秦野研究所
信頼性保証部門責任者 [redacted]