

最終報告書訂正版

2-メチルパレルアルデヒドのラットを用いる 反復投与毒性・生殖発生毒性併合試験

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試験番号 R-12-010

被験物質 2-メチルバレルアルデヒド

試験項目 反復投与毒性ならびに生殖発生毒性試験

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保管期間 試験終了後10年間
その後の保管については試験委託者と協議する。

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本試験は、「新規化学物質等に係る試験の方法について」(平成23年3月31日付け 薬食発0331第7号厚生労働省医薬食品局長、平成23・03・29製局第5号経済産業省製造産業局長、環境企発第110331009号環境省総合環境政策局長通知)に準拠し、「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成23年3月31日付け 薬食発0331第8号厚生労働省医薬食品局長、平成23・03・29製局第6号経済産業省製造産業局長、環境企発第110331010号環境省総合環境政策局長通知)を遵守して実施した。

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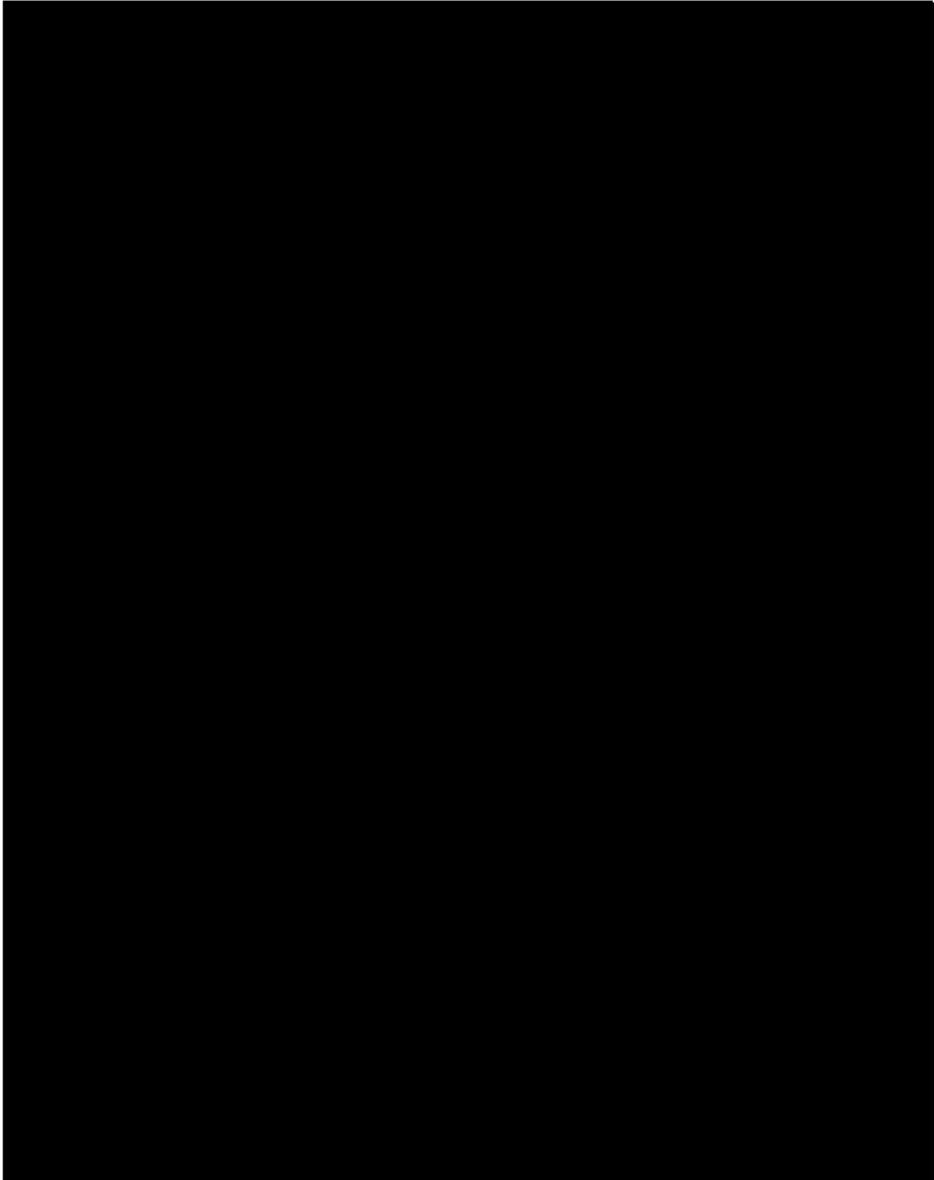
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尿検査
病理学検査

被験物質管理
検体調製
化学分析



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要約

今回、2-メチルバレルアルデヒドの雌雄動物の反復投与毒性および回復性、ならびに生殖能力に対する影響および新生児の発育に及ぼす影響を検討することを目的として、反復投与毒性ならびに生殖発生毒性試験を化審法ガイドラインに従って実施した。被験物質をトウモロコシ油(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2週間および交配期間、妊娠期間を通して哺育4日まで41~47日間投与した。なお、母動物は自然分娩させ、出生児は哺育4日、母動物は哺育5日に剖検した。また、雌の非交配群として0および1000 mg/kgの用量にサテライト群(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投与群の各5例、雌の非交配群のサテライト群の各5例は、42日間投与した後、14日間飼育して剖検した。

1. 親動物所見

投与期間中の一般状態の変化として、1000 mg/kg投与群の雄および非交配雌(サテライト群)で投与後に一過性の流涎、交配雌および非交配雌(サテライト群)でよろめき歩行、非交配雌(サテライト群)で自発運動の低下、雄、交配雌および非交配雌(サテライト群)で耳介および四肢の発赤が観察された。詳細な症状観察では、投与30日に1000 mg/kg投与群の雄1例で皮膚色の潮紅が観察された。いずれの所見も投与後3時間から7時間以内に消失した。

投与期間終了時の自発運動量測定において、1000 mg/kg投与群の分娩雌で区画移動数および立ち上がり回数の減少がみられた。

投与期間終了時の器官重量測定において、1000 mg/kg投与群の非交配雌(サテライト群)では、肝臓の重量が、分娩雌では脾臓の重量が増加した。

投与期間終了時の病理組織学検査において、250 mg/kg以上の投与群の雄および分娩雌に、前胃の角化亢進、扁平上皮細胞層の過形成、粘膜下織への炎症細胞浸潤、粘膜固有層および粘膜下織の水腫が観察され、1000 mg/kg投与群の分娩雌では限局性にびらんも観察された。1000 mg/kg投与群の非交配雌(サテライト群)にも、前胃の角化亢進、扁平上皮細胞層の過形成、粘膜下織への炎症細胞浸潤、粘膜固有層および粘膜下織の水腫が観察された。

投与期間中にみられた一般状態所見は回復期間中には観察されず、回復期間終了後の自発運動量測定および器官重量測定においても投与期間終了時にみられた変化は認められなかった。回復期間終了時の病理組織学検査 g18

前胃の角化亢進が雄および非交配雌(サテライト群)に、扁平上皮細胞層の過形成および粘膜下織への炎症細胞浸潤が非交配雌(サテライト群)に観察されたが、投与終了時と比較して所見の程度および頻度は軽減した。

2. 生殖発生毒性学的所見および出生児所見

生殖発生毒性は認められず、出生児においても被験物質投与による影響は認められなかった。

3. 無毒性量

以上の結果から、本試験条件下における 2-メチルバレルアルデヒドの親動物に対する一般毒性学的無毒性量は、一般状態および胃に観察された病理組織学変化から雌雄ともに 62.5 mg/kg/day、生殖発生毒性学的な無毒性量および次世代児に対する無毒性量は、いずれの投与群にも被験物質投与による影響はみられなかったことから 1000 mg/kg/day と考えられた。

また、一般毒性学的変化は 14 日間の回復期間終了後に回復性を示すことが明らかとなった。

試験目的

雌雄ラットの交配前(2週間)および交配期間中(最長2週間)、ならびに雄では交配期間終了後を通して計42日間、生殖能を評価した交配雌では妊娠期間を通して周産期(哺育4日まで)に41~47日間、非交配雌のサテライト群では雄と同様の期間に、2-メチルバレルアルデヒドを強制経口投与し、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。

試験ガイドラインと GLP

本試験は、「新規化学物質等に係る試験の方法について:以下、化審法ガイドライン」(平成23年3月31日付け 薬食発0331第7号厚生労働省医薬食品局長、平成23・03・29製局第5号経済産業省製造産業局長、環境企発第110331009号環境省総合環境政策局長通知)に準拠し、「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成23年3月31日付け 薬食発0331第8号厚生労働省医薬食品局長、平成23・03・29製局第6号経済産業省製造産業局長、環境企発第110331010号環境省総合環境政策局長通知)を遵守して実施した。

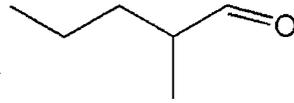
動物愛護

全ての実験操作は、「動物の愛護及び管理に関する法律」(昭和48年10月1日法律第105号、平成24年9月5日一部改正)、「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」(平成18年4月28日、環境省告示第88号)および「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」(平成18年6月1日、科発第0601001号)を遵守し、「財団法人食品薬品安全センター秦野研究所動物実験に関する指針」(平成2年10月1日、平成22年10月1日改正)に基づいて実施した。本試験における動物実験計画は、秦野研究所動物実験委員会の審査を受け、承認されている(動物実験承認番号:1120199A)。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2-メチルバレルアルデヒド(別名:2-メチルペンタナール、CAS No.:123-15-9、分子式: $C_6H_{12}O$ 、分子量:100.16、外観:無色~ほとんど無色透明の液体、刺激臭、引火性、純度:98.1%、沸点:119℃、比重:0.8108(20/20)、屈折率:1.4002($n_{20/D}$)、ロット番号:JPQXD、Annex A、以下、2-MV)は[REDACTED]より購入し(被験物質入手:2012年7月3日)、使用時まで冷蔵・遮光・密閉下(実測値3~7℃)で保管した。2-MV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赤外吸収スペクトルを測定し、スペクトルに変化がないことを他試験(試験番号 M-12-020)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 週齢の Sprague-Dawley (SD) 系 [CrI:CD (SD)、SPF] ラット雄 55 匹、雌 83 匹を購入し、1 号室に収容した。入荷日も含めて 15 日間、検疫と飼育環境への馴化のため飼育した。その間毎日、動物の一般状態を観察し、入荷日(検疫 1 日)および検疫終了日に体重を測定した。検疫・馴化期間中は動物の尾にフェルトペンで馴化番号を記し、飼育ケージに試験番号、性別および馴化番号を記入した動物カードを掛けて識別した。また、雌動物については、検疫 3 日から毎日、性周期を観察した。入荷動物の入荷時および検疫終了時の体重は下記の通りであった。

動物入荷日	:2012 年 10 月 1 日
入荷時体重	:雄 247.0~277.7 g、雌 179.9~211.1 g
検疫終了日	:2012 年 10 月 15 日
検疫終了時体重	:雄 338.6~422.1 g、雌 212.7~275.6 g

検疫・馴化の結果、入荷した動物において、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。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 4 匹を除外し、体重別層化無作為抽出法により群分けを行った。群分けした動物には一連の動物番号を割り当て、フェルトペンで尾に動物番号を標識し、色彩の異なった動物カードに試験番号、性別および動物番号を記入して飼育ケージに掛けた。群分けから棄却した雄動物 7 匹、雌動物 11 匹、性周期の観察結果により除外した 4 匹は全て余剰動物とし、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、雄動物、分娩した雌動物ならびにサテライト群の動物は、解剖前に絶食させた)。雌動物は分娩例全例について、妊娠 18 日から哺育 4 日までラット用プラスチック製繁殖ケージ(350w×400d×180h mm)に 1 匹ずつ収容し、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 21.5~24.0℃、湿度は 50.0~72.0%であった。また、供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを確認した。

3. 投与検体

1) 調製

被験物質を秤量し、媒体(トウモロコシ油、製造元:ナカライテスク、製造番号:V2K9025)に溶解させ、25 w/v%溶液を調製した。さらに25 w/v%溶液を媒体によって希釈し、6.25ならびに1.5625 w/v%溶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 3~6°C)で保管し、安定性の保証期間内に使用した。

2) 安定性試験

秦野研究所で、投与に先立ち、1.5625 および 25 w/v%濃度の投与検体について、冷蔵、遮光条件下(実測値 3~4°C)における8日間の安定性を確認した後、本試験の動物実験を開始した(安定性試験開始日:2012年10月9日、8日目:2012年10月17日、Annex B)。

3) 含量の測定

本試験の初回調製検体(調製日:2012年10月15日)について、1.5625、6.25 および 25 w/v%濃度の調製検体の含量を測定した。その結果、平均含量は調製指示濃度の101.8~102.9%であり、各測定値のばらつきは平均値の98.7~100.9%で規定範囲内にあった(Annex C)。

調製検体中の被験物質濃度は以下の方法で測定した。投与検体の1 mLを正確にとり、アセトンで適宜希釈し、検量線の範囲内となるように試料溶液を調製した。これらの試料溶液とIS溶液を1:1(v/v)の割合で混合し、測定用試料溶液とした。測定用試料溶液は、投与検体の採取からn=3で調製した。

試料溶液および標準溶液を以下に示すガス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2-MV濃度を算出した。

ガスクロマトグラフ測定条件

検出器	水素炎イオン化検出器(FID)
分析カラム	TC-624(長さ30 m、内径0.53 mm、膜厚3.0 μm、GLサイエンス)
キャリアガス	ヘリウム
カラム温度	測定用標準溶液:70°C(0分)→5°C/分→90°C(0分)→30°C/分→120°C(0分) 測定用試料溶液:70°C(0分)→5°C/分→90°C(0分)→30°C/分→250°C(5分)
注入口設定温度	250°C
検出器設定温度	250°C
試料注入量	2 μL
試料注入方式	スプリット
オートインジェクタ洗浄液	アセトン
システムの適合性	測定開始前および測定終了後に測定用標準溶液(約100 μg/mL)を1回ずつ測定し、2-MVのピーク保持時間およびISに対するピーク面積比の変動率(測定開始前に対する測定終了後の偏差%)を確認した。変動率の許容基準は、ピーク保持時間が±3.0%以内、ピーク面積比が±5.0%以内とした。

4. 投与量の設定および投与方法

本試験の投与量は、「2-メチルパレルアルデヒドのラットを用いる反復投与毒性・生殖発生毒性併合試験(予備試験)」(試験番号:R-12-009)の結果をもとに設定した。すなわち、0(媒体、トウモロコシ油)、100、300 および 1000 mg/kg の 2-MV を 8 週齢の雌雄各 3 匹の SD 系ラットに 14 日間、反復強制経口投与した。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。

雌の 1000 mg/kg 投与群において、胆汁酸濃度が対照群の約 3 倍に増加した。同様の変化は雄では認められず、雌雄ともに肝臓の逸脱酵素に変化はなかったが、肝臓重量は雌雄ともに増加傾向がみられた。したがって、1000 mg/kg の 2-MV は肝臓に影響を及ぼす可能性が示唆された。本試験の投与期間は予備試験の約 3 倍(42 日間)であるが、これらの変化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、肝臓に影響が認められた用量である 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。

本試験では、雄動物は交配前 2 週間、交配期間(14 日間)を通して剖検前日まで(総投与回数 42 回)、雌動物は交配前 2 週間、交配期間、妊娠期間を通して分娩後の哺育 4 日まで、交尾が確認されなかった雌は剖検前日まで(総投与回数 42 回)、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、非妊娠雌の反復毒性を評価するために設定したサテライト群では投与 42 日まで、経口的に 1 日 1 回、1 週 7 回、午前中(9 時 2 分~12 時 00 分)に投与した。投与容量は 4 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トウモロコシ油を同様に投与した。投与経路は化審法ガイドラインに拠り、ラット用胃管による強制経口投与とした。

本試験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 (w/v%)	投与容量 (mL/kg)	動物番号	
					雄	雌
対照群	トウモロコシ油 (媒体)	0	0	4	M01001~M01012*	F01001~F01012
低用量群	2-MV	62.5	1.5625	4	M02013~M02024	F02013~F02024
中用量群	2-MV	250	6.25	4	M03025~M03036	F03025~F03036
高用量群	2-MV	1000	25	4	M04037~M04048*	F04037~F04048
対照群 (サテライト群)	トウモロコシ油 (媒体)	0	0	4	-	F05049~F05058*
高用量群 (サテライト群)	2-MV	1000	25	4	-	F06059~F06068*

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

5. 検査法

1) 親動物 (F_0)

① 一般状態の観察

全例について、飼育期間中は毎日 1 回、投与期間中は投与前後の毎日 2 回以上観察した。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 8、15、24、30、36 および 42 日、未交尾例はさらに投与 49 日、回復期間中は回復 7 および 14 日に、スコアリング法による詳細な症状観察を行った。さらに、分娩例は哺育 0 日から 4 日の間に 1 回観察した。観察は、いずれも 13 時 10 分～14 時 44 分の間に行った。

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

④ 機能検査

雄では、投与 42 日の詳細な症状観察に引き続き、各群動物番号の若い 5 例について、刺激に対する感覚運動反応を検査し、握力測定、自発運動測定は、投与 38 日に検査した。雌では、分娩例は投与期間が近接し、分娩から日数が経過した各群 5 例について、刺激に対する感覚運動反応、握力測定、自発運動測定を検査した。サテライト群では、投与 42 日の詳細な症状観察に引き続き、各群 5 例について、刺激に対する感覚運動反応を検査し、握力測定、自発運動測定は、投与 41 日に検査した。さらに、投与最終週に実施した自発運動測定で、1000 mg/kg 投与群の雌において自発運動量の減少がみられたため、回復 14 日の詳細な症状観察後に、回復例全例について自発運動測定を実施した。

(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

置設置場所に運搬し、速やかに自発運動測定を開始した。

⑤体重測定

雄および雌動物のサテライト群は、投与 1(投与開始日)、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。未交尾例は投与 21、28、35、42、49 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

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

⑦尿検査

雄動物および雌動物のサテライト群を検査対象とし、投与 37 日の検査では各群動物番号の若い 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 4～8 時間の時点で採取した蓄尿で、その他の項目は約 24 時間の蓄尿で行った。

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

⑧性周期観察

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

⑨交配

投与 15 日の 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、膣栓を確認し、同居中の雌の膣垢標本を作製して鏡検した。膣内に膣栓あるいは膣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い、午前と午後に観察し、15 時までには分娩が完了した例について、その日を哺育 0 日(分娩日)とした。分娩状態の直接観察は観察可能な動物について行い、直接観察できなかった動物についても、分娩後の一般状態および産児の状態から異常の有無を判断した。分娩後は、哺育状態を哺育 1~4 日の間、毎日観察した。分娩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。また、雌の投与終了時剖検では、分娩例について哺育 5 日に投与期間が近接した各群 5 例、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) 血液学検査用:抗凝固剤 EDTA-2K
- 2) 血液学検査用:抗凝固剤 クエン酸ナトリウム
- 3) 血液生化学検査用:抗凝固剤 ヘパリン

⑫血液学検査

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

項目	測定法	使用機器
赤血球数(RBC)	電気抵抗検出法	血液自動分析装置 XT-2000iV(シスメックス)
白血球数(WBC)	半導体レーザを用いた フローサイトメトリー法	同上
白血球分類	同上	同上
網状赤血球比率(RET%)	同上	同上
血色素量(HGB)	SLSヘモグロビン法	同上
平均赤血球容積(MCV)	計算(HCT×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血液生化学検査

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

項目	測定法	使用機器
総蛋白濃度(TP)	ビウレット法	自動分析装置 JCA-BM6010(日本電子)
アルブミン濃度(rALB)	BCG法	同上
グルコース濃度(Glc)	ヘキソキナーゼ・G-6-PDH法	同上
総コレステロール濃度(TC)	コレステロールオキシダーゼ・HMMPS法	同上
トリグリセリド濃度(TG)	GPO・HMMPS法、グリセリン消去法	同上
リン脂質濃度(PL)	コリンオキシダーゼ・DAOS法	同上
尿素窒素濃度(BUN)	ウレアーゼ・G-LDH法、ウレアーゼ律速系	同上
クレアチニン濃度(cre)	Jaffé法	同上
γ-グルタミルトランスアミナーゼ活性(γ-GTP)	IFCC法	同上
アルカリフォスファターゼ活性(ALP)	GSCC法	同上
アスパラギン酸アミノトランスフェラーゼ活性(AST)	IFCC法	同上
アラニンアミノトランスフェラーゼ活性(ALT)	IFCC法	同上
乳酸脱水素酵素活性(LDH)	JSCC標準化対応法	同上
カルシウム濃度(Ca)	OCPC法	同上
総ビリルビン濃度(tbil)	酵素法	同上
無機リン濃度(IP)	モリブデン酸直接法	同上
胆汁酸濃度(TBA)	酵素サイクリング法	同上
A/G比	計算(rALB/(TP- rALB))	同上
ナトリウムイオン濃度(Na)	イオン電極法	全自動電解質分析装置 EA05(エイアントテュー)
カリウムイオン濃度(K)	同上	同上
塩素イオン濃度(Cl)	同上	同上

⑭剖検および器官重量

雄動物およびサテライト群の投与終了時剖検例は投与 42 日の翌日に、雌動物の分娩例は哺育 4 日の翌日に、交尾が確認されなかった雌(対照群の 1 例:動物番号 F01009、62.5 mg/kg 投与群の 1 例:動物番号 F02016)は投与 52 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 F03025、100 mg/kg 投与群の 1 例:動物番号 F04043)は妊娠 26 日相当日に、雄動物およびサテライト群の回復観察例は回復 15 日に、それぞれ剖検した。

血液学、血液生化学検査を実施する動物はペントバルビタールナトリウム麻酔下で採血し、これ以外の動物はペントバルビタールナトリウム麻酔下で放血致死させた。

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、精巣上部、前立腺、精嚢および凝固腺、卵巣、子宮、膣、膀胱、大腿骨および大腿骨髄、骨格筋、坐骨神経、乳腺、および病変部を採取し、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。精巣および精巣上部はブアン液に固定(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、未交尾例および未分娩例の器官重量値は評価対象から除外した。

⑮病理組織学検査

剖検した動物のうち、雄およびサテライト群の投与終了時剖検では対照群ならびに高用量群の動物番号が若い各 5 例、雌の投与終了時剖検では分娩例について哺育 5 日に投与期間が近接し可能な限り分娩から日数が経過している対照群ならびに高用量群の 5 例について、組織学検査対象器官のヘマトキシリン・エオジン(HE)標本作製し、病理組織学検査を実施した。

また、剖検時に異常所見がみられた器官・組織(精巣上部および卵巣)に関しても同様に HE 標本作製して病理組織学検査を実施し、さらに胃については各群 5 例および病変がみられた例について観察した。

投与終了時の病理組織観察結果において、被験物質投与による変化が胃にみられたことから、回復期間終了時には胃および病変部(肝臓)について検査を実施した。

2) 出生児(F₁)

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

②剖検

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

6. データの解析法

性周期の変化した動物の頻度、交尾率、受胎率、出生児の形態異常の出現頻度については Fisher の直接確率検定を行った(有意水準:5%)。

2-MV 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、2-MV 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、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意性について検定(有意水準:5%)を行った。分散が一意である場合には、一元配置型の分散分析(有意水準:5%)を行い、群間に有意性が認められる場合は、Dunnett 法により多重比較を行った(有意水準:5%)。一方、いずれかの群で分散が 0 となる場合および分散が一意でない場合には、Kruskal-Wallis の順位検定(有意水準:5%)を行い、群間に有意性が認められる場合には、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

2012 年 10 月 4 日、11:00 から受変電設備の定期点検のために停電した。これに伴い動物飼育室内の照明が消え、空調(送風および温湿度制御機能)が停止した。照明は 14:26 に、空調は 14:28 に再開した。停電時の動物飼育室内の温湿度に異常はなく、いずれの動物の一般状態にも変化は認められなかったことから、試験への影響はないと判断した。

2012 年 10 月 26 日、本館電灯用回路の主配線用遮断器が 10:21 と 14:15 に作動した。これに伴い 10:21~10:37(16 分間)、14:15~14:16(1 分間)に動物飼育室内の照明が消えた。また、電源供給配線工事のために 16:02~16:07(5 分間)に停電し、この間も照明が消えた。停電の時間は短く、いずれの動物の一般状態にも変化は認められなかったことから、試験への影響はないと判断した。

2012 年 11 月 26 日、分娩例 4 例(動物番号 F01010、F03027、F03030、F04041)の詳細な症状観察が実施できなかった。分娩例の詳細な症状観察は哺育 0 日から 4 日の間に 1 回実施する計画になっていたが、この 4 例は交配開始後、翌日に交尾が確認された動物で、かつ妊娠 21 日相当日に出産したため、観察実施予定の 2012 年 11 月 26 日には哺育 5 日となってしまった。上記 4 例以外の動物は全て哺育期間中の詳細な症状観察を実施し、いずれの群においても評価ができる十分な観察数を得ていることから、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～Table 4, Appendix 1～Appendix 4)

投与期間中の一般状態の変化として、1000 mg/kg 投与群において投与後の一過性の流涎が、雄では投与 7 日以降に 3 例で散見され、非交配雌 (サテライト群) の 1 例では投与 8 日および 28 日に観察された。また、投与後に耳介および四肢の発赤が、雄で 11 例、雌で 11 例、非交配雌 (サテライト群) で 9 例に観察され、投与 9 日以降、投与期間を通して散見された。さらに、雌ではよろめき歩行が投与 7 日に 1 例で観察され、非交配雌 (サテライト群) では投与 7 日から投与 12 日の投与後に自発運動の低下が 2 例、よろめき歩行が 3 例に観察された。自発運動の低下は投与 17、28、36 日、よろめき歩行は投与 17 日にも各 1 例に観察された。いずれの所見も投与後 3 時間から 7 時間以内に消失した。

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

回復期間中の観察では、雌雄とも一般状態に変化は観察されなかった。

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

雄では、投与 30 日に 1000 mg/kg 投与群の 1 例で皮膚色の潮紅が観察された。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、排尿および排糞数にも対照群と比較して差はなかった。

雌では、いずれの観察項目および観察項目には変化は認められず、排尿および排糞数にも対照群と比較して差はなかった。

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

投与期間中、雄の体重は対照群と同様に推移し、対照群と 2-MV 各投与群との間に有意差は認められなかった。

生殖能を評価した雌の 2-MV 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。反復投与毒性を評価した非交配雌 (サテライト群) においても、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。

回復期間中の雄の体重は、回復 7 日に 1000mg/kg 投与群で有意 ($P<0.05$) に増加した。雌の体重推移には、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。

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

雄では、250 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 ($P<0.01$) に増加したが、それ以降、投与終了時まで、対照群と 2-MV 各投与群の摂餌量に有意差は認められなかった。

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 ($P<0.05$) に増加し、250 mg/kg 投与群においては投与 7～8 日の摂餌量が対照群と比較して有意 ($P<0.05$) に低下した。それ以降、交配前、妊娠期間中、哺育期間中を通して、対照群との間に有意差は認められなかった。

1000 mg/kg 投与群の非交配雌 (サテライト群) では、投与 7～8 日の摂餌量が対照群と比較して有意に低下 ($P<0.05$) した。

回復期間の雄では、回復 12～13 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 (Table 15～Table 22, Appendix 15～Appendix 22)

投与最終週に下記の試験を実施した。分娩雌では自発運動量の有意な減少が認められたことから、自発運動量測定のみ回復期間終了時にも実施した。なお、回復期間終了時の自発運動量測定は性差を確認するために、雌雄ともに実施した。

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

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、サテライト群を含む雌雄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～Appendix 19)

雄では、250 mg/kg 投与群の後肢握力が有意($P<0.01$)に増加したが、用量依存的な変化ではなかった。

雌では、分娩雌、非交配雌(サテライト群)ともに対照群と 2-MV 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～Appendix 22)

雄では、区画移動数および立ち上がり回数には対照群と 2-MV 各投与群との間に統計学的な有意差はなかった。

分娩雌では、1000 mg/kg 投与群において、検査開始後 10 分～15 分および 15 分～20 分の区画移動数が有意($P<0.05$)に減少し、10 分～15 分の立ち上がり回数も有意($P<0.01$)に減少した。

1000 mg/kg 投与群の非交配雌(サテライト群)では、検査開始後 15 分～20 分の立ち上がり回数が有意($P<0.05$)に増加した。250 mg/kg 以下の投与群では雌雄ともに区画移動数および立ち上がり回数には対照群と比較して差はなかった。

回復期間終了時の検査では、雌雄ともに対照群と 1000 mg/kg 投与群の区画移動数および立ち上がり回数に有意差は認められなかった。

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

①投与期間終了時

雌雄ともに、対照群と 2-MV 各投与群との間に有意差は認められなかった。

②回復期間終了時

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。

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

①投与期間終了時

雄では、対照群と 2-MV 各投与群との間に有意差は認められなかった。

分娩雌では、62.5 mg/kg 投与群において好中球比率が有意($P<0.01$)に増加し、リンパ球比率が有意($P<0.01$)に減少した。また、250 mg/kg 投与群の単球比率が有意($P<0.05$)に増加した。

非交配雌(サテライト群)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。

②回復期間終了時

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。

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

①投与期間終了時

雄では、いずれの検査項目にも対照群と2-MV各投与群との間に有意差は認められなかった。

分娩雌では、対照群と2-MV各投与群との間に有意差は認められなかった。

1000 mg/kg投与群の非交配雌(サテライト群)では、総蛋白濃度(P<0.05)、アルブミン濃度およびカルシウム濃度(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投与群において胆汁酸濃度が有意(P<0.05)に減少した。

非交配雌(サテライト群)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。

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

①投与期間終了時

雄では、62.5 mg/kg投与群において精囊の実重量(P<0.05)および相対重量(P<0.01)が有意に増加し、250 mg/kg投与群において精巣上体の実重量、前立腺の実重量および相対重量、精囊の実重量および相対重量が有意(P<0.05)に増加した。

分娩雌では、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)に増加した。

1000 mg/kg投与群の非交配雌(サテライト群)では、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、右腎臓および左右合計重量も有意(P<0.05)に増加した。

②回復期間終了時

雄では、心臓および左腎臓の実重量が有意(P<0.05)に増加した。

非交配雌(サテライト群)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。

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

①雄の投与期間終了時屠殺例

前胃粘膜の水腫様が250 mg/kg投与群の2例、1000 mg/kg投与群の7例に認められた。1000 mg/kg投与群の1例では前胃粘膜の肥厚も伴っていた。

片側の精巣上体尾部に黄白色の結節が、62.5および1000 mg/kg投与群で各1例観察された。

②雄の回復期間終了時屠殺例

前胃粘膜の水腫様が、1000 mg/kg投与群の1例に観察され、同例では腺胃粘膜に黒色の陥凹部も認められた。

③雌の投与期間終了時屠殺例(哺育5日剖検)

前胃粘膜の水腫様が、対照群および62.5 mg/kgに各1例、250 mg/kg投与群の5例、1000 mg/kg投与群の10例に認められた。これらの動物のうち、250 mg/kgの1例および1000 mg/kg投与群の2例では前胃粘膜が陥凹し、黒色を呈していた。また、1000 mg/kg投与群の1例では前胃粘膜の肥厚も伴っていた。対照群の1例で腺胃粘膜に陥凹部が観察され、1例で右側

卵巣に嚢腫が認められ赤色液が貯留していた。

④サテライト群の投与期間終了時屠殺例

前胃粘膜の水腫様が 1000 mg/kg 投与群の 4 例に、前胃粘膜の肥厚が同群の 3 例に観察された。また、対照群の 1 例では回腸に憩室が認められた。

⑤サテライト群の回復期間終了時屠殺例

肝臓の横隔膜結節が 1000 mg/kg 投与群の 1 例に観察された。

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

胃については、被験物質投与によると考えられる変化が剖検時に認められたために全ての投与群について病理組織学検査を実施した。

①雄の投与期間終了時屠殺例

前胃では、角化亢進、扁平上皮細胞層の過形成、粘膜下織への炎症細胞浸潤、粘膜固有層および粘膜下織の水腫が、250 mg/kg 以上の投与群で観察された。1000 mg/kg 投与群では、いずれの所見も対照群と比較して所見の程度は強く、頻度も高かった。扁平上皮細胞層の過形成は、250 mg/kg 投与群においても高頻度であった。

腺胃では、粘膜下織の水腫、粘液の増加、粘膜下織への炎症細胞浸潤が対照群を含む各投与群に認められたが、程度および頻度には差はなかった。

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が、両群間の程度に差はなかった。

肝臓では、門脈周囲性に肝細胞の脂肪化および小肉芽腫が、腎臓では皮質に好塩基性尿細管、髓質に鉍質沈着が、甲状腺では限局性のリンパ球浸潤、異所性胸腺組織、鰓後体遺残が、前立腺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、それぞれ観察されたがいずれの所見も両群間で程度および頻度に差はなかった。

その他、対照群では心臓に限局性の変性/線維化が、肺に限局性の泡沫細胞の集簇、出血、骨化生、動脈周囲の鉍質沈着が、副腎束状帯に空胞化が、62.5 mg/kg 投与群では精巣上体尾部に精子肉芽腫(解剖時病変部)が、1000 mg/kg 投与群では脾臓の間質にリンパ球浸潤が、ハーダー腺の間質にリンパ球浸潤が、それぞれ各 1 例に観察された。

上記以外の組織学検査対象器官・組織には、病理組織学的変化は観察されなかった。

②雄の回復期間終了時屠殺例

前胃では、角化亢進、粘膜下織への炎症細胞浸潤が 1000 mg/kg 投与群に観察され、角化亢進の程度は対照群と比較して強く、高頻度にみられた。

腺胃では、粘膜下織への炎症細胞浸潤、粘膜下織の水腫、粘液の増加が、対照群および 1000 mg/kg 投与群に観察されたが、いずれの所見にも程度および頻度に両群間で差はなかった。

③雌の投与期間終了時屠殺例(哺育 5 日剖検)

前胃では、角化亢進、扁平上皮細胞層の過形成が 250 mg/kg 以上の投与群で観察され、所見の程度は対照群と比較して強く、高頻度にみられた。また、粘膜固有層および粘膜下織の水腫が、対照群

を含む各投与群に観察され、1000 mg/kg 投与群では対照群と比較して高頻度にみられた。粘膜下織への炎症細胞浸潤および限局性のびらんが、対照群および 250 mg/kg 以上の投与群に観察された。炎症細胞浸潤は 250 mg/kg 以上の投与群で頻度が増し、1000 mg/kg 投与群では程度も増強した。

腺胃では、粘液の増加が 62.5 mg/kg 以上の各投与群で観察され、250 mg/kg 投与群で程度も強く高頻度にみられた。粘膜下織の水腫が対照群を含む各投与群に観察されたが、程度および頻度には対照群と比較して差はなかった。

肝臓では、門脈周囲性に肝細胞の脂肪化が、対照群および 1000 mg/kg 投与群に観察されたが、程度および頻度に差はなかった。また、小肉芽腫が 1000 mg/kg 投与群にのみ観察され頻度に有意差がみられたが、ごく軽度の変化であった。

脾臓では褐色色素の沈着および髓外造血像が、対照群および 1000 mg/kg 投与群の全例に観察されたが、程度に差はなかった。

その他、腎臓では皮質に好塩基性尿細管が、甲状腺に鰓後体遺残が、胸腺の委縮が、肺胞内に泡沫細胞集簇が、対照群および 1000 mg/kg 投与群に、それぞれ観察されたが、程度および頻度に差はなかった。

また、対照群では、腎臓間質にリンパ球浸潤、近位尿細管上皮に空胞変性が、上皮小体では細胞質の空胞化が、膵臓の間質にリンパ球浸潤が、卵巣に嚢胞(解剖時病変部)が、骨髄に脂髄が観察された。

上記以外の組織学検査対象器官・組織には、病理組織学的変化は観察されなかった。

④サテライト群の投与期間終了時屠殺例

前胃では、角化亢進、扁平上皮細胞の過形成、粘膜下織への炎症細胞浸潤が、1000 mg/kg 投与群に観察され、程度および頻度に有意差がみられた。また、粘膜固有層および粘膜下織の水腫が対照群に 1 例、1000 mg/kg 投与群に 4 例認められ、程度も増強傾向を示した。

腺胃では、粘膜下織に炎症細胞浸潤、粘液の増加が 1000 mg/kg 投与群に各 1 例観察されたが、ごく軽度な変化であった。粘膜下織の水腫が対照群および 1000 mg/kg 投与群で観察されたが、程度および頻度に両群間で差はなかった。

肝臓では、門脈周囲性に肝細胞の脂肪化および小肉芽腫が対照群および 1000 mg/kg 投与群に観察されたが、両群間に程度および頻度に差はなかった。

脾臓では、褐色色素の沈着および髓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が、両群間の程度に差はなかった。

腎臓では、皮質に好塩基性尿細管が、間質に炎症細胞浸潤が、対照群および 1000 mg/kg 投与群に観察され、このうち 1000 mg/kg 投与群の 1 例では炎症細胞浸潤が腎盂にも観察された。しかし、これらの所見の程度および頻度には両群間に差はなかった。

子宮内腔の拡張、ハーダー腺間質にリンパ球浸潤、大腿骨骨髄の髓外造血が、対照群および 1000 mg/kg 投与群に観察されたが、いずれの所見も両群間に程度および頻度に差はなかった。なお、子宮の所見は発情前期に伴った変化であった。

その他、甲状腺では限局性のリンパ球浸潤、異所性胸腺、鰓後体遺残が、上皮小体では細胞質の空胞化が、胸腺では委縮が、肺では肺胞腔に泡沫細胞の集簇が、対照群および(あるいは)1000 mg/kg 投与群に観察されたが、いずれの所見も両群間に程度および頻度に差はなかった。

上記以外の組織学検査対象器官・組織には、病理組織学的変化は観察されなかった。

⑤サテライト群の回復期間終了時屠殺例

胃では、前胃の角化亢進、扁平上皮細胞の過形成、粘膜下織への炎症細胞浸潤が1000 mg/kg 投与群に観察された。角化亢進、扁平上皮細胞の過形成の程度および頻度に有意差がみられ、粘膜下織への炎症細胞浸潤の頻度に有意差がみられた。

腺胃では、粘液の増加が1000 mg/kg 投与群に観察され、粘膜下織の水腫が対照群および1000 mg/kg 投与群に観察されたが、いずれの所見にも程度および頻度に両群間で差はなかった。

肝臓では、横隔膜結節(解剖時病変部)が1000 mg/kg 投与群の1例に観察され、結節周囲の漿膜下に線維化および、結節領域の類洞にうっ血が観察された。

2. 生殖能力

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

62.5 mg/kg 投与群の1例(動物番号 F02024)において、投与開始後に性周期が4~5日の間隔で回帰しなくなったが、その他の動物は4~5日の間隔で性周期は正常に回帰した。

交配の結果、対照群および62.5 mg/kg 投与群の各1例(動物番号 F01009 および F02016)を除く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の発情回数に、対照群と2-MV 各投与群との間に有意差は認められなかった。

250 mg/kg 投与群および1000 mg/kg 投与群の各1例(動物番号 F03025 および F04043)は、交尾は確認されたが妊娠していなかった。それ以外の動物は、妊娠が確認され、いずれの投与群においても交尾率および受胎率には被験物質投与の影響は認められなかった。

2) 出産率および妊娠期間 (Table 37, Appendix 37)

出産率および妊娠期間は、対照群と2-MV 各投与群との間に有意差は認められなかった。

3) 分娩および哺育状態 (Table 37, Appendix 37)

全ての妊娠動物は妊娠21~23日に出産し、分娩状態および哺育状態に異常は認められなかった。

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

250 mg/kg 投与群および1000 mg/kg 投与群の各1例(動物番号 F03025 および F04043)では、妊娠25日までに分娩が確認されなかった。剖検の結果、着床痕および妊娠黄体は認められず、不妊と判断した。

黄体数、着床数および着床率には、対照群と2-MV 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)

250 mg/kg 投与群では、生児出産率が対照群と比較して有意 ($P < 0.05$) に高かった。

分娩率、出生率、新生児生存率および性比には、対照群と 2-MV 各投与群との間に有意差は認められなかった。

2) 体重 (Table 38, Appendix 38)

哺育 0 および 4 日における出生児の体重には、対照群と 2-MV 各投与群との間に有意差は認められなかった。

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

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)、あるいは死後経過が進み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 日の出生児剖検の内部器官観察の結果、62.5 mg/kg 投与群の雌 1 匹 (母動物番号 F02013) で両側性の腎盂拡張が観察された。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 (2 週間) および交配期間中、ならびに雄では交配期間終了後を通して計 42 日間、生殖能を評価した交配雌では妊娠期間を通して周産期 (哺育 4 日まで) に 41~47 日間、非交配雌のサテライト群では雄と同様の期間に、2-メチルバレルアルデヒドを強制経口投与し、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. 親動物

投与期間中に 1000 mg/kg 投与群の雌雄に観察された一般状態の変化、詳細な症状観察結果および自発運動量の減少は 250 mg/kg 以下の投与群には観察されていないことから、被験物質投与に起因した変化と考えられた。また、病理組織学検査の結果、250 mg/kg 以上の投与群の雌雄には、被験物質投与によると考えられた変化が胃に認められた。

本被験物質は眼および皮膚に刺激性を示すことが知られている²⁾。刺激性物質の経口投与により、投与後の一過性の流涎、自発運動の減少、胃の組織学的変化が観察される場合がある。本被験物質の類縁化合物であるバレルアルデヒドのラットを用いる 90 日間反復経口投与毒性試験³⁾においても、流涎や胃の変化は観察されている。しかし、今回、2-メチルバレルアルデヒド投与により 1000 mg/kg 投与群では、さらに耳介および四肢の発赤やよろめき歩行が観察された。耳介および四肢の発赤は動物が一過性の血圧低下を示し、それに付随してよろめき歩行が観察されたとも考えられる。これらのことを総合的に判断し、今回認められた上述の変化は 2-メチルバレルアルデヒドの刺激性とともに神経系にも起因した

変化であると考えられた。

2週間の回復期間により、病理学検査以外の変化は消失した。また、胃の病理組織学的な変化も雌雄ともに、投与終了時と比較して所見の程度および頻度は軽減したことから、これらの変化は回復性のある変化と考えられた。

体重には、雌雄ともに被験物質投与による影響は認められなかった。なお、1000 mg/kg 投与群の雄では回復7日の体重が対照群と比較して有意な高値を示したが、僅かな変化であることから偶発的な変化であると判断した。

摂餌量は、250 mg/kg 投与群以上の雌雄において、試験期間中に有意差がみられる測定点が散見されたが、いずれも僅かな変化であること、体重推移には被験物質投与による影響は認められていないことから偶発的な変化であると判断した。

尿検査には、被験物質投与の影響を示唆する変化は認められなかった。

血液学検査の結果、雌雄ともに被験物質投与による影響は認められなかった。なお、分娩雌の62.5 mg/kg および250 mg/kg 投与群において白血球分類比に差がみられたが、白血球数に変動がないこと、1000 mg/kg 投与群には認められていないことから毒性学的意義はないと判断した。

血液生化学検査の結果、投与期間終了時の検査において、1000 mg/kg 投与群の非交配雌(サテライト群)では、総蛋白濃度、アルブミン濃度およびカルシウム濃度が増加した。しかし、増加の程度は僅かであること、肝臓、腎臓、上皮小体および甲状腺機能、骨代謝の異常を示す病理組織学的所見は観察されていないことから、被験物質投与による影響ではなく偶発的な変化であると判断した。

また、回復期間終了時の血液生化学検査において、1000 mg/kg 投与群の雄では胆汁酸濃度が減少した。しかし、投与期間終了時の検査では同様の変化がなく、回復期間終了時の肝臓重量、血液生化学検査および病理組織学検査においても肝臓機能障害を示唆する変化は認められていない。また、予備試験では胆汁酸の増加がみられ再現性がないこと、同種試験の背景データ(N=40、最小値～最大値:4.9～58.3 mg/dL、平均値±2SD:15.8±24.1 mg/dL)範囲内であることから、被験物質投与による変化ではないと判断した。

投与最終週に実施した握力検査では、250 mg/kg 投与群の雄の後肢握力が増加した。しかし、用量依存的な変化ではないこと、病理組織学検査においても坐骨神経および骨格筋には異常はないことから、被験物質投与による変化ではないと判断した。

投与最終週に実施した自発運動測定時に、1000 mg/kg 投与群の非交配雌(サテライト群)では立ち上がり回数が増加したが、検査開始後15分～20分の5分間のみ有意に増加していることから、偶発的な変化であると判断した。

投与期間終了時の器官重量測定において、1000 mg/kg 投与群の非交配雌(サテライト群)では、肝臓の重量が、分娩雌では脾臓の重量が増加した。肝臓重量の増加は、本被験物質の予備試験¹⁾においても同投与量で増加傾向が認められている。いずれも被験物質投与による影響と考えられたが、血液生化学検査および血液学検査においては、肝臓障害あるいは貧血や造血能の異常を示唆する変化は認められず、肝臓および脾臓の病理組織学検査においても異常は観察されなかった。その他、精巣上体、

前立腺、精嚢にみられた重量変化は、1000 mg/kg 投与群では認められていないこと、これらの臓器に被験物質投与に起因すると考えられた病理組織学的変化は観察されなかったことから被験物質投与による変化ではないと考えられた。

投与期間終了時の病理組織学検査では、上述の胃以外には被験物質投与に起因したと考えられる変化は認められなかった。

2. 生殖発生毒性および出生児

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

250 mg/kg 投与群では、生児出産率が高い値を示した。しかし、着床数および分娩日死亡児数には被験物質投与による変化はみられていないことから、対照群に分娩日の死亡児数が多い動物が 2 例（母動物番号 F01004 および F01005）観察されたことに起因する偶発的な変化と考えられた。

出生児の生存性および体重に被験物質投与の影響はみられず、死亡児には外表奇形および内部器官異常は観察されなかった。

哺育 4 日の出生児剖検の結果、62.5 mg/kg 投与群の雌 1 匹で両側性の腎盂拡張が観察されたが、その他の動物に外表奇形および内部器官異常は観察されなかったことから、偶発的な変化であると判断した。

3. 無毒性量

以上の結果から、本試験条件下における 2-MV の親動物に対する一般毒性学的無毒性量は、一般状態および胃に観察された病理組織学変化から雌雄ともに 62.5 mg/kg/day、生殖発生毒性学的な無毒性量および次世代児に対する無毒性量は、いずれの投与群にも被験物質投与による影響はみられなかったことから 1000 mg/kg/day と考えられた。

参考文献

- 1) 2-メチルバレルアルデヒド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)
- 2) Chemical Book, Methyl valeraldehyde (123-15-9), <http://www.chemicalbook.com>
- 3) 国際的に汎用されている添加物(香料)の指定に向けた試験-バレルアルデヒドのラットを用いる 90 日間反復経口投与毒性試験-

Annex A



試験成績書

2012年07月03日

東京化成工業株式会社 品質保証部
 〒103-0023
 東京都中央区日本橋本町4丁目10
 TEL: 03(5640)8850 FAX: 03(5640)8851

製品名: 2-Methylvaleraldehyde			
製品コード: M0596	等級: EP	製品ロット: JPQXD	判定: 合格
項目	結果	規格値	
純度(GC)	98.1 %	95.0 %以上	
比重 (20/20)	0.8108	0.8080 ~ 0.8120	
屈折率 n _D 20/D	1.4002	1.3980 ~ 1.4010	

Annex B

安定性試験結果

試験番号	R-12-010
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被験物質：2-メチルバレルアルデヒド
ロット番号：JPQXD
媒体：トウモロコシ油

調製年月日 2012年10月9日
測定年月日 A 2012年10月9日(調製直後)
B 2012年10月12日(調製後3日)
C 2012年10月17日(調製後8日)
保管条件 冷蔵、遮光

調製濃度 (mg/mL)	A				B					C				
	試料 番号	測定濃度 (mg/mL)	含量 ^{a)} (%)	ばらつき ^{b)} (%)	試料 番号	測定濃度 (mg/mL)	含量 ^{a)} (%)	ばらつき ^{b)} (%)	残存率 ^{c)} (%)	試料 番号	測定濃度 (mg/mL)	含量 ^{a)} (%)	ばらつき ^{b)} (%)	残存率 ^{c)} (%)
15.625	1	15.67	100.3	99.7	13	16.43	105.2	99.8	104.5	28	15.69	100.4	99.9	99.8
	2	15.70	100.5	99.9	14	16.54	105.9	100.5	105.2	29	15.78	101.0	100.4	100.4
	3	15.81	101.2	100.6	15	16.41	105.0	99.7	104.4	30	15.67	100.3	99.7	99.7
	平均	15.72	100.7	/	平均	16.46	105.4	/	104.7	平均	15.71	100.6	/	100.0
250	4	255.9	102.4	99.7	16	268.6	107.4	100.1	104.6	31	252.4	101.0	99.1	98.3
	5	255.7	102.3	99.6	17	270.3	108.1	100.8	105.3	32	255.7	102.3	100.4	99.6
	6	258.6	103.4	100.7	18	265.8	106.3	99.1	103.5	33	255.8	102.3	100.5	99.6
	平均	256.7	102.7	/	平均	268.2	107.3	/	104.5	平均	254.6	101.9	/	99.2

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

安定性の判断基準(溶液検体)

調製直後および保管後の平均含量がそれぞれ調製濃度の90.0~110.0%、また、各測定値のばらつきがそれぞれ平均値の90.0~110.0%以内であり、かつ、調製直後の測定平均値に対する保管後の残存率が平均値の90.0%以上を示す期間。

Annex C

試験番号	R-12-010
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含 量 試 験 結 果

被験物質：2-メチルパレルアルデヒド

調製年月日：2012年10月15日

ロット番号：JPQXD

測定年月日：2012年10月15日

媒 体：トウモロコシ油

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
19	15.625	15.70	15.90	100.5	101.8	98.7
20		16.04		102.7		100.9
21		15.97		102.2		100.4
22	62.5	64.19	64.15	102.7	102.6	100.1
23		64.12		102.6		100.0
24		64.15		102.6		100.0
25	250	257.3	257.2	102.9	102.9	100.0
26		257.6		103.0		100.2
27		256.9		102.8		99.9

含量の判断基準(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 2-Methylvaleraldehyde 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: corn oil)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2-MV 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	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde 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			
Control (vehicle: corn oil)	Number of females	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
	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
2-MV 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
	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
	Skin, Reddening of the extremities	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Reddening of the auricle	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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									
Control (vehicle: corn oil)	Number of females	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
	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	5
2-MV 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	5
	General appearance, No abnormality	10	8	10	5	10	7	10	8	10	8	10	7	10	8	10	6	10	8	10	7	10	8	10	7	10	9	5
	Skin, Reddening of the extremities	0	2	0	5	0	3	0	2	0	2	0	3	0	2	0	1	0	2	0	2	0	3	0	2	0	3	0
	Skin, Reddening of the auricle	0	2	0	5	0	3	0	2	0	2	0	3	0	2	0	1	0	2	0	2	0	3	0	2	0	3	0
	Behavior, Decrease in locomotor activity	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde 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: corn oil)	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2-MV 1000 mg/kg	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde 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: corn oil)	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
2-MV 62.5 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
2-MV 250 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
2-MV 1000 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
	General appearance, No abnormality	11	11	11	7	11	6	11	5	11	9	11	8	11	9	11	8	11	5	11	7	11	6	11	7	11	8	11	7
	Skin, Reddening of the extremities	0	0	0	4	0	5	0	6	0	2	0	3	0	2	0	3	0	6	0	4	0	5	0	4	0	3	0	4
	Skin, Reddening of the auricle	0	0	0	4	0	5	0	6	0	2	0	3	0	2	0	3	0	6	0	4	0	5	0	4	0	3	0	4
	Behavior, Decrease in locomotor activity	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	2	0	0	0	0	0	0	0
	Behavior, Staggering gait	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: corn oil)	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6	6	
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6	6	
2-MV 62.5 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	2	2	
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	2	2	
2-MV 250 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	0	0		
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	0	0		
2-MV 1000 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	5	5		
	General appearance, No abnormality	11	8	11	6	11	9	11	9	11	10	11	9	11	10	11	5	3	
	Skin, Reddening of the extremities	0	3	0	5	0	2	0	2	0	1	0	2	0	0	0	0	0	
	Skin, Reddening of the auricle	0	3	0	5	0	2	0	2	0	1	0	2	0	0	0	0	0	
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	2	
	Behavior, Staggering gait	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde 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: corn oil)	Number of dams	5	5	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	5	5	11	11	11	11	11	11	11	11	11
2-MV 62.5 mg/kg	Number of dams	7	7	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	7	7	11	11	11	11	11	11	11	11	11
2-MV 250 mg/kg	Number of dams	9	9	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	9	9	11	11	11	11	11	11	11	11	11
2-MV 1000 mg/kg	Number of dams	4	4	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	4	4	11	9	11	8	11	8	11	11	11
	Skin, Reddening of the extremities.	0	0	0	2	0	2	0	2	0	0	0
	Skin, Reddening of the auricle.	0	0	0	0	0	2	0	1	0	0	0
	Behavior, Decrease in locomotor activity.	0	0	0	0	0	1	0	1	0	0	0
	Behavior, Staggering gait.	0	0	0	0	0	1	0	1	0	1	0

Pre: Before administration, Post: after administration.

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

Table 5. Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery ^a		
				8	15	24	30	36	42	7	14	
[Skin/mucous membranes color] Flush	Control (vehicle: corn oil)	12	0 ^b	0	0	0	0	0	0	0	0	0
	2-MV 62.5 mg/kg	12	0	0	0	0	0	0	0	0	0	0
	2-MV 250 mg/kg	12	0	0	0	0	0	0	0	0	0	0
	2-MV 1000 mg/kg	12	0	0	0	0	1	0	0	0	0	0
[Urination] (frequency/30sec)	Control (vehicle: corn oil)	12	0 ^c	3	1	1	0	1	0	1	1	1
	2-MV 62.5 mg/kg	12	0	4	4	3	0	2	0	0	0	0
	2-MV 250 mg/kg	12	1	0	0	2	2	2	1	0	0	0
	2-MV 1000 mg/kg	12	1	2	1	0	1	2	0	0	0	1
[Defecation] (frequency/30sec)	Control (vehicle: corn oil)	12	3 ^c	0	0	0	0	0	0	0	0	0
	2-MV 62.5 mg/kg	12	1	0	0	0	0	0	0	0	0	0
	2-MV 250 mg/kg	12	0	0	0	0	0	0	0	0	0	0
	2-MV 1000 mg/kg	12	2	1	0	3	1	2	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 2-Methylvaleraldehyde by oral administration in rats

Table 6-1. Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						The lactation period				
				8	15	24	30	36	42			49		
[Urination] (frequency/30sec)	Control (vehicle: corn oil)	12	1 ^a	1	0	0	0	1	0	(1)	0	(1)	0	(10)
	2-MV 62.5 mg/kg	12	0	1	0	0	0	1	0	(1)	0	(1)	0	(11)
	2-MV 250 mg/kg	12	0	0	0	0	0	0					0	(9)
	2-MV 1000 mg/kg	12	0	0	1	0	0	1					0	(10)
[Defecation] (frequency/30sec)	Control (vehicle: corn oil)	12	0 ^a	0	0	0	0	0	0	(1)	0	(1)	1	(10)
	2-MV 62.5 mg/kg	12	0	0	0	0	1	0	0	(1)	0	(1)	0	(11)
	2-MV 250 mg/kg	12	0	0	0	0	0	0					0	(9)
	2-MV 1000 mg/kg	12	0	0	0	0	0	0					1	(10)

^a Values represent total score of each group.
 Figures in parentheses indicate number of animals.

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

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

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery ^a	
				8	15	24	30	36	42	7	14
[Straub tail] Tail elevation	Control (vehicle: corn oil)	10	0	0	0	0	0	0	0	0	0
	2-MV 1000 mg/kg	10	1 ^b	0	0	0	0	0	0	0	0
[Urination] (frequency/30sec)	Control (vehicle: corn oil)	10	1 ^c	2	0	1	2	0	0	1	0
	2-MV 1000 mg/kg	10	0	3	0	1	0	0	0	0	0
[Defecation] (frequency/30sec)	Control (vehicle: corn oil)	10	0 ^c	0	0	0	0	0	0	0	0
	2-MV 1000 mg/kg	10	0	0	0	0	0	0	0	0	0

^a The recovery test was performed in 5 animals for each of the 0 and 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 2-Methylvaleraldehyde by oral administration in rats

Table 7-1. Body weights of male rats

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of males	12	12	12	12
Days of administration				
1	379.3 ± 14.9	383.6 ± 14.7	384.1 ± 15.6	386.8 ± 15.6
4	389.5 ± 16.7	395.1 ± 18.1	397.1 ± 19.3	396.6 ± 16.3
7	398.5 ± 18.5	402.3 ± 19.2	408.0 ± 22.9	405.4 ± 17.2
14	416.8 ± 23.8	422.1 ± 21.9	431.4 ± 30.0	424.8 ± 20.3
21	437.8 ± 26.3	441.8 ± 25.2	452.7 ± 35.7	443.1 ± 23.5
28	461.7 ± 32.2	467.9 ± 30.1	472.8 ± 41.2	468.2 ± 28.2
35	483.6 ± 38.8	482.8 ± 29.1	487.9 ± 43.1	489.3 ± 32.5
42	492.2 ± 40.4	494.0 ± 33.2	502.2 ± 45.3	501.1 ± 32.7

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 2-Methylvaleraldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)	2-MV 1000 mg/kg
Number of males	5	5
Days of recovery		
1	473.8 ± 37.7	518.6 ± 30.4
7	487.2 ± 38.1	535.9 ± 27.9 *
14	492.8 ± 44.4	544.7 ± 26.5

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 2-Methylvaleraldehyde by oral administration in rats

Table 8-1. Body weights of female rats

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of females	12	12	11	11
Days of administration				
1	246.7 ± 11.1	243.9 ± 14.6	242.5 ± 12.0	242.2 ± 14.8
4	254.1 ± 11.9	253.6 ± 13.9	248.8 ± 12.1	247.5 ± 11.4
7	254.4 ± 13.2	256.7 ± 17.2	253.7 ± 12.7	253.2 ± 15.2
14	264.1 ± 17.1	270.8 ± 23.7	259.6 ± 13.7	262.0 ± 16.8

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: corn oil)	2-MV 1000 mg/kg
Number of females	10	10
Days of administration		
1	245.7 ± 10.0	243.8 ± 11.3
4	253.8 ± 8.5	251.3 ± 9.8
7	261.4 ± 8.0	259.2 ± 9.5
14	273.1 ± 8.9	269.0 ± 11.6
21	283.1 ± 8.6	277.7 ± 10.9
28	290.4 ± 11.3	284.5 ± 11.5
35	299.6 ± 13.0	296.3 ± 11.5
42	303.5 ± 12.1	300.0 ± 10.4

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: corn oil)	2-MV 1000 mg/kg
Number of females	5	5
Days of recovery		
1	303.5 ± 12.1	299.3 ± 11.7
7	314.2 ± 9.8	301.1 ± 8.8
14	311.0 ± 10.8	298.5 ± 14.9

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 2-Methylvaleraldehyde by oral administration in rats

Table 9. Body weights of dams during pregnancy

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of dams	11	11	11	11
Days of pregnancy				
0	276.8 ± 17.4	281.1 ± 22.9	265.7 ± 13.8	275.3 ± 18.9
7	311.4 ± 25.6	315.0 ± 24.3	303.4 ± 16.2	314.6 ± 19.6
14	347.4 ± 30.6	352.7 ± 28.4	340.8 ± 20.8	348.1 ± 21.1
20	430.1 ± 38.8	436.9 ± 29.4	418.8 ± 25.9	424.4 ± 25.6

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 2-Methylvaleraldehyde by oral administration in rats

Table 10. Body weights of dams during lactation

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of dams	11	11	11	11
Days of lactation				
0	332.6 ± 40.2	329.2 ± 35.1	309.7 ± 23.5	336.9 ± 22.2
4	333.2 ± 31.8	336.0 ± 26.4	322.7 ± 27.5	346.4 ± 27.7

Each value shows mean ± S.D. (g).

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

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

Table 11-1. Food consumption of male rats

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of males	12	12	12	12
Days of administration				
1	23.7 ± 1.7	25.6 ± 2.8	28.5 ± 3.0 **	26.2 ± 3.6
7	24.1 ± 1.9	22.7 ± 3.2	24.1 ± 3.1	22.9 ± 2.8
14	20.8 ± 3.5	22.1 ± 3.8	24.0 ± 3.4	23.5 ± 3.0
29	25.6 ± 3.3	24.5 ± 2.1	24.7 ± 2.9	24.5 ± 3.8
35	22.4 ± 3.9	23.6 ± 2.7	22.4 ± 2.1	21.9 ± 2.7
41	22.4 ± 2.5	22.4 ± 2.8	23.5 ± 2.7	23.5 ± 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 2-Methylvaleraldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)		2-MV 1000 mg/kg	
Number of males	5		5	
Days of recovery	6	27.3 ± 4.0	30.8 ± 1.9	
	12	27.2 ± 2.5	31.1 ± 1.3 *	

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 2-Methylvaleraldehyde by oral administration in rats

Table 12-1. Food consumption of female rats

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of females	12	12	11	11
Days of administration				
1	18.0 ± 3.2	19.3 ± 2.2	20.0 ± 2.3	21.3 ± 2.7 *
7	19.3 ± 2.0	19.1 ± 2.7	16.5 ± 2.9 *	17.5 ± 2.4
14	16.2 ± 3.7	17.6 ± 4.6	18.1 ± 2.1	18.1 ± 2.4

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: corn oil)	2-MV 1000 mg/kg
Number of females	10	10
Days of administration		
1	20.4 ± 2.2	20.8 ± 3.4
7	19.4 ± 3.1	16.6 ± 2.6 *
14	19.5 ± 3.2	20.2 ± 1.5
21	19.4 ± 1.4	18.5 ± 3.4
29	19.0 ± 2.3	19.3 ± 2.4
35	16.8 ± 3.3	17.3 ± 2.3
41	16.1 ± 1.6	17.1 ± 2.8

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: corn oil)	2-MV 1000 mg/kg
Number of females	5	5
Days of recovery		
6	22.4 ± 2.9	18.9 ± 3.1
12	21.6 ± 2.9	23.1 ± 1.9

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 2-Methylvaleraldehyde by oral administration in rats

Table 13. Food consumption in dams during pregnancy

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of dams	11	11	11	11
Days of pregnancy				
0	19.8 ± 3.3	19.7 ± 3.1	18.9 ± 2.6	20.6 ± 1.7
7	24.5 ± 3.8	24.0 ± 3.3	23.0 ± 3.7	23.0 ± 2.9
14	23.8 ± 3.8	24.0 ± 2.4	22.8 ± 3.4	22.9 ± 2.3
20	20.3 ± 5.8	17.7 ± 3.6	15.9 ± 4.5	21.2 ± 3.4

Each value shows mean ± S.D. (g).

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

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

Table 14. Food consumption in dams during lactation

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg	
Number of dams	11	11	11	11	
Days of lactation	3	33.2 ± 11.8	36.9 ± 8.0	36.0 ± 8.9	38.1 ± 6.0

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 2-Methylvaleraldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Male				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Prayer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100

Values represent % of animals showing normal responses.

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

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

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
<u>Female, dam</u>				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Prayer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
<u>Female, satellite groups</u>				
Number of animals	5			5
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Prayer's reaction	100			100
Withdrawal reflex	100			100
Eyelid reflex	100			100

Values represent % of animals showing normal responses.

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

Table 17. Assessment of grip strength of male rats

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of males	5	5	5	5
Administration period				
Forelimb	0.434 ± 0.146	0.546 ± 0.134	0.472 ± 0.112	0.649 ± 0.109
Hindlimb	0.174 ± 0.049	0.203 ± 0.014	0.264 ± 0.026 **	0.224 ± 0.024

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 2-Methylvaleraldehyde by oral administration in rats

Table 18. Assessment of grip strength of female rats

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of females	5	5	5	5
Administration period				
Forelimb	0.665 ± 0.151	0.678 ± 0.064	0.554 ± 0.110	0.725 ± 0.121
Hindlimb	0.327 ± 0.087	0.347 ± 0.132	0.253 ± 0.084	0.367 ± 0.122

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 2-Methylvaleraldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)	2-MV 1000 mg/kg
Number of females	5	5
Administration period		
Forelimb	0.683 ± 0.056	0.691 ± 0.136
Hindlimb	0.233 ± 0.092	0.273 ± 0.087

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 2-Methylvaleraldehyde by oral administration in rats

Table 20. Motor activity of male rats

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of males	5	5	5	5
Administration period				
Ambulation (counts)				
5min	1171 ± 142	1222 ± 25	1276 ± 416	1142 ± 93
10min	1088 ± 226	1183 ± 151	1221 ± 391	1028 ± 111
15min	984 ± 265	954 ± 72	1122 ± 223	823 ± 323
20min	770 ± 437	682 ± 305	878 ± 340	688 ± 246
Total	4013 ± 997	4041 ± 342	4497 ± 1331	3681 ± 691
Rearing (counts)				
5min	40 ± 4	38 ± 8	40 ± 9	35 ± 6
10min	26 ± 9	31 ± 12	33 ± 8	28 ± 8
15min	23 ± 8	21 ± 6	29 ± 11	19 ± 11
20min	15 ± 10	13 ± 8	18 ± 2	14 ± 8
Total	104 ± 28	104 ± 21	120 ± 13	96 ± 27
Recovery period				
Ambulation (counts)				
5min	1186 ± 155			1100 ± 202
10min	1099 ± 193			1004 ± 185
15min	1010 ± 124			773 ± 361
20min	787 ± 183			727 ± 277
Total	4083 ± 591			3604 ± 970
Rearing (counts)				
5min	38 ± 6			34 ± 13
10min	28 ± 10			25 ± 8
15min	19 ± 5			19 ± 13
20min	16 ± 8			16 ± 5
Total	101 ± 22			93 ± 31

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 2-Methylvaleraldehyde by oral administration in rats

Table 21. Motor activity of female rats

Group	Control (vehicle: corn oil)		2-MV 62.5 mg/kg		2-MV 250 mg/kg		2-MV 1000 mg/kg	
Number of females	5		5		5		5	
Administration period								
Ambulation (counts)								
5min	1198	± 49	1164	± 123	1116	± 497	1044	± 156
10min	931	± 107	932	± 209	1005	± 384	749	± 140
15min	805	± 171	708	± 268	759	± 548	224	± 147 *
20min	550	± 277	676	± 278	627	± 453	74	± 73 *
Total	3483	± 424	<u>3481</u>	± <u>634</u>	3508	± 1845	2091	± 322
Rearing (counts)								
5min	28	± 6	34	± 8	28	± 10	29	± 5
10min	16	± 6	20	± 9	16	± 4	13	± 4
15min	18	± 10	8	± 6	11	± 8	1	± 2 **
20min	6	± 7	9	± 9	6	± 11	0	± 0
Total	68	± 16	71	± 21	61	± 27	44	± 6

Each value shows mean±S.D.

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

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

Table 22. Motor activity of female rats, satellite group

Group	Control (vehicle: corn oil)		2-MV 1000 mg/kg	
Number of females	5		5	
Administration period				
Ambulation (counts)				
5min	1104	± 133	1130	± 237
10min	1014	± 105	1129	± 286
15min	986	± 260	1013	± 337
20min	729	± 179	969	± 184
Total	3833	± 447	<u>4241</u>	± <u>1014</u>
Rearing (counts)				
5min	33	± 9	35	± 3
10min	25	± 10	35	± 12
15min	32	± 12	32	± 14
20min	14	± 6	28	± 12 *
Total	104	± 4	130	± 24
Recovery period				
Ambulation (counts)				
5min	1174	± 166	1200	± 349
10min	1079	± 166	1029	± 319
15min	870	± 206	1037	± 343
20min	611	± 210	882	± 434
Total	3734	± 567	4149	± 1358
Rearing (counts)				
5min	39	± 12	39	± 15
10min	32	± 12	27	± 10
15min	25	± 11	21	± 8
20min	13	± 10	19	± 13
Total	109	± 35	106	± 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 2-Methylvaleraldehyde by oral administration in rats

Table 23-1. Urinalysis in male rats

Group	Number of males	Quality ^{a)}																							
		Color		Turbidity		pH					Protein				Glucose		Ketone			Bilirubin	Occult blood			Urobilinogen	
		Light yellow	Yellow	-	+	6.0	6.5	7.0	7.5	8.0	±	+	2+	3+	-	±	-	±	+	-	-	±	±	+	2+
Control (vehicle: corn oil)	5	4	1	4	1	0	2	0	2	1	0	1	4	0	5	0	0	1	4	5	5	0	2	3	0
2-MV 62.5 mg/kg	5	4	1	5	0	0	2	2	0	1	1	2	1	1	4	1	1	2	2	5	4	1	4	0	1
2-MV 250 mg/kg	5	4	1	5	0	0	0	2	0	3	0	4	2	0	5	0	0	1	4	5	5	0	4	1	0
2-MV 1000 mg/kg	5	5	0	5	0	2	2	1	0	0	0	2	3	0	5	0	0	1	4	5	5	0	1	4	0

Group	Number of males	Urinary sediments ^{a)}								Urine volume ^{b)} (mL/24hr)	Specific gravity ^{b)}	Electrolyte, density ^{b)} (mEq/L)			Electrolyte, gross volume ^{b)} (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells		Na			K	Cl	Na	K	Cl	
		-	-	-	-	±	+	-	±								
Control (vehicle: corn oil)	5	5	5	5	1	3	1	5	0	12.5 ±6.0	1.062 ±0.016	89.9 ±34.8	159.9 ±23.1	111.0 ±57.3	1.17 ±0.63	1.95 ±0.77	1.45 ±0.84
2-MV 62.5 mg/kg	5	5	5	5	1	4	0	5	0	12.8 ±5.5	1.060 ±0.015	96.2 ±32.8	165.5 ±31.1	114.4 ±38.0	1.10 ±0.28	1.99 ±0.48	1.32 ±0.31
2-MV 250 mg/kg	5	5	5	5	1	4	0	4	1	12.9 ±3.1	1.057 ±0.014	98.0 ±27.1	159.8 ±25.3	115.7 ±41.4	1.21 ±0.20	2.00 ±0.25	1.41 ±0.31
2-MV 1000 mg/kg	5	5	5	5	2	3	0	5	0	14.9 ±7.2	1.063 ±0.019	110.9 ±42.3	156.6 ±22.1	134.0 ±49.6	1.42 ±0.15	2.24 ±0.79	1.75 ±0.34

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

Turbidity, -: negative; +: slight

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL

Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL

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

Bilirubin, -: negative

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

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

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

Crystals, -: not observed; ±: a few; +: abundant

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

a), values represent as number of animals

b), values represent as mean ± S.D.

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

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

Group	Number of males	Quality ^{a)}																			
		Color		Turbidity		pH			Protein			Glucose		Ketone		Bilirubin	Occult blood		Urobilinogen		
		Light yellow	Yellow	-	6.5	7.5	8.0	±	+	2+	-	-	±	+	-	-	±	+	±	+	2+
Control (vehicle: corn oil)	5	4	1	5	1	2	2	1	3	1	5	1	2	2	5	5	0	3	1	1	
2-MV 1000 mg/kg	5	5	0	5	1	1	3	0	3	2	5	1	1	3	5	4	1	1	4	0	

Group	Number of males	Urinary sediments ^{b)}						Urine volume ^{b)} (mL/24hr)	Specific gravity ^{b)}	Electrolyte, density ^{b)} (mEq/L)			Electrolyte, gross volume ^{b)} (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	Na			K	Cl	Na	K	Cl	
		-	-	-	-	±	-			-	-	-	-	-	-
Control (vehicle: corn oil)	5	5	5	5	1	4	5	14.4 ±3.9	1.067 ±0.013	128.8 ±42.0	190.9 ±20.7	154.3 ±42.5	1.78 ±0.48	2.75 ±0.79	2.11 ±0.32
2-MV 1000 mg/kg	5	5	5	5	1	4	5	17.6 ±3.0	1.064 ±0.011	128.1 ±22.0	202.9 ±29.9	140.7 ±18.1	2.20 ±0.15	3.52 ±0.43	2.44 ±0.26

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

Turbidity, -: negative

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

Glucose, -: negative

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

Bilirubin, -: negative

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

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

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

Crystals, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

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

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

Group	Number of females	Quality ^{a)}																			
		Color		Turbidity		pH				Protein			Glucose		Ketone			Bilirubin	Occult blood	Urobilinogen	
		Light yellow	Yellow	-	6.0	6.5	7.0	7.5	-	±	+	2+	-	±	-	±	+	-	-	±	+
Control (vehicle: corn oil)	5	4	1	5	0	3	1	1	1	2	1	1	4	1	1	3	1	5	5	3	2
2-MV 1000 mg/kg	5	5	0	5	2	2	1	0	1	1	3	0	5	0	1	3	1	5	5	3	2

Group	Number of females	Urinary sediments ^{a)}						Urine volume ^{b)} (mL/24hr)	Specific gravity ^{b)}	Electrolyte, density ^{b)} (mEq/L)			Electrolyte, gross volume ^{b)} (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	Na			K	Cl	Na	K	Cl	
		-	-	-	-	±	-			-	-	-	-	-	-
Control (vehicle: corn oil)	5	5	5	5	1	4	5	12.0 ±5.7	1.057 ±0.024	85.9 ±21.8	143.0 ±14.1	98.6 ±36.6	1.09 ±0.55	1.71 ±0.79	1.31 ±0.68
2-MV 1000 mg/kg	5	5	5	5	2	3	5	10.1 ±4.4	1.060 ±0.016	93.5 ±46.5	144.1 ±38.6	107.8 ±45.7	0.83 ±0.30	1.41 ±0.64	1.01 ±0.45

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

Turbidity, -: negative

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

Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL

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

Bilirubin, -: negative

Occult blood, -: negative

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

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

Crystals, -: not

a), values represent as number of animals

b), values represent as mean ± S.D.

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

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

Group	Number of females	Quality ^{a)}													
		Color	Turbidity	pH			Protein		Glucose	Ketone		Bilirubin	Occult blood	Urobilinogen	
		Light yellow	-	7.0	7.5	8.0	-	±	-	-	±	-	-	±	
Control (vehicle: corn oil)	5	5	5	4	0	1	2	3	5	4	1	5	5	5	
2-MV 1000 mg/kg	5	5	5	3	2	0	2	3	5	5	0	5	5	5	

Group	Number of females	Urinary sediments ^{a)}							Urine volume ^{b)} (mL/24hr)	Specific gravity ^{b)}	Electrolyte, density ^{b)} (mEq/L)			Electrolyte, gross volume ^{b)} (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells	Na			K	Cl	Na	K	Cl	
		-	-	-	-	±	-									
Control (vehicle: corn oil)	5	5	5	5	2	3	5	15.9 ±9.5	1.053 ±0.020	104.6 ±41.0	159.1 ±47.8	119.9 ±51.0	1.36 ±0.27	2.19 ±0.49	1.57 ±0.43	
2-MV 1000 mg/kg	5	5	5	5	1	4	5	15.5 ±3.7	1.049 ±0.015	97.6 ±33.2	164.7 ±41.8	104.1 ±41.5	1.45 ±0.47	2.47 ±0.60	1.55 ±0.56	

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

Turbidity, -: negative

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

Glucose, -: negative

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

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal

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

Crystals, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

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

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

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of males	5	5	5	5
RBC ($\times 10^4/\mu\text{L}$)	818 \pm 20	827 \pm 29	839 \pm 27	837 \pm 18
Hemoglobin (g/dL)	15.1 \pm 0.2	14.7 \pm 0.4	15.1 \pm 0.5	15.3 \pm 0.4
Hematocrit (%)	42.8 \pm 1.0	41.4 \pm 1.2	42.2 \pm 1.1	43.7 \pm 1.9
MCV (fL)	52.4 \pm 2.2	50.0 \pm 1.0	50.4 \pm 1.4	52.3 \pm 1.9
MCH (pg)	18.5 \pm 0.6	17.7 \pm 0.4	18.0 \pm 0.4	18.3 \pm 0.3
MCHC (g/dL)	35.3 \pm 0.6	35.5 \pm 0.4	35.7 \pm 0.5	35.0 \pm 0.6
Platelet ($\times 10^4/\mu\text{L}$)	107.9 \pm 14.2	107.6 \pm 7.9	107.4 \pm 11.4	103.8 \pm 13.7
PT (sec)	16.0 \pm 3.5	16.4 \pm 2.7	17.1 \pm 2.4	16.8 \pm 1.6
APTT (sec)	23.0 \pm 2.7	23.8 \pm 2.4	23.8 \pm 1.2	24.7 \pm 1.4
WBC ($\times 10^2/\mu\text{L}$)	79.6 \pm 11.0	87.4 \pm 18.9	92.1 \pm 7.8	88.2 \pm 21.8
Differential leukocyte count (%)				
Neutrophil	17.3 \pm 5.3	19.6 \pm 5.4	20.4 \pm 6.2	17.6 \pm 4.7
Eosinophil	1.6 \pm 0.7	1.4 \pm 0.4	1.0 \pm 0.4	1.2 \pm 0.4
Basophil	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Monocyte	4.5 \pm 1.4	4.1 \pm 0.9	3.4 \pm 0.8	4.2 \pm 1.0
Lymphocyte	76.5 \pm 6.9	74.8 \pm 6.2	75.2 \pm 7.2	77.0 \pm 5.8
Reticulocyte count (%)	2.74 \pm 0.34	2.96 \pm 0.42	3.29 \pm 0.56	3.28 \pm 0.30

Each value shows mean \pm S.D.

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

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

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

Group	Control (vehicle: corn oil)		2-MV 1000 mg/kg	
	5		5	
Number of males				
RBC ($\times 10^4/\mu\text{L}$)	808	± 77	864	± 21
Hemoglobin (g/dL)	14.7	± 0.7	15.1	± 0.4
Hematocrit (%)	42.7	± 1.3	43.8	± 1.2
MCV (fL)	53.2	± 4.2	50.8	± 1.4
MCH (pg)	18.3	± 1.0	17.4	± 0.3
MCHC (g/dL)	34.4	± 0.8	34.4	± 0.6
Platelet ($\times 10^4/\mu\text{L}$)	86.5	± 45.2	112.5	± 13.2
PT (sec)	16.6	± 2.2	17.6	± 1.8
APTT (sec)	24.4	± 2.8	25.0	± 1.4
WBC ($\times 10^2/\mu\text{L}$)	73.6	± 16.1	84.6	± 25.7
Differential leukocyte count (%)				
Neutrophil	24.5	± 3.6	21.4	± 7.5
Eosinophil	1.9	± 0.5	1.6	± 0.5
Basophil	0.0	± 0.0	0.0	± 0.0
Monocyte	3.6	± 0.9	3.9	± 1.2
Lymphocyte	70.1	± 4.5	73.1	± 6.8
Reticulocyte count (%)	3.89	± 0.26	3.70	± 0.36

Each value shows mean \pm S.D.

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

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

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

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of females	5	5	5	5
RBC ($\times 10^4/\mu\text{L}$)	697 \pm 62	675 \pm 43	637 \pm 14	640 \pm 48
Hemoglobin (g/dL)	13.3 \pm 0.7	13.1 \pm 0.7	12.6 \pm 0.3	12.8 \pm 0.9
Hematocrit (%)	39.0 \pm 0.9	39.2 \pm 1.6	37.7 \pm 1.2	39.0 \pm 2.4
MCV (fL)	56.1 \pm 3.6	58.1 \pm 2.6	59.2 \pm 2.2	61.1 \pm 3.0
MCH (pg)	19.2 \pm 0.7	19.4 \pm 0.4	19.7 \pm 0.5	19.9 \pm 0.6
MCHC (g/dL)	34.2 \pm 1.2	33.5 \pm 0.7	33.3 \pm 0.7	32.7 \pm 0.6
Platelet ($\times 10^4/\mu\text{L}$)	117.1 \pm 11.0	112.8 \pm 17.3	99.0 \pm 30.0	110.1 \pm 16.1
PT (sec)	11.7 \pm 0.7	11.5 \pm 0.6	11.7 \pm 1.0	11.8 \pm 0.8
APTT (sec)	18.0 \pm 1.8	18.2 \pm 1.5	17.4 \pm 1.4	17.5 \pm 2.7
WBC ($\times 10^2/\mu\text{L}$)	136.3 \pm 16.6	133.9 \pm 35.5	135.2 \pm 22.6	135.0 \pm 27.6
Differential leukocyte count (%)				
Neutrophil	32.1 \pm 4.3	47.4 \pm 6.9 **	38.9 \pm 5.2	34.3 \pm 7.1
Eosinophil	0.8 \pm 0.1	0.5 \pm 0.4	0.5 \pm 0.5	0.4 \pm 0.2
Basophil	0.0 \pm 0.1	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Monocyte	3.5 \pm 0.6	3.7 \pm 0.7	4.6 \pm 0.5 *	3.3 \pm 0.6
Lymphocyte	63.6 \pm 3.9	48.4 \pm 7.5 **	56.0 \pm 4.6	61.9 \pm 7.7
Reticulocyte count (%)	7.11 \pm 3.92	8.06 \pm 0.83	7.11 \pm 2.56	9.31 \pm 2.40

Each value shows mean \pm S.D.

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

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

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

Group	Control (vehicle: corn oil)		2-MV 1000 mg/kg	
	5		5	
Number of females				
RBC ($\times 10^4/\mu\text{L}$)	774	± 23	788	± 31
Hemoglobin (g/dL)	14.7	± 0.4	14.6	± 0.5
Hematocrit (%)	42.0	± 1.2	41.8	± 1.5
MCV (fL)	54.3	± 2.2	53.0	± 1.2
MCH (pg)	19.0	± 0.7	18.5	± 0.4
MCHC (g/dL)	35.0	± 0.3	35.0	± 0.6
Platelet ($\times 10^4/\mu\text{L}$)	95.8	± 7.3	96.6	± 4.2
PT (sec)	11.8	± 0.3	11.8	± 0.5
APTT (sec)	19.3	± 0.8	19.3	± 1.6
WBC ($\times 10^2/\mu\text{L}$)	67.8	± 9.7	58.4	± 19.0
Differential leukocyte count (%)				
Neutrophil	12.3	± 4.2	12.3	± 2.9
Eosinophil	1.7	± 0.9	1.1	± 0.4
Basophil	0.0	± 0.0	0.0	± 0.0
Monocyte	1.8	± 0.7	2.6	± 0.5
Lymphocyte	84.1	± 4.6	84.0	± 3.2
Reticulocyte count (%)	3.75	± 0.78	3.70	± 1.13

Each value shows mean \pm S.D.

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

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

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

Group	Control (vehicle: corn oil)		2-MV 1000 mg/kg	
	5		5	
Number of females				
RBC ($\times 10^4/\mu\text{L}$)	774	± 19	786	± 48
Hemoglobin (g/dL)	14.5	± 0.3	14.6	± 0.7
Hematocrit (%)	41.8	± 1.1	41.9	± 1.6
MCV (fL)	54.1	± 0.4	53.4	± 1.5
MCH (pg)	18.7	± 0.2	18.6	± 0.4
MCHC (g/dL)	34.6	± 0.3	34.8	± 0.7
Platelet ($\times 10^4/\mu\text{L}$)	101.8	± 8.7	95.9	± 7.8
PT (sec)	11.6	± 0.7	11.6	± 0.5
APTT (sec)	20.1	± 1.8	19.9	± 1.2
WBC ($\times 10^2/\mu\text{L}$)	37.0	± 7.1	40.9	± 7.6
Differential leukocyte count (%)				
Neutrophil	15.4	± 3.6	13.4	± 1.7
Eosinophil	2.3	± 0.6	2.3	± 0.9
Basophil	0.0	± 0.0	0.0	± 0.0
Monocyte	3.0	± 0.6	3.6	± 1.1
Lymphocyte	79.4	± 4.1	80.7	± 2.0
Reticulocyte count (%)	2.62	± 0.29	2.63	± 0.32

Each value shows mean \pm S.D.

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

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

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

Group		Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of males		5	5	5	5
Total protein	g/dL	5.6 ± 0.3	5.4 ± 0.1	5.6 ± 0.3	5.5 ± 0.1
Albumin	g/dL	3.5 ± 0.1	3.5 ± 0.1	3.5 ± 0.1	3.5 ± 0.1
A/G		1.72 ± 0.14	1.77 ± 0.13	1.66 ± 0.06	1.80 ± 0.12
Glucose	mg/dL	155 ± 14	142 ± 6	155 ± 9	137 ± 12
Total cholesterol	mg/dL	48 ± 6	47 ± 8	51 ± 10	52 ± 8
Triglyceride	mg/dL	46 ± 6	36 ± 19	41 ± 10	47 ± 18
Phospholipid	mg/dL	87 ± 10	80 ± 11	84 ± 10	91 ± 11
AST	U/L	51 ± 7	56 ± 7	56 ± 6	49 ± 5
ALT	U/L	25 ± 5	26 ± 5	30 ± 4	22 ± 3
γ-GTP	U/L	1 ± 1	0 ± 0	0 ± 0	1 ± 1
LDH	U/L	103 ± 41	173 ± 108	118 ± 75	72 ± 20
Bile acid	μmol/L	12.6 ± 7.0	9.8 ± 4.5	11.1 ± 3.4	11.8 ± 4.3
BUN	mg/dL	13 ± 1	14 ± 2	15 ± 2	13 ± 1
Creatinine	mg/dL	0.5 ± 0.1	0.4 ± 0.0	0.5 ± 0.0	0.5 ± 0.1
Total bilirubin	mg/dL	0.06 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.01
ALP	U/L	347 ± 62	327 ± 68	372 ± 77	324 ± 81
Inorganic phosphorus	mg/dL	5.9 ± 0.4	5.8 ± 0.7	6.0 ± 0.4	6.0 ± 0.6
Ca	mg/dL	9.2 ± 0.2	9.3 ± 0.2	9.2 ± 0.4	9.3 ± 0.2
Na	mEq/L	144.7 ± 0.4	144.5 ± 1.1	144.3 ± 0.5	143.7 ± 0.9
K	mEq/L	3.97 ± 0.32	3.81 ± 0.05	3.82 ± 0.10	4.02 ± 0.15
Cl	mEq/L	106.9 ± 1.0	108.1 ± 1.4	107.3 ± 1.2	105.8 ± 1.2

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 2-Methylvaleraldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	2-MV 1000 mg/kg
Number of males		5	5
Total protein	g/dL	5.9 ± 0.4	5.6 ± 0.2
Albumin	g/dL	3.8 ± 0.3	3.6 ± 0.1
A/G		1.79 ± 0.16	1.82 ± 0.11
Glucose	mg/dL	138 ± 20	150 ± 12
Total cholesterol	mg/dL	53 ± 6	53 ± 13
Triglyceride	mg/dL	18 ± 9	28 ± 17
Phospholipid	mg/dL	81 ± 12	86 ± 13
AST	U/L	64 ± 7	61 ± 7
ALT	U/L	29 ± 3	27 ± 6
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	144 ± 107	304 ± 165
Bile acid	μmol/L	12.3 ± 3.2	7.3 ± 2.8 *
BUN	mg/dL	18 ± 1	15 ± 2
Creatinine	mg/dL	0.6 ± 0.1	0.5 ± 0.0
Total bilirubin	mg/dL	0.05 ± 0.02	0.06 ± 0.01
ALP	U/L	264 ± 55	261 ± 32
Inorganic phosphorus	mg/dL	5.8 ± 0.6	5.9 ± 0.4
Ca	mg/dL	9.1 ± 0.2	9.2 ± 0.2
Na	mEq/L	143.2 ± 0.8	142.6 ± 0.8
K	mEq/L	3.99 ± 0.32	3.91 ± 0.25
Cl	mEq/L	107.3 ± 2.0	106.1 ± 1.4

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of females		5	5	5	5
Total protein	g/dL	5.6 ± 0.4	5.7 ± 0.2	5.7 ± 0.5	5.8 ± 0.3
Albumin	g/dL	3.9 ± 0.3	4.0 ± 0.1	3.8 ± 0.3	4.0 ± 0.3
A/G		2.20 ± 0.10	2.32 ± 0.20	2.05 ± 0.18	2.20 ± 0.34
Glucose	mg/dL	124 ± 25	139 ± 15	137 ± 5	135 ± 15
Total cholesterol	mg/dL	54 ± 10	59 ± 20	59 ± 20	53 ± 11
Triglyceride	mg/dL	45 ± 30	31 ± 9	35 ± 15	44 ± 29
Phospholipid	mg/dL	112 ± 9	112 ± 28	106 ± 26	109 ± 27
AST	U/L	85 ± 33	81 ± 10	68 ± 6	71 ± 11
ALT	U/L	47 ± 10	41 ± 6	37 ± 4	38 ± 4
γ-GTP	U/L	0 ± 0	1 ± 1	0 ± 0	0 ± 0
LDH	U/L	227 ± 50	141 ± 49	158 ± 85	128 ± 55
Bile acid	μmol/L	17.7 ± 9.2	10.0 ± 3.3	7.8 ± 3.3	11.2 ± 3.1
BUN	mg/dL	12 ± 4	13 ± 2	10 ± 2	13 ± 3
Creatinine	mg/dL	0.5 ± 0.1	0.6 ± 0.0	0.5 ± 0.1	0.6 ± 0.1
Total bilirubin	mg/dL	0.08 ± 0.01	0.07 ± 0.02	0.07 ± 0.01	0.07 ± 0.02
ALP	U/L	166 ± 47	226 ± 105	157 ± 39	139 ± 52
Inorganic phosphorus	mg/dL	6.4 ± 0.5	6.8 ± 1.0	6.8 ± 0.7	6.3 ± 0.6
Ca	mg/dL	9.6 ± 0.5	9.8 ± 0.3	9.8 ± 0.3	9.9 ± 0.2
Na	mEq/L	141.6 ± 1.2	142.1 ± 0.9	142.5 ± 3.1	141.6 ± 1.8
K	mEq/L	3.21 ± 0.31	3.35 ± 0.37	3.33 ± 0.29	3.44 ± 0.37
Cl	mEq/L	103.7 ± 3.0	106.9 ± 2.1	108.3 ± 2.0	106.1 ± 2.2

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 2-Methylvaleraldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	2-MV 1000 mg/kg
Number of females		5	5
Total protein	g/dL	5.7 ± 0.3	6.1 ± 0.2 *
Albumin	g/dL	4.0 ± 0.1	4.4 ± 0.2 **
A/G		2.40 ± 0.31	2.61 ± 0.31
Glucose	mg/dL	123 ± 12	131 ± 8
Total cholesterol	mg/dL	65 ± 8	67 ± 10
Triglyceride	mg/dL	17 ± 9	16 ± 3
Phospholipid	mg/dL	116 ± 7	130 ± 19
AST	U/L	57 ± 9	49 ± 3
ALT	U/L	22 ± 4	18 ± 2
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	98 ± 48	79 ± 36
Bile acid	μmol/L	13.7 ± 7.1	10.0 ± 1.3
BUN	mg/dL	17 ± 3	18 ± 1
Creatinine	mg/dL	0.6 ± 0.1	0.6 ± 0.0
Total bilirubin	mg/dL	0.09 ± 0.01	0.08 ± 0.01
ALP	U/L	179 ± 56	131 ± 25
Inorganic phosphorus	mg/dL	4.7 ± 0.6	4.8 ± 0.9
Ca	mg/dL	9.3 ± 0.1	9.8 ± 0.2 **
Na	mEq/L	142.3 ± 1.2	142.9 ± 1.1
K	mEq/L	3.66 ± 0.26	3.69 ± 0.33
Cl	mEq/L	107.3 ± 1.4	107.4 ± 0.9

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: corn oil)	2-MV 1000 mg/kg
Number of females		5	5
Total protein	g/dL	6.1 ± 0.3	6.1 ± 0.3
Albumin	g/dL	4.2 ± 0.3	4.2 ± 0.3
A/G		2.19 ± 0.29	2.29 ± 0.19
Glucose	mg/dL	123 ± 15	133 ± 13
Total cholesterol	mg/dL	67 ± 3	70 ± 14
Triglyceride	mg/dL	15 ± 6	19 ± 7
Phospholipid	mg/dL	118 ± 13	123 ± 19
AST	U/L	53 ± 9	57 ± 10
ALT	U/L	22 ± 7	25 ± 7
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	66 ± 35	62 ± 12
Bile acid	μmol/L	51.2 ± 76.7	16.2 ± 7.3
BUN	mg/dL	18 ± 3	18 ± 3
Creatinine	mg/dL	0.6 ± 0.1	0.6 ± 0.1
Total bilirubin	mg/dL	0.08 ± 0.02	0.08 ± 0.01
ALP	U/L	143 ± 42	153 ± 23
Inorganic phosphorus	mg/dL	3.8 ± 0.5	4.3 ± 0.6
Ca	mg/dL	9.3 ± 0.3	9.4 ± 0.2
Na	mEq/L	142.8 ± 1.3	142.6 ± 0.9
K	mEq/L	3.65 ± 0.26	3.51 ± 0.08
Cl	mEq/L	108.3 ± 1.5	107.2 ± 0.6

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: corn oil)		2-MV 62.5 mg/kg		2-MV 250 mg/kg		2-MV 1000 mg/kg	
Number of males		7		12		12		7	
Body weight	(g)	482.5 ± 38.3		471.1 ± 32.9		478.1 ± 43.6		465.2 ± 27.9	
Brain	(mg)	1992.5 ± 76.7		1968.6 ± 72.1		1996.8 ± 90.9		1974.9 ± 67.9	
	(mg/g)	4.146 ± 0.280		4.199 ± 0.344		4.202 ± 0.339		4.261 ± 0.322	
Thymus	(mg)	329.2 ± 91.8		276.7 ± 73.7		252.6 ± 71.6		266.9 ± 64.7	
	(mg/g)	0.685 ± 0.201		0.585 ± 0.135		0.529 ± 0.138		0.575 ± 0.137	
Heart	(mg)	1376.3 ± 96.0		1405.3 ± 156.9		1385.5 ± 107.1		1323.2 ± 72.1	
	(mg/g)	2.855 ± 0.062		2.978 ± 0.187		2.909 ± 0.222		2.849 ± 0.145	
Liver	(mg)	13468.6 ± 2034.7		13082.3 ± 1588.6		13490.5 ± 1758.5		13472.3 ± 1178.6	
	(mg/g)	27.843 ± 2.754		27.700 ± 1.671		28.163 ± 1.796		28.963 ± 1.829	
Kidney (R)	(mg)	1506.3 ± 167.0		1529.7 ± 122.6		1529.0 ± 148.5		1547.0 ± 117.2	
	(mg/g)	3.124 ± 0.281		3.247 ± 0.133		3.206 ± 0.235		3.330 ± 0.223	
Kidney (L)	(mg)	1520.1 ± 171.3		1538.1 ± 106.0		1513.5 ± 104.5		1522.1 ± 102.7	
	(mg/g)	3.155 ± 0.299		3.268 ± 0.141		3.183 ± 0.276		3.276 ± 0.187	
Kidneys	(mg)	3026.3 ± 331.9		3067.8 ± 221.5		3042.6 ± 249.0		3069.2 ± 218.4	
	(mg/g)	6.279 ± 0.565		6.516 ± 0.246		6.389 ± 0.498		6.606 ± 0.407	
Spleen	(mg)	758.8 ± 63.6		857.1 ± 189.6		793.6 ± 89.0		772.1 ± 76.1	
	(mg/g)	1.575 ± 0.108		1.816 ± 0.366		1.663 ± 0.151		1.665 ± 0.196	
Testis (R)	(mg)	1603.0 ± 108.1		1664.8 ± 138.4		1625.3 ± 104.6		1618.2 ± 153.9	
	(mg/g)	3.334 ± 0.265		3.536 ± 0.183		3.423 ± 0.350		3.479 ± 0.258	
Testis (L)	(mg)	1583.7 ± 121.5		1674.4 ± 144.7		1644.5 ± 87.9		1597.7 ± 153.1	
	(mg/g)	3.297 ± 0.323		3.558 ± 0.219		3.467 ± 0.365		3.435 ± 0.255	
Testes	(mg)	3186.7 ± 225.5		3339.2 ± 276.4		3269.8 ± 187.8		3215.9 ± 305.0	
	(mg/g)	6.630 ± 0.585		7.093 ± 0.382		6.890 ± 0.709		6.914 ± 0.506	
Epididymis (R)	(mg)	596.0 ± 34.2		637.6 ± 40.9		644.8 ± 47.2		614.9 ± 46.2	
	(mg/g)	1.239 ± 0.089		1.358 ± 0.104		1.363 ± 0.194		1.323 ± 0.075	
Epididymis (L)	(mg)	590.1 ± 34.7		630.6 ± 42.6		632.0 ± 36.9		588.0 ± 42.1	
	(mg/g)	1.227 ± 0.089		1.342 ± 0.098		1.333 ± 0.154		1.266 ± 0.084	
Epididymides	(mg)	1186.1 ± 67.6		1268.2 ± 80.1		1276.8 ± 76.2 *		1202.9 ± 86.0	
	(mg/g)	2.467 ± 0.176		2.700 ± 0.195		2.696 ± 0.341		2.588 ± 0.153	

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 2-Methylvaleraldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		2-MV 62.5 mg/kg		2-MV 250 mg/kg		2-MV 1000 mg/kg	
Number of males		7		12		12		7	
Prostate, ventral	(mg)	492.6 ±	117.5	650.8 ±	186.6	665.1 ±	87.5 *	548.9 ±	67.3
	(mg/g)	1.032 ±	0.293	1.392 ±	0.424	1.406 ±	0.242 *	1.180 ±	0.125
Seminal vesicles	(mg)	1450.5 ±	383.9	1826.3 ±	239.5 *	1813.2 ±	232.9 *	1617.1 ±	266.1
	(mg/g)	2.990 ±	0.704	3.895 ±	0.594 **	3.825 ±	0.616 *	3.465 ±	0.482
Thyroid gland	(mg)	15.7 ±	2.3	18.3 ±	3.2	19.0 ±	3.9	17.2 ±	4.6
	(mg/g)	0.033 ±	0.005	0.039 ±	0.007	0.040 ±	0.008	0.037 ±	0.010
Adrenal gland (R)	(mg)	25.7 ±	3.1	25.7 ±	3.1	26.7 ±	3.8	29.6 ±	4.9
	(mg/g)	0.053 ±	0.005	0.055 ±	0.007	0.056 ±	0.009	0.064 ±	0.011
Adrenal gland (L)	(mg)	27.0 ±	3.8	26.6 ±	4.1	27.4 ±	4.5	31.1 ±	4.0
	(mg/g)	0.056 ±	0.008	0.057 ±	0.010	0.058 ±	0.009	0.067 ±	0.011
Adrenal glands	(mg)	52.7 ±	6.8	52.3 ±	7.0	54.1 ±	8.1	60.7 ±	8.8
	(mg/g)	0.109 ±	0.013	0.111 ±	0.016	0.114 ±	0.018	0.131 ±	0.022

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 2-Methylvaleraldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		2-MV 1000 mg/kg	
Number of males		5		5	
Body weight	(g)	466.3	± 43.2	512.9	± 28.3
Brain	(mg)	1985.0	± 81.5	2045.0	± 79.8
	(mg/g)	4.282	± 0.368	3.990	± 0.082
Thymus	(mg)	280.0	± 34.1	265.2	± 92.8
	(mg/g)	0.601	± 0.053	0.513	± 0.159
Heart	(mg)	1284.0	± 139.4	1481.2	± 107.4 *
	(mg/g)	2.751	± 0.055	2.889	± 0.150
Liver	(mg)	11799.3	± 2096.8	14050.8	± 1765.3
	(mg/g)	25.178	± 2.691	27.323	± 2.115
Kidney (R)	(mg)	1457.8	± 66.5	1652.9	± 232.8
	(mg/g)	3.139	± 0.181	3.213	± 0.294
Kidney (L)	(mg)	1398.9	± 75.4	1639.4	± 181.7 *
	(mg/g)	3.013	± 0.208	3.191	± 0.205
Kidneys	(mg)	2856.7	± 135.2	3292.4	± 414.4
	(mg/g)	6.152	± 0.378	6.404	± 0.497
Spleen	(mg)	783.8	± 92.4	881.4	± 138.9
	(mg/g)	1.685	± 0.172	1.719	± 0.261
Testis (R)	(mg)	1656.1	± 188.6	1698.0	± 123.1
	(mg/g)	3.586	± 0.594	3.320	± 0.327
Testis (L)	(mg)	1621.8	± 142.2	1724.7	± 96.4
	(mg/g)	3.509	± 0.514	3.370	± 0.248
Testes	(mg)	3277.9	± 329.6	3422.7	± 215.6
	(mg/g)	7.095	± 1.105	6.689	± 0.572
Epididymis (R)	(mg)	647.8	± 70.6	686.9	± 38.6
	(mg/g)	1.405	± 0.250	1.343	± 0.109
Epididymis (L)	(mg)	619.8	± 52.0	675.4	± 47.2
	(mg/g)	1.343	± 0.208	1.319	± 0.094
Epididymides	(mg)	1267.6	± 122.3	1362.3	± 83.2
	(mg/g)	2.748	± 0.458	2.661	± 0.198

Each value shows mean ± S.D.

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

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

Group		Control (vehicle: corn oil)		2-MV 1000 mg/kg	
Number of males		5		5	
Prostate, ventral	(mg)	600.3	± 132.0	591.9	± 109.1
	(mg/g)	1.285	± 0.237	1.150	± 0.176
Seminal vesicles	(mg)	1609.2	± 207.4	1681.6	± 235.0
	(mg/g)	3.503	± 0.752	3.285	± 0.471
Thyroid gland	(mg)	18.5	± 5.4	17.8	± 3.7
	(mg/g)	0.041	± 0.015	0.035	± 0.007
Adrenal gland (R)	(mg)	24.0	± 4.4	26.5	± 8.0
	(mg/g)	0.052	± 0.013	0.052	± 0.019
Adrenal gland (L)	(mg)	26.3	± 3.7	26.3	± 3.5
	(mg/g)	0.057	± 0.011	0.051	± 0.009
Adrenal glands	(mg)	50.3	± 8.0	52.8	± 11.1
	(mg/g)	0.109	± 0.025	0.104	± 0.027

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 2-Methylvaleraldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)		2-MV 62.5 mg/kg		2-MV 250 mg/kg		2-MV 1000 mg/kg	
	11		11		11		11	
Number of females								
Body weight	(g)	302.2 ± 29.2	309.5 ± 24.0	289.8 ± 23.1	306.1 ± 19.9			
Brain	(mg)	1870.6 ± 51.5	1872.1 ± 49.8	1860.8 ± 85.6	1884.1 ± 92.4			
	(mg/g)	6.242 ± 0.631	6.081 ± 0.493	6.441 ± 0.321	6.169 ± 0.346			
Thymus	(mg)	192.5 ± 54.4	169.9 ± 55.0	159.8 ± 50.1	221.9 ± 78.6			
	(mg/g)	0.638 ± 0.170	0.545 ± 0.162	0.549 ± 0.163	0.720 ± 0.233			
Heart	(mg)	973.3 ± 91.8	974.9 ± 82.3	921.9 ± 72.1	980.8 ± 61.6			
	(mg/g)	3.225 ± 0.180	3.153 ± 0.181	3.185 ± 0.165	3.212 ± 0.224			
Liver	(mg)	10138.9 ± 1157.7	9887.7 ± 808.0	9661.8 ± 828.6	10741.7 ± 704.3			
	(mg/g)	33.572 ± 2.489	32.098 ± 3.437	33.427 ± 2.580	35.109 ± 1.098			
Kidney (R)	(mg)	962.8 ± 87.8	951.4 ± 55.4	930.3 ± 85.2	1009.6 ± 113.2			
	(mg/g)	3.203 ± 0.338	3.083 ± 0.205	3.212 ± 0.175	3.299 ± 0.311			
Kidney (L)	(mg)	955.7 ± 84.6	953.5 ± 51.4	893.8 ± 75.1	995.2 ± 102.0			
	(mg/g)	3.183 ± 0.361	3.091 ± 0.201	3.087 ± 0.150	3.254 ± 0.294			
Kidneys	(mg)	1918.5 ± 169.9	1904.9 ± 104.0	1824.1 ± 155.9	2004.8 ± 213.1			
	(mg/g)	6.386 ± 0.692	6.174 ± 0.398	6.298 ± 0.301	6.552 ± 0.596			
Spleen	(mg)	635.8 ± 137.4	667.0 ± 89.7	624.8 ± 84.0	749.2 ± 104.4 *			
	(mg/g)	2.094 ± 0.357	2.157 ± 0.258	2.158 ± 0.270	2.450 ± 0.333 *			
Ovary (R)	(mg)	53.3 ± 8.7	52.9 ± 7.8	54.4 ± 8.0	55.7 ± 13.6			
	(mg/g)	0.177 ± 0.031	0.171 ± 0.025	0.188 ± 0.023	0.181 ± 0.038			
Ovary (L)	(mg)	52.1 ± 9.9	51.3 ± 5.3	45.7 ± 8.8	54.9 ± 8.3			
	(mg/g)	0.172 ± 0.025	0.167 ± 0.021	0.157 ± 0.024	0.179 ± 0.022			
Ovaries	(mg)	105.4 ± 12.3	104.2 ± 7.1	100.1 ± 13.0	110.6 ± 20.8			
	(mg/g)	0.349 ± 0.026	0.338 ± 0.027	0.345 ± 0.030	0.360 ± 0.056			
Uterus	(mg)	615.6 ± 123.6	595.0 ± 67.6	588.9 ± 111.3	604.8 ± 82.8			
	(mg/g)	2.033 ± 0.326	1.923 ± 0.160	2.040 ± 0.407	1.979 ± 0.271			
Thyroid gland	(mg)	17.6 ± 4.4	15.1 ± 2.6	16.0 ± 3.5	16.6 ± 3.0			
	(mg/g)	0.058 ± 0.015	0.049 ± 0.010	0.056 ± 0.016	0.054 ± 0.009			
Adrenal gland (R)	(mg)	37.6 ± 4.6	38.6 ± 3.7	39.5 ± 7.4	40.4 ± 3.9			
	(mg/g)	0.125 ± 0.017	0.126 ± 0.016	0.137 ± 0.030	0.132 ± 0.013			
Adrenal gland (L)	(mg)	41.0 ± 4.6	41.3 ± 4.1	43.0 ± 5.0	43.4 ± 4.3			
	(mg/g)	0.136 ± 0.018	0.134 ± 0.015	0.149 ± 0.020	0.142 ± 0.013			
Adrenal glands	(mg)	78.6 ± 8.4	79.9 ± 7.4	82.5 ± 12.0	83.8 ± 7.7			
	(mg/g)	0.262 ± 0.032	0.260 ± 0.030	0.286 ± 0.049	0.274 ± 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 2-Methylvaleraldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)			2-MV 1000 mg/kg		
	Number of females	5		5		
Body weight	(g)	285.5 ±	17.5	283.7 ±	9.9	
Brain	(mg)	1838.0 ±	78.6	1812.6 ±	72.0	
	(mg/g)	6.453 ±	0.409	6.393 ±	0.275	
Thymus	(mg)	293.9 ±	57.1	289.0 ±	33.5	
	(mg/g)	1.027 ±	0.185	1.016 ±	0.089	
Heart	(mg)	877.6 ±	28.1	913.8 ±	47.5	
	(mg/g)	3.083 ±	0.216	3.222 ±	0.141	
Liver	(mg)	7034.1 ±	690.4	7868.4 ±	324.9 *	
	(mg/g)	24.607 ±	1.335	27.757 ±	1.299 **	
Kidney (R)	(mg)	852.3 ±	67.8	946.4 ±	52.6 *	
	(mg/g)	2.993 ±	0.291	3.340 ±	0.229	
Kidney (L)	(mg)	851.3 ±	70.7	921.2 ±	25.2	
	(mg/g)	2.985 ±	0.227	3.252 ±	0.187	
Kidneys	(mg)	1703.6 ±	133.6	1867.5 ±	75.0 *	
	(mg/g)	5.978 ±	0.507	6.592 ±	0.401	
Spleen	(mg)	537.2 ±	56.2	532.0 ±	65.8	
	(mg/g)	1.887 ±	0.221	1.876 ±	0.218	
Ovary (R)	(mg)	34.9 ±	3.7	39.1 ±	8.5	
	(mg/g)	0.123 ±	0.016	0.138 ±	0.030	
Ovary (L)	(mg)	37.5 ±	5.5	35.8 ±	7.7	
	(mg/g)	0.132 ±	0.020	0.126 ±	0.025	
Ovaries	(mg)	72.4 ±	6.6	74.9 ±	7.4	
	(mg/g)	0.254 ±	0.029	0.264 ±	0.023	
Uterus	(mg)	470.5 ±	245.9	895.2 ±	475.4	
	(mg/g)	1.689 ±	1.004	3.145 ±	1.661	
Thyroid gland	(mg)	14.4 ±	1.5	14.6 ±	3.8	
	(mg/g)	0.051 ±	0.008	0.051 ±	0.013	
Adrenal gland (R)	(mg)	28.8 ±	3.6	30.1 ±	1.1	
	(mg/g)	0.101 ±	0.013	0.106 ±	0.005	
Adrenal gland (L)	(mg)	29.6 ±	3.3	31.5 ±	1.4	
	(mg/g)	0.104 ±	0.014	0.111 ±	0.006	
Adrenal glands	(mg)	58.4 ±	6.6	61.6 ±	2.0	
	(mg/g)	0.205 ±	0.027	0.218 ±	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 2-Methylvaleraldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		2-MV 1000 mg/kg	
Number of females		5		5	
Body weight	(g)	291.3	± 10.2	281.5	± 10.7
Brain	(mg)	1918.9	± 79.5	1813.9	± 75.7
	(mg/g)	6.598	± 0.467	6.447	± 0.225
Thymus	(mg)	216.8	± 34.1	259.1	± 70.6
	(mg/g)	0.747	± 0.135	0.919	± 0.238
Heart	(mg)	900.2	± 47.4	936.0	± 59.8
	(mg/g)	3.096	± 0.249	3.331	± 0.275
Liver	(mg)	7043.1	± 445.0	7140.7	± 613.2
	(mg/g)	24.179	± 1.361	25.363	± 1.897
Kidney (R)	(mg)	953.5	± 82.6	906.1	± 42.0
	(mg/g)	3.280	± 0.352	3.221	± 0.152
Kidney (L)	(mg)	903.7	± 79.1	893.2	± 48.0
	(mg/g)	3.109	± 0.344	3.174	± 0.134
Kidneys	(mg)	1857.2	± 160.1	1799.3	± 81.1
	(mg/g)	6.389	± 0.692	6.394	± 0.250
Spleen	(mg)	538.9	± 93.7	538.0	± 64.1
	(mg/g)	1.854	± 0.343	1.911	± 0.213
Ovary (R)	(mg)	41.1	± 4.7	41.9	± 7.4
	(mg/g)	0.142	± 0.018	0.149	± 0.030
Ovary (L)	(mg)	42.1	± 6.1	40.8	± 3.7
	(mg/g)	0.145	± 0.021	0.145	± 0.016
Ovaries	(mg)	83.2	± 9.7	82.7	± 10.9
	(mg/g)	0.286	± 0.035	0.295	± 0.046
Uterus	(mg)	600.6	± 206.7	504.2	± 126.1
	(mg/g)	2.054	± 0.657	1.785	± 0.408
Thyroid gland	(mg)	14.8	± 2.2	16.3	± 6.3
	(mg/g)	0.051	± 0.007	0.058	± 0.022
Adrenal gland (R)	(mg)	33.3	± 7.5	31.4	± 4.4
	(mg/g)	0.115	± 0.028	0.112	± 0.017
Adrenal gland (L)	(mg)	34.9	± 6.0	33.5	± 5.3
	(mg/g)	0.120	± 0.023	0.120	± 0.020
Adrenal glands	(mg)	68.3	± 13.3	64.9	± 9.2
	(mg/g)	0.235	± 0.050	0.231	± 0.035

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 2-Methylvaleraldehyde by oral administration in rats

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

Findings	Group Grade	Control (vehicle: corn oil)		2-MV 62.5 mg/kg		2-MV 250 mg/kg		2-MV 1000 mg/kg	
		-	P	-	P	-	P	-	P
Epididymis									
Nodule, yellowish white, caudal, unilateral		7	0	11	1	12	0	6	1
Forestomach									
Edematous, mucosa		7	0	12	0	10	2	0	7
Thickening, mucosa		7	0	12	0	12	0	6	1

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

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

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

Findings	Group Grade	Control (vehicle: corn oil)		2-MV 1000 mg/kg	
		-	P	-	P
Forestomach					
Edematous, mucosa		5	0	4	1
Glandular stomach					
Recessed area, mucosa, black color		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 2-Methylvaleraldehyde by oral administration in rats

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

Findings	Group Grade	Control (vehicle: corn oil)		2-MV 62.5 mg/kg		2-MV 250 mg/kg		2-MV 1000 mg/kg	
		-	P	-	P	-	P	-	P
Forestomach									
Edematous, mucosa		10	1	10	1	6	5	1	10
Recessed area, mucosa, black color		11	0	11	0	10	1	9	2
Thickening, mucosa		11	0	11	0	11	0	10	1
Glandular stomach									
Recessed area, mucosa		10	1	11	0	11	0	11	0
Ovary									
Cystic ovarian bursa, reddish fluid, right		10	1	11	0	11	0	11	0

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

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

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

Findings	Group Grade	Control (vehicle: corn oil)		2-MV 1000 mg/kg	
		-	P	-	P
Forestomach					
Edematous, mucosa		5	0	1	4
Thickening, mucosa		5	0	2	3
Ileum					
Diverticulum		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 2-Methylvaleraldehyde by oral administration in rats

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

Findings	Group Grade	Control (vehicle: corn oil)		2-MV 1000 mg/kg	
		-	P	-	P
Liver					
Diaphragmatic nodule		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 2-Methylvaleraldehyde by oral administration in rats

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

Findings	Group Grade	Control (vehicle: control)						2-MV 62.5 mg/kg						2-MV 250 mg/kg						2-MV 1000 mg/kg									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5					2	0						12	0							12	5						2
Spinal cord		5					2	0						12	0							12	5						2
Pituitary gland		5					2	0						12	0							12	5						2
Submandibular gland		5					2	0						12	0							12	5						2
Sublingual gland		5					2	0						12	0							12	5						2
Lymph node, submandibular		5					2	0						12	0							12	5						2
Thyroid gland																													
Cellular infiltration, lymphocyte, focal		5	0	0	0	0	0	2	0	0	0	0	0	0	12	0	0	0	0	0	0	12	4	1	0	0	0	0	2
Ectopic thymic tissue		5					0	2	0					0	12	0						0	12	3					2
Ultimobranchial body		4					1	2	0					0	12	0						0	12	3					2
Parathyroid gland		5					2	0						12	0							12	5						2
Thymus		5					2	0						12	0							12	5						2
Heart																													
Degeneration/fibrosis, myocardial, focal		4	1	0	0	0	0	2	0	0	0	0	0	0	12	0	0	0	0	0	0	12	5	0	0	0	0	0	2
Trachea		5					2	0						12	0							12	5						2
Lung																													
Accumulation, foam cell, alveolus		4	1	0	0	0	0	2	0	0	0	0	0	0	12	0	0	0	0	0	0	12	5	0	0	0	0	0	2
Hemorrhage, focal		4	1	0	0	0	0	2	0	0	0	0	0	0	12	0	0	0	0	0	0	12	5	0	0	0	0	0	2
Metaplasia, osseous, focal		4	1	0	0	0	0	2	0	0	0	0	0	0	12	0	0	0	0	0	0	12	5	0	0	0	0	0	2
Mineralization, focal, arterial wall		4	1	0	0	0	0	2	0	0	0	0	0	0	12	0	0	0	0	0	0	12	5	0	0	0	0	0	2
Bronchus		5					2	0						12	0							12	5						2
Liver																													
Fatty change, hepatocyte, periportal		2	1	2	0	0	0	2	0	0	0	0	0	0	12	0	0	0	0	0	0	12	1	4	0	0	0	0	2
Microgranuloma		2	3	0	0	0	0	2	0	0	0	0	0	0	12	0	0	0	0	0	0	12	3	2	0	0	0	0	2
Pancreas																													
Cellular infiltration, lymphocyte, interstitial		5	0	0	0	0	0	2	0	0	0	0	0	0	12	0	0	0	0	0	0	12	4	1	0	0	0	0	2

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

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

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

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

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

Findings	Group Grade	Control (vehicle: control)						2-MV 62.5 mg/kg						2-MV 250 mg/kg						2-MV 1000 mg/kg													
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE				
Stomach																																	
Forestomach																																	
Cellular infiltration, inflammatory, submucosa		5	0	0	0	0	2	5	0	0	0	0	7	6	1	0	0	0	5	0	3	4	0	0								**,#	
Edema, lamina propria/ submucosa		5	0	0	0	0	2	5	0	0	0	0	7	5	2	0	0	0	5	2	5	0	0	0								*,#	
Hyperkeratosis		5	0	0	0	0	2	5	0	0	0	0	7	4	3	0	0	0	5	0	0	0	7	0								**,#	
Hyperplasia, squamous cell		5	0	0	0	0	2	5	0	0	0	0	7	2	5	0	0	0	5	*,#	0	0	4	3	0								**,#
Glandular stomach																																	
Cellular infiltration, inflammatory, submucosa		3	2	0	0	0	2	4	1	0	0	0	7	6	1	0	0	0	5	7	0	0	0	0									
Edema, submucosa		0	5	0	0	0	2	2	2	1	0	0	7	3	3	1	0	0	5	2	5	0	0	0									
Increase, mucus		4	1	0	0	0	2	4	1	0	0	0	7	5	2	0	0	0	5	6	1	0	0	0									
Duodenum		5					2	0				12	0				12	5												2			
Jejunum		5					2	0				12	0				12	5												2			
Ileum		5					2	0				12	0				12	5												2			
Cecum		5					2	0				12	0				12	5												2			
Colon		5					2	0				12	0				12	5												2			
Rectum		5					2	0				12	0				12	5												2			
Lymph node, mesenteric		5					2	0				12	0				12	5												2			
Spleen																																	
Deposit, pigment, brown		0	5	0	0	0	2	0	0	0	0	0	12	0	0	0	0	0	12	0	4	1	0	0								2	
Hematopoiesis, extramedullary		0	3	2	0	0	2	0	0	0	0	0	12	0	0	0	0	0	12	0	1	3	1	0								2	
Kidney																																	
Basophilic tubule, cortex		3	2	0	0	0	2	0	0	0	0	0	12	0	0	0	0	0	12	3	2	0	0	0								2	
Mineralization, medulla		5	0	0	0	0	2	0	0	0	0	0	12	0	0	0	0	0	12	4	1	0	0	0								2	
Urinary bladder		5					2	0				12	0				12	5												2			

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

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

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

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

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

Findings	Group Grade	Control (vehicle: control)						2-MV 62.5 mg/kg						2-MV 250 mg/kg						2-MV 1000 mg/kg								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Adrenal gland																												
Vacuolation, zona fasciculata		4	1	0	0	0	2	0	0	0	0	0	12	0	0	0	0	0	12	5	0	0	0	0	0	2		
Testis		5					2	0				12	0				12	5						2				
Epididymis																												
Granuloma, spermatic, caudal, unilateral		5				0	2	0				1	11	0				0	12	5				0	2			
Prostate																												
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0	2	0	0	0	0	0	12	0	0	0	0	0	12	4	1	0	0	0	0	2		
Seminal vesicle		5					2	0				12	0				12	5						2				
Coagulating gland		5					2	0				12	0				12	5						2				
Eyeball		5					2	0				12	0				12	5						2				
Harderian gland																												
Cellular infiltration, lymphocyte, interstitial		5	0	0	0	0	2	0	0	0	0	0	12	0	0	0	0	0	12	4	1	0	0	0	0	2		
Sciatic nerve		5					2	0				12	0				12	5						2				
Skeletal muscle		5					2	0				12	0				12	5						2				
Femur		5					2	0				12	0				12	5						2				
Marrow, femur		5					2	0				12	0				12	5						2				

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

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

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

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

Table 33-2. Histopathological findings of male rats at the end of the recovery period [H.E. staining]

Findings	Group Grade	Control (vehicle: control)						2-MV 1000 mg/kg							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Stomach															
Forestomach															
Cellular infiltration, inflammatory, submucosa		5	0	0	0	0		3	2	0	0	0			
Hyperplasia, squamous cell		5	0	0	0	0		0	5	0	0	0			** , ##
Glandular stomach															
Cellular infiltration, inflammatory, submucosa		3	2	0	0	0		3	2	0	0	0			
Edema, submucosa		3	2	0	0	0		2	2	1	0	0			
Increase, mucus		4	1	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.

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

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

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

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

Findings	Group Grade	Control (vehicle: control)						2-MV 62.5 mg/kg						2-MV 250 mg/kg						2-MV 1000 mg/kg									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5					6	0						11	0							11	5						6
Spinal cord		5					6	0						11	0							11	5						6
Pituitary gland		5					6	0						11	0							11	5						6
Submandibular gland		5					6	0						11	0							11	5						6
Sublingual gland		5					6	0						11	0							11	5						6
Lymph node, submandibular		5					6	0						11	0							11	5						6
Thyroid gland																													
Ultimobranchial body		3					2	6	0			0	11	0			0	11				4					1	6	
Parathyroid gland																													
Vacuolation, cytoplasmic		4	1	0	0	0		6	0	0	0	0	0	11	0	0	0	0	0	0	11	5	0	0	0	0	0		6
Thymus																													
Atrophy		1	3	0	1	0		6	0	0	0	0	0	11	0	0	0	0	0	0	11	1	4	0	0	0	0		6
Heart		5					6	0						11	0							11	5						6
Trachea		5					6	0						11	0							11	5						6
Lung																													
Accumulation, foam cell, alveolus		3	2	0	0	0		6	0	0	0	0	0	11	0	0	0	0	0	0	11	3	2	0	0	0	0		6
Bronchus		5					6	0						11	0							11	5						6
Liver																													
Fatty change, hepatocyte, periportal		2	2	0	1	0		6	0	0	0	0	0	11	0	0	0	0	0	0	11	4	1	0	0	0	0		6
Microgranuloma		5	0	0	0	0		6	0	0	0	0	0	11	0	0	0	0	0	0	11	1	4	0	0	0	0		6 #
Pancreas																													
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0		6	0	0	0	0	0	11	0	0	0	0	0	0	11	5	0	0	0	0	0		6

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

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

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

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

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

Findings	Group Grade	Control (vehicle: control)						2-MV 62.5 mg/kg						2-MV 250 mg/kg						2-MV 1000 mg/kg									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Stomach																													
Forestomach																													
Cellular infiltration, inflammatory, submucosa		4	1	0	0	0	6	6	0	0	0	0	5	1	6	0	0	0	4	#	0	1	9	0	0	1	**	##	
Edema, lamina propria/ submucosa		4	0	1	0	0	6	5	1	0	0	0	5	2	0	1	4	0	4	1	4	3	2	0	1	#			
Erosion, focal		4	1	0	0	0	6	6	0	0	0	0	5	6	1	0	0	0	4	6	2	2	0	0	1				
Hyperkeratosis		5	0	0	0	0	6	6	0	0	0	0	5	0	1	3	3	0	4	**	##	0	0	6	4	0	1	**	##
Hyperplasia, squamous cell		5	0	0	0	0	6	6	0	0	0	0	5	0	3	4	0	0	4	**	##	0	0	6	4	0	1	**	##
Glandular stomach																													
Edema, submucosa		4	1	0	0	0	6	3	3	0	0	0	5	5	2	0	0	0	4	6	3	1	0	0	1				
Increase, mucus		5	0	0	0	0	6	4	2	0	0	0	5	2	5	0	0	0	4	*	#	6	4	0	0	0	1		
Duodenum		5					6	0				11	0				11	5					6						
Jejunum		5					6	0				11	0				11	5					6						
Ileum		5					6	0				11	0				11	5					6						
Cecum		5					6	0				11	0				11	5					6						
Colon		5					6	0				11	0				11	5					6						
Rectum		5					6	0				11	0				11	5					6						
Lymph node, mesenteric		5					6	0				11	0				11	5					6						
Spleen																													
Deposit, pigment, brown		0	1	4	0	0	6	0	0	0	0	0	11	0	0	0	0	0	11	0	2	3	0	0	6				
Hematopoiesis, extramedullary		0	1	2	2	0	6	0	0	0	0	0	11	0	0	0	0	0	11	0	0	3	2	0	6				

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

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

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

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

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

Findings	Group Grade	Control (vehicle: control)						2-MV 62.5 mg/kg						2-MV 250 mg/kg						2-MV 1000 mg/kg								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Kidney																												
	Basophilic tubule, cortex	4	1	0	0	0	6	0	0	0	0	0	11	0	0	0	0	0	11	4	1	0	0	0	6	6		
	Cellular infiltration, lymphocyte, interstitial	3	2	0	0	0	6	0	0	0	0	0	11	0	0	0	0	0	11	5	0	0	0	0	6	6		
	Degeneration, vacuolar, epithelium, proximal tubule	4	0	1	0	0	6	0	0	0	0	0	11	0	0	0	0	0	11	5	0	0	0	0	6	6		
	Urinary bladder	5					6	0				11	0				11	5					6	6				
	Adrenal gland	5					6	0				11	0				11	5					6	6				
Ovary																												
	Cyst	5					1	5	0				0	11	0				0	11	5					0	6	6
	Uterus	5					6	0				11	0				11	5					6	6				
	Vagina	5					6	0				11	0				11	5					6	6				
	Eyeball	5					6	0				11	0				11	5					6	6				
	Harderian gland	5					6	0				11	0				11	5					6	6				
	Sciatic nerve	5					6	0				11	0				11	5					6	6				
	Skeletal muscle	5					6	0				11	0				11	5					6	6				
	Femur	5					6	0				11	0				11	5					6	6				
Marrow, femur																												
	Fatty marrow	4	1	0	0	0	6	0	0	0	0	0	11	0	0	0	0	0	11	5	0	0	0	0	6	6		

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde 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]

Findings	Group Grade	Control (vehicle: control)						2-MV 1000 mg/kg							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5						5							
Spinal cord		5						5							
Pituitary gland		5						5							
Submandibular gland		5						5							
Sublingual gland		5						5							
Lymph node, submandibular		5						5							
Thyroid gland															
Cellular infiltration, lymphocyte, focal		5	0	0	0	0		4	1	0	0	0			
Ectopic thymic tissue		5					0	4						1	
Ultimobranchial body		4					1	3						2	
Parathyroid gland															
Vacuolation, cytoplasmic		4	0	0	0	0	1	4	1	0	0	0			
Thymus															
Atrophy		4	1	0	0	0		5	0	0	0	0			
Heart		5						5							
Trachea		5						5							
Lung															
Accumulation, foam cell, alveolus		4	1	0	0	0		5	0	0	0	0			
Bronchus		5						5							
Liver															
Fatty change, hepatocyte, periportal		0	4	1	0	0		2	3	0	0	0			
Microgranuloma		3	2	0	0	0		0	5	0	0	0			
Pancreas		5						5							
Stomach															
Forestomach															
Cellular infiltration, inflammatory, submucosa		5	0	0	0	0		0	1	4	0	0		**	##
Edema, lamina propria/ submucosa		4	1	0	0	0		1	1	2	1	0			
Hyperkeratosis		5	0	0	0	0		0	0	2	3	0		**	##
Hyperplasia, squamous cell		5	0	0	0	0		0	2	2	1	0		**	##
Glandular stomach															
Cellular infiltration, inflammatory, submucosa		5	0	0	0	0		4	1	0	0	0			
Edema, submucosa		4	1	0	0	0		3	1	1	0	0			
Increase, mucus		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.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde 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]

Findings	Group Grade	Control (vehicle: control)						2-MV 1000 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Duodenum		5						5						
Jejunum		5						5						
Ileum		5						5						
Cecum		5						5						
Colon		5						5						
Rectum		5						5						
Lymph node, mesenteric		5						5						
Spleen														
Deposit, pigment, brown		0	2	3	0	0		0	3	2	0	0		
Hematopoiesis, extramedullary		0	4	0	1	0		0	4	1	0	0		
Kidney														
Basophilic tubule, cortex		4	1	0	0	0		4	1	0	0	0		
Cellular infiltration, inflammatory, interstitial		4	1	0	0	0		2	3 ^{a)}	0	0	0		
Urinary bladder		5						5						
Adrenal gland		5						5						
Ovary		5						5						
Uterus														
Dilatation, lumen		4	1	0	0	0		2	3	0	0	0		
Vagina		5						5						
Eyeball		5						5						
Harderian gland														
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0		4	1	0	0	0		
Sciatic nerve		5						5						
Skeletal muscle		5						5						
Femur		5						5						
Marrow, femur														
Increase, hematopoiesis		3	2	0	0	0		3	2	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.
a) Inflammatory cells were infiltrated into the pelvis.
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

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

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

Findings	Group Grade	Control (Vehicle)						2-MV 1000 mg/kg							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Nodule, hepatodiaphragmatic ^{a)}		0					0	5	0					1	4
Stomach															
Forestomach															
Cellular infiltration, inflammatory, submucosa		5	0	0	0	0			1	4	0	0	0		#
Hyperkeratosis		5	0	0	0	0			0	5	0	0	0		** , ##
Hyperplasia, squamous cell		5	0	0	0	0			0	5	0	0	0		** , ##
Glandular stomach															
Edema, submucosa		4	1	0	0	0			3	2	0	0	0		
Increase, mucus		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.

a), Fibrosis was observed in serosa around the nodule, and congestion was observed in sinusoid.

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

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

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

Table 35. Results of observations about estrous cycle

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of animals examined	12	12	12	12
<u>Pre-treatment period</u>				
Number of animals showing type of cycle				
4-day cycle	9	9	10	6
4/5-day cycle	1	2	2	3
5-day cycle	2	1	0	3
Mean length of estrous cycle in days; Mean±S.D. (N)	4.2 ± 0.4 (12)	4.2 ± 0.3 (12)	4.1 ± 0.2 (12)	4.4 ± 0.4 (12)
<u>Treatment period</u>				
Number of animals showing each type of cycle				
4-day cycle	10	10	10	7
4/5-day cycle	0	0	1	3
5-day cycle	2	1	1	2
irregular	0	1	0	0
Mean length of estrous cycle in days; Mean±S.D. (N)	4.2 ± 0.4 (12)	4.1 ± 0.3 (11)	4.1 ± 0.3 (12)	4.3 ± 0.4 (12)
Frequency of animals that show				
abnormal estrous cycles after the treatment	0 / 12	1 / 12	0 / 12	0 / 12
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.0 ± 0.0 (11)	1.0 ± 0.0 (11)	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 2-Methylvaleraldehyde by oral administration in rats

Table 36. Results of observations about reproductive performance

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of mated pairs [A]	12	12	12	12
Number of copulated pairs [B]	11	11	12	12
Copulation index [(B/A)×100,%]	91.7	91.7	100.0	100.0
Number of fertile males [C]	11	11	11	11
Fertility index [(C/B)×100,%]	100.0	100.0	91.7	91.7
Pairing days until copulation ;Mean±S.D.(N)	3.1 ± 1.1 (11)	3.2 ± 1.1 (11)	2.3 ± 1.1 (12)	2.8 ± 1.4 (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 (F₁)

Group	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of dams	11	11	11	11
Gestation length (days)				
Mean ± S.D. per dam	22.0 ± 0.4	21.8 ± 0.6	21.8 ± 0.4	21.8 ± 0.4
Number of corpora lutea				
Total	173	175	171	176
Mean ± S.D. per dam	15.7 ± 1.3	15.9 ± 1.4	15.5 ± 1.5	16.0 ± 2.0
Number of implantation scars				
Total	166	173	168	166
Mean ± S.D. per dam	15.1 ± 1.8	15.7 ± 1.5	15.3 ± 1.4	15.1 ± 2.9
Implantation index (%) ^{a)}	95.8 ± 6.8	98.8 ± 2.6	98.3 ± 2.9	94.1 ± 11.7
Delivery index (dams,%) ^{b)}	100.0	100.0	100.0	100.0
Number of offspring at birth				
Total	154	167	162	155
Mean ± S.D. per dam	14.0 ± 1.9	15.2 ± 1.1	14.7 ± 1.6	14.1 ± 2.9
Number of live offspring at birth				
Male	71	74	83	67
Female	70	88	77	82
Total	141	162	160	149
Mean ± S.D. per dam	12.8 ± 2.3	14.7 ± 1.4	14.5 ± 1.6	13.5 ± 3.3
Sex ratio ^{c)}				
Mean ± S.D. per dam	0.51 ± 0.12	0.45 ± 0.13	0.51 ± 0.14	0.43 ± 0.13
Number of dead offspring				
Total	13	5	2	6
Mean ± S.D. per dam	1.2 ± 2.0	0.5 ± 0.7	0.2 ± 0.4	0.5 ± 1.2
Delivery index (offspring) ^{d)}				
Mean% ± S.D. per dam	92.8 ± 6.8	96.8 ± 4.1	96.5 ± 5.3	93.4 ± 7.5
Birth index ^{e)}				
Mean% ± S.D. per dam	84.9 ± 10.3	93.8 ± 5.6	95.3 ± 5.1 *	89.9 ± 13.0
Live birth index ^{f)}				
Mean% ± S.D. per dam	92.2 ± 13.6	96.9 ± 4.6	98.8 ± 2.7	95.9 ± 9.3
Number of offspring on day 4				
Male	71	74	83	64
Female	68	87	75	79
Sex ratio ^{g)}				
Mean ± S.D. per dam	0.52 ± 0.12	0.46 ± 0.13	0.51 ± 0.13	0.43 ± 0.14
Viability index ^{h)}				
Mean% ± S.D. per dam	98.9 ± 2.6	99.3 ± 2.3	98.7 ± 4.3	96.6 ± 4.1
Number of external abnormalities ^{b)}	0	1	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.8 ± 2.5	0.0 ± 0.0	0.0 ± 0.0

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

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

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

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

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

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

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

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

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

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

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

Group		Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Number of dams		11	11	11	11
Male					
Days after birth					
	0	6.8 ± 0.5	6.4 ± 0.5	6.3 ± 0.5	6.4 ± 0.7
	4	11.0 ± 1.5	10.4 ± 1.4	9.6 ± 1.5	10.6 ± 1.8
Number of dams		11	11	11	11
Female					
Days after birth					
	0	6.5 ± 0.5	6.2 ± 0.4	6.0 ± 0.4	6.1 ± 0.6
	4	10.6 ± 1.6	10.1 ± 1.1	9.3 ± 1.4	10.1 ± 1.7

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

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 39. General conditions in offspring (F₁) before weaning

Group	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
Control (vehicle: corn oil)	Number of offspring	141	141	140	139	139
	General appearance, No abnormality	141	140	139	139	139
	General appearance, Death		1	1		
2-MV 62.5 mg/kg	Number of offspring	162	162	161	161	161
	General appearance, No abnormality	162	161	161	161	161
	General appearance, Death		1			
2-MV 250 mg/kg	Number of offspring	160	160	160	160	160
	General appearance, No abnormality	160	160	160	160	158
	General appearance, Death					2
2-MV 1000 mg/kg	Number of offspring	149	149	146	144	143
	General appearance, No abnormality	149	146	144	143	143
	General appearance, Death		3	2	1	

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

Table 40. Morphological observations of offspring (F₁)

Dose	Control (vehicle: corn oil)	2-MV 62.5 mg/kg	2-MV 250 mg/kg	2-MV 1000 mg/kg
Dead offspring				
Number of dead offspring ^{a)}	15	6	4	12
Number of missing offspring	1	1	1	4
Number of dead offspring examined ^{b)}	14 (6)	5 (0)	3 (0)	8 (0)
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)	141	162	160	149
Number of live offspring with external changes	0	0	0	0

Number of live offspring examined (postnatal day 4)	139	161	158	143
Number of live offspring with external changes	0	0	0	0
Number of live offspring with visceral changes	0	1	0	0
Dilatation of renal pelvis	0	1	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 because of their autolysis.

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

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

Control (vehicle: corn oil)

Male No.	Days of recovery														
	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 2-Methylvaleraldehyde by oral administration in rats

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

2-MV 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

∴ General appearance, No abnormality.

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

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

2-MV 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	12	12	12	12	9	9	4	4	2	2
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	4	4	2	2		

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

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

2-MV 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,b	-	-	-	-	a,b	-	-	-	a,b								
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	7	0	4	0	5	0	6	0	3	0	6	0	2	0	1	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	7	0	4	0	5	0	6	0	3	0	6	0	2	0	1	0	
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Skin, Reddening of the extremities.

b: Skin, Reddening of the auricle.

c: Behavior, Staggering gait.

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

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

Control (vehicle: corn oil)

Female No.	Days of recovery														
	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 2-Methylvaleraldehyde by oral administration in rats

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

2-MV 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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 2-Methylvaleraldehyde by oral administration in rats

Appendix 3-1. General conditions in dams during pregnancy

Control (vehicle: corn oil)

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

Control (vehicle: corn oil)

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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6	6
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6	6

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

Appendix 3-2. General conditions in dams during pregnancy

2-MV 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

2-MV 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	2	2
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	2	2

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

Appendix 3-3. General conditions in dams during pregnancy

2-MV 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	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11

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

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

2-MV 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	Post
F03025	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11

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

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

Appendix 3-4. General conditions in dams during pregnancy

2-MV 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,b	-	-	-	a,b	-	-	-	-	-	-	-	a,b	-	-	-	-	-	-	-	-	-	-	-	a,b		
F04038	-	-	-	-	-	a,b	-	a,b	-	-	-	-	-	-	-	-	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b		
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,b,c	-	a,b	-	-	-	a,b	-	-		
F04040	-	-	-	-	-	a,b	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,b	-	-	-	-		
F04041	-	-	-	a,b	-	a,b	-	a,b	-	-	-	a,b	-	-	-	-	-	a,b	-	-	-	-	-	-	-	-	-	a,b		
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,b	-	-	-	-	-	-	-	-	-	-		
F04043	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	a,b	>	>	>	a,b	>	>	>	a,b	>	>
F04044	-	-	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b	-	a,b
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,b	-	-	-	a,b	-	a,b	-	-	-	-		
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F04047	-	-	-	a,b,c,d	-	a,b	-	a,b,c,d	-	a,b,c	-	a,b,c	-	a,b	-	-	-	-	-	-										
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11		
-	11	11	11	7	11	6	11	5	11	9	11	8	11	9	11	8	11	5	11	7	11	6	11	7	11	8	11	7		
a	0	0	0	4	0	5	0	6	0	2	0	3	0	2	0	3	0	6	0	4	0	5	0	4	0	3	0	4		
b	0	0	0	4	0	5	0	6	0	2	0	3	0	2	0	3	0	6	0	4	0	5	0	4	0	3	0	4		
c	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	2	0	0	0	0	0	0	0	0		
d	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0		

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Skin, Reddening of the extremities.

b: Skin, Reddening of the auricle.

c: Behavior, Decrease in locomotor activity.

d: Behavior, Staggering gait.

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

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

2-MV 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,b	-	-	-	a,b	-	a,b	-	a,b	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04038	-	-	-	a,b	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	a,b	-	-	-	-	-	-	c,d	-	-	-	-	-	-	-
F04041	-	a,b	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04043	>	> a,b	>	> a,b	>	> a,b	>	> a,b	>	> a,b	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>
F04044	-	-	-	a,b	-	-	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	c	-	-	-	c	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047	-	a,b	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	5	5	0	0	0	0	0	0	0	0
-	11	8	11	6	11	9	11	9	11	10	11	9	11	10	11	11	5	3	0	0	0	0	0	0	0	0
a	0	3	0	5	0	2	0	2	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	3	0	5	0	2	0	2	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Skin, Reddening of the extremities.

b: Skin, Reddening of the auricle.

c: Behavior, Decrease in locomotor activity.

d: Behavior, Staggering gait.

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

Appendix 4-1. General conditions in dams during lactation

Control (vehicle: corn oil)

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	#	#	-	-	-	-	-	-	-	-	-	-
F01010	#	#	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-
F01012	#	#	-	-	-	-	-	-	-	-	-	-
Number of dams	5	5	11	11	11	11	11	11	11	11	11	11
-	5	5	11	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 2-Methylvaleraldehyde by oral administration in rats

Appendix 4-2. General conditions in dams during lactation

2-MV 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	-	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-	-
F02019	#	#	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-	-
F02024	#	#	-	-	-	-	-	-	-	-	-	-
Number of dams	7	7	11	11	11	11	11	11	11	11	11	11
-	7	7	11	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 2-Methylvaleraldehyde by oral administration in rats

Appendix 4-3. General conditions in dams during lactation

2-MV 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	
F03026	-	-	-	-	-	-	-	-	-	-	-	-
F03027	#	#	-	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-	-
F03030	#	#	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-	-
F03032	-	-	-	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-	-
F03034	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	9	9	11	11	11	11	11	11	11	11	11	11
-	9	9	11	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 2-Methylvaleraldehyde by oral administration in rats

Appendix 4-4. General conditions in dams during lactation

2-MV 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	#	#	-	-	-	-	-	c	-	-	-
F04038	-	-	-	-	-	-	-	-	-	-	-
F04039	-	-	-	-	-	-	-	-	-	-	-
F04040	#	#	-	-	-	-	-	-	-	-	-
F04041	#	#	-	c	-	c,d	-	c,d	-	-	-
F04042	#	#	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	-	b,a	-	b,a	-	-	-
F04045	#	#	-	c	-	-	-	-	-	-	-
F04046	#	#	-	-	-	-	-	-	-	-	-
F04047	#	#	-	-	-	c,d	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-
Number of dams	4	4	11	11	11	11	11	11	11	11	11
-	4	4	11	9	11	8	11	8	11	11	11
a	0	0	0	0	0	1	0	1	0	0	0
b	0	0	0	0	0	1	0	1	0	0	0
c	0	0	0	2	0	2	0	2	0	0	0
d	0	0	0	0	0	2	0	1	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: Skin, Reddening of the extremities.

b: Skin, Reddening of the auricle.

c: Behavior, Decrease in locomotor activity.

d: Behavior, Staggering gait.

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

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

Control (vehicle: corn oil)

Male No.	Observations made while handling ^{b)}										Open-field observations ^{c)}																			
	skin/mucous membranes color										Urination										Defecation									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14		Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14		
M01001	2	2	2	2	2	2	2				0	2	0	1	0	0	0				0	0	0	0	0	0	0			
M01002	2	2	2	2	2	2	2				0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M01003	2	2	2	2	2	2	2				0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M01004	2	2	2	2	2	2	2				0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M01005	2	2	2	2	2	2	2				0	0	0	0	0	0	0				3	0	0	0	0	0	0			
M01006	2	2	2	2	2	2	2				0	0	0	0	0	1	0				0	0	0	0	0	0	0			
M01007	2	2	2	2	2	2	2				0	1	0	0	0	0	0				0	0	0	0	0	0	0			
M01008	2	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0	1	0		0	0	0	0	0	0	0	0	0	0
M01009	2	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0
M01010	2	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0	0	1		0	0	0	0	0	0	0	0	0	0
M01011	2	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0
M01012	2	2	2	2	2	2	2	2	2		0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0		0	3	1	1	0	1	0	1	1		3	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)		(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)		

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery
 Skin color / Mucous membranes [2, normal; 1, abnormal (flush)]
 Urination [frequency/30sec]
 Defecation [frequency/30sec]

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

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

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

2-MV 62.5 mg/kg

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

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

Skin color / Mucous membranes [2, normal; 1, abnormal (flush)]

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

2-MV 250 mg/kg

Male No.	Observations made while handling ^{b)}							Open-field observations ^{c)}													
	skin/mucous membranes color							Urination				Defecation									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M03025	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03026	2	2	2	2	2	2	2	0	0	0	1	1	1	0	0	0	0	0	0	0	0
M03027	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03028	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03029	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03030	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03031	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03032	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03033	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03034	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03035	2	2	2	2	2	2	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M03036	2	2	2	2	2	2	2	1	0	0	0	1	1	1	0	0	0	0	0	0	0
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1	0	0	2	2	2	1	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 8 of treatment; ^c day 7 of recovery

Skin color / Mucuous membranes [2, normal; 1, abnormal (flush)]

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

2-MV 1000 mg/kg

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

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery
 Skin color / Mucous membranes [2, normal; 1, abnormal (flush)]
 Urination [frequency/30sec]
 Defecation [frequency/30sec]

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

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

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

Control (vehicle: corn oil)

Female No.	Open-field observations ^{o)}																		
	Urination										Defecation								
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c	Pre	T8	T15	T24	T30	T36	T42	T49	L	
F01001	0	0	0	0	0	0			0	0	0	0	0	0	0			0	
F01002	0	0	0	0	0	0			0	0	0	0	0	0	0			1	
F01003	0	0	0	0	0	0			0	0	0	0	0	0	0			0	
F01004	0	0	0	0	0	0			0	0	0	0	0	0	0			0	
F01005	0	0	0	0	0	0			0	0	0	0	0	0	0			0	
F01006	0	0	0	0	0	0			0	0	0	0	0	0	0			0	
F01007	0	0	0	0	0	0			0	0	0	0	0	0	0			0	
F01008	0	0	0	0	0	0			0	0	0	0	0	0	0			0	
F01009	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0		
F01010	1	1	0	0	0	0			0	0	0	0	0	0	0			0	
F01011	0	0	0	0	0	0			0	0	0	0	0	0	0			0	
F01012	0	0	0	0	0	1			0	0	0	0	0	0	0			0	
Total score	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)	

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde by oral administration in rats
 Appendix 6-1-2. Detailed clinical observations of female rats

2-MV 62.5 mg/kg

Female No.	Open-field observations ^{o)}																	
	Urination									Defecation								
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c	Pre	T8	T15	T24	T30	T36	T42	T49	L
F02013	0	0	0	0	0	1			0	0	0	0	0	0	0			0
F02014	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02015	0	0	0	0	0	0			0	0	0	0	0	1	0			0
F02016	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	
F02017	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02018	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02019	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02020	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02021	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02022	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02023	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02024	0	1	0	0	0	0			0	0	0	0	0	0	0			0
Total score	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

2-MV 250 mg/kg

Female No.	Open-field observations ^{o)}																	
	Urination									Defecation								
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c	Pre	T8	T15	T24	T30	T36	T42	T49	L
F03025	0	0	0	0	0	0				0	0	0	0	0	0			
F03026	0	0	0	0	0	0		0		0	0	0	0	0	0			0
F03027	0	0	0	0	0	0				0	0	0	0	0	0			
F03028	0	0	0	0	0	0		0		0	0	0	0	0	0			0
F03029	0	0	0	0	0	0		0		0	0	0	0	0	0			0
F03030	0	0	0	0	0	0				0	0	0	0	0	0			
F03031	0	0	0	0	0	0		0		0	0	0	0	0	0			0
F03032	0	0	0	0	0	0		0		0	0	0	0	0	0			0
F03033	0	0	0	0	0	0		0		0	0	0	0	0	0			0
F03034	0	0	0	0	0	0		0		0	0	0	0	0	0			0
F03035	0	0	0	0	0	0		0		0	0	0	0	0	0			0
F03036	0	0	0	0	0	0		0		0	0	0	0	0	0			0
Total score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(9)		(12)	(12)	(12)	(12)	(12)	(12)	(0)		(9)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde by oral administration in rats
Appendix 6-1-4. Detailed clinical observations of female rats

2-MV 1000 mg/kg

Female No.	Open-field observations ^{c)}																	
	Urination									Defecation								
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c	Pre	T8	T15	T24	T30	T36	T42	T49	L
F04037	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04038	0	0	0	0	0	0			0	0	0	0	0	0	0			1
F04039	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04040	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04041	0	0	0	0	0	0				0	0	0	0	0	0			
F04042	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04043	0	0	0	0	0	0				0	0	0	0	0	0			
F04044	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04045	0	0	1	0	0	1			0	0	0	0	0	0	0			0
F04046	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04047	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04048	0	0	0	0	0	0			0	0	0	0	0	0	0			0
Total score	0	0	1	0	0	1			0	0	0	0	0	0	0			1
(N)	(12)	(12)	(12)	(12)	(12)	(12)			(10)	(12)	(12)	(12)	(12)	(12)	(12)			(10)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

Control (vehicle: corn oil)

Female No.	Open-field observations ^{o)}																										
	Straub tail										Urination				Defecation												
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F05049	2	2	2	2	2	2	2			0	2	0	0	1	0	0			0	0	0	0	0	0	0		
F05050	2	2	2	2	2	2	2			0	0	0	1	0	0	0			0	0	0	0	0	0	0		
F05051	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05052	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05053	2	2	2	2	2	2	2			0	0	0	0	1	0	0			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	0	0	0	0	0	0	0	0	0
F05055	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05056	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05057	2	2	2	2	2	2	2	2	2	1	0	0	0	0	0	0	1	0	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	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	2	0	1	2	0	0	1	0	0	0	0	0	0	0	0	0	0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	

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

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

2-MV 1000 mg/kg

Female No.	Open-field observations ^{c)}																											
	Straub tail										Urination					Defecation												
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14		Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F06059	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0	0		
F06060	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0	0		
F06061	2	2	2	2	2	2	2			0	0	0	1	0	0	0			0	0	0	0	0	0	0	0		
F06062	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0	0		
F06063	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	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	0	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	0	0	0	0	0	0	0	0	0	0
F06066	3	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F06067	2	2	2	2	2	2	2	2	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F06068	2	2	2	2	2	2	2	2	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	3:1	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	0	3	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	

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

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

Control (vehicle: corn oil)

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M01001	394.0	408.7	420.9	455.6	471.6	507.0	545.0	543.3
M01002	373.6	374.3	382.6	392.2	416.3	446.3	479.4	467.4
M01003	372.2	375.6	388.1	414.2	436.2	455.4	476.7	480.4
M01004	374.8	382.0	385.0	395.5	416.6	443.1	458.8	458.4
M01005	391.9	402.5	411.0	429.3	458.6	490.9	514.8	518.1
M01006	364.9	376.6	392.2	409.7	441.2	473.0	497.6	511.7
M01007	406.1	419.9	432.7	453.4	478.8	509.8	545.7	566.2
M01008	358.0	370.1	376.8	379.8	386.1	401.2	419.4	426.5
M01009	382.7	389.5	398.7	406.1	432.4	459.6	472.5	490.2
M01010	392.2	405.3	409.7	430.0	448.4	458.5	478.4	488.6
M01011	381.7	396.5	410.4	433.4	451.0	474.5	485.0	511.3
M01012	359.0	372.4	373.5	402.8	416.8	421.5	430.4	444.8
Number of males	12	12	12	12	12	12	12	12
Mean	379.3	389.5	398.5	416.8	437.8	461.7	483.6	492.2
S.D.	14.9	16.7	18.5	23.8	26.3	32.2	38.8	40.4

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

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

2-MV 62.5 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M02013	393.6	413.5	425.0	441.7	464.3	486.5	505.5	515.5
M02014	385.1	403.0	406.0	415.4	437.4	464.1	483.2	481.0
M02015	400.6	417.0	419.9	434.2	461.5	483.7	491.6	473.6
M02016	396.5	403.9	411.0	427.0	440.9	458.3	462.7	484.3
M02017	359.9	366.0	370.5	390.3	412.9	443.1	466.0	470.8
M02018	371.9	384.4	387.6	393.3	415.1	433.0	442.6	453.5
M02019	378.0	389.8	400.0	427.6	450.3	485.3	494.0	514.6
M02020	394.9	406.7	416.7	450.3	476.0	504.9	522.1	534.0
M02021	387.8	392.0	393.9	417.3	425.0	437.5	449.3	458.1
M02022	367.2	377.6	381.7	403.2	420.6	452.7	479.8	494.2
M02023	365.6	369.3	383.7	406.0	413.6	437.1	458.7	481.7
M02024	402.6	418.4	431.4	459.3	483.6	528.3	538.2	567.0
Number of males	12	12	12	12	12	12	12	12
Mean	383.6	395.1	402.3	422.1	441.8	467.9	482.8	494.0
S.D.	14.7	18.1	19.2	21.9	25.2	30.1	29.1	33.2
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

2-MV 250 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M03025	363.3	376.8	384.1	404.0	410.3	425.9	443.4	451.7
M03026	372.5	374.6	386.3	406.1	417.4	423.4	435.7	457.2
M03027	396.7	413.1	421.9	456.3	484.2	505.8	514.7	535.7
M03028	360.0	369.5	381.4	396.8	417.0	428.4	435.2	444.5
M03029	377.9	398.1	409.5	425.4	445.3	464.4	481.6	497.8
M03030	396.5	415.6	431.6	458.0	485.1	515.3	533.9	555.1
M03031	394.1	403.2	413.7	442.8	466.6	497.1	508.1	520.6
M03032	399.3	420.0	441.4	475.0	509.0	537.9	556.3	573.8
M03033	389.2	402.5	409.6	436.2	464.7	480.4	498.8	508.4
M03034	409.6	424.8	438.0	460.4	473.4	490.4	514.6	521.9
M03035	373.7	389.6	405.3	439.4	466.0	491.6	506.1	524.1
M03036	376.9	376.8	373.3	376.8	393.8	413.5	426.1	436.0
Number of males	12	12	12	12	12	12	12	12
Mean	384.1	397.1	408.0	431.4	452.7	472.8	487.9	502.2
S.D.	15.6	19.3	22.9	30.0	35.7	41.2	43.1	45.3
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

2-MV 1000 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M04037	375.2	387.7	402.2	418.4	440.1	467.5	487.1	503.1
M04038	390.5	405.3	422.6	435.3	451.8	481.5	511.9	522.6
M04039	384.1	401.5	407.9	429.5	430.5	450.3	459.9	478.8
M04040	393.7	404.0	404.2	426.8	456.3	480.5	501.2	497.7
M04041	391.9	401.3	403.5	421.8	444.4	466.4	474.6	467.0
M04042	382.6	392.0	397.4	425.2	446.2	468.9	500.3	516.3
M04043	356.0	362.1	368.9	379.1	394.8	411.1	428.3	435.8
M04044	399.5	400.2	410.5	416.5	449.4	490.7	520.8	538.0
M04045	362.3	371.7	382.8	404.4	408.0	427.7	452.5	479.1
M04046	402.1	400.6	409.9	432.5	455.6	488.3	494.2	508.1
M04047	404.9	417.9	429.6	456.6	484.7	515.7	550.0	557.6
M04048	399.0	415.3	425.3	450.9	454.8	469.4	490.8	508.7
Number of males	12	12	12	12	12	12	12	12
Mean	386.8	396.6	405.4	424.8	443.1	468.2	489.3	501.1
S.D.	15.6	16.3	17.2	20.3	23.5	28.2	32.5	32.7
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Male No.	Days of recovery		
	1	7	14
M01008	427.7	435.1	432.4
M01009	497.4	513.8	529.3
M01010	487.8	497.6	503.4
M01011	515.3	527.6	536.3
M01012	440.9	461.9	462.8
Number of males	5	5	5
Mean	473.8	487.2	492.8
S.D.	37.7	38.1	44.4

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

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

2-MV 1000 mg/kg

Male No.	Days of recovery		
	1	7	14
M04044	539.8	549.1	562.8
M04045	483.4	501.3	517.6
M04046	505.5	527.3	528.9
M04047	559.4	575.7	581.4
M04048	505.1	526.3	532.8
Number of males	5	5	5
Mean	518.6	535.9	544.7
S.D.	30.4	27.9	26.5
Significance	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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Female No.	Days of administration								
	1	4	7	14	21	28	35	42	49
F01001	264.1	264.3	261.1	283.6					
F01002	250.5	254.9	254.1	263.4					
F01003	254.8	261.1	262.8	258.7					
F01004	231.1	233.7	232.9	237.0					
F01005	241.5	253.9	260.6	271.2					
F01006	251.2	271.5	271.5	282.3					
F01007	243.7	256.0	255.7	265.3					
F01008	244.7	250.6	252.9	258.7					
F01009	241.6	249.4	245.4	258.3	289.0	304.2	289.9	295.7	300.0
F01010	265.5	270.6	275.6	296.3					
F01011	241.2	246.3	245.1	245.1					
F01012	230.9	236.5	234.8	249.1					
Number of females	12	12	12	12					
Mean	246.7	254.1	254.4	264.1					
S.D.	11.1	11.9	13.2	17.1					

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

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

2-MV 62.5 mg/kg

Female No.	Days of administration								
	1	4	7	14	21	28	35	42	49
F02013	254.3	257.5	258.4	276.9					
F02014	234.2	252.1	257.6	267.3					
F02015	232.4	251.7	258.8	266.9					
F02016	240.6	245.7	238.6	252.9	283.8	319.6	301.7	302.5	311.6
F02017	233.2	249.2	254.1	267.1					
F02018	235.6	235.4	236.6	250.8					
F02019	257.5	259.1	260.1	285.3					
F02020	244.5	255.3	252.4	259.3					
F02021	270.6	279.2	284.3	292.8					
F02022	224.1	233.4	235.8	237.2					
F02023	235.0	247.3	252.1	264.0					
F02024	264.7	277.2	292.1	328.9					
Number of females	12	12	12	12					
Mean	243.9	253.6	256.7	270.8					
S.D.	14.6	13.9	17.2	23.7					
Significance	NS	NS	NS	NS	---	---	---	---	---
Statistical method	AN	AN	AN	AN	NA	NA	NA	NA	NA

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

NS: Not significantly different from the control group.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

2-MV 250 mg/kg

Female No.	Days of administration			
	1	4	7	14
F03025	235.4	238.1	229.9	252.8
F03026	246.7	252.1	253.8	252.7
F03027	228.3	232.5	239.9	255.6
F03028	243.1	245.7	258.1	265.2
F03029	256.7	254.0	264.5	267.9
F03030	252.8	251.1	260.0	269.8
F03031	244.3	259.7	260.1	269.1
F03032	258.1	270.6	273.1	276.8
F03033	250.3	259.1	263.9	272.5
F03034	236.3	242.0	246.5	246.5
F03035	227.1	234.2	234.0	233.1
F03036	224.3	235.4	236.6	246.4
Number of females	11	11	11	11
Mean	242.5	248.8	253.7	259.6
S.D.	12.0	12.1	12.7	13.7
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

2-MV 1000 mg/kg

Female No.	Days of administration			
	1	4	7	14
F04037	241.2	239.0	247.7	252.1
F04038	255.0	259.0	271.4	279.1
F04039	236.4	240.2	240.3	250.5
F04040	226.2	237.1	235.5	237.6
F04041	243.7	247.5	258.5	271.5
F04042	266.9	267.1	272.5	286.6
F04043	248.6	255.5	255.7	266.5
F04044	229.6	244.5	248.9	246.4
F04045	254.5	254.5	262.7	275.4
F04046	220.3	238.4	240.2	255.5
F04047	257.8	262.1	273.7	280.2
F04048	233.1	233.5	234.2	247.6
Number of females	11	11	11	11
Mean	242.2	247.5	253.2	262.0
S.D.	14.8	11.4	15.2	16.8
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F05049	238.2	255.5	261.5	275.2	290.8	303.1	313.9	316.3
F05050	228.7	234.0	248.5	255.7	264.5	264.8	274.1	279.3
F05051	248.8	253.2	270.3	284.7	289.6	304.8	316.4	315.6
F05052	239.4	254.2	262.3	272.7	276.2	287.8	294.7	292.6
F05053	255.4	258.8	257.2	267.5	279.1	288.7	290.9	300.7
F05054	257.7	264.4	264.9	279.3	288.9	292.2	300.3	304.4
F05055	252.5	257.7	274.7	281.7	292.1	295.1	310.2	314.3
F05056	250.0	259.7	264.3	278.0	287.9	289.5	294.0	296.9
F05057	233.5	245.4	250.8	263.3	279.3	295.7	309.0	314.9
F05058	252.7	254.7	259.7	272.7	282.5	282.2	292.3	300.2
Number of females	10	10	10	10	10	10	10	10
Mean	245.7	253.8	261.4	273.1	283.1	290.4	299.6	303.5
S.D.	10.0	8.5	8.0	8.9	8.6	11.3	13.0	12.1

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

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

2-MV 1000 mg/kg

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F06059	243.6	257.3	253.8	253.0	265.3	280.8	287.0	284.0
F06060	249.1	257.2	263.7	267.5	283.7	295.6	308.7	303.4
F06061	254.2	257.6	267.1	281.2	286.9	294.9	301.3	302.5
F06062	260.4	262.5	271.8	281.2	290.3	286.8	303.0	309.2
F06063	246.5	247.7	258.7	273.4	281.0	279.5	298.9	304.0
F06064	236.1	250.0	262.7	271.7	280.5	287.8	299.9	304.8
F06065	229.2	243.4	251.0	260.5	263.9	275.3	284.4	289.3
F06066	252.6	258.0	268.2	284.4	290.2	303.8	314.6	318.1
F06067	224.6	228.9	240.3	251.2	261.5	266.1	279.4	289.4
F06068	241.4	250.0	255.0	265.8	274.1	274.0	286.2	295.4
Number of females	10	10	10	10	10	10	10	10
Mean	243.8	251.3	259.2	269.0	277.7	284.5	296.3	300.0
S.D.	11.3	9.8	9.5	11.6	10.9	11.5	11.5	10.4
Significance	NS	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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Female No.	Days of recovery		
	1	7	14
F05054	301.1	309.4	309.4
F05055	306.1	313.1	309.5
F05056	288.6	306.1	303.1
F05057	321.9	331.2	329.5
F05058	299.6	311.2	303.7
Number of females	5	5	5
Mean	303.5	314.2	311.0
S.D.	12.1	9.8	10.8

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

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

2-MV 1000 mg/kg

Female No.	Days of recovery		
	1	7	14
F06064	303.7	302.4	303.2
F06065	291.9	292.8	280.4
F06066	317.4	315.5	320.5
F06067	287.6	295.8	291.4
F06068	296.0	298.8	296.8
Number of females	5	5	5
Mean	299.3	301.1	298.5
S.D.	11.7	8.8	14.9
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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 9-1. Body weights of dams during pregnancy

Control (vehicle: corn oil)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	310.5	357.3	403.0	488.2
F01002	272.5	305.7	332.2	411.3
F01003	271.5	293.2	322.0	407.9
F01004	250.4	277.6	307.9	388.7
F01005	277.0	314.1	351.2	429.3
F01006	287.4	330.8	374.6	470.2
F01007	284.6	328.4	382.2	483.1
F01008	270.9	303.0	337.2	400.2
F01010	298.0	341.6	366.4	463.8
F01011	260.3	279.8	313.7	386.1
F01012	262.2	294.0	330.9	402.5
Number of dams	11	11	11	11
Mean	276.8	311.4	347.4	430.1
S.D.	17.4	25.6	30.6	38.8

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

Appendix 9-2. Body weights of dams during pregnancy

2-MV 62.5 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	286.8	324.2	357.6	428.3
F02014	273.5	316.5	358.1	439.6
F02015	271.8	315.8	353.1	437.7
F02017	269.0	303.2	339.4	427.7
F02018	268.8	298.8	336.7	419.1
F02019	301.0	351.5	395.1	468.5
F02020	264.8	287.0	315.0	387.6
F02021	303.3	333.5	375.2	468.7
F02022	246.6	278.7	320.5	414.3
F02023	276.6	302.3	328.7	422.8
F02024	330.2	353.6	400.3	491.7
Number of dams	11	11	11	11
Mean	281.1	315.0	352.7	436.9
S.D.	22.9	24.3	28.4	29.4
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 9-3. Body weights of dams during pregnancy

2-MV 250 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F03025	255.4 >	303.1 >	322.3 >	303.7 >	300.4 >
F03026	268.3	304.3	345.8	424.4	
F03027	253.1	294.2	327.0	418.1	
F03028	268.0	313.5	349.2	413.4	
F03029	278.4	334.2	387.9	486.7	
F03030	267.8	296.9	338.7	410.7	
F03031	269.8	303.4	326.8	411.7	
F03032	286.5	320.1	359.1	429.1	
F03033	274.3	301.2	334.9	411.7	
F03034	269.4	309.4	347.1	422.9	
F03035	238.8	274.8	313.3	390.9	
F03036	247.8	285.8	319.5	387.4	
Number of dams	11	11	11	11	
Mean	265.7	303.4	340.8	418.8	
S.D.	13.8	16.2	20.8	25.9	
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 9-4. Body weights of dams during pregnancy

2-MV 1000 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F04037	265.7	302.1	333.7	419.6	
F04038	301.0	334.2	379.4	468.9	
F04039	260.4	295.2	329.2	402.8	
F04040	246.7	285.8	315.9	391.3	
F04041	271.6	305.7	328.2	413.0	
F04042	309.5	347.8	371.6	439.2	
F04043	268.4 >	308.1 >	305.3 >	301.0 >	313.0 >
F04044	281.1	325.6	360.8	413.1	
F04045	268.7	315.9	353.7	419.8	
F04046	263.0	309.0	345.0	408.7	
F04047	292.8	338.4	373.0	471.8	
F04048	268.3	300.4	338.8	419.9	
Number of dams	11	11	11	11	
Mean	275.3	314.6	348.1	424.4	
S.D.	18.9	19.6	21.1	25.6	
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 10-1. Body weights of dams during lactation

Control (vehicle: corn oil)

Dam No.	Days of lactation	
	0	4
F01001	390.4	387.6
F01002	321.1	330.0
F01003	312.1	330.2
F01004	256.1	287.6
F01005	317.4	339.1
F01006	373.0	286.8
F01007	366.9	369.1
F01008	328.7	323.5
F01010	371.3	363.4
F01011	289.1	310.0
F01012	332.2	338.1
Number of dams	11	11
Mean	332.6	333.2
S.D.	40.2	31.8

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

Appendix 10-2. Body weights of dams during lactation

2-MV 62.5 mg/kg

Dam No.	Days of lactation	
	0	4
F02013	348.2	340.4
F02014	348.2	337.0
F02015	301.7	339.1
F02017	306.1	311.4
F02018	292.4	319.8
F02019	373.5	367.3
F02020	299.6	303.3
F02021	347.3	375.7
F02022	287.6	314.2
F02023	323.8	313.3
F02024	392.4	374.3
Number of dams	11	11
Mean	329.2	336.0
S.D.	35.1	26.4
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 10-3. Body weights of dams during lactation

2-MV 250 mg/kg

Dam No.	Days of lactation	
	0	4
F03026	322.3	335.6
F03027	296.9	293.2
F03028	307.6	273.3
F03029	337.1	365.3
F03030	334.4	335.0
F03031	286.8	321.2
F03032	337.7	346.1
F03033	320.7	344.3
F03034	312.8	331.9
F03035	276.0	293.6
F03036	274.2	310.4
Number of dams	11	11
Mean	309.7	322.7
S.D.	23.5	27.5
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 10-4. Body weights of dams during lactation

2-MV 1000 mg/kg

Dam No.	Days of lactation	
	0	4
F04037	322.8	329.6
F04038	346.0	399.6
F04039	325.5	321.9
F04040	300.4	311.8
F04041	330.2	324.4
F04042	364.0	375.0
F04044	344.8	358.9
F04045	331.1	333.1
F04046	345.6	349.9
F04047	379.5	376.1
F04048	316.0	330.5
Number of dams	11	11
Mean	336.9	346.4
S.D.	22.2	27.7
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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Male No.	Days of administration					
	1	7	14	29	35	41
M01001	25.9	24.0	23.7	25.7	25.5	19.1
M01002	21.9	24.5	14.2	28.6	15.8	23.7
M01003	23.8	25.0	22.7	23.8	24.4	20.9
M01004	23.2	22.3	18.9	25.1	25.7	20.7
M01005	27.0	26.2	24.0	29.6	25.9	24.3
M01006	24.3	23.1	23.2	26.4	23.4	25.9
M01007	24.4	26.6	25.7	31.6	26.5	23.8
M01008	22.6	19.6	16.6	21.3	16.3	17.8
M01009	21.6	23.3	16.7	23.8	22.7	21.3
M01010	23.9	25.9	22.2	24.7	23.7	24.9
M01011	21.4	24.8	19.7	26.6	21.6	24.5
M01012	24.0	23.3	21.5	20.3	17.1	22.1
Number of males	12	12	12	12	12	12
Mean	23.7	24.1	20.8	25.6	22.4	22.4
S.D.	1.7	1.9	3.5	3.3	3.9	2.5

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

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

2-MV 62.5 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02013	30.4	26.5	26.5	24.1	23.2	21.0
M02014	24.5	22.1	18.8	22.8	21.9	19.8
M02015	28.2	24.3	21.0	24.4	20.7	16.7
M02016	28.0	25.3	21.8	25.5	29.3	25.3
M02017	24.4	20.9	23.1	25.8	24.1	25.1
M02018	25.3	18.4	15.3	21.6	22.8	21.7
M02019	23.8	22.5	24.2	27.6	24.7	25.0
M02020	28.9	26.6	27.1	26.8	24.1	24.7
M02021	25.9	21.9	18.6	24.7	19.3	19.3
M02022	22.4	18.8	20.2	23.9	23.5	24.2
M02023	20.7	18.1	20.4	20.7	22.8	23.7
M02024	24.4	26.6	27.9	26.6	27.3	22.5
Number of males	12	12	12	12	12	12
Mean	25.6	22.7	22.1	24.5	23.6	22.4
S.D.	2.8	3.2	3.8	2.1	2.7	2.8
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

2-MV 250 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03025	25.8	20.9	22.0	22.0	23.1	21.2
M03026	29.6	23.1	23.5	24.2	22.5	26.1
M03027	27.9	25.4	24.1	25.8	22.7	26.3
M03028	27.5	21.6	23.4	23.0	18.1	22.1
M03029	30.4	25.1	22.3	25.4	21.4	23.3
M03030	31.6	29.9	28.3	28.3	23.3	26.6
M03031	26.2	24.1	24.9	26.6	21.2	24.9
M03032	30.5	27.4	31.4	29.4	27.2	26.6
M03033	33.8	24.5	25.4	27.0	22.1	25.2
M03034	30.0	24.5	22.9	23.3	20.6	19.7
M03035	24.9	25.2	21.6	22.8	22.7	20.0
M03036	23.4	17.7	17.7	19.1	23.8	20.4
Number of males	12	12	12	12	12	12
Mean	28.5	24.1	24.0	24.7	22.4	23.5
S.D.	3.0	3.1	3.4	2.9	2.1	2.7
Significance	**	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

2-MV 1000 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04037	26.1	21.4	24.5	24.8	23.0	21.8
M04038	29.2	22.0	20.0	26.6	19.9	24.1
M04039	28.3	22.8	19.8	16.0	21.6	22.2
M04040	24.5	21.1	25.1	26.2	19.2	21.9
M04041	27.0	22.3	23.2	21.7	20.8	19.9
M04042	25.7	21.3	23.3	24.5	21.2	27.2
M04043	20.2	22.0	18.4	20.3	17.4	20.5
M04044	28.6	28.9	24.7	31.1	27.1	29.0
M04045	25.5	21.2	24.0	24.0	22.5	24.0
M04046	19.1	20.4	22.8	27.5	21.3	23.3
M04047	29.2	23.3	27.1	26.4	25.4	23.3
M04048	31.4	28.6	28.8	25.3	23.9	24.4
Number of males	12	12	12	12	12	12
Mean	26.2	22.9	23.5	24.5	21.9	23.5
S.D.	3.6	2.8	3.0	3.8	2.7	2.6
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Male No.	Days of recovery	
	6	12
M01008	21.2	23.4
M01009	29.1	28.5
M01010	25.9	27.6
M01011	31.6	26.4
M01012	28.7	30.0
Number of males	5	5
Mean	27.3	27.2
S.D.	4.0	2.5

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

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

2-MV 1000 mg/kg

Male No.	Days of recovery	
	6	12
M04044	30.7	30.2
M04045	28.3	30.5
M04046	30.4	33.0
M04047	31.3	30.0
M04048	33.5	31.7
Number of males	5	5
Mean	30.8	31.1
S.D.	1.9	1.3
Significance	NS	*
Statistical method	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Female No.	Days of administration						
	1	7	14	29	35	41	48
F01001	20.1	22.4	14.4				
F01002	13.4	19.1	16.0				
F01003	15.7	17.4	16.1				
F01004	12.8	17.6	16.5				
F01005	21.2	22.2	16.9				
F01006	20.4	21.1	20.6				
F01007	19.5	20.4	14.5				
F01008	18.8	19.9	11.2				
F01009	19.6	15.9	12.4	16.7	9.3	14.6	17.0
F01010	23.0	18.8	24.9				
F01011	14.7	18.0	17.1				
F01012	17.1	18.3	13.3				
Number of females	12	12	12				
Mean	18.0	19.3	16.2				
S.D.	3.2	2.0	3.7				

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

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

2-MV 62.5 mg/kg

Female No.	Days of administration						
	1	7	14	29	35	41	48
F02013	18.5	19.7	15.8				
F02014	23.7	20.2	21.0				
F02015	18.9	17.5	20.0				
F02016	19.9	17.9	10.5	23.0	6.8	17.3	18.4
F02017	18.9	19.3	21.2				
F02018	16.6	15.6	15.0				
F02019	21.9	20.5	15.6				
F02020	15.0	17.7	15.6				
F02021	20.1	19.9	13.6				
F02022	18.5	16.4	17.6				
F02023	19.4	17.8	16.5				
F02024	19.8	26.2	28.3				
Number of females	12	12	12				
Mean	19.3	19.1	17.6				
S.D.	2.2	2.7	4.6				
Significance	NS	NS	NS	---	---	---	---
Statistical method	DU	DU	AN	NA	NA	NA	NA

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

2-MV 250 mg/kg

Female No.	Days of administration		
	1	7	14
F03025	20.7	16.9	9.3
F03026	15.6	20.6	17.7
F03027	20.2	15.0	18.1
F03028	21.4	13.0	20.1
F03029	24.7	13.4	19.3
F03030	21.0	12.7	15.6
F03031	21.6	19.8	19.5
F03032	19.1	19.5	20.8
F03033	18.2	19.3	20.2
F03034	20.7	16.0	14.2
F03035	19.4	15.5	17.1
F03036	18.2	16.7	16.6
Number of females	11	11	11
Mean	20.0	16.5	18.1
S.D.	2.3	2.9	2.1
Significance	NS	*	NS
Statistical method	DU	DU	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

2-MV 1000 mg/kg

Female No.	Days of administration		
	1	7	14
F04037	17.4	14.0	16.8
F04038	20.8	17.9	19.9
F04039	20.8	17.9	13.6
F04040	17.2	14.5	19.3
F04041	24.5	13.9	20.7
F04042	24.0	21.3	18.9
F04043	17.5	18.7	13.6
F04044	19.3	18.5	17.4
F04045	25.3	17.9	21.8
F04046	22.0	18.6	18.2
F04047	22.1	19.0	17.9
F04048	20.8	18.9	15.0
Number of females	11	11	11
Mean	21.3	17.5	18.1
S.D.	2.7	2.4	2.4
Significance	*	NS	NS
Statistical method	DU	DU	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Female No.	Days of administration						
	1	7	14	21	29	35	41
F05049	18.5	23.8	20.6	18.2	14.4	21.2	13.7
F05050	20.8	17.1	17.4	20.2	21.4	13.1	16.5
F05051	23.0	22.3	24.5	20.9	21.3	17.0	15.0
F05052	18.1	18.0	20.1	17.9	17.5	16.1	14.2
F05053	18.2	20.8	16.7	19.6	20.4	18.7	16.9
F05054	21.8	17.2	14.9	19.7	20.4	17.1	18.5
F05055	22.9	17.0	20.4	19.4	19.2	13.3	17.4
F05056	22.4	20.3	16.0	20.7	17.6	17.1	17.5
F05057	17.1	22.9	23.3	16.7	17.1	22.3	14.8
F05058	21.3	14.3	20.9	20.4	20.5	12.4	16.3
Number of females	10	10	10	10	10	10	10
Mean	20.4	19.4	19.5	19.4	19.0	16.8	16.1
S.D.	2.2	3.1	3.2	1.4	2.3	3.3	1.6

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

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

2-MV 1000 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06059	15.1	18.3	19.2	12.3	15.4	17.4	13.1
F06060	14.6	18.6	22.4	12.9	15.4	20.3	11.4
F06061	22.4	16.0	21.0	20.1	19.9	15.2	18.3
F06062	25.8	12.8	21.5	20.0	22.5	11.9	16.5
F06063	21.0	15.0	17.8	22.4	20.0	18.0	18.8
F06064	22.2	18.2	19.4	17.4	18.0	18.8	18.4
F06065	20.6	21.8	21.0	19.3	19.8	17.8	18.9
F06066	21.3	14.4	20.1	19.4	20.6	19.1	16.3
F06067	22.3	15.1	21.5	20.6	21.6	16.8	19.8
F06068	22.6	15.9	18.2	20.7	19.8	18.1	19.2
Number of females	10	10	10	10	10	10	10
Mean	20.8	16.6	20.2	18.5	19.3	17.3	17.1
S.D.	3.4	2.6	1.5	3.4	2.4	2.3	2.8
Significance	NS	*	NS	NS	NS	NS	NS
Statistical method	TT	TT	AW	AW	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Female No.	Days of recovery	
	6	12
F05054	22.1	20.3
F05055	18.5	21.1
F05056	22.3	17.7
F05057	26.6	25.1
F05058	22.3	23.9
Number of females	5	5
Mean	22.4	21.6
S.D.	2.9	2.9

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

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

2-MV 1000 mg/kg

Female No.	Days of recovery	
	6	12
F06064	15.8	21.8
F06065	17.1	22.3
F06066	17.4	21.3
F06067	23.4	25.6
F06068	20.8	24.6
Number of females	5	5
Mean	18.9	23.1
S.D.	3.1	1.9
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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 13-1. Food consumption in dams during pregnancy

Control (vehicle: corn oil)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	22.3	28.8	30.4	26.1
F01002	17.2	23.9	22.5	16.2
F01003	17.9	19.2	20.0	25.0
F01004	19.3	21.3	20.7	7.7
F01005	17.2	22.0	24.5	18.2
F01006	16.8	22.1	25.3	25.1
F01007	23.1	29.8	30.8	22.8
F01008	20.6	24.3	22.9	15.5
F01010	26.1	24.7	22.9	26.3
F01011	15.2	22.0	19.8	18.3
F01012	21.8	31.0	22.0	22.1
Number of dams	11	11	11	11
Mean	19.8	24.5	23.8	20.3
S.D.	3.3	3.8	3.8	5.8

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

Appendix 13-2. Food consumption in dams during pregnancy

2-MV 62.5 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	18.4	25.0	23.6	18.0
F02014	24.2	23.8	26.2	22.3
F02015	21.2	23.0	22.5	11.0
F02017	19.3	23.7	24.4	17.2
F02018	18.8	19.9	25.0	13.9
F02019	21.4	30.3	23.4	21.4
F02020	14.7	21.8	20.5	16.8
F02021	18.4	26.3	28.4	21.4
F02022	16.1	21.1	21.8	14.4
F02023	19.2	20.9	21.7	17.1
F02024	25.2	28.7	26.4	20.9
Number of dams	11	11	11	11
Mean	19.7	24.0	24.0	17.7
S.D.	3.1	3.3	2.4	3.6
Significance	NS	NS	NS	NS
Statistical method	AN	AN	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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 13-3. Food consumption in dams during pregnancy

2-MV 250 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03025	18.0 >	25.9 >	12.3 >	15.7 >
F03026	20.6	26.6	23.3	22.2
F03027	19.0	22.9	23.1	10.7
F03028	20.9	26.4	20.2	15.6
F03029	22.0	29.8	32.7	12.2
F03030	18.2	24.9	20.5	20.3
F03031	15.7	18.4	21.4	12.3
F03032	20.0	22.3	22.0	17.8
F03033	19.3	18.0	20.7	20.1
F03034	21.7	22.2	22.1	20.9
F03035	14.1	19.0	23.0	9.4
F03036	16.0	22.3	22.0	13.9
Number of dams	11	11	11	11
Mean	18.9	23.0	22.8	15.9
S.D.	2.6	3.7	3.4	4.5
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of β -Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 13-4. Food consumption in dams during pregnancy

2-MV 1000 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	19.4	19.7	22.3	19.3
F04038	21.0	21.2	21.5	24.8
F04039	17.3	22.7	20.3	19.9
F04040	19.7	19.2	22.0	16.5
F04041	22.2	26.0	23.0	22.0
F04042	19.8	24.2	22.3	20.4
F04043	18.2 >	19.5 >	10.5 >	15.0 >
F04044	21.3	24.2	23.4	18.4
F04045	22.3	29.0	26.3	19.2
F04046	22.6	23.5	25.1	21.9
F04047	19.3	20.5	26.5	29.2
F04048	22.2	23.0	19.5	21.3
Number of dams	11	11	11	11
Mean	20.6	23.0	22.9	21.2
S.D.	1.7	2.9	2.3	3.4
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 14-1. Food consumption in dams during lactation

Control (vehicle: corn oil)

Dam No.	Days of lactation
	3
F01001	31.7
F01002	39.7
F01003	45.4
F01004	33.3
F01005	36.4
F01006	0.0
F01007	35.5
F01008	30.6
F01010	35.8
F01011	36.0
F01012	41.2
Number of dams	11
Mean	33.2
S.D.	11.8

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

Appendix 14-2. Food consumption in dams during lactation

2-MV 62.5 mg/kg

Dam No.	Days of lactation
	3
F02013	31.1
F02014	32.2
F02015	46.4
F02017	31.1
F02018	47.6
F02019	28.7
F02020	43.2
F02021	45.4
F02022	42.5
F02023	30.0
F02024	27.6
Number of dams	11
Mean	36.9
S.D.	8.0
Significance	NS
Statistical method	AN

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

NS: Not significantly different from the control group.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 14-3. Food consumption in dams during lactation

2-MV 250 mg/kg

Dam No.	Days of lactation
	3
F03026	35.8
F03027	37.4
F03028	15.4
F03029	44.1
F03030	32.7
F03031	37.4
F03032	36.9
F03033	48.6
F03034	34.1
F03035	29.1
F03036	45.0
Number of dams	11
Mean	36.0
S.D.	8.9
Significance	NS
Statistical method	AN

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

NS: Not significantly different from the control group.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 14-4. Food consumption in dams during lactation

2-MV 1000 mg/kg

Dam No.	Days of lactation
	3
F04037	34.0
F04038	51.7
F04039	35.2
F04040	35.5
F04041	34.3
F04042	33.9
F04044	33.2
F04045	42.4
F04046	34.8
F04047	38.0
F04048	45.9
Number of dams	11
Mean	38.1
S.D.	6.0
Significance	NS
Statistical method	AN

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

NS: Not significantly different from the control group.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

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

Control (vehicle: corn oil)

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M01001	2	2	2	2	+	+	+
M01002	2	2	2	2	+	+	+
M01003	2	2	2	2	+	+	+
M01004	2	2	2	2	+	+	+
M01005	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

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

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

2-MV 62.5 mg/kg

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer'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 2-Methylvaleraldehyde by oral administration in rats

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

2-MV 250 mg/kg

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer'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 2-Methylvaleraldehyde by oral administration in rats

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

2-MV 1000 mg/kg

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer'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 2-Methylvaleraldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F01002	2	2	2	2	+	+	+
F01003	2	2	2	2	+	+	+
F01005	2	2	2	2	+	+	+
F01006	2	2	2	2	+	+	+
F01011	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 2-Methylvaleraldehyde by oral administration in rats

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

2-MV 62.5 mg/kg

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F02014	2	2	2	2	+	+	+
F02015	2	2	2	2	+	+	+
F02017	2	2	2	2	+	+	+
F02022	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 2-Methylvaleraldehyde by oral administration in rats

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

2-MV 250 mg/kg

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F03028	2	2	2	2	+	+	+
F03029	2	2	2	2	+	+	+
F03031	2	2	2	2	+	+	+
F03033	2	2	2	2	+	+	+
F03035	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 2-Methylvaleraldehyde by oral administration in rats

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

2-MV 1000 mg/kg

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F04037	2	2	2	2	+	+	+
F04040	2	2	2	2	+	+	+
F04045	2	2	2	2	+	+	+
F04046	2	2	2	2	+	+	+
F04047	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 2-Methylvaleraldehyde by oral administration in rats

Appendix 16-5. Functional findings of female rats and female rats at the end of the dosing period

Control (vehicle: corn oil)

Female, satellite groups

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer'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 2-Methylvaleraldehyde by oral administration in rats

Appendix 16-6. Functional findings of male rats and female rats at the end of the dosing period

2-MV 1000 mg/kg

Female, satellite groups

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer'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 2-Methylvaleraldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M01001	0.340	0.173
M01002	0.265	0.122
M01003	0.553	0.165
M01004	0.614	0.157
M01005	0.398	0.254
Number of males	5	5
Mean	0.434	0.174
S.D.	0.146	0.049

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

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

2-MV 62.5 mg/kg

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M02013	0.385	0.222
M02014	0.545	0.203
M02015	0.564	0.202
M02016	0.487	0.183
M02017	0.750	0.203
Number of males	5	5
Mean	0.546	0.203
S.D.	0.134	0.014

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

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

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M03025	0.490	0.276
M03026	0.294	0.262
M03027	0.446	0.223
M03028	0.563	0.294
M03029	0.567	0.267
Number of males	5	5
Mean	0.472	0.264 **
S.D.	0.112	0.026

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

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

2-MV 1000 mg/kg

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M04037	0.653	0.240
M04038	0.679	0.206
M04039	0.483	0.241
M04040	0.644	0.190
M04041	0.787	0.243
Number of males	5	5
Mean	0.649	0.224
S.D.	0.109	0.024

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

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

Control (vehicle: corn oil)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F01002	0.618	0.191
F01003	0.563	0.335
F01005	0.777	0.433
F01006	0.863	0.323
F01010	0.502	0.354
Number of females	5	5
Mean	0.665	0.327
S.D.	0.151	0.087

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

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

2-MV 62.5 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F02014	0.677	0.412
F02015	0.601	0.492
F02017	0.664	0.377
F02022	0.670	0.140
F02024	0.780	0.315
Number of females	5	5
Mean	0.678	0.347
S.D.	0.064	0.132

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

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

2-MV 250 mg/kg

	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F03027	0.531	0.286
F03028	0.406	0.158
F03029	0.652	0.365
F03030	0.672	0.275
F03031	0.508	0.180
Number of females	5	5
Mean	0.554	0.253
S.D.	0.110	0.084

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

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

2-MV 1000 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
F04040	0.626	0.476
F04041	0.705	0.496
F04045	0.630	0.310
F04046	0.742	0.201
F04047	0.923	0.350
Number of females	5	5
Mean	0.725	0.367
S.D.	0.121	0.122

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

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

Control (vehicle: corn oil)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F05049	0.670	0.235
F05050	0.598	0.166
F05051	0.708	0.194
F05052	0.750	0.391
F05053	0.687	0.179
Number of females	5	5
Mean	0.683	0.233
S.D.	0.056	0.092

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

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

2-MV 1000 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F06059	0.817	0.382
F06060	0.855	0.161
F06061	0.636	0.224
F06062	0.585	0.266
F06063	0.561	0.330
Number of females	5	5
Mean	0.691	0.273
S.D.	0.136	0.087

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

Appendix 20-1. Motor activity of male rats

Control (vehicle: corn oil)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1387	1306	1342	1280	5315	47	36	34	29	146
M01002	1176	940	949	1065	4130	40	18	21	20	99
M01003	990	772	606	193	2561	39	19	11	3	72
M01004	1148	1162	949	487	3746	35	22	21	10	88
M01005	1152	1261	1073	825	4311	39	37	26	15	117
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1171	1088	984	770	4013	40	26	23	15	104
S.D.	142	226	265	437	997	4	9	8	10	28

Male No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01008	1163	991	1051	549	3754	33	16	18	9	76
M01009	1360	1263	1118	968	4709	38	29	15	9	91
M01010	1053	995	809	692	3549	45	31	15	26	117
M01011	1024	903	980	756	3663	32	21	24	16	93
M01012	1331	1345	1094	972	4742	42	42	24	22	130
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1186	1099	1010	787	4083	38	28	19	16	101
S.D.	155	193	124	183	591	6	10	5	8	22

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

Appendix 20-2. Motor activity of male rats

2-MV 62.5 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02013	1237	1281	996	857	4371	35	38	25	10	108
M02014	1251	918	854	773	3796	33	13	18	24	88
M02015	1201	1267	924	200	3592	40	28	15	1	84
M02016	1192	1215	953	987	4347	32	33	20	16	101
M02017	1229	1235	1043	593	4100	51	44	29	13	137
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1222	1183	954	682	4041	38	31	21	13	104
S.D.	25	151	72	305	342	8	12	6	8	21

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

Appendix 20-3. Motor activity of male rats

2-MV 250 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03025	744	772	779	514	2809	34	38	29	17	118
M03026	1079	866	1053	751	3749	54	24	38	19	135
M03027	1877	1701	1376	1415	6369	45	25	11	19	100
M03028	1355	1400	1199	742	4696	38	41	30	14	123
M03029	1326	1366	1204	968	4864	30	38	36	20	124
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1276	1221	1122	878	4497	40	33	29	18	120
S.D.	416	391	223	340	1331	9	8	11	2	13

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

Appendix 20-4. Motor activity of male rats

2-MV 1000 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04037	1251	1163	1035	1094	4543	37	31	26	24	118
M04038	1042	992	705	630	3369	38	28	18	18	102
M04039	1226	1091	1071	559	3947	41	39	31	13	124
M04040	1120	1025	999	708	3852	26	21	17	1	65
M04041	1072	868	307	449	2696	32	20	3	14	69
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1142	1028	823	688	3681	35	28	19	14	96
S.D.	93	111	323	246	691	6	8	11	8	27

Male No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04044	1036	796	330	496	2658	35	24	10	14	83
M04045	835	841	431	382	2489	20	12	2	10	44
M04046	1214	1133	1044	1048	4439	34	26	23	19	102
M04047	1045	1026	999	850	3920	27	28	33	22	110
M04048	1371	1226	1060	859	4516	54	33	26	13	126
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1100	1004	773	727	3604	34	25	19	16	93
S.D.	202	185	361	277	970	13	8	13	5	31

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

Appendix 21-1. Motor activity of female rats

Control (vehicle: corn oil)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01002	1120	879	883	624	3506	24	17	33	4	78
F01003	1253	1095	718	626	3692	36	24	9	13	82
F01005	1196	902	1059	881	4038	28	11	22	13	74
F01006	1201	813	748	496	3258	21	10	11	0	42
F01010	1219	966	615	122	2922	29	17	17	0	63
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1198	931	805	550	3483	28	16	18	6	68
S.D.	49	107	171	277	424	6	6	10	7	16

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

Appendix 21-2. Motor activity of female rats

2-MV 62.5 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02014	1096	891	747	536	3270	40	22	12	6	80
F02015	1085	608	621	584	2898	21	5	5	2	33
F02017	1053	1035	876	353	<u>3317</u>	38	26	15	1	80
F02022	1340	1171	997	1059	<u>4567</u>	30	26	7	21	84
F02024	1246	957	299	849	<u>3351</u>	39	20	1	16	76
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1164	932	708	676	<u>3481</u>	34	20	8	9	71
S.D.	123	209	268	278	<u>634</u>	8	9	6	9	21

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

Appendix 21-3. Motor activity of female rats

2-MV 250 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03027	670	809	167	412	2058	13	13	0	2	28
F03028	648	630	407	136	1821	24	20	9	0	53
F03029	1316	1093	968	924	4301	39	20	17	26	102
F03030	1102	869	673	407	3051	33	13	19	2	67
F03031	1844	1626	1580	1257	6307	31	15	10	0	56
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1116	1005	759	627	3508	28	16	11	6	61
S.D.	497	384	548	453	1845	10	4	8	11	27

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

Appendix 21-4. Motor activity of female rats

2-MV 1000 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04040	893	663	264	44	1864	26	17	4	0	47
F04041	992	736	394	183	2305	29	8	1	0	38
F04045	1078	736	309	112	2235	28	10	0	0	38
F04046	1296	985	126	0	2407	25	16	2	0	43
F04047	960	627	27	32	1646	38	15	0	0	53
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1044	749	224 *	74 *	2091	29	13	1 **	0	44
S.D.	156	140	147	73	322	5	4	2	0	6

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

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

Control (vehicle: corn oil)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05049	1113	1070	1153	976	4312	33	21	35	17	106
F05050	977	1062	725	822	3586	26	38	23	18	105
F05051	1215	1008	1309	501	4033	35	12	51	6	104
F05052	1251	1095	1017	687	4050	47	27	25	8	107
F05053	962	836	725	661	3184	25	28	24	20	97
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1104	1014	986	729	3833	33	25	32	14	104
S.D.	133	105	260	179	447	9	10	12	6	4

Female No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05054	1061	1161	839	578	3639	36	47	19	12	114
F05055	1381	896	999	489	3765	56	25	34	10	125
F05056	1104	1009	968	856	3937	35	33	33	16	117
F05057	1006	1006	523	347	2882	24	16	9	0	49
F05058	1320	1323	1019	784	4446	43	39	29	28	139
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1174	1079	870	611	3734	39	32	25	13	109
S.D.	166	166	206	210	567	12	12	11	10	35

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

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

2-MV 1000 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06059	1353	1338	1351	1241	5283	40	37	43	39	159
F06060	763	712	565	755	<u>2795</u>	33	25	14	43	115
F06061	1325	1436	1349	1014	<u>5124</u>	33	54	48	16	151
F06062	1097	1011	892	851	<u>3851</u>	35	25	24	17	101
F06063	1114	1149	906	984	<u>4153</u>	34	36	30	26	126
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1130	1129	1013	969	<u>4241</u>	35	35	32	28 *	130
S.D.	237	286	337	184	<u>1014</u>	3	12	14	12	24

Female No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06064	1078	963	1204	1190	4435	35	20	19	35	109
F06065	974	938	722	811	3445	17	16	7	13	53
F06066	1346	1042	1027	917	4332	46	25	26	23	120
F06067	1738	1539	1523	1301	6101	59	38	26	25	148
F06068	866	664	709	191	2430	39	37	25	1	102
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1200	1029	1037	882	4149	39	27	21	19	106
S.D.	349	319	343	434	1358	15	10	8	13	35

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

Appendix 23-1-1. Urinalysis in male rats

Control (vehicle: corn oil)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	Light yellow	+	7.5	2+	-	+	-	-	+	-	-	-	+	-
M01002	Light yellow	-	6.5	2+	-	+	-	-	±	-	-	-	-	-
M01003	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M01004	Light yellow	-	8.0	2+	-	+	-	-	+	-	-	-	±	-
M01005	Yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			M01001	12.3	1.052	90.7	147.2	102.2
M01002	5.7	1.077	39.3	153.1	28.8	0.22	0.87	0.16
M01003	22.2	1.039	83.0	133.8	98.8	1.84	2.97	2.19
M01004	10.3	1.072	100.7	172.5	142.2	1.04	1.78	1.46
M01005	12.0	1.071	135.9	193.0	182.8	1.63	2.32	2.19
Number of males	5	5	5	5	5	5	5	5
Mean	12.5	1.062	89.9	159.9	111.0	1.17	1.95	1.45
±S.D.	6.0	0.016	34.8	23.1	57.3	0.63	0.77	0.84

Turbidity, -: negative; +: slight

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL

Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL

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

Bilirubin, -: negative

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

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

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

Crystals, -: not observed; ±: a few; +: abundant

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

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

Appendix 23-1-2. Urinalysis in male rats

2-MV 62.5 mg/kg

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02013	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
M02014	Yellow	-	7.0	3+	±	+	-	-	2+	-	-	-	±	-
M02015	Light yellow	-	6.5	2+	-	+	-	±	±	-	-	-	-	-
M02016	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	±	-
M02017	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			M02013	21.6	1.038	41.8	112.1	52.4
M02014	9.6	1.060	97.0	171.3	119.6	0.93	1.64	1.15
M02015	7.1	1.078	123.2	187.7	144.4	0.87	1.33	1.03
M02016	13.7	1.056	98.3	168.6	110.0	1.35	2.31	1.51
M02017	12.1	1.068	120.7	187.6	145.7	1.46	2.27	1.76
Number of males	5	5	5	5	5	5	5	5
Mean	12.8	1.060	96.2	165.5	114.4	1.10	1.99	1.32
±S.D.	5.5	0.015	32.8	31.1	38.0	0.28	0.48	0.31

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

Turbidity, -: negative; +: slight

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL

Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL

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

Bilirubin, -: negative

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

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

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

Crystals, -: not observed; ±: a few; +: abundant

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

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

Appendix 23-1-3. Urinalysis in male rats

2-MV 250 mg/kg

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03025	Yellow	-	7.0	2+	-	+	-	-	+	-	-	-	±	±
M03026	Light yellow	-	8.0	+	-	+	-	-	±	-	-	-	±	-
M03027	Light yellow	-	8.0	+	-	+	-	-	±	-	-	-	±	-
M03028	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
M03029	Light yellow	-	7.0	+	-	+	-	-	±	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			M03025	9.6	1.070	106.3	177.5	150.5
M03026	11.2	1.069	136.3	193.6	169.7	1.53	2.17	1.90
M03027	12.4	1.059	94.4	146.3	87.7	1.17	1.81	1.09
M03028	13.3	1.048	91.9	150.9	92.3	1.22	2.01	1.23
M03029	17.8	1.038	61.3	130.6	78.2	1.09	2.32	1.39
Number of males	5	5	5	5	5	5	5	5
Mean	12.9	1.057	98.0	159.8	115.7	1.21	2.00	1.41
±S.D.	3.1	0.014	27.1	25.3	41.4	0.20	0.25	0.31

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

Turbidity, -: negative; +: slight

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL

Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL

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

Bilirubin, -: negative

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

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

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

Crystals, -: not observed; ±: a few; +: abundant

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

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

Appendix 23-1-4. Urinalysis in male rats

2-MV 1000 mg/kg

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04037	Light yellow	-	6.0	+	-	±	-	-	±	-	-	-	-	-
M04038	Light yellow	-	6.0	2+	-	+	-	-	+	-	-	-	-	-
M04039	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	±	-
M04040	Light yellow	-	7.0	2+	-	+	-	-	+	-	-	-	±	-
M04041	Light yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			M04037	25.8	1.036	57.2	123.8	69.7
M04038	11.6	1.077	142.5	185.9	192.9	1.65	2.16	2.24
M04039	18.7	1.048	75.4	155.2	99.3	1.41	2.90	1.86
M04040	10.0	1.077	126.1	160.7	143.6	1.26	1.61	1.44
M04041	8.6	1.076	153.1	157.6	164.7	1.32	1.36	1.42
Number of males	5	5	5	5	5	5	5	5
Mean	14.9	1.063	110.9	156.6	134.0	1.42	2.24	1.75
±S.D.	7.2	0.019	42.3	22.1	49.6	0.15	0.79	0.34

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

Turbidity, -: negative; +: slight

Protein, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL

Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL

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

Bilirubin, -: negative

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

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

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

Crystals, -: not observed; ±: a few; +: abundant

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

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

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

Control (vehicle: corn oil)

Male No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01008	Light yellow	-	8.0	+	-	+	-	-	+	-	-	-	±	-
M01009	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M01010	Yellow	-	6.5	2+	-	+	-	-	2+	-	-	-	±	-
M01011	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	-	-
M01012	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			M01008	12.3	1.069	100.8	219.5	152.3
M01009	16.8	1.064	149.9	204.9	155.8	2.52	3.44	2.62
M01010	9.8	1.086	191.5	176.9	221.6	1.88	1.73	2.17
M01011	19.8	1.050	87.8	183.0	106.1	1.74	3.62	2.10
M01012	13.3	1.067	114.2	170.0	135.5	1.52	2.26	1.80
Number of males	5	5	5	5	5	5	5	5
Mean	14.4	1.067	128.8	190.9	154.3	1.78	2.75	2.11
±S.D.	3.9	0.013	42.0	20.7	42.5	0.48	0.79	0.32

Turbidity, -: negative

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

Glucose, -: negative

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

Bilirubin, -: negative

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

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

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

Crystals, -: not observed; ±: a few

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

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

2-MV 1000 mg/kg

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04044	Light yellow	-	8.0	+	-	+	-	±	+	-	-	-	±	-
M04045	Light yellow	-	7.5	+	-	-	-	-	±	-	-	-	-	-
M04046	Light yellow	-	8.0	2+	-	+	-	-	+	-	-	-	±	-
M04047	Light yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-
M04048	Light yellow	-	8.0	+	-	±	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			M04044	13.9	1.080	149.7	249.5	154.1
M04045	22.2	1.048	94.8	187.8	117.1	2.10	4.17	2.60
M04046	16.6	1.066	146.0	209.3	154.1	2.42	3.47	2.56
M04047	17.5	1.065	121.5	169.5	125.0	2.13	2.97	2.19
M04048	17.8	1.061	128.4	198.5	153.0	2.29	3.53	2.72
Number of males	5	5	5	5	5	5	5	5
Mean	17.6	1.064	128.1	202.9	140.7	2.20	3.52	2.44
±S.D.	3.0	0.011	22.0	29.9	18.1	0.15	0.43	0.26

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

Turbidity, -: negative

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

Glucose, -: negative

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

Bilirubin, -: negative

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

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

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

Crystals, -: not observed; ±: a few

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

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

Control (vehicle: corn oil)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05049	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	±	-
F05050	Light yellow	-	7.0	±	-	±	-	-	±	-	-	-	±	-
F05051	Light yellow	-	6.5	±	-	±	-	-	+	-	-	-	±	-
F05052	Yellow	-	6.5	2+	±	+	-	-	+	-	-	-	-	-
F05053	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			F05049	12.0	1.054	115.1	165.4	131.5
F05050	14.2	1.048	81.3	148.2	112.3	1.15	2.10	1.59
F05051	14.0	1.044	91.4	136.2	116.0	1.28	1.91	1.62
F05052	2.3	1.098	54.4	135.0	37.1	0.13	0.31	0.09
F05053	17.3	1.040	87.2	130.4	96.3	1.51	2.26	1.67
Number of females	5	5	5	5	5	5	5	5
Mean	12.0	1.057	85.9	143.0	98.6	1.09	1.71	1.31
±S.D.	5.7	0.024	21.8	14.1	36.6	0.55	0.79	0.68

Turbidity, -: negative
 Protein, -: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL
 Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL
 Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL
 Bilirubin, -: negative
 Occult blood, -: negative
 Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL
 Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
 Crystals, -: not observed; ±: a few

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

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

2-MV 1000 mg/kg

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06059	Light yellow	-	6.0	±	-	±	-	-	±	-	-	-	-	-
F06060	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	±	-
F06061	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-
F06062	Light yellow	-	6.0	+	-	+	-	-	+	-	-	-	±	-
F06063	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	-	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			F06059	7.2	1.069	132.8	188.1	140.4
F06060	5.1	1.084	149.7	152.7	155.1	0.76	0.78	0.79
F06061	9.9	1.045	37.0	84.1	38.1	0.37	0.83	0.38
F06062	11.7	1.058	75.7	160.4	111.5	0.89	1.88	1.30
F06063	16.5	1.046	72.3	135.2	94.0	1.19	2.23	1.55
Number of females	5	5	5	5	5	5	5	5
Mean	10.1	1.060	93.5	144.1	107.8	0.83	1.41	1.01
±S.D.	4.4	0.016	46.5	38.6	45.7	0.30	0.64	0.45

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

Turbidity, -: negative

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

Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL

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

Bilirubin, -: negative

Occult blood, -: negative

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

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

Crystals, -: not observed; ±: a few

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

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

Control (vehicle: corn oil)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05054	Light yellow	-	7.0	±	-	±	-	-	±	-	-	-	±	-
F05055	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	-	-
F05056	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F05057	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	-	-
F05058	Light yellow	-	8.0	-	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			F05054	16.8	1.050	105.9	173.8	131.3
F05055	11.3	1.060	124.9	158.8	126.1	1.41	1.79	1.42
F05056	10.0	1.072	135.4	188.9	178.6	1.35	1.89	1.79
F05057	32.1	1.020	33.7	77.7	37.7	1.08	2.49	1.21
F05058	9.5	1.063	123.2	196.5	125.9	1.17	1.87	1.20
Number of females	5	5	5	5	5	5	5	5
Mean	15.9	1.053	104.6	159.1	119.9	1.36	2.19	1.57
±S.D.	9.5	0.020	41.0	47.8	51.0	0.27	0.49	0.43

Turbidity, -: negative
 Protein, -: negative; ±: 10 ≤ and < 30 mg/dL
 Glucose, -: negative
 Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL
 Bilirubin, -: negative
 Occult blood, -: negative
 Urobilinogen, ±: normal
 Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
 Crystals, -: not observed; ±: a few

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

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

2-MV 1000 mg/kg

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06064	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	-
F06065	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F06066	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	-
F06067	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	±	-
F06068	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	-	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
			F06064	13.8	1.064	128.6	204.3	158.5
F06065	19.0	1.026	43.5	94.9	45.6	0.83	1.80	0.87
F06066	15.3	1.055	118.8	168.2	122.4	1.82	2.57	1.87
F06067	10.3	1.056	104.2	187.4	102.4	1.07	1.93	1.05
F06068	19.1	1.042	92.9	168.6	91.7	1.77	3.22	1.75
Number of females	5	5	5	5	5	5	5	5
Mean	15.5	1.049	97.6	164.7	104.1	1.45	2.47	1.55
±S.D.	3.7	0.015	33.2	41.8	41.5	0.47	0.60	0.56

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

Turbidity, -: negative

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

Glucose, -: negative

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

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal

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

Crystals, -: not observed; ±: a few

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

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

Control (vehicle: corn oil)

Male No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
M01001	837	15.0	41.7	49.8	17.9	36.0	127.5	12.6	22.5
M01002	803	14.8	42.0	52.3	18.4	35.2	101.3	14.9	19.6
M01003	790	15.3	44.1	55.8	19.4	34.7	101.3	14.1	21.9
M01004	831	15.4	43.1	51.9	18.5	35.7	117.4	21.6	26.9
M01005	827	15.0	43.1	52.1	18.1	34.8	92.1	16.8	24.2
Number of males	5	5	5	5	5	5	5	5	5
Mean	818	15.1	42.8	52.4	18.5	35.3	107.9	16.0	23.0
S.D.	20	0.2	1.0	2.2	0.6	0.6	14.2	3.5	2.7

Male No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M01001	70.3	10.3	1.3	0.0	2.6	85.8	3.24
M01002	71.4	22.8	2.8	0.0	5.2	69.2	2.41
M01003	82.2	19.6	1.8	0.0	6.2	72.4	2.91
M01004	76.7	20.6	1.0	0.0	4.7	73.7	2.62
M01005	97.4	13.4	1.2	0.0	3.8	81.6	2.52
Number of males	5	5	5	5	5	5	5
Mean	79.6	17.3	1.6	0.0	4.5	76.5	2.74
S.D.	11.0	5.3	0.7	0.0	1.4	6.9	0.34

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

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

2-MV 62.5 mg/kg

Male No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
M02013	821	14.4	40.2	49.0	17.5	35.8	98.5	13.2	21.4
M02014	826	14.3	41.1	49.8	17.3	34.8	106.7	15.4	24.1
M02015	791	14.4	40.3	50.9	18.2	35.7	109.6	16.6	23.9
M02016	828	15.1	42.4	51.2	18.2	35.6	119.6	16.3	22.0
M02017	871	15.2	42.9	49.3	17.5	35.4	103.5	20.6	27.6
Number of males	5	5	5	5	5	5	5	5	5
Mean	827	14.7	41.4	50.0	17.7	35.5	107.6	16.4	23.8
S.D.	29	0.4	1.2	1.0	0.4	0.4	7.9	2.7	2.4

Male No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M02013	115.4	13.5	1.0	0.1	3.9	81.5	2.77
M02014	85.5	27.0	2.1	0.0	3.9	67.0	2.67
M02015	63.2	22.2	1.4	0.0	5.5	70.9	2.62
M02016	92.0	15.3	1.2	0.0	3.0	80.5	3.15
M02017	81.0	20.1	1.5	0.0	4.4	74.0	3.61
Number of males	5	5	5	5	5	5	5
Mean	87.4	19.6	1.4	0.0	4.1	74.8	2.96
S.D.	18.9	5.4	0.4	0.0	0.9	6.2	0.42

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

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

2-MV 250 mg/kg

Male No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
M03025	825	15.1	43.0	52.1	18.3	35.1	94.4	17.5	24.4
M03026	802	14.7	41.2	51.4	18.3	35.7	99.7	14.9	21.8
M03027	841	14.8	41.1	48.9	17.6	36.0	110.3	14.5	23.3
M03028	870	15.9	43.7	50.2	18.3	36.4	124.2	20.4	24.8
M03029	858	14.9	42.2	49.2	17.4	35.3	108.2	18.0	24.5
Number of males	5	5	5	5	5	5	5	5	5
Mean	839	15.1	42.2	50.4	18.0	35.7	107.4	17.1	23.8
S.D.	27	0.5	1.1	1.4	0.4	0.5	11.4	2.4	1.2

Male No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M03025	81.0	20.2	0.9	0.0	4.2	74.7	3.08
M03026	96.9	21.1	0.8	0.0	3.2	74.9	4.23
M03027	98.0	14.9	0.9	0.0	2.8	81.4	2.72
M03028	97.8	15.6	0.6	0.0	2.6	81.2	3.24
M03029	86.7	30.4	1.7	0.0	4.3	63.6	3.19
Number of males	5	5	5	5	5	5	5
Mean	92.1	20.4	1.0	0.0	3.4	75.2	3.29
S.D.	7.8	6.2	0.4	0.0	0.8	7.2	0.56

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

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

2-MV 1000 mg/kg

Male No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
M04037	813	14.7	41.5	51.0	18.1	35.4	107.6	18.5	26.2
M04038	830	15.1	42.4	51.1	18.2	35.6	107.1	14.9	22.9
M04039	861	15.6	44.3	51.5	18.1	35.2	95.9	16.5	23.7
M04040	845	15.3	44.1	52.2	18.1	34.7	122.4	15.7	25.2
M04041	836	15.8	46.4	55.5	18.9	34.1	85.9	18.3	25.7
Number of males	5	5	5	5	5	5	5	5	5
Mean	837	15.3	43.7	52.3	18.3	35.0	103.8	16.8	24.7
S.D.	18	0.4	1.9	1.9	0.3	0.6	13.7	1.6	1.4

Male No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M04037	96.4	15.7	0.7	0.0	4.0	79.6	3.20
M04038	98.1	23.6	1.4	0.0	5.2	69.8	3.48
M04039	52.0	17.3	1.7	0.0	5.0	76.0	3.69
M04040	85.9	20.2	1.2	0.0	4.3	74.3	3.05
M04041	108.8	11.1	1.1	0.1	2.6	85.1	2.97
Number of males	5	5	5	5	5	5	5
Mean	88.2	17.6	1.2	0.0	4.2	77.0	3.28
S.D.	21.8	4.7	0.4	0.0	1.0	5.8	0.30

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

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

Control (vehicle: corn oil)

Male No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
M01008	678	13.4	40.6	59.9	19.8	33.0	7.9	13.9	21.3
M01009	865	14.8	42.4	49.0	17.1	34.9	119.9	19.7	25.3
M01010	836	15.0	43.3	51.8	17.9	34.6	98.4	17.5	28.5
M01011	860	15.3	43.7	50.8	17.8	35.0	113.0	16.1	22.4
M01012	803	15.0	43.6	54.3	18.7	34.4	93.5	15.6	24.3
Number of males	5	5	5	5	5	5	5	5	5
Mean	808	14.7	42.7	53.2	18.3	34.4	86.5	16.6	24.4
S.D.	77	0.7	1.3	4.2	1.0	0.8	45.2	2.2	2.8

Male No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M01008	64.2	19.9	1.2	0.0	2.6	76.3	3.84
M01009	80.2	21.5	1.7	0.0	4.0	72.8	4.23
M01010	89.6	27.7	1.8	0.0	3.2	67.3	4.08
M01011	83.6	25.3	2.4	0.0	3.2	69.1	3.65
M01012	50.2	27.9	2.4	0.0	4.8	64.9	3.66
Number of males	5	5	5	5	5	5	5
Mean	73.6	24.5	1.9	0.0	3.6	70.1	3.89
S.D.	16.1	3.6	0.5	0.0	0.9	4.5	0.26

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

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

2-MV 1000 mg/kg

Male No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
M04044	863	15.1	45.0	52.1	17.5	33.6	94.3	19.1	23.7
M04045	886	15.5	45.0	50.8	17.5	34.4	112.1	18.3	26.8
M04046	864	14.7	42.1	48.7	17.0	34.9	125.6	19.0	23.8
M04047	875	15.3	43.9	50.2	17.5	34.9	124.7	14.9	24.5
M04048	830	14.7	43.2	52.0	17.7	34.0	105.9	16.9	26.1
Number of males	5	5	5	5	5	5	5	5	5
Mean	864	15.1	43.8	50.8	17.4	34.4	112.5	17.6	25.0
S.D.	21	0.4	1.2	1.4	0.3	0.6	13.2	1.8	1.4

Male No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M04044	95.0	16.7	2.1	0.0	5.8	75.4	3.70
M04045	113.0	10.8	1.3	0.0	4.4	83.5	3.78
M04046	95.3	28.2	1.7	0.0	3.0	67.1	4.20
M04047	74.2	23.7	0.9	0.0	3.4	72.0	3.64
M04048	45.7	27.6	2.2	0.0	2.8	67.4	3.20
Number of males	5	5	5	5	5	5	5
Mean	84.6	21.4	1.6	0.0	3.9	73.1	3.70
S.D.	25.7	7.5	0.5	0.0	1.2	6.8	0.36

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

Control (vehicle: corn oil)

Female No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
F01002	666	13.1	39.3	59.0	19.7	33.3	112.4	11.3	15.4
F01003	667	13.3	38.7	58.0	19.9	34.4	111.1	12.8	20.3
F01005	693	12.9	38.7	55.8	18.6	33.3	135.5	11.7	17.7
F01006	804	14.6	40.3	50.1	18.2	36.2	118.5	10.8	18.8
F01010	654	12.7	37.8	57.8	19.4	33.6	108.0	11.9	18.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	697	13.3	39.0	56.1	19.2	34.2	117.1	11.7	18.0
S.D.	62	0.7	0.9	3.6	0.7	1.2	11.0	0.7	1.8

Female No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F01002	144.9	36.1	0.9	0.1	3.0	59.9	11.92
F01003	144.6	31.5	0.7	0.0	3.1	64.7	8.42
F01005	152.1	33.9	0.7	0.0	3.5	61.9	6.71
F01006	110.7	24.9	0.8	0.0	4.4	69.9	1.07
F01010	129.2	34.0	0.9	0.1	3.4	61.6	7.43
Number of females	5	5	5	5	5	5	5
Mean	136.3	32.1	0.8	0.0	3.5	63.6	7.11
S.D.	16.6	4.3	0.1	0.1	0.6	3.9	3.92

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

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

2-MV 62.5 mg/kg

Female No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
F02014	722	13.8	40.8	56.5	19.1	33.8	136.0	12.6	19.1
F02015	691	13.1	38.1	55.1	19.0	34.4	126.7	11.2	16.5
F02017	702	13.7	40.8	58.1	19.5	33.6	102.5	11.1	16.6
F02022	631	12.3	37.3	59.1	19.5	33.0	100.6	11.2	19.8
F02024	627	12.6	38.8	61.9	20.1	32.5	98.3	11.2	18.8
Number of females	5	5	5	5	5	5	5	5	5
Mean	675	13.1	39.2	58.1	19.4	33.5	112.8	11.5	18.2
S.D.	43	0.7	1.6	2.6	0.4	0.7	17.3	0.6	1.5

Female No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F02014	109.3	38.3	1.0	0.0	2.9	57.8	7.14
F02015	144.3	45.0	0.5	0.0	3.8	50.7	7.69
F02017	179.7	44.8	0.1	0.1	3.0	52.0	7.90
F02022	147.7	55.0	0.3	0.0	3.9	40.8	8.19
F02024	88.7	53.7	0.8	0.0	4.7	40.8	9.38
Number of females	5	5	5	5	5	5	5
Mean	133.9	47.4 **	0.5	0.0	3.7	48.4 **	8.06
S.D.	35.5	6.9	0.4	0.0	0.7	7.5	0.83

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

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

2-MV 250 mg/kg

Female No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
F03027	647	12.8	37.2	57.5	19.8	34.4	85.8	12.2	16.1
F03028	648	12.4	36.7	56.6	19.1	33.8	85.3	10.9	18.1
F03029	618	12.1	36.8	59.5	19.6	32.9	83.2	10.5	15.6
F03030	647	12.8	39.0	60.3	19.8	32.8	152.6	13.0	18.2
F03031	627	12.8	39.0	62.2	20.4	32.8	88.3	11.8	18.9
Number of females	5	5	5	5	5	5	5	5	5
Mean	637	12.6	37.7	59.2	19.7	33.3	99.0	11.7	17.4
S.D.	14	0.3	1.2	2.2	0.5	0.7	30.0	1.0	1.4

Female No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F03027	144.2	39.6	0.3	0.0	3.7	56.4	5.83
F03028	124.4	41.5	0.5	0.0	4.6	53.4	3.35
F03029	163.8	42.7	0.2	0.0	4.8	52.3	8.42
F03030	103.6	29.8	1.3	0.1	5.0	63.8	9.91
F03031	139.8	40.7	0.2	0.0	4.9	54.2	8.02
Number of females	5	5	5	5	5	5	5
Mean	135.2	38.9	0.5	0.0	4.6 *	56.0	7.11
S.D.	22.6	5.2	0.5	0.0	0.5	4.6	2.56

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

Appendix 26-1-4. Hematological findings of female rats at the end of the dosing period

2-MV 1000 mg/kg

Female No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
F04040	633	12.6	38.7	61.1	19.9	32.6	118.9	10.9	15.5
F04041	588	11.8	36.7	62.4	20.1	32.2	81.8	12.4	17.4
F04045	616	12.1	36.8	59.7	19.6	32.9	117.4	12.2	21.0
F04046	648	13.5	42.1	65.0	20.8	32.1	112.0	10.9	14.4
F04047	716	13.8	40.9	57.1	19.3	33.7	120.2	12.6	19.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	640	12.8	39.0	61.1	19.9	32.7	110.1	11.8	17.5
S.D.	48	0.9	2.4	3.0	0.6	0.6	16.1	0.8	2.7

Female No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F04040	169.6	25.1	0.2	0.0	3.1	71.6	11.27
F04041	116.8	39.3	0.3	0.0	3.2	57.2	8.18
F04045	155.5	31.0	0.5	0.0	3.1	65.4	8.73
F04046	102.1	33.0	0.4	0.0	2.8	63.8	12.14
F04047	131.0	43.3	0.6	0.0	4.4	51.7	6.21
Number of females	5	5	5	5	5	5	5
Mean	135.0	34.3	0.4	0.0	3.3	61.9	9.31
S.D.	27.6	7.1	0.2	0.0	0.6	7.7	2.40

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

Control (vehicle: corn oil)

Female No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
F05049	750	14.9	42.8	57.1	19.9	34.8	84.6	11.6	18.2
F05050	807	15.2	43.3	53.7	18.8	35.1	103.4	12.3	19.1
F05051	789	14.1	40.3	51.1	17.9	35.0	98.9	11.9	20.1
F05052	765	14.7	41.5	54.2	19.2	35.4	99.2	11.8	20.2
F05053	761	14.6	42.2	55.5	19.2	34.6	93.0	11.5	19.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	774	14.7	42.0	54.3	19.0	35.0	95.8	11.8	19.3
S.D.	23	0.4	1.2	2.2	0.7	0.3	7.3	0.3	0.8

Female No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F05049	69.3	10.6	3.3	0.0	2.0	84.1	5.05
F05050	52.4	9.0	1.0	0.0	1.5	88.5	3.22
F05051	77.6	9.0	1.3	0.0	2.1	87.6	3.77
F05052	74.0	14.2	1.4	0.0	0.9	83.5	3.08
F05053	65.5	18.8	1.7	0.0	2.7	76.8	3.62
Number of females	5	5	5	5	5	5	5
Mean	67.8	12.3	1.7	0.0	1.8	84.1	3.75
S.D.	9.7	4.2	0.9	0.0	0.7	4.6	0.78

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

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

2-MV 1000 mg/kg

Female No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
F06059	821	14.8	42.0	51.2	18.0	35.2	98.1	11.8	17.1
F06060	810	14.9	43.2	53.3	18.4	34.5	90.4	11.0	18.3
F06061	755	14.0	40.8	54.0	18.5	34.3	94.6	12.1	20.8
F06062	798	15.1	43.1	54.0	18.9	35.0	99.6	12.0	19.8
F06063	756	14.2	39.7	52.5	18.8	35.8	100.5	12.1	20.7
Number of females	5	5	5	5	5	5	5	5	5
Mean	788	14.6	41.8	53.0	18.5	35.0	96.6	11.8	19.3
S.D.	31	0.5	1.5	1.2	0.4	0.6	4.2	0.5	1.6

Female No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F06059	76.6	14.6	1.2	0.0	2.1	82.1	3.36
F06060	73.3	10.3	1.6	0.0	2.2	85.9	3.02
F06061	53.3	8.3	0.6	0.0	2.4	88.7	5.70
F06062	59.7	14.4	0.7	0.0	3.0	81.9	3.20
F06063	29.0	14.1	1.4	0.0	3.1	81.4	3.20
Number of females	5	5	5	5	5	5	5
Mean	58.4	12.3	1.1	0.0	2.6	84.0	3.70
S.D.	19.0	2.9	0.4	0.0	0.5	3.2	1.13

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

Control (vehicle: corn oil)

Female No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
F05054	753	14.0	40.4	53.7	18.6	34.7	117.0	12.5	20.6
F05055	759	14.5	41.5	54.7	19.1	34.9	96.1	10.9	17.7
F05056	791	14.6	42.9	54.2	18.5	34.0	100.0	12.2	22.6
F05057	770	14.3	41.5	53.9	18.6	34.5	96.0	11.3	20.2
F05058	796	14.9	42.9	53.9	18.7	34.7	99.8	11.3	19.6
Number of females	5	5	5	5	5	5	5	5	5
Mean	774	14.5	41.8	54.1	18.7	34.6	101.8	11.6	20.1
S.D.	19	0.3	1.1	0.4	0.2	0.3	8.7	0.7	1.8

Female No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F05054	36.4	18.5	2.2	0.0	3.8	75.5	2.69
F05055	34.5	16.2	1.7	0.0	3.5	78.6	2.69
F05056	49.3	9.2	1.8	0.0	2.6	86.4	2.85
F05057	31.7	15.8	2.8	0.0	2.5	78.9	2.77
F05058	33.3	17.1	3.0	0.0	2.4	77.5	2.12
Number of females	5	5	5	5	5	5	5
Mean	37.0	15.4	2.3	0.0	3.0	79.4	2.62
S.D.	7.1	3.6	0.6	0.0	0.6	4.1	0.29

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

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

2-MV 1000 mg/kg

Female No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
F06064	710	13.4	39.7	55.9	18.9	33.8	90.4	12.0	19.0
F06065	821	15.1	43.5	53.0	18.4	34.7	102.5	11.9	20.7
F06066	774	14.6	40.9	52.8	18.9	35.7	103.3	11.6	20.7
F06067	795	14.9	42.4	53.3	18.7	35.1	98.2	10.8	18.1
F06068	831	14.9	43.2	52.0	17.9	34.5	85.3	11.7	20.8
Number of females	5	5	5	5	5	5	5	5	5
Mean	786	14.6	41.9	53.4	18.6	34.8	95.9	11.6	19.9
S.D.	48	0.7	1.6	1.5	0.4	0.7	7.8	0.5	1.2

Female No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F06064	51.2	15.6	1.8	0.0	3.5	79.1	3.10
F06065	40.6	11.3	3.9	0.0	2.5	82.3	2.54
F06066	42.2	13.1	2.1	0.0	5.2	79.6	2.80
F06067	40.7	12.5	1.5	0.0	2.7	83.3	2.39
F06068	29.7	14.5	2.4	0.0	4.0	79.1	2.34
Number of females	5	5	5	5	5	5	5
Mean	40.9	13.4	2.3	0.0	3.6	80.7	2.63
S.D.	7.6	1.7	0.9	0.0	1.1	2.0	0.32

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

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

Control (vehicle: corn oil)																
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01001	5.8	3.7	1.76	178	56	57	101	49	24	0	158	7.1	12	0.5	0.07	268
M01002	5.6	3.5	1.67	152	52	47	89	48	25	1	77	14.8	12	0.5	0.05	408
M01003	5.3	3.5	1.94	144	42	42	77	63	32	1	108	23.5	13	0.5	0.06	318
M01004	5.9	3.6	1.57	156	50	42	88	48	22	0	119	11.3	14	0.4	0.07	327
M01005	5.3	3.3	1.65	143	42	43	78	49	20	1	51	6.3	12	0.4	0.06	412
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.5	1.72	155	48	46	87	51	25	1	103	12.6	13	0.5	0.06	347
S.D.	0.3	0.1	0.14	14	6	6	10	7	5	1	41	7.0	1	0.1	0.01	62

Control (vehicle: corn oil)					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01001	5.8	9.6	144.7	4.50	107.2
M01002	5.7	9.1	145.3	3.66	106.4
M01003	5.5	9.2	144.6	3.95	108.0
M01004	6.0	9.3	144.2	3.84	105.4
M01005	6.5	9.0	144.5	3.91	107.4
Number of males	5	5	5	5	5
Mean	5.9	9.2	144.7	3.97	106.9
S.D.	0.4	0.2	0.4	0.32	1.0

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

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

2-MV 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 μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M02013	5.3	3.4	1.79	134	41	17	71	57	27	0	96	8.2	13	0.4	0.06	268
M02014	5.6	3.4	1.55	139	50	33	82	66	34	0	280	8.2	15	0.5	0.06	381
M02015	5.5	3.6	1.89	150	56	18	84	57	26	0	284	4.6	12	0.4	0.08	243
M02016	5.3	3.4	1.79	141	53	61	95	53	22	0	162	11.7	16	0.4	0.07	348
M02017	5.4	3.5	1.84	147	36	50	69	46	23	0	42	16.4	13	0.4	0.07	394
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.5	1.77	142	47	36	80	56	26	0	173	9.8	14	0.4	0.07	327
S.D.	0.1	0.1	0.13	6	8	19	11	7	5	0	108	4.5	2	0.0	0.01	68
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	AN	AN	AN	AN	AN	AN	KW	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.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 62.5 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M02013	4.8	9.2	142.9	3.84	107.7
M02014	5.5	9.1	146.0	3.86	109.6
M02015	5.7	9.3	144.9	3.73	109.5
M02016	6.4	9.6	144.7	3.82	107.4
M02017	6.6	9.4	144.1	3.78	106.3
Number of males	5	5	5	5	5
Mean	5.8	9.3	144.5	3.81	108.1
S.D.	0.7	0.2	1.1	0.05	1.4
Significance	NS	NS	NS	NS	NS
Statistical method	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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

2-MV 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 μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M03025	5.3	3.3	1.65	161	40	45	69	51	26	0	108	6.3	13	0.5	0.07	407
M03026	5.5	3.4	1.62	140	66	24	95	50	28	1	60	15.3	16	0.4	0.06	347
M03027	5.5	3.5	1.75	154	55	43	92	62	33	0	149	10.2	15	0.5	0.07	321
M03028	6.0	3.7	1.61	163	49	42	82	61	36	0	230	10.5	16	0.5	0.06	298
M03029	5.6	3.5	1.67	157	44	52	82	54	26	0	45	13.4	13	0.5	0.06	489
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.5	1.66	155	51	41	84	56	30	0	118	11.1	15	0.5	0.06	372
S.D.	0.3	0.1	0.06	9	10	10	10	6	4	0	75	3.4	2	0.0	0.01	77
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	AN	AN	AN	AN	AN	AN	KW	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.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 250 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M03025	5.3	8.6	143.9	3.72	107.6
M03026	6.3	9.2	143.7	3.89	107.6
M03027	6.2	9.2	145.1	3.71	106.9
M03028	6.0	9.6	144.4	3.85	108.7
M03029	6.1	9.2	144.5	3.94	105.5
Number of males	5	5	5	5	5
Mean	6.0	9.2	144.3	3.82	107.3
S.D.	0.4	0.4	0.5	0.1	1.2
Significance	NS	NS	NS	NS	NS
Statistical method	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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 27-1-4. Biochemical findings of male rats at the end of the dosing period

2-MV 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 μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04037	5.5	3.5	1.75	133	55	61	99	46	21	0	85	6.1	13	0.5	0.06	275
M04038	5.5	3.4	1.62	137	64	70	106	50	27	1	87	12.2	12	0.4	0.05	342
M04039	5.4	3.5	1.84	127	53	38	85	54	24	1	48	10.3	13	0.5	0.06	439
M04040	5.7	3.7	1.85	158	41	32	81	41	18	1	51	17.9	11	0.4	0.06	224
M04041	5.3	3.5	1.94	129	49	32	85	53	21	0	87	12.7	15	0.5	0.07	340
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.5	1.80	137	52	47	91	49	22	1	72	11.8	13	0.5	0.06	324
S.D.	0.1	0.1	0.12	12	8	18	11	5	3	1	20	4.3	1	0.1	0.01	81
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	AN	AN	AN	AN	AN	AN	KW	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.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 1000 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04037	5.4	9.2	142.4	4.21	105.7
M04038	5.8	9.6	144.3	3.92	104.6
M04039	5.9	9.0	143.3	4.04	104.9
M04040	5.9	9.5	144.1	3.83	106.4
M04041	6.9	9.2	144.5	4.08	107.5
Number of males	5	5	5	5	5
Mean	6	9.3	143.7	4.02	105.8
S.D.	0.6	0.2	0.9	0.15	1.2
Significance	NS	NS	NS	NS	NS
Statistical method	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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Control (vehicle: corn oil)

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01008	5.7	3.6	1.71	128	45	11	68	58	30	0	46	15.5	18	0.6	0.08	244
M01009	6.3	4.1	1.86	158	62	31	96	68	28	0	314	13.8	18	0.6	0.05	255
M01010	6.2	4.0	1.82	158	56	17	91	59	26	0	117	9.0	16	0.6	0.05	268
M01011	5.7	3.8	2.00	134	52	22	78	75	33	0	175	14.6	17	0.5	0.05	352
M01012	5.4	3.3	1.57	113	50	10	71	60	28	0	69	8.8	20	0.5	0.04	202
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	3.8	1.79	138	53	18	81	64	29	0	144	12.3	18	0.6	0.05	264
S.D.	0.4	0.3	0.16	20	6	9	12	7	3	0	107	3.2	1	0.1	0.02	55

Control (vehicle: corn oil)

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01008	6.1	9.0	143.9	4.22	109.6
M01009	6.5	9.3	142.1	4.40	104.8
M01010	5.9	9.2	142.7	3.89	105.7
M01011	5.2	9.2	143.2	3.81	107.7
M01012	5.1	8.7	144.0	3.61	108.8
Number of males	5	5	5	5	5
Mean	5.8	9.1	143.2	3.99	107.3
S.D.	0.6	0.2	0.8	0.32	2.0

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

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

2-MV 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 μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04044	5.7	3.7	1.85	168	59	54	96	70	33	0	414	7.4	12	0.5	0.05	249
M04045	5.6	3.7	1.95	153	35	36	70	61	24	0	472	11.9	15	0.6	0.07	272
M04046	5.4	3.5	1.84	147	48	15	78	64	34	0	141	4.6	18	0.5	0.06	285
M04047	5.8	3.6	1.64	145	69	14	102	52	20	0	379	7.0	16	0.5	0.05	288
M04048	5.4	3.5	1.84	135	52	19	85	60	24	0	114	5.7	16	0.5	0.05	210
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.6	1.82	150	53	28	86	61	27	0	304	7.3	15	0.5	0.06	261
S.D.	0.2	0.1	0.11	12	13	17	13	7	6	0	165	2.8	2	0.0	0.01	32
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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 1000 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04044	5.6	9.5	141.6	3.87	104.3
M04045	6.6	9.4	143.0	4.22	106.2
M04046	5.7	9.0	143.4	3.64	108.1
M04047	5.9	9.2	141.8	4.10	106.6
M04048	5.9	9.0	143.2	3.72	105.5
Number of males	5	5	5	5	5
Mean	5.9	9.2	142.6	3.91	106.1
S.D.	0.4	0.2	0.8	0.25	1.4
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Control (vehicle: corn oil)																	
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	
F01002	5.7	3.9	2.17	126	67	28	118	69	48	0	157	32.9	12	0.5	0.07	133	
F01003	5.6	3.9	2.29	126	40	85	99	69	44	0	203	8.2	17	0.5	0.10	209	
F01005	6.1	4.1	2.05	145	59	69	121	75	53	0	261	17.7	10	0.6	0.07	164	
F01006	4.9	3.4	2.27	83	50	19	115	144	59	0	285	13.9	7	0.6	0.08	217	
F01010	5.8	4.0	2.22	142	53	25	108	69	33	0	229	15.9	13	0.5	0.07	108	
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.6	3.9	2.20	124	54	45	112	85	47	0	227	17.7	12	0.5	0.08	166	
S.D.	0.4	0.3	0.10	25	10	30	9	33	10	0	50	9.2	4	0.1	0.01	47	

Control (vehicle: corn oil)						
Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L	
F01002	6.0	9.6	142.1	3.27	105.3	
F01003	5.9	9.7	139.9	3.38	104.1	
F01005	6.1	9.9	141.8	3.12	103.6	
F01006	7.0	8.8	143.2	2.72	98.8	
F01010	6.9	10.0	140.9	3.55	106.8	
Number of females	5	5	5	5	5	
Mean	6.4	9.6	141.6	3.21	103.7	
S.D.	0.5	0.5	1.2	0.31	3.0	

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

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

2-MV 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 μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F02014	5.6	3.9	2.29	155	51	38	99	87	44	1	72	10.7	15	0.6	0.05	409
F02015	5.4	3.9	2.60	135	57	32	119	84	49	0	157	15.2	15	0.5	0.09	203
F02017	5.8	3.9	2.05	151	90	30	146	64	36	2	209	8.4	11	0.6	0.06	172
F02022	6.0	4.2	2.33	137	60	39	123	86	42	0	135	9.3	15	0.6	0.06	147
F02024	5.7	4.0	2.35	117	36	16	72	84	34	0	132	6.3	11	0.6	0.07	200
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	4.0	2.32	139	59	31	112	81	41	1	141	10.0	13	0.6	0.07	226
S.D.	0.2	0.1	0.20	15	20	9	28	10	6	1	49	3.3	2	0.0	0.02	105
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	KW	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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 62.5 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F02014	6.4	9.9	142.8	2.93	104.1
F02015	6.6	9.5	140.5	3.63	105.7
F02017	8.5	10.2	142.4	3.67	107.0
F02022	6.6	9.5	142.3	2.95	108.5
F02024	5.9	9.7	142.4	3.55	109.4
Number of females	5	5	5	5	5
Mean	6.8	9.8	142.1	3.35	106.9
S.D.	1.0	0.3	0.9	0.37	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).

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 28-1-3. Biochemical findings of female rats at the end of the dosing period

2-MV 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
F03027	5.6	3.6	1.80	140	48	44	88	72	41	0	207	7.8	9	0.5	0.08	122
F03028	5.0	3.4	2.13	140	44	17	82	74	32	0	71	5.4	7	0.6	0.05	119
F03029	5.8	3.9	2.05	142	93	55	148	70	39	0	246	10.9	10	0.5	0.08	173
F03030	6.3	4.2	2.00	133	56	33	104	64	39	0	201	11.2	13	0.6	0.06	213
F03031	5.6	3.9	2.29	132	54	24	107	59	35	1	63	3.9	12	0.5	0.07	156
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.8	2.05	137	59	35	106	68	37	0	158	7.8	10	0.5	0.07	157
S.D.	0.5	0.3	0.18	5	20	15	26	6	4	0	85	3.3	2	0.1	0.01	39
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).

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 250 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F03027	6.8	9.8	144.9	2.91	108.7
F03028	8.0	9.9	145.5	3.54	111.2
F03029	6.9	9.9	141.1	3.30	107.4
F03030	6.3	10.2	143.3	3.23	108.4
F03031	6.1	9.3	137.9	3.66	105.7
Number of females	5	5	5	5	5
Mean	6.8	9.8	142.5	3.33	108.3
S.D.	0.7	0.3	3.1	0.29	2.0
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).

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

2-MV 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 μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F04040	6.0	4.4	2.75	156	69	83	153	63	38	0	105	15.3	11	0.6	0.09	220
F04041	5.3	3.6	2.12	120	41	16	84	81	32	0	77	8.8	13	0.6	0.06	122
F04045	6.0	4.1	2.16	124	52	31	104	85	43	0	150	7.5	12	0.5	0.07	80
F04046	5.7	3.9	2.17	145	56	66	116	59	38	1	96	11.6	10	0.5	0.06	152
F04047	5.9	3.8	1.81	130	45	24	90	69	40	0	214	12.8	18	0.7	0.05	119
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	4.0	2.20	135	53	44	109	71	38	0	128	11.2	13	0.6	0.07	139
S.D.	0.3	0.3	0.34	15	11	29	27	11	4	0	55	3.1	3	0.1	0.02	52
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	KW	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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F04040	6.4	9.8	141.8	3.87	106.2
F04041	7.3	9.6	144.5	2.94	109.1
F04045	6.3	10.2	140.5	3.44	104.7
F04046	5.9	9.8	140.2	3.24	103.3
F04047	5.8	10.0	140.8	3.73	107.3
Number of females	5	5	5	5	5
Mean	6.3	9.9	141.6	3.44	106.1
S.D.	0.6	0.2	1.8	0.37	2.2
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).

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Control (vehicle: corn oil)																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05049	5.9	4.0	2.11	132	72	33	117	72	25	0	167	11.7	15	0.6	0.10	262
F05050	5.5	3.9	2.44	111	57	11	108	59	21	0	115	25.0	17	0.5	0.10	157
F05051	5.5	4.0	2.67	130	62	14	118	51	26	0	45	14.6	21	0.6	0.11	135
F05052	5.6	4.1	2.73	109	60	10	113	48	17	0	63	5.7	15	0.5	0.08	132
F05053	6.1	4.1	2.05	132	74	16	126	57	22	0	100	11.4	15	0.6	0.08	209
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	4.0	2.40	123	65	17	116	57	22	0	98	13.7	17	0.6	0.09	179
S.D.	0.3	0.1	0.31	12	8	9	7	9	4	0	48	7.1	3	0.1	0.01	56

Control (vehicle: corn oil)					
Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05049	5.0	9.2	142.2	4.04	107.2
F05050	4.4	9.2	143.9	3.56	109.1
F05051	5.7	9.3	140.6	3.82	106.0
F05052	4.3	9.2	142.3	3.47	108.2
F05053	4.3	9.4	142.3	3.42	105.9
Number of females	5	5	5	5	5
Mean	4.7	9.3	142.3	3.66	107.3
S.D.	0.6	0.1	1.2	0.26	1.4

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

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

2-MV 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	4.4	2.59	139	53	12	105	50	19	0	71	9.6	20	0.6	0.07	106
F06060	6.3	4.4	2.32	125	64	16	123	54	16	0	119	10.6	16	0.6	0.09	141
F06061	5.9	4.2	2.47	137	65	17	127	46	18	0	38	9.9	18	0.6	0.10	103
F06062	6.0	4.3	2.53	119	76	19	144	48	20	0	53	8.2	17	0.6	0.07	145
F06063	6.2	4.7	3.13	133	78	18	153	46	19	0	114	11.7	18	0.7	0.07	158
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	4.4	2.61	131	67	16	130	49	18	0	79	10.0	18	0.6	0.08	131
S.D.	0.2	0.2	0.31	8	10	3	19	3	2	0	36	1.3	1	0.0	0.01	25
Significance	*	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06059	6.3	9.9	142.0	4.25	106.5
F06060	4.6	9.8	142.5	3.61	106.8
F06061	4.4	9.5	141.9	3.57	107.3
F06062	4.6	9.8	143.6	3.64	107.8
F06063	3.9	9.9	144.3	3.36	108.7
Number of females	5	5	5	5	5
Mean	4.8	9.8	142.9	3.69	107.4
S.D.	0.9	0.2	1.1	0.33	0.9
Significance	NS	**	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 28-3-1. Biochemical findings of female rats at the end of the recovery period

Control (vehicle: corn oil)																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05054	5.9	3.8	1.81	104	63	12	107	60	22	0	38	186.9	23	0.7	0.10	149
F05055	6.0	4.3	2.53	129	70	19	120	52	18	0	94	11.3	19	0.6	0.07	82
F05056	6.5	4.6	2.42	127	71	22	140	44	18	0	43	36.7	16	0.5	0.09	154
F05057	6.3	4.3	2.15	144	65	16	115	45	16	0	112	13.4	15	0.5	0.07	197
F05058	5.8	3.9	2.05	113	66	8	109	65	34	0	41	7.8	18	0.6	0.05	131
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	4.2	2.19	123	67	15	118	53	22	0	66	51.2	18	0.6	0.08	143
S.D.	0.3	0.3	0.29	15	3	6	13	9	7	0	35	76.7	3	0.1	0.02	42

Control (vehicle: corn oil)						
Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L	
F05054	4.0	8.9	141.3	4.08	106.9	
F05055	4.0	9.2	143.0	3.41	108.3	
F05056	4.1	9.6	141.8	3.52	106.6	
F05057	3.0	9.5	144.7	3.54	109.9	
F05058	3.7	9.3	143.4	3.70	109.6	
Number of females	5	5	5	5	5	
Mean	3.8	9.3	142.8	3.65	108.3	
S.D.	0.5	0.3	1.3	0.26	1.5	

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

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

2-MV 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	5.7	4.0	2.35	124	67	27	125	54	18	0	63	26.8	15	0.6	0.09	146
F06065	6.0	4.0	2.00	143	72	19	126	55	34	0	43	11.8	17	0.6	0.08	129
F06066	5.9	4.2	2.47	151	52	21	99	51	21	0	69	9.4	20	0.7	0.07	134
F06067	6.5	4.6	2.42	127	68	8	115	51	21	0	61	12.3	14	0.5	0.07	178
F06068	6.4	4.4	2.20	121	91	19	152	74	32	0	76	20.6	22	0.6	0.07	176
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	4.2	2.29	133	70	19	123	57	25	0	62	16.2	18	0.6	0.08	153
S.D.	0.3	0.3	0.19	13	14	7	19	10	7	0	12	7.3	3	0.1	0.01	23
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	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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06064	3.9	9.3	141.9	3.50	107.1
F06065	4.2	9.3	142.3	3.58	106.7
F06066	3.8	9.3	142.3	3.46	108.3
F06067	4.1	9.5	142.4	3.59	107.0
F06068	5.3	9.7	144.2	3.40	106.9
Number of females	5	5	5	5	5
Mean	4.3	9.4	142.6	3.51	107.2
S.D.	0.6	0.2	0.9	0.08	0.6
Significance	NS	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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Control (vehicle: corn oil)

Male No.	Body	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)
M01001	526.3	2050.3	3.896	395.4	0.751	1492.0	2.835	17236.8	32.751	1644.3	3.124	1736.7	3.300	3381.0	6.424	758.7	1.442
M01002	444.9	1893.8	4.257	193.9	0.436	1258.3	2.828	12881.2	28.953	1369.8	3.079	1352.8	3.041	2722.6	6.120	739.6	1.662
M01003	455.6	1978.7	4.343	482.8	1.060	1335.1	2.930	10873.1	23.865	1328.8	2.917	1438.7	3.158	2767.5	6.074	699.7	1.536
M01004	436.4	1955.3	4.481	338.0	0.775	1258.8	2.885	12056.6	27.627	1416.4	3.246	1414.2	3.241	2830.6	6.486	718.5	1.646
M01005	496.9	2131.2	4.289	284.6	0.573	1388.6	2.795	12886.8	25.934	1431.7	2.881	1426.4	2.871	2858.1	5.752	854.5	1.720
M01006	485.9	1982.1	4.079	281.6	0.580	1424.7	2.932	13830.2	28.463	1791.9	3.688	1790.2	3.684	3582.1	7.372	701.8	1.444
M01007	531.6	1955.9	3.679	328.0	0.617	1476.4	2.777	14515.7	27.306	1560.9	2.936	1481.4	2.787	3042.3	5.723	838.5	1.577
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	482.5	1992.5	4.146	329.2	0.685	1376.3	2.855	13468.6	27.843	1506.3	3.124	1520.1	3.155	3026.3	6.279	758.8	1.575
S.D.	38.3	76.7	0.280	91.8	0.201	96.0	0.062	2034.7	2.754	167.0	0.281	171.3	0.299	331.9	0.565	63.6	0.108

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

Control (vehicle: corn oil)

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	1540.7	2.927	1436.6	2.730	2977.3	5.657	581.6	1.105	593.6	1.128	1175.2	2.233
M01002	1418.2	3.188	1414.5	3.179	2832.7	6.367	581.1	1.306	563.3	1.266	1144.4	2.572
M01003	1619.7	3.555	1663.1	3.650	3282.8	7.205	544.9	1.196	538.3	1.182	1083.2	2.378
M01004	1640.8	3.760	1613.4	3.697	3254.2	7.457	602.2	1.380	611.5	1.401	1213.7	2.781
M01005	1644.2	3.309	1650.9	3.322	3295.1	6.631	635.1	1.278	614.0	1.236	1249.1	2.514
M01006	1585.8	3.264	1562.3	3.215	3148.1	6.479	583.6	1.201	570.8	1.175	1154.4	2.376
M01007	1771.5	3.332	1745.4	3.283	3516.9	6.616	643.3	1.210	639.1	1.202	1282.4	2.412
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1603.0	3.334	1583.7	3.297	3186.7	6.630	596.0	1.239	590.1	1.227	1186.1	2.467
S.D.	108.1	0.265	121.5	0.323	225.5	0.585	34.2	0.089	34.7	0.089	67.6	0.176

Control (vehicle: corn oil)

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	399.6	0.759	1858.1	3.530	16.6	0.032	28.4	0.054	31.1	0.059	59.5	0.113
M01002	658.2	1.479	1477.1	3.320	11.3	0.025	28.6	0.064	31.4	0.071	60.0	0.135
M01003	303.9	0.667	696.8	1.529	16.0	0.035	23.2	0.051	26.0	0.057	49.2	0.108
M01004	576.1	1.320	1256.1	2.878	18.0	0.041	21.7	0.050	21.9	0.050	43.6	0.100
M01005	553.9	1.115	1658.0	3.337	18.0	0.036	24.4	0.049	23.9	0.048	48.3	0.097
M01006	474.3	0.976	1707.4	3.514	14.3	0.029	23.8	0.049	24.8	0.051	48.6	0.100
M01007	482.0	0.907	1499.7	2.821	15.8	0.030	29.6	0.056	30.2	0.057	59.8	0.112
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	492.6	1.032	1450.5	2.990	15.7	0.033	25.7	0.053	27.0	0.056	52.7	0.109
S.D.	117.5	0.293	383.9	0.704	2.3	0.005	3.1	0.005	3.8	0.008	6.8	0.013

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

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

2-MV 62.5 mg/kg																	
Male 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)
M02013	495.9	1885.8	3.803	266.5	0.537	1452.2	2.928	14572.3	29.386	1562.2	3.150	1660.2	3.348	3222.4	6.498	875.4	1.765
M02014	459.0	2046.2	4.458	245.6	0.535	1355.5	2.953	13083.3	28.504	1448.5	3.156	1483.4	3.232	2931.9	6.388	839.5	1.829
M02015	458.5	2073.1	4.521	225.2	0.491	1261.6	2.752	12070.8	26.327	1406.4	3.067	1425.6	3.109	2832.0	6.177	588.3	1.283
M02016	462.2	1950.0	4.219	303.0	0.656	1415.5	3.063	12587.8	27.235	1463.5	3.166	1496.9	3.239	2960.4	6.405	1001.0	2.166
M02017	448.1	1977.1	4.412	302.9	0.676	1464.2	3.268	12889.0	28.764	1474.0	3.289	1559.6	3.480	3033.6	6.770	882.5	1.969
M02018	427.9	1902.8	4.447	187.3	0.438	1143.4	2.672	11161.4	26.084	1474.3	3.445	1425.6	3.332	2899.9	6.777	768.5	1.796
M02019	493.6	2067.5	4.189	198.3	0.402	1568.8	3.178	13156.5	26.654	1708.8	3.462	1710.5	3.465	3419.3	6.927	654.2	1.325
M02020	508.6	1888.1	3.712	449.4	0.884	1548.8	3.045	15060.7	29.612	1687.5	3.318	1675.3	3.294	3362.8	6.612	1037.1	2.039
M02021	436.9	1989.1	4.553	211.3	0.484	1300.2	2.976	11210.4	25.659	1346.2	3.081	1390.2	3.182	2736.4	6.263	532.4	1.219
M02022	467.8	2031.5	4.343	337.5	0.721	1435.2	3.068	11944.7	25.534	1529.3	3.269	1513.0	3.234	3042.3	6.503	924.6	1.976
M02023	452.0	1913.6	4.234	266.1	0.589	1226.0	2.712	12746.0	28.199	1523.2	3.370	1501.8	3.323	3025.0	6.692	1074.4	2.377
M02024	542.1	1898.2	3.502	326.9	0.603	1691.7	3.121	16505.0	30.446	1732.5	3.196	1614.5	2.978	3347.0	6.174	1107.6	2.043
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	471.1	1968.6	4.199	276.7	0.585	1405.3	2.978	13082.3	27.700	1529.7	3.247	1538.1	3.268	3067.8	6.516	857.1	1.816
S.D.	32.9	72.1	0.344	73.7	0.135	156.9	0.187	1588.6	1.671	122.6	0.133	106.0	0.141	221.5	0.246	189.6	0.366
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	KW	AN	AN	AN	AN	AN	AN	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).

DU: Analysis by Dunnett's test

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

2-MV 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	1822.8	3.676	1923.1	3.878	3745.9	7.554	692.1	1.396	725.6	1.463	1417.7	2.859
M02014	1570.4	3.421	1626.0	3.542	3196.4	6.964	599.7	1.307	617.8	1.346	1217.5	2.653
M02015	1590.1	3.468	1606.7	3.504	3196.8	6.972	654.8	1.428	642.8	1.402	1297.6	2.830
M02016	1562.3	3.380	1567.8	3.392	3130.1	6.772	607.9	1.315	621.2	1.344	1229.1	2.659
M02017	1665.7	3.717	1615.0	3.604	3280.7	7.321	608.5	1.358	591.9	1.321	1200.4	2.679
M02018	1596.9	3.732	1567.2	3.663	3164.1	7.394	616.9	1.442	594.3	1.389	1211.2	2.831
M02019	1555.4	3.151	1581.8	3.205	3137.2	6.356	613.9	1.244	628.1	1.272	1242.0	2.516
M02020	1713.1	3.368	1596.2	3.138	3309.3	6.507	619.3	1.218	585.1	1.150	1204.4	2.368
M02021	1565.8	3.584	1622.5	3.714	3188.3	7.298	597.6	1.368	601.5	1.377	1199.1	2.745
M02022	1722.0	3.681	1690.0	3.613	3412.0	7.294	637.0	1.362	606.7	1.297	1243.7	2.659
M02023	1596.1	3.531	1679.7	3.716	3275.8	7.247	722.0	1.597	681.9	1.509	1403.9	3.106
M02024	2017.1	3.721	2017.0	3.721	4034.1	7.442	681.6	1.257	670.0	1.236	1351.6	2.493
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1664.8	3.536	1674.4	3.558	3339.2	7.093	637.6	1.358	630.6	1.342	1268.2	2.700
S.D.	138.4	0.183	144.7	0.219	276.4	0.382	40.9	0.104	42.6	0.098	80.1	0.195
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	KW	DU	AN	DU	AN

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

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

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	540.9	1.091	1898.3	3.828	18.0	0.036	30.2	0.061	32.4	0.065	62.6	0.126
M02014	807.4	1.759	2089.4	4.552	13.8	0.030	29.1	0.063	33.6	0.073	62.7	0.137
M02015	988.5	2.156	2247.2	4.901	16.0	0.035	21.6	0.047	22.5	0.049	44.1	0.096
M02016	958.8	2.074	1841.2	3.984	22.7	0.049	24.7	0.053	26.3	0.057	51.0	0.110
M02017	464.2	1.036	1477.3	3.297	22.3	0.050	23.0	0.051	22.4	0.050	45.4	0.101
M02018	484.2	1.132	1425.0	3.330	14.4	0.034	23.5	0.055	25.1	0.059	48.6	0.114
M02019	745.4	1.510	1770.6	3.587	16.3	0.033	26.4	0.053	26.8	0.054	53.2	0.108
M02020	548.3	1.078	1766.0	3.472	15.8	0.031	22.1	0.043	22.1	0.043	44.2	0.087
M02021	685.2	1.568	2009.4	4.599	16.4	0.038	23.5	0.054	25.0	0.057	48.5	0.111
M02022	556.8	1.190	1807.5	3.864	21.6	0.046	30.3	0.065	31.1	0.066	61.4	0.131
M02023	580.8	1.285	1955.8	4.327	21.2	0.047	27.8	0.062	28.8	0.064	56.6	0.125
M02024	449.4	0.829	1628.3	3.004	20.8	0.038	25.9	0.048	22.8	0.042	48.7	0.090
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	650.8	1.392	1826.3	3.895	18.3	0.039	25.7	0.055	26.6	0.057	52.3	0.111
S.D.	186.6	0.424	239.5	0.594	3.2	0.007	3.1	0.007	4.1	0.010	7.0	0.016
Significance	NS	NS	*	**	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DT	DU	DU	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).

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-3. Organ weights of male rats at the end of the dosing period

2-MV 250 mg/kg																	
Male No.	Body weight (g)	Brain (mg/g)		Thymus (mg/g)		Heart (mg/g)		Liver (mg/g)		Kidney (R) (mg/g)		Kidney (L) (mg/g)		Kidneys (mg/g)		Spleen (mg/g)	
M03025	431.5	1997.5	4.629	196.3	0.455	1253.9	2.906	11930.0	27.648	1439.7	3.337	1453.5	3.368	2893.2	6.705	799.0	1.852
M03026	435.5	1974.4	4.534	170.3	0.391	1445.9	3.320	12591.1	28.912	1487.3	3.415	1541.6	3.540	3028.9	6.955	799.3	1.835
M03027	509.3	1985.2	3.898	212.0	0.416	1350.5	2.652	14638.5	28.742	1562.5	3.068	1528.4	3.001	3090.9	6.069	802.5	1.576
M03028	420.6	1946.4	4.628	285.5	0.679	1253.7	2.981	12157.5	28.905	1401.8	3.333	1417.4	3.370	2819.2	6.703	610.4	1.451
M03029	472.4	2006.9	4.248	296.1	0.627	1317.8	2.790	13294.0	28.141	1517.3	3.212	1478.5	3.130	2995.8	6.342	787.5	1.667
M03030	527.6	1934.0	3.666	185.5	0.352	1424.2	2.699	16924.3	32.078	1666.7	3.159	1601.6	3.036	3268.3	6.195	848.0	1.607
M03031	495.7	2002.7	4.040	385.9	0.778	1316.7	2.656	13168.9	26.566	1358.4	2.740	1356.3	2.736	2714.7	5.476	844.8	1.704
M03032	545.2	2271.4	4.166	367.5	0.674	1526.6	2.800	15380.1	28.210	1903.8	3.492	1731.4	3.176	3635.2	6.668	794.4	1.457
M03033	485.6	1954.6	4.025	239.1	0.492	1563.0	3.219	12540.1	25.824	1616.0	3.328	1620.7	3.338	3236.7	6.665	734.9	1.513
M03034	498.0	2004.8	4.026	186.5	0.374	1377.5	2.766	13792.8	27.696	1532.8	3.078	1536.0	3.084	3068.8	6.162	865.5	1.738
M03035	502.4	1954.9	3.891	283.5	0.564	1507.8	3.001	14974.5	29.806	1436.6	2.859	1400.5	2.788	2837.1	5.647	956.3	1.903
M03036	412.8	1929.1	4.673	222.8	0.540	1288.2	3.121	10494.5	25.423	1425.5	3.453	1496.3	3.625	2921.8	7.078	681.1	1.650
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	478.1	1996.8	4.202	252.6	0.529	1385.5	2.909	13490.5	28.163	1529.0	3.206	1513.5	3.183	3042.6	6.389	793.6	1.663
S.D.	43.6	90.9	0.339	71.6	0.138	107.1	0.222	1758.5	1.796	148.5	0.235	104.5	0.276	249.0	0.498	89.0	0.151
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	KW	AN	AN	AN	AN	AN	AN	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).

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

2-MV 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	1677.4	3.887	1649.2	3.822	3326.6	7.709	738.3	1.711	649.5	1.505	1387.8	3.216
M03026	1544.7	3.547	1631.2	3.746	3175.9	7.293	658.8	1.513	616.2	1.415	1275.0	2.928
M03027	1791.9	3.518	1819.1	3.572	3611.0	7.090	647.0	1.270	684.2	1.343	1331.2	2.614
M03028	1515.6	3.603	1535.0	3.650	3050.6	7.253	615.9	1.464	592.4	1.408	1208.3	2.873
M03029	1541.2	3.262	1589.3	3.364	3130.5	6.627	623.3	1.319	602.3	1.275	1225.6	2.594
M03030	1427.8	2.706	1515.9	2.873	2943.7	5.579	549.2	1.041	604.4	1.146	1153.6	2.187
M03031	1625.2	3.279	1623.6	3.275	3248.8	6.554	660.0	1.331	648.5	1.308	1308.5	2.640
M03032	1670.3	3.064	1634.9	2.999	3305.2	6.062	678.8	1.245	662.5	1.215	1341.3	2.460
M03033	1727.1	3.557	1730.6	3.564	3457.7	7.120	638.9	1.316	643.4	1.325	1282.3	2.641
M03034	1600.9	3.215	1575.0	3.163	3175.9	6.377	634.3	1.274	605.2	1.215	1239.5	2.489
M03035	1733.4	3.450	1709.5	3.403	3442.9	6.853	604.1	1.202	581.6	1.158	1185.7	2.360
M03036	1648.3	3.993	1720.5	4.168	3368.8	8.161	688.5	1.668	694.2	1.682	1382.7	3.350
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1625.3	3.423	1644.5	3.467	3269.8	6.890	644.8	1.363	632.0	1.333	1276.8	2.696
S.D.	104.6	0.350	87.9	0.365	187.8	0.709	47.2	0.194	36.9	0.154	76.2	0.341
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	KW	DU	AN	DU	AN

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

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

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	722.2	1.674	1757.5	4.073	21.0	0.049	31.4	0.073	33.6	0.078	65.0	0.151
M03026	555.5	1.276	1835.8	4.215	12.8	0.029	21.6	0.050	22.1	0.051	43.7	0.100
M03027	712.7	1.399	1599.3	3.140	22.4	0.044	27.1	0.053	29.7	0.058	56.8	0.112
M03028	722.3	1.717	1831.5	4.354	17.8	0.042	27.0	0.064	25.0	0.059	52.0	0.124
M03029	643.4	1.362	1478.0	3.129	13.7	0.029	26.2	0.055	27.0	0.057	53.2	0.113
M03030	597.6	1.133	1803.6	3.418	26.6	0.050	24.6	0.047	25.6	0.049	50.2	0.095
M03031	569.8	1.149	1962.4	3.959	16.6	0.033	24.2	0.049	23.8	0.048	48.0	0.097
M03032	528.4	0.969	2046.3	3.753	18.6	0.034	28.6	0.052	33.3	0.061	61.9	0.114
M03033	755.5	1.556	1812.1	3.732	17.9	0.037	34.4	0.071	35.1	0.072	69.5	0.143
M03034	813.4	1.633	2206.1	4.430	17.8	0.036	29.3	0.059	27.4	0.055	56.7	0.114
M03035	685.8	1.365	1410.2	2.807	21.5	0.043	22.4	0.045	23.5	0.047	45.9	0.091
M03036	674.6	1.634	2016.1	4.884	21.7	0.053	23.6	0.057	22.9	0.055	46.5	0.113
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	665.1	1.406	1813.2	3.825	19.0	0.040	26.7	0.056	27.4	0.058	54.1	0.114
S.D.	87.5	0.242	232.9	0.616	3.9	0.008	3.8	0.009	4.5	0.009	8.1	0.018
Significance	*	*	*	*	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DT	DU	DU	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).

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-4. Organ weights of male rats at the end of the dosing period

2-MV 1000 mg/kg

Male 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)	
M04037	480.5	1934.8	4.027	206.2	0.429	1252.4	2.606	13660.8	28.430	1406.7	2.928	1404.3	2.923	2811.0	5.850	746.3	1.553	
M04038	497.3	2037.9	4.098	286.7	0.577	1426.4	2.868	14579.8	29.318	1677.2	3.373	1644.6	3.307	3321.8	6.680	725.6	1.459	
M04039	458.7	2083.3	4.542	323.7	0.706	1382.1	3.013	12265.7	26.740	1550.6	3.380	1524.6	3.324	3075.2	6.704	888.4	1.937	
M04040	475.1	1891.5	3.981	178.5	0.376	1353.8	2.850	15173.7	31.938	1503.5	3.165	1524.7	3.209	3028.2	6.374	735.6	1.548	
M04041	446.0	1981.0	4.442	250.0	0.561	1320.0	2.960	12095.5	27.120	1493.8	3.349	1440.5	3.230	2934.3	6.579	867.2	1.944	
M04042	483.7	1916.9	3.963	364.9	0.754	1309.0	2.706	13873.6	28.682	1732.2	3.581	1670.2	3.453	3402.4	7.034	757.6	1.566	
M04043	414.8	1978.9	4.771	258.0	0.622	1218.7	2.938	12656.7	30.513	1465.3	3.533	1446.1	3.486	2911.4	7.019	683.9	1.649	
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Mean	465.2	1974.9	4.261	266.9	0.575	1323.2	2.849	13472.3	28.963	1547.0	3.330	1522.1	3.276	3069.2	6.606	772.1	1.665	
S.D.	27.9	67.9	0.322	64.7	0.137	72.1	0.145	1178.6	1.829	117.2	0.223	102.7	0.187	218.4	0.407	76.1	0.196	
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	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	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).

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-4 (continued). Organ weights of male rats at the end of the dosing period

2-MV 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)
M04037	1451.3	3.020	1436.8	2.990	2888.1	6.011	563.4	1.173	524.8	1.092	1088.2	2.265
M04038	1849.1	3.718	1805.8	3.631	3654.9	7.349	658.9	1.325	636.2	1.279	1295.1	2.604
M04039	1558.9	3.399	1530.2	3.336	3089.1	6.734	594.4	1.296	600.9	1.310	1195.3	2.606
M04040	1606.4	3.381	1651.2	3.475	3257.6	6.857	662.8	1.395	617.9	1.301	1280.7	2.696
M04041	1690.6	3.791	1690.6	3.791	3381.2	7.581	619.0	1.388	602.7	1.351	1221.7	2.739
M04042	1743.4	3.604	1688.7	3.491	3432.1	7.096	654.0	1.352	599.1	1.239	1253.1	2.591
M04043	1427.5	3.441	1380.8	3.329	2808.3	6.770	551.8	1.330	534.1	1.288	1085.9	2.618
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1618.2	3.479	1597.7	3.435	3215.9	6.914	614.9	1.323	588.0	1.266	1202.9	2.588
S.D.	153.9	0.258	153.1	0.255	305.0	0.506	46.2	0.075	42.1	0.084	86.0	0.153
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	KW	DU	AN	DU	AN

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

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 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	650.9	1.355	1558.1	3.243	12.1	0.025	31.2	0.065	30.4	0.063	61.6	0.128
M04038	555.0	1.116	1813.7	3.647	17.2	0.035	22.4	0.045	25.6	0.051	48.0	0.097
M04039	548.4	1.196	1537.5	3.352	23.5	0.051	28.3	0.062	30.7	0.067	59.0	0.129
M04040	454.3	0.956	1788.5	3.764	16.6	0.035	38.6	0.081	37.6	0.079	76.2	0.160
M04041	520.5	1.167	1851.6	4.152	12.0	0.027	30.5	0.068	33.6	0.075	64.1	0.144
M04042	614.9	1.271	1688.7	3.491	22.8	0.047	27.1	0.056	27.1	0.056	54.2	0.112
M04043	498.0	1.201	1081.6	2.608	16.4	0.040	29.4	0.071	32.7	0.079	62.1	0.150
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	548.9	1.180	1617.1	3.465	17.2	0.037	29.6	0.064	31.1	0.067	60.7	0.131
S.D.	67.3	0.125	266.1	0.482	4.6	0.010	4.9	0.011	4.0	0.011	8.8	0.022
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DT	DU	DU	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).

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Control (vehicle: corn oil)

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		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)
M01008	404.5	1916.2	4.737	246.0	0.608	1102.1	2.725	9225.2	22.806	1376.5	3.403	1293.6	3.198	2670.1	6.601	674.3	1.667
M01009	500.6	2114.4	4.224	291.8	0.583	1384.3	2.765	13932.3	27.831	1535.3	3.067	1498.5	2.993	3033.8	6.060	915.7	1.829
M01010	480.0	1924.7	4.010	330.3	0.688	1319.6	2.749	13581.3	28.294	1432.2	2.984	1370.4	2.855	2802.6	5.839	787.3	1.640
M01011	506.3	1958.0	3.867	280.4	0.554	1434.0	2.832	12209.3	24.115	1517.0	2.996	1403.4	2.772	2920.4	5.768	723.9	1.430
M01012	439.9	2011.5	4.573	251.4	0.571	1179.8	2.682	10048.2	22.842	1427.8	3.246	1428.7	3.248	2856.5	6.494	817.8	1.859
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	466.3	1985.0	4.282	280.0	0.601	1284.0	2.751	11799.3	25.178	1457.8	3.139	1398.9	3.013	2856.7	6.152	783.8	1.685
S.D.	43.2	81.5	0.368	34.1	0.053	139.4	0.055	2096.8	2.691	66.5	0.181	75.4	0.208	135.2	0.378	92.4	0.172

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

Control (vehicle: corn oil)

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	1772.3	4.381	1722.7	4.259	3495.0	8.640	671.4	1.660	630.7	1.559	1302.1	3.219
M01009	1430.7	2.858	1485.0	2.966	2915.7	5.824	562.0	1.123	566.5	1.132	1128.5	2.254
M01010	1514.8	3.156	1485.7	3.095	3000.5	6.251	590.4	1.230	571.0	1.190	1161.4	2.420
M01011	1896.8	3.746	1804.4	3.564	3701.2	7.310	679.7	1.342	639.8	1.264	1319.5	2.606
M01012	1665.9	3.787	1611.3	3.663	3277.2	7.450	735.6	1.672	691.0	1.571	1426.6	3.243
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1656.1	3.586	1621.8	3.509	3277.9	7.095	647.8	1.405	619.8	1.343	1267.6	2.748
S.D.	188.6	0.594	142.2	0.514	329.6	1.105	70.6	0.250	52.0	0.208	122.3	0.458

Control (vehicle: corn oil)

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	588.2	1.454	1780.2	4.401	26.3	0.065	27.5	0.068	27.3	0.067	54.8	0.135
M01009	755.1	1.508	1396.3	2.789	13.0	0.026	19.4	0.039	23.4	0.047	42.8	0.085
M01010	490.2	1.021	1421.6	2.962	21.3	0.044	19.1	0.040	21.7	0.045	40.8	0.085
M01011	712.3	1.407	1589.9	3.140	14.5	0.029	26.0	0.051	28.7	0.057	54.7	0.108
M01012	455.6	1.036	1858.0	4.224	17.2	0.039	28.0	0.064	30.6	0.070	58.6	0.133
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	600.3	1.285	1609.2	3.503	18.5	0.041	24.0	0.052	26.3	0.057	50.3	0.109
S.D.	132.0	0.237	207.4	0.752	5.4	0.015	4.4	0.013	3.7	0.011	8.0	0.025

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

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

2-MV 1000 mg/kg																	
Male 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)
M04044	523.5	2104.3	4.020	282.4	0.539	1629.8	3.113	15751.1	30.088	1737.5	3.319	1715.3	3.277	3452.8	6.596	875.8	1.673
M04045	476.7	1935.3	4.060	230.9	0.484	1415.2	2.969	12175.2	25.541	1488.7	3.123	1517.4	3.183	3006.1	6.306	766.0	1.607
M04046	502.9	2037.3	4.051	281.3	0.559	1386.4	2.757	13105.7	26.060	1569.2	3.120	1558.8	3.100	3128.0	6.220	1084.1	2.156
M04047	553.6	2137.9	3.862	393.6	0.711	1560.1	2.818	16116.9	29.113	2019.5	3.648	1922.9	3.473	3942.4	7.121	939.0	1.696
M04048	507.7	2010.2	3.959	137.7	0.271	1414.3	2.786	13105.3	25.813	1449.8	2.856	1482.7	2.920	2932.5	5.776	741.9	1.461
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	512.9	2045.0	3.990	265.2	0.513	1481.2	2.889	14050.8	27.323	1652.9	3.213	1639.4	3.191	3292.4	6.404	881.4	1.719
S.D.	28.3	79.8	0.082	92.8	0.159	107.4	0.150	1765.3	2.115	232.8	0.294	181.7	0.205	414.4	0.497	138.9	0.261
Significance	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS
Statistical method	TT	TT	AW	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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

2-MV 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	1618.2	3.091	1631.9	3.117	3250.1	6.208	644.2	1.231	630.5	1.204	1274.7	2.435
M04045	1856.6	3.895	1803.4	3.783	3660.0	7.678	705.5	1.480	657.8	1.380	1363.3	2.860
M04046	1602.4	3.186	1670.0	3.321	3272.4	6.507	722.2	1.436	723.7	1.439	1445.9	2.875
M04047	1806.0	3.262	1851.3	3.344	3657.3	6.606	716.5	1.294	728.1	1.315	1444.6	2.609
M04048	1607.0	3.165	1666.7	3.283	3273.7	6.448	646.1	1.273	637.0	1.255	1283.1	2.527
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1698.0	3.320	1724.7	3.370	3422.7	6.689	686.9	1.343	675.4	1.319	1362.3	2.661
S.D.	123.1	0.327	96.4	0.248	215.6	0.572	38.6	0.109	47.2	0.094	83.2	0.198
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.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

2-MV 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	563.8	1.077	1283.5	2.452	12.4	0.024	21.7	0.041	28.2	0.054	49.9	0.095
M04045	473.6	0.993	1718.1	3.604	15.9	0.033	40.7	0.085	31.7	0.066	72.4	0.152
M04046	510.1	1.014	1764.3	3.508	21.8	0.043	23.1	0.046	24.1	0.048	47.2	0.094
M04047	702.5	1.269	1908.6	3.448	19.2	0.035	22.2	0.040	23.5	0.042	45.7	0.083
M04048	709.7	1.398	1733.6	3.415	19.6	0.039	24.6	0.048	24.1	0.047	48.7	0.096
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	591.9	1.150	1681.6	3.285	17.8	0.035	26.5	0.052	26.3	0.051	52.8	0.104
S.D.	109.1	0.176	235.0	0.471	3.7	0.007	8.0	0.019	3.5	0.009	11.1	0.027
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.

TT: Analysis by Student's t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Control (vehicle: corn oil)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		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	364.1	1837.2	5.046	121.3	0.333	1133.4	3.113	12029.5	33.039	943.3	2.591	909.0	2.497	1852.3	5.087	787.4	2.163
F01002	296.5	1882.7	6.350	217.1	0.732	956.9	3.227	9328.4	31.462	854.7	2.883	813.4	2.743	1668.1	5.626	614.0	2.071
F01003	308.2	1825.8	5.924	293.6	0.953	957.8	3.108	10027.8	32.537	981.5	3.185	1018.6	3.305	2000.1	6.490	594.5	1.929
F01004	262.2	1867.4	7.122	105.3	0.402	891.4	3.400	9674.9	36.899	849.5	3.240	879.3	3.354	1728.8	6.593	563.1	2.148
F01005	295.8	1920.2	6.492	216.2	0.731	1038.8	3.512	9693.4	32.770	911.0	3.080	947.0	3.201	1858.0	6.281	549.9	1.859
F01006	273.2	1940.5	7.103	150.8	0.552	810.1	2.965	8518.3	31.180	979.6	3.586	967.5	3.541	1947.1	7.127	373.0	1.365
F01007	334.2	1955.6	5.852	216.7	0.648	995.6	2.979	10333.9	30.921	978.6	2.928	945.8	2.830	1924.4	5.758	755.3	2.260
F01008	290.4	1841.0	6.340	186.5	0.642	926.9	3.192	9507.4	32.739	964.6	3.322	945.5	3.256	1910.1	6.577	757.0	2.607
F01009	299.5 a)	1912.6 a)	6.386 a)	296.2 a)	0.989 a)	823.4 a)	2.749 a)	9689.3 a)	32.352 a)	887.1 a)	2.962 a)	827.6 a)	2.763 a)	1714.7 a)	5.725 a)	467.4 a)	1.561 a)
F01010	323.1	1783.5	5.520	245.6	0.760	1074.6	3.326	12078.7	37.384	1089.3	3.371	1066.7	3.301	2156.0	6.673	843.5	2.611
F01011	280.1	1865.3	6.659	174.7	0.624	899.8	3.212	9188.5	32.804	904.9	3.231	908.2	3.242	1813.1	6.473	617.7	2.205
F01012	296.8	1856.9	6.256	189.2	0.637	1020.5	3.438	11147.2	37.558	1134.1	3.821	1111.5	3.745	2245.6	7.566	538.2	1.813
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	302.2	1870.6	6.242	192.5	0.638	973.3	3.225	10138.9	33.572	962.8	3.203	955.7	3.183	1918.5	6.386	635.8	2.094
S.D.	29.2	51.5	0.631	54.4	0.170	91.8	0.180	1157.7	2.489	87.8	0.338	84.6	0.361	169.9	0.692	137.4	0.357

a) Excluded from data analysis (not copulated).

Appendix 30-1-1 (continued). Organ weights of female rats at the end of the dosing period

Control (vehicle: corn oil)

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	62.5	0.172	61.8	0.170	124.3	0.341	729.4	2.003	18.3	0.050	35.9	0.099	38.7	0.106	74.6	0.205
F01002	47.1	0.159	51.7	0.174	98.8	0.333	606.1	2.044	19.0	0.064	37.9	0.128	39.2	0.132	77.1	0.260
F01003	36.8	0.119	53.0	0.172	89.8	0.291	428.0	1.389	15.0	0.049	29.5	0.096	34.5	0.112	64.0	0.208
F01004	50.8	0.194	41.4	0.158	92.2	0.352	531.1	2.026	14.2	0.054	39.3	0.150	39.7	0.151	79.0	0.301
F01005	63.2	0.214	45.6	0.154	108.8	0.368	561.2	1.897	24.8	0.084	37.6	0.127	49.3	0.167	86.9	0.294
F01006	62.7	0.230	33.4	0.122	96.1	0.352	656.0	2.401	10.0	0.037	32.9	0.120	37.3	0.137	70.2	0.257
F01007	60.7	0.182	59.7	0.179	120.4	0.360	755.2	2.260	21.6	0.065	40.9	0.122	45.4	0.136	86.3	0.258
F01008	56.9	0.196	55.6	0.191	112.5	0.387	568.4	1.957	14.5	0.050	36.4	0.125	41.9	0.144	78.3	0.270
F01009	44.5 a)	0.149 a)	42.7 a)	0.143 a)	87.2 a)	0.291 a)	350.9 a)	1.172 a)	17.7 a)	0.059 a)	29.2 a)	0.097 a)	23.8 a)	0.079 a)	53.0 a)	0.177 a)
F01010	52.6	0.163	61.2	0.189	113.8	0.352	854.6	2.645	15.0	0.046	45.6	0.141	44.0	0.136	89.6	0.277
F01011	46.1	0.165	44.9	0.160	91.0	0.325	504.0	1.799	22.7	0.081	34.9	0.125	35.7	0.127	70.6	0.252
F01012	46.5	0.157	65.0	0.219	111.5	0.376	577.1	1.944	18.6	0.063	43.2	0.146	45.2	0.152	88.4	0.298
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	53.3	0.177	52.1	0.172	105.4	0.349	615.6	2.033	17.6	0.058	37.6	0.125	41.0	0.136	78.6	0.262
S.D.	8.7	0.031	9.9	0.025	12.3	0.026	123.6	0.326	4.4	0.015	4.6	0.017	4.6	0.018	8.4	0.032

a) Excluded from data analysis (not copulated).

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

Appendix 30-1-2. Organ weights of female rats at the end of the dosing period

2-MV 62.5 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)
F02013	308.0	1820.9	5.912	229.4	0.745	889.6	2.888	9140.8	29.678	886.0	2.877	884.3	2.871	1770.3	5.748	485.4	1.576
F02014	313.5	1931.8	6.162	284.2	0.907	960.9	3.065	9801.4	31.264	979.9	3.126	970.7	3.096	1950.6	6.222	709.7	2.264
F02015	305.8	1849.0	6.046	112.8	0.369	916.1	2.996	9638.3	31.518	952.8	3.116	1011.1	3.306	1963.9	6.422	682.9	2.233
F02016	319.4 a)	1762.0 a)	5.517 a)	430.3 a)	1.347 a)	899.7 a)	2.817 a)	10298.2 a)	32.242 a)	899.1 a)	2.815 a)	948.5 a)	2.970 a)	1847.6 a)	5.785 a)	608.6 a)	1.905 a)
F02017	283.7	1814.6	6.396	138.1	0.487	911.3	3.212	10588.0	37.321	903.3	3.184	923.6	3.256	1826.9	6.440	573.4	2.021
F02018	302.8	1919.0	6.338	164.1	0.542	1053.9	3.481	11163.3	36.867	982.8	3.246	986.9	3.259	1969.7	6.505	641.9	2.120
F02019	352.9	1873.4	5.309	175.0	0.496	1137.9	3.224	9883.1	28.005	950.6	2.694	961.8	2.725	1912.4	5.419	697.1	1.975
F02020	282.0	1864.8	6.613	104.1	0.369	908.9	3.223	8678.2	30.774	913.7	3.240	916.9	3.251	1830.6	6.491	589.6	2.091
F02021	329.7	1839.6	5.580	171.2	0.519	953.3	2.891	11172.8	33.888	1007.0	3.054	999.6	3.032	2006.6	6.086	728.0	2.208
F02022	280.3	1880.9	6.710	122.1	0.436	934.5	3.334	10054.9	35.872	860.1	3.068	855.1	3.051	1715.2	6.119	670.7	2.393
F02023	303.9	1969.9	6.482	149.6	0.492	966.4	3.180	9295.0	30.586	1042.0	3.429	998.9	3.287	2040.9	6.716	786.3	2.587
F02024	342.4	1829.7	5.344	217.9	0.636	1091.0	3.186	9349.0	27.304	987.2	2.883	980.0	2.862	1967.2	5.745	772.2	2.255
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	309.5	1872.1	6.081	169.9	0.545	974.9	3.153	9887.7	32.098	951.4	3.083	953.5	3.091	1904.9	6.174	667.0	2.157
S.D.	24.0	49.8	0.493	55.0	0.162	82.3	0.181	808.0	3.437	55.4	0.205	51.4	0.201	104.0	0.398	89.7	0.258
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	KW	AN	AN	DU	KW	AN	AN	DU	DU

a) Excluded from data analysis (not copulated).

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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 30-1-2 (continued). Organ weights of female rats at the end of the dosing period

2-MV 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	53.7	0.174	46.8	0.152	100.5	0.326	653.1	2.120	12.8	0.042	33.5	0.109	37.2	0.121	70.7	0.230
F02014	59.1	0.189	59.3	0.189	118.4	0.378	622.9	1.987	14.0	0.045	41.8	0.133	47.7	0.152	89.5	0.285
F02015	52.9	0.173	43.4	0.142	96.3	0.315	584.2	1.910	12.9	0.042	42.3	0.138	45.6	0.149	87.9	0.287
F02016	43.3 a)	0.136 a)	48.4 a)	0.152 a)	91.7 a)	0.287 a)	445.3 a)	1.394 a)	14.9 a)	0.047 a)	32.6 a)	0.102 a)	32.7 a)	0.102 a)	65.3 a)	0.204 a)
F02017	37.6	0.133	55.1	0.194	92.7	0.327	603.7	2.128	15.3	0.054	36.7	0.129	41.7	0.147	78.4	0.276
F02018	64.7	0.214	44.4	0.147	109.1	0.360	561.4	1.854	13.7	0.045	39.9	0.132	41.6	0.137	81.5	0.269
F02019	61.6	0.175	47.5	0.135	109.1	0.309	755.5	2.141	18.8	0.053	36.1	0.102	37.3	0.106	73.4	0.208
F02020	47.1	0.167	51.8	0.184	98.9	0.351	498.2	1.767	21.1	0.075	35.6	0.126	38.2	0.135	73.8	0.262
F02021	45.3	0.137	58.1	0.176	103.4	0.314	579.0	1.756	15.0	0.045	36.2	0.110	37.5	0.114	73.7	0.224
F02022	56.7	0.202	51.0	0.182	107.7	0.384	530.9	1.894	15.1	0.054	44.2	0.158	41.2	0.147	85.4	0.305
F02023	50.3	0.166	54.7	0.180	105.0	0.346	586.7	1.931	12.9	0.042	35.8	0.118	38.1	0.125	73.9	0.243
F02024	53.0	0.155	52.6	0.154	105.6	0.308	569.8	1.664	15.0	0.044	43.0	0.126	48.0	0.140	91.0	0.266
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	52.9	0.171	51.3	0.167	104.2	0.338	595.0	1.923	15.1	0.049	38.6	0.126	41.3	0.134	79.9	0.260
S.D.	7.8	0.025	5.3	0.021	7.1	0.027	67.6	0.160	2.6	0.010	3.7	0.016	4.1	0.015	7.4	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	KW	KW	AN	AN	AN	AN	AN	KW	AN	AN	AN	AN

a) Excluded from data analysis (not copulated).

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).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 30-1-3. Organ weights of female rats at the end of the dosing period

2-MV 250 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)
F03025	300.4 b)	1977.8 b)	6.584 b)	261.6 b)	0.871 b)	930.3 b)	3.097 b)	9793.0 b)	32.600 b)	1100.0 b)	3.662 b)	1032.2 b)	3.436 b)	2132.2 b)	7.098 b)	459.4 b)	1.529 b)
F03026	313.0	1889.7	6.037	185.6	0.593	947.9	3.028	9503.1	30.361	874.7	2.795	913.6	2.919	1788.3	5.713	678.9	2.169
F03027	261.0	1758.9	6.739	148.3	0.568	809.9	3.103	9285.9	35.578	819.6	3.140	811.3	3.108	1630.9	6.249	652.3	2.499
F03028	254.5	1744.2	6.853	99.0	0.389	831.3	3.266	9177.5	36.061	858.8	3.374	793.5	3.118	1652.3	6.492	433.4	1.703
F03029	327.2	1964.9	6.005	129.8	0.397	966.9	2.955	11902.8	36.378	1072.9	3.279	991.5	3.030	2064.4	6.309	719.5	2.199
F03030	297.7	1827.6	6.139	201.9	0.678	958.8	3.221	9647.0	32.405	913.7	3.069	844.5	2.837	1758.2	5.906	695.4	2.336
F03031	293.8	1914.3	6.516	214.8	0.731	931.2	3.170	10255.1	34.905	980.7	3.338	956.8	3.257	1937.5	6.595	590.7	2.011
F03032	310.7	1948.6	6.272	128.5	0.414	956.2	3.078	8964.7	28.853	1035.5	3.333	950.5	3.059	1986.0	6.392	542.5	1.746
F03033	297.3	1838.0	6.182	217.4	0.731	977.4	3.288	9327.5	31.374	988.6	3.325	936.4	3.150	1925.0	6.475	582.3	1.959
F03034	291.6	1991.2	6.829	205.6	0.705	1043.7	3.579	9477.6	32.502	978.1	3.354	981.0	3.364	1959.1	6.718	702.9	2.410
F03035	269.5	1791.3	6.647	67.4	0.250	865.3	3.211	9749.0	36.174	834.2	3.095	799.0	2.965	1633.2	6.060	630.1	2.338
F03036	271.5	1800.2	6.631	159.2	0.586	852.2	3.139	8989.7	33.111	876.3	3.228	853.9	3.145	1730.2	6.373	644.4	2.373
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	289.8	1860.8	6.441	159.8	0.549	921.9	3.185	9661.8	33.427	930.3	3.212	893.8	3.087	1824.1	6.298	624.8	2.158
S.D.	23.1	85.6	0.321	50.1	0.163	72.1	0.165	828.6	2.580	85.2	0.175	75.1	0.150	155.9	0.301	84.0	0.270
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	KW	AN	AN	DU	KW	AN	AN	DU	DU

b) Excluded from data analysis (not pregnant).

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 30-1-3 (continued). Organ weights of female rats at the end of the dosing period

2-MV 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	54.0 b)	0.180 b)	49.4 b)	0.164 b)	103.4 b)	0.344 b)	1131.3 b)	3.766 b)	11.3 b)	0.038 b)	31.7 b)	0.106 b)	39.6 b)	0.132 b)	71.3 b)	0.237 b)
F03026	49.4	0.158	49.9	0.159	99.3	0.317	511.4	1.634	13.5	0.043	33.5	0.107	35.8	0.114	69.3	0.221
F03027	47.7	0.183	41.2	0.158	88.9	0.341	761.5	2.918	25.0	0.096	44.3	0.170	43.6	0.167	87.9	0.337
F03028	50.0	0.196	41.3	0.162	91.3	0.359	562.7	2.211	13.7	0.054	32.9	0.129	35.7	0.140	68.6	0.270
F03029	56.5	0.173	68.0	0.208	124.5	0.381	641.9	1.962	13.5	0.041	41.0	0.125	46.1	0.141	87.1	0.266
F03030	62.1	0.209	34.9	0.117	97.0	0.326	699.5	2.350	15.3	0.051	32.2	0.108	38.3	0.129	70.5	0.237
F03031	48.0	0.163	41.5	0.141	89.5	0.305	628.2	2.138	15.3	0.052	43.8	0.149	48.6	0.165	92.4	0.314
F03032	73.4	0.236	50.3	0.162	123.7	0.398	742.5	2.390	18.3	0.059	40.3	0.130	46.7	0.150	87.0	0.280
F03033	55.2	0.186	45.9	0.154	101.1	0.340	500.1	1.682	13.9	0.047	40.3	0.136	44.0	0.148	84.3	0.284
F03034	57.1	0.196	40.6	0.139	97.7	0.335	498.2	1.709	13.7	0.047	40.3	0.138	42.5	0.146	82.8	0.284
F03035	53.0	0.197	49.2	0.183	102.2	0.379	488.1	1.811	15.1	0.056	56.1	0.208	50.9	0.189	107.0	0.397
F03036	45.8	0.169	40.4	0.149	86.2	0.317	444.0	1.635	18.9	0.070	29.7	0.109	40.5	0.149	70.2	0.259
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	54.4	0.188	45.7	0.157	100.1	0.345	588.9	2.040	16.0	0.056	39.5	0.137	43.0	0.149	82.5	0.286
S.D.	8.0	0.023	8.8	0.024	13.0	0.030	111.3	0.407	3.5	0.016	7.4	0.030	5.0	0.020	12.0	0.049
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	KW	KW	AN	AN	AN	AN	AN	KW	AN	AN	AN	AN

b) Excluded from data analysis (not pregnant).

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 30-1-4. Organ weights of female rats at the end of the dosing period

2-MV 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)	
F04037	300.5	1937.1	6.446	118.6	0.395	931.8	3.101	11008.2	36.633	984.8	3.277	931.6	3.100	1916.4	6.377	520.8	1.733	
F04038	336.2	1920.5	5.712	318.1	0.946	1015.0	3.019	12044.1	35.824	1087.6	3.235	1035.8	3.081	2123.4	6.316	862.1	2.564	
F04039	290.8	1896.0	6.520	163.6	0.563	994.7	3.421	10565.1	36.331	1052.0	3.618	1049.1	3.608	2101.1	7.225	907.5	3.121	
F04040	283.8	1791.4	6.312	200.4	0.706	927.6	3.268	9865.5	34.762	802.3	2.827	840.7	2.962	1643.0	5.789	744.0	2.622	
F04041	280.6	1875.0	6.682	162.4	0.579	1009.7	3.598	9888.2	35.239	854.6	3.046	869.9	3.100	1724.5	6.146	731.3	2.606	
F04042	337.6	1961.2	5.809	233.0	0.690	996.2	2.951	11619.4	34.418	1017.9	3.015	1036.4	3.070	2054.3	6.085	803.1	2.379	
F04043	313.0 b)	1907.9 b)	6.096 b)	287.9 b)	0.920 b)	979.5 b)	3.129 b)	10907.7 b)	34.849 b)	1081.6 b)	3.456 b)	1067.3 b)	3.410 b)	2148.9 b)	6.865 b)	613.2 b)	1.959 b)	
F04044	313.1	1931.5	6.169	402.8	1.286	1070.4	3.419	11317.1	36.145	1175.8	3.755	1148.7	3.669	2324.5	7.424	790.2	2.524	
F04045	293.9	1660.4	5.650	208.9	0.711	894.2	3.043	10136.5	34.490	1053.0	3.583	1020.3	3.472	2073.3	7.054	651.5	2.217	
F04046	313.2	1993.3	6.364	232.0	0.741	1076.8	3.438	10796.8	34.473	1146.8	3.662	1144.6	3.655	2291.4	7.316	753.9	2.407	
F04047	322.7	1913.2	5.929	186.6	0.578	964.4	2.989	10590.2	32.817	979.3	3.035	920.3	2.852	1899.6	5.887	784.6	2.431	
F04048	294.5	1845.7	6.267	214.0	0.727	908.0	3.083	10327.1	35.067	951.7	3.232	949.4	3.224	1901.1	6.455	692.3	2.351	
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
Mean	306.1	1884.1	6.169	221.9	0.720	980.8	3.212	10741.7	35.109	1009.6	3.299	995.2	3.254	2004.8	6.552	749.2	2.450	
S.D.	19.9	92.4	0.346	78.6	0.233	61.6	0.224	704.3	1.098	113.2	0.311	102.0	0.294	213.1	0.596	104.4	0.333	
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	KW	AN	AN	DU	KW	AN	AN	DU	DU	

b) Excluded from data analysis (not pregnant).

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 30-1-4 (continued). Organ weights of female rats at the end of the dosing period

2-MV 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	53.5	0.178	61.0	0.203	114.5	0.381	621.8	2.069	14.9	0.050	38.7	0.129	46.0	0.153	84.7	0.282
F04038	73.2	0.218	65.4	0.195	138.6	0.412	612.8	1.823	17.1	0.051	42.6	0.127	44.6	0.133	87.2	0.259
F04039	43.2	0.149	53.2	0.183	96.4	0.331	746.9	2.568	15.2	0.052	33.5	0.115	38.2	0.131	71.7	0.247
F04040	39.9	0.141	41.3	0.146	81.2	0.286	560.5	1.975	20.5	0.072	41.2	0.145	38.0	0.134	79.2	0.279
F04041	52.2	0.186	48.9	0.174	101.1	0.360	524.2	1.868	13.8	0.049	45.5	0.162	48.6	0.173	94.1	0.335
F04042	54.3	0.161	49.1	0.145	103.4	0.306	597.1	1.769	20.6	0.061	47.1	0.140	51.4	0.152	98.5	0.292
F04043	51.6 b)	0.165 b)	47.3 b)	0.151 b)	98.9 b)	0.316 b)	581.7 b)	1.858 b)	16.4 b)	0.052 b)	26.5 b)	0.085 b)	28.2 b)	0.090 b)	54.7 b)	0.175 b)
F04044	75.1	0.240	61.9	0.198	137.0	0.438	739.2	2.361	17.2	0.055	39.9	0.127	39.9	0.127	79.8	0.255
F04045	57.7	0.196	55.5	0.189	113.2	0.385	544.1	1.851	12.8	0.044	38.9	0.132	42.3	0.144	81.2	0.276
F04046	41.3	0.132	55.1	0.176	96.4	0.308	551.2	1.760	21.4	0.068	38.2	0.122	41.8	0.133	80.0	0.255
F04047	76.3	0.236	66.7	0.207	143.0	0.443	659.4	2.043	13.8	0.043	41.8	0.130	45.8	0.142	87.6	0.271
F04048	46.0	0.156	45.4	0.154	91.4	0.310	496.1	1.685	15.6	0.053	36.9	0.125	41.1	0.140	78.0	0.265
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	55.7	0.181	54.9	0.179	110.6	0.360	604.8	1.979	16.6	0.054	40.4	0.132	43.4	0.142	83.8	0.274
S.D.	13.6	0.038	8.3	0.022	20.8	0.056	82.8	0.271	3.0	0.009	3.9	0.013	4.3	0.013	7.7	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	KW	KW	AN	AN	AN	AN	AN	KW	AN	AN	AN	AN

b) Excluded from data analysis (not pregnant).

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 30-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: corn oil)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		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	298.2	1842.9	6.180	306.5	1.028	861.5	2.889	6873.9	23.051	787.1	2.640	805.5	2.701	1592.6	5.341	552.4	1.852
F05050	261.0	1735.0	6.648	202.7	0.777	882.3	3.380	6149.6	23.562	844.2	3.234	823.5	3.155	1667.7	6.390	487.2	1.867
F05051	306.1	1805.2	5.897	293.6	0.959	896.1	2.927	8080.3	26.398	906.3	2.961	955.6	3.122	1861.9	6.083	487.4	1.592
F05052	280.7	1856.5	6.614	360.1	1.283	909.6	3.240	7077.7	25.214	936.0	3.335	889.7	3.170	1825.7	6.504	535.8	1.909
F05053	281.7	1950.5	6.924	306.8	1.089	838.7	2.977	6988.8	24.809	787.8	2.797	782.3	2.777	1570.1	5.574	623.4	2.213
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	285.5	1838.0	6.453	293.9	1.027	877.6	3.083	7034.1	24.607	852.3	2.993	851.3	2.985	1703.6	5.978	537.2	1.887
S.D.	17.5	78.6	0.409	57.1	0.185	28.1	0.216	690.4	1.335	67.8	0.291	70.7	0.227	133.6	0.507	56.2	0.221

Appendix 30-2-1 (continued). Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: corn oil)

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	36.2	0.121	29.1	0.098	65.3	0.219	272.9	0.915	13.3	0.045	32.2	0.108	33.1	0.111	65.3	0.219
F05050	34.5	0.132	37.0	0.142	71.5	0.274	899.5	3.446	15.6	0.060	28.5	0.109	29.9	0.115	58.4	0.224
F05051	31.9	0.104	43.2	0.141	75.1	0.245	385.7	1.260	12.3	0.040	27.1	0.089	25.2	0.082	52.3	0.171
F05052	40.6	0.145	41.7	0.149	82.3	0.293	418.4	1.491	15.9	0.057	23.9	0.085	27.5	0.098	51.4	0.183
F05053	31.4	0.111	36.6	0.130	68.0	0.241	375.8	1.334	14.8	0.053	32.5	0.115	32.2	0.114	64.7	0.230
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	34.9	0.123	37.5	0.132	72.4	0.254	470.5	1.689	14.4	0.051	28.8	0.101	29.6	0.104	58.4	0.205
S.D.	3.7	0.016	5.5	0.020	6.6	0.029	245.9	1.004	1.5	0.008	3.6	0.013	3.3	0.014	6.6	0.027

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

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

2-MV 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	267.3	1801.3	6.739	232.5	0.870	893.5	3.343	7625.0	28.526	980.7	3.669	956.7	3.579	1937.4	7.248	514.2	1.924
F06060	290.8	1926.0	6.623	322.2	1.108	924.2	3.178	7418.3	25.510	929.4	3.196	905.3	3.113	1834.7	6.309	477.9	1.643
F06061	285.7	1739.4	6.088	298.4	1.044	910.4	3.187	8107.9	28.379	915.8	3.205	903.2	3.161	1819.0	6.367	580.7	2.033
F06062	291.9	1829.4	6.267	295.4	1.012	985.2	3.375	8103.4	27.761	1018.4	3.489	938.9	3.217	1957.3	6.705	619.3	2.122
F06063	282.7	1766.8	6.250	296.3	1.048	855.5	3.026	8087.3	28.607	887.5	3.139	901.7	3.190	1789.2	6.329	468.1	1.656
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	283.7	1812.6	6.393	289.0	1.016	913.8	3.222	7868.4	27.757	946.4	3.340	921.2	3.252	1867.5	6.592	532.0	1.876
S.D.	9.9	72.0	0.275	33.5	0.089	47.5	0.141	324.9	1.299	52.6	0.229	25.2	0.187	75.0	0.401	65.8	0.218
Significance	NS	NS	NS	NS	NS	NS	NS	*	**	*	NS	NS	NS	*	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 30-2-2 (continued). Organ weights of female rats at the end of the dosing period, satellite group

2-MV 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	36.3	0.136	33.3	0.125	69.6	0.260	427.1	1.598	11.1	0.042	30.4	0.114	31.4	0.117	61.8	0.231
F06060	35.6	0.122	47.8	0.164	83.4	0.287	406.4	1.398	11.7	0.040	30.2	0.104	29.7	0.102	59.9	0.206
F06061	30.0	0.105	35.1	0.123	65.1	0.228	1135.6	3.975	19.5	0.068	30.1	0.105	33.3	0.117	63.4	0.222
F06062	41.2	0.141	36.2	0.124	77.4	0.265	996.8	3.415	17.9	0.061	31.5	0.108	32.3	0.111	63.8	0.219
F06063	52.6	0.186	26.4	0.093	79.0	0.279	1510.0	5.341	12.7	0.045	28.5	0.101	30.8	0.109	59.3	0.210
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	39.1	0.138	35.8	0.126	74.9	0.264	895.2	3.145	14.6	0.051	30.1	0.106	31.5	0.111	61.6	0.218
S.D.	8.5	0.030	7.7	0.025	7.4	0.023	475.4	1.661	3.8	0.013	1.1	0.005	1.4	0.006	2.0	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	TT	TT	TT	TT	TT	TT	AW	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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 30-3-1. Organ weights of female rats at the end of the recovery period

Control (vehicle: corn oil)																	
Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		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)
F05054	287.2	2013.4	7.010	215.4	0.750	951.0	3.311	6561.7	22.847	973.6	3.390	904.2	3.148	1877.8	6.538	641.2	2.233
F05055	294.9	1830.0	6.205	173.0	0.587	852.7	2.891	6665.6	22.603	825.9	2.801	805.8	2.732	1631.7	5.533	411.0	1.394
F05056	281.8	1971.0	6.994	234.2	0.831	950.4	3.373	7049.1	25.015	976.3	3.465	919.7	3.264	1896.0	6.728	488.8	1.735
F05057	307.5	1844.8	5.999	198.8	0.647	863.3	2.807	7633.7	24.825	938.9	3.053	867.1	2.820	1806.0	5.873	538.7	1.752
F05058	285.3	1935.3	6.783	262.6	0.920	883.8	3.098	7305.5	25.606	1052.8	3.690	1021.5	3.580	2074.3	7.271	614.9	2.155
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	291.3	1918.9	6.598	216.8	0.747	900.2	3.096	7043.1	24.179	953.5	3.280	903.7	3.109	1857.2	6.389	538.9	1.854
S.D.	10.2	79.5	0.467	34.1	0.135	47.4	0.249	445.0	1.361	82.6	0.352	79.1	0.344	160.1	0.692	93.7	0.343

Appendix 30-3-1 (continued). Organ weights of female rats at the end of the recovery period

Control (vehicle: corn oil)																	
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	42.7	0.149	43.8	0.153	86.5	0.301	544.3	1.895	16.5	0.057	40.0	0.139	41.1	0.143	81.1	0.282	
F05055	32.9	0.112	36.9	0.125	69.8	0.237	342.4	1.161	11.6	0.039	24.3	0.082	27.2	0.092	51.5	0.175	
F05056	42.5	0.151	35.3	0.125	77.8	0.276	651.5	2.312	15.5	0.055	30.1	0.107	35.6	0.126	65.7	0.233	
F05057	42.3	0.138	44.6	0.145	86.9	0.283	910.9	2.962	16.9	0.055	30.0	0.098	30.6	0.100	60.6	0.197	
F05058	45.0	0.158	50.1	0.176	95.1	0.333	553.8	1.941	13.6	0.048	42.2	0.148	40.2	0.141	82.4	0.289	
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	41.1	0.142	42.1	0.145	83.2	0.286	600.6	2.054	14.8	0.051	33.3	0.115	34.9	0.120	68.3	0.235	
S.D.	4.7	0.018	6.1	0.021	9.7	0.035	206.7	0.657	2.2	0.007	7.5	0.028	6.0	0.023	13.3	0.050	

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

Appendix 30-3-2. Organ weights of female rats at the end of the recovery period

2-MV 1000 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)
F06064	287.3	1749.2	6.088	379.7	1.322	918.0	3.195	7044.4	24.519	905.2	3.151	920.3	3.203	1825.5	6.354	614.1	2.137
F06065	271.0	1761.2	6.499	195.6	0.722	867.2	3.200	6507.9	24.014	841.7	3.106	813.3	3.001	1655.0	6.107	541.4	1.998
F06066	296.8	1914.3	6.450	228.4	0.770	901.3	3.037	7468.0	25.162	915.6	3.085	929.2	3.131	1844.8	6.216	560.4	1.888
F06067	272.8	1769.1	6.485	252.1	0.924	1014.8	3.720	6668.4	24.444	908.8	3.331	919.9	3.372	1828.7	6.703	536.6	1.967
F06068	279.5	1875.9	6.712	239.8	0.858	978.9	3.502	8014.9	28.676	959.1	3.431	883.4	3.161	1842.5	6.592	437.3	1.565
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	281.5	1813.9	6.447	259.1	0.919	936.0	3.331	7140.7	25.363	906.1	3.221	893.2	3.174	1799.3	6.394	538.0	1.911
S.D.	10.7	75.7	0.225	70.6	0.238	59.8	0.275	613.2	1.897	42.0	0.152	48.0	0.134	81.1	0.250	64.1	0.213
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 30-3-2 (continued). Organ weights of female rats at the end of the recovery period

2-MV 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	32.2	0.112	35.5	0.124	67.7	0.236	707.4	2.462	25.3	0.088	25.3	0.088	24.6	0.086	49.9	0.174
F06065	52.7	0.194	45.8	0.169	98.5	0.363	466.0	1.720	16.6	0.061	34.9	0.129	37.9	0.140	72.8	0.269
F06066	40.3	0.136	41.9	0.141	82.2	0.277	537.8	1.812	13.9	0.047	34.8	0.117	37.0	0.125	71.8	0.242
F06067	40.0	0.147	41.3	0.151	81.3	0.298	402.4	1.475	17.9	0.066	33.8	0.124	32.9	0.121	66.7	0.245
F06068	44.1	0.158	39.7	0.142	83.8	0.300	407.5	1.458	8.0	0.029	28.0	0.100	35.2	0.126	63.2	0.226
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	41.9	0.149	40.8	0.145	82.7	0.295	504.2	1.785	16.3	0.058	31.4	0.112	33.5	0.120	64.9	0.231
S.D.	7.4	0.030	3.7	0.016	10.9	0.046	126.1	0.408	6.3	0.022	4.4	0.017	5.3	0.020	9.2	0.035
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Findings	Group	Control (vehicle: control)					2-MV 1000 mg/kg				
	Animal No.	M01	M01	M01	M01	M01	M04	M04	M04	M04	M04
		008	009	010	011	012	044	045	046	047	048
Forestomach											
Edematous, mucosa		-	-	-	-	-	-	-	-	P	-
Glandular stomach											
Recessed area, mucosa, black color		-	-	-	-	-	-	-	-	P	-

- : No abnormal changes P : Non-graded change

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

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

Group	Control (vehicle: control)											2-MV 62.5 mg/kg											2-MV 250 mg/kg											2-MV 1000 mg/kg															
	Animal No.																																																
Findings	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F04														
Fate	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	
	NC											NC											NP											NP															
Forestomach																																																	
Edematous, mucosa	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	-	-	-	-	-	-	-	-	P	-	P	P	P	P	-	-	-	-	-	-	-
Recessed area, mucosa, black color	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-
Thickening, mucosa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Glandular stomach																																																	
Recessed area, mucosa	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ovary																																																	
Cystic ovarian bursa, reddish fluid, right	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

Fate : blanks, Subjected to autopsy on day 5 of lactation; NC, Not copulated; NP, Not pregnant.

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

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

Findings	Group Animal No.	Control (vehicle: control)					2-MV 1000 mg/kg				
		F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063
Forestomach											
Edematous, mucosa		-	-	-	-	-	P	P	P	P	-
Thickening, mucosa		-	-	-	-	-	-	P	P	-	P
Ileum											
Diverticulum		-	-	-	P	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

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

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

Findings	Group	Control (vehicle: control)					2-MV 1000 mg/kg				
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		054	055	056	057	058	064	065	066	067	068
Liver											
Diaphragmatic nodule		-	-	-	-	-	-	-	-	-	P

- : No abnormal changes P : Non-graded change

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

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

Findings	Group Animal No.	Control (vehicle: control)						2-MV 62.5 mg/kg								2-MV 250 mg/kg								2-MV 1000 mg/kg																																		
		M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043																			
Kidney							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	±	-	-	±	-						NE	NE						
Basophilic tubule, cortex		-	-	±	-	±																																																				
Mineralization, medulla		-	-	-	-	-																																																				
Urinary bladder							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Adrenal gland							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Vacuolation, zona fasciculata		±	-	-	-	-																																																				
Testis							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Epididymis							NE	NE														NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Granuloma, spermatic, caudal unilateral		-	-	-	-	-																																																				
Prostate							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Cellular infiltration, lymphocyte, interstitial		±	-	-	-	-																																																		±		
Seminal vesicle							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Coagulating gland							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Eyeball							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Harderian gland							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Cellular infiltration, lymphocyte, interstitial		-	-	-	-	-																																																		±		
Sciatic nerve							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Skeletal muscle							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Femur							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											NE	NE	
Marrow, femur							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE											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 2-Methylvaleraldehyde 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 Animal No.	Control (vehicle: control)					2-MV 1000 mg/kg				
		M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
Stomach											
Forestomach											
Cellular infiltration, inflammatory, submucosa		-	-	-	-	-	±	-	±	-	-
Hyperplasia, squamous cell		-	-	-	-	-	±	±	±	±	±
Glandular stomach											
Cellular infiltration, inflammatory, submucosa		-	-	±	±	-	±	-	-	±	-
Edema, submucosa		-	±	±	-	-	+	-	±	±	-
Increase, mucus		-	-	±	-	-	-	-	-	-	±

- : 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 2-Methylvaleraldehyde by oral administration in rats

Appendix 34-1. Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Findings	Group Animal No. Fate	Control (vehicle: control)											2-MV 62.5 mg/kg												2-MV 250 mg/kg												2-MV 1000 mg/kg											
		F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	
		001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047
Brain		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Pituitary gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Thyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Ultimobranchial body			P								P																																					
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Vacuolation, cytoplasmic											±																																					
Thymus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Atrophy			*								±																																					
Heart		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Trachea		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Lung		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Accumulation, foam cell, alveolus			±			±																																										
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Liver		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Fatty change, hepatocyte, periportal			±	±							2+																																					
Microgranuloma																																																
Pancreas		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Cellular infiltration, lymphocyte, interstitial			±																																													
Stomach																																																
Forestomach		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Cellular infiltration, inflammatory, submucosa																																																
Edema, lamina propria/submucosa																																																
Erosion, focal																																																
Hyperkeratosis																																																
Hyperplasia, squamous cell																																																
Glandular stomach		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		
Edema, submucosa																																																
Increase, mucus																																																

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Fate: blank, Subjected to autopsy on day 5 of lactation; NC, not copulated; NP, Not pregnant

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde by oral administration in rats
 Appendix 34-1 (continued). Histopathological findings of female rats at the end of the dosing period [H.E. staining]

Findings	Group Animal No.	Control (vehicle: control)										2-MV 62.5 mg/kg										2-MV 250 mg/kg										2-MV 1000 mg/kg									
		F01					F02					F03					F04					F05					F06					F07									
		F01	F01	F01	F01	F01	F02	F02	F02	F02	F02	F03	F03	F03	F03	F03	F04	F04	F04	F04	F04	F05	F05	F05	F05	F05	F06	F06	F06	F06	F06	F07	F07	F07	F07	F07					
		NC										NC										NP										NP									
	Fate	NC										NC										NP										NP									
Duodenum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Jejunum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Ileum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Cecum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Colon		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Rectum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Lymph node, mesenteric		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Spleen		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Deposit, pigment, brown		±	+	+	+	+																																			
Hematopoiesis, extramedullary		+	2+	+	±	2+																																			
Kidney		NP	NP	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE													
Basophilic tubule, cortex		-	-	-	-	±																																			
Cellular infiltration, lymphocyte, interstitial		-	±	-	-	±																																			
Degeneration, vacuolar, epithelium, proximal tubule		-	-	-	+	-																																			
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Adrenal gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Ovary		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Cyst		-	-	-	-	P																																			
Uterus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Vagina		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Eyeball		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Harderian gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Sciatic nerve		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Skeletal muscle		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Femur		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Marrow, femur		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE					
Fatty marrow		-	-	-	±	-																																			

-: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
 P: Non-graded change NE: Not examined M: Missing A: Autolysis
 Fate: blank, Subjected to autopsy on day 5 of lactation; NC, not copulated; NP, Not pregnant

Combined repeat dose and reproductive/developmental toxicity screening test of 2-Methylvaleraldehyde 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]

Findings	Group Animal No.	Control (vehicle: control)					2-MV 1000 mg/kg				
		F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063
Brain		-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-
Thyroid gland											
Cellular infiltration, lymphocyte, focal		-	-	-	-	-	-	-	-	±	-
Ectopic thymic tissue		-	-	-	-	-	-	-	-	-	P
Ultimobranchial body		-	-	-	P	-	-	-	P	-	P
Parathyroid gland					M						
Vacuolation, cytoplasmic		-	-	-	-	-	-	-	-	-	±
Thymus											
Atrophy		-	±	-	-	-	-	-	-	-	-
Heart		-	-	-	-	-	-	-	-	-	-
Trachea		-	-	-	-	-	-	-	-	-	-
Lung											
Accumulation, foam cell, alveolus		-	±	-	-	-	-	-	-	-	-
Bronchus		-	-	-	-	-	-	-	-	-	-
Liver											
Fatty change, hepatocyte, periportal		±	±	+	±	±	±	-	±	±	-
Microgranuloma		±	-	±	-	-	±	±	±	±	±
Pancreas		-	-	-	-	-	-	-	-	-	-
Stomach											
Forestomach											
Cellular infiltration, inflammatory, submucosa		-	-	-	-	-	+	±	+	+	+
Edema, lamina propria/ submucosa		-	-	-	-	±	-	2+	±	+	+
Hyperkeratosis		-	-	-	-	-	2+	2+	+	+	2+
Hyperplasia, squamous cell		-	-	-	-	-	±	±	+	+	2+
Glandular stomach											
Cellular infiltration, inflammatory, submucosa		-	-	-	-	-	±	-	-	-	-
Edema, submucosa		±	-	-	-	-	+	±	-	-	-
Increase, mucus		-	-	-	-	-	-	±	-	-	-

- : 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 2-Methylvaleraldehyde 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]

Findings	Group Animal No.	Control (vehicle: control)					2-MV 1000 mg/kg				
		F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063
Duodenum		-	-	-	-	-	-	-	-	-	-
Jejunum		-	-	-	-	-	-	-	-	-	-
Ileum		-	-	-	-	-	-	-	-	-	-
Cecum		-	-	-	-	-	-	-	-	-	-
Colon		-	-	-	-	-	-	-	-	-	-
Rectum		-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric		-	-	-	-	-	-	-	-	-	-
Spleen											
Deposit, pigment, brown		+	±	±	+	+	+	+	±	±	±
Hematopoiesis, extramedullary		±	±	±	2+	±	±	±	+	±	±
Kidney											
Basophilic tubule, cortex		±	-	-	-	-	-	-	-	-	±
Cellular infiltration, inflammatory, interstitial		-	±	-	-	-	± ^{a)}	±	-	±	-
Urinary bladder		-	-	-	-	-	-	-	-	-	-
Adrenal gland		-	-	-	-	-	-	-	-	-	-
Ovary		-	-	-	-	-	-	-	-	-	-
Uterus		-	-	-	-	-	-	-	-	-	-
Dilatation, lumen		-	±	-	-	-	-	-	±	±	±
Vagina		-	-	-	-	-	-	-	-	-	-
Eyeball		-	-	-	-	-	-	-	-	-	-
Harderian gland		-	-	-	-	-	-	-	-	-	-
Cellular infiltration, lymphocyte, interstitial		-	-	±	-	-	-	-	±	-	-
Sciatic nerve		-	-	-	-	-	-	-	-	-	-
Skeletal muscle		-	-	-	-	-	-	-	-	-	-
Femur		-	-	-	-	-	-	-	-	-	-
Marrow, femur											
Increase, hematopoiesis		-	-	±	±	-	-	-	±	±	-

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

a) Inflammatory cells were infiltrated into the pelvis.

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

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

Findings	Group Animal No.	Control (vehicle: control)					2-MV 1000 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
Liver		054	055	056	057	058	064	065	066	067	068
Nodule, hepatodiaphragmatic ^{a)}		NE	NE	NE	NE	NE	NE	NE	NE	NE	P
Stomach											
Forestomach											
Cellular infiltration, inflammatory, submucosa		-	-	-	-	-	±	-	±	±	±
Hyperkeratosis		-	-	-	-	-	±	±	±	±	±
Hyperplasia, squamous cell		-	-	-	-	-	±	±	±	±	±
Glandular stomach											
Edema, submucosa		-	±	-	-	-	±	±	-	-	-
Increase, mucus		-	-	-	-	-	±	-	-	-	-

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

a), Fibrosis was observed in serosa around the nodule, and congestion was observed in sinusoid.

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

Appendix 35-1. Results of observations about estrous cycle

Control (vehicle: corn oil)

Animal No.	Pre-mating period						Mating period	Times of vaginal estrus observed
	Pre-treatment period			Treatment period				
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)		
F01001	DDPEDDPEDDPEDD	4-day	4.0	PEDDDEDDPEDDPE	4-day	4.0	DDP PL	1
F01002	DPEDDPEDDPEDDP	4-day	4.0	EDDPEDDPEDDPED	4-day	4.0	DP PL	1
F01003	DPEDDPEDDPEDDP	4-day	4.0	EDDPEDDPEDDPED	4-day	4.0	DP PL	1
F01004	PEDDDEDDPEDDDD	4/5-day	4.5	EDDPEDDDEDDPED	4-day	4.0	DP PL	1
F01005	DEDDPEDDDEDDPE	4-day	4.0	DDPEDDDEDDPEDD	4-day	4.0	D PL	1
F01006	DEDDDEDDPEDDPE	4-day	4.0	DDPEDDDEDDDEDD	4-day	4.0	P PL	1
F01007	DPEDDPEEDDPEED	5-day	5.0	DPPEDDPEEDDDPE	5-day	5.0	DDPP PL	1
F01008	DPEDDDPEDDP PED	5-day	5.0	DPPEDDPEEDDDPE	5-day	5.0	DDD PL	1
F01009	DDPEDDPEDDPEDD	4-day	4.0	PEDDPEDDPEDDPE	4-day	4.0	DDDDDDDDDDDD	
F01010	EDDPEDDDEDDPED	4-day	4.0	DDEDDPEDDPEDDP	4-day	4.0	PL	1
F01011	DPEDDPEDDPEDDDD	4-day	4.0	EDDDEDDDEDDDED	4-day	4.0	DP PL	1
F01012	DDPEDDPEDDPEDD	4-day	4.0	PEDDPEDDPEDDPE	4-day	4.0	DDP PL	1
Mean			4.2			4.2		1.0
S.D.			0.4			0.4		0.0
(N)			(12)			(12)		(11)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

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

Appendix 35-2. Results of observations about estrous cycle

2-MV 62.5 mg/kg

Animal No.	Pre-mating period				Mating period			Times of vaginal estrus observed
	Pre-treatment period		Treatment period		Mating period			
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F02013	DDPEDDPEDDPEDD	4-day	4.0	PEDDPEDDDEDDPE	4-day	4.0	DDP PL	1
F02014	DEDDPEDDDEDDPE	4-day	4.0	DDDEDDDEDDPEDD	4-day	4.0	P PL	1
F02015	DEDDPEDDPEDDDE	4-day	4.0	DDPEDDPEDDPEDD	4-day	4.0	P PL	1
F02016	DDPEDDPEDDPEDD	4-day	4.0	PEDDPEDDPEDDPE	4-day	4.0	DDDDDDDDDDDDDD	
F02017	PEDDPEDDPEDDPE	4-day	4.0	DDPEDDPEDDPEDD	4-day	4.0	P PL	1
F02018	DDPEDDDEDDPEDD	4-day	4.0	PEDDPEDDPEDDPE	4-day	4.0	DDP PL	1
F02019	DDPEDDPEDDPEDD	4-day	4.0	PEDDPEDDPEDDPE	4-day	4.0	DDP PL	1
F02020	DPEDDPEDDPEDDP	4-day	4.0	EDDPEDDPEDDPED	4-day	4.0	DP PL	1
F02021	DDEDDDPEDDDEED	5-day	5.0	DDPEDDPEEDDDPE	5-day	5.0	DDPP PL	1
F02022	DEDDPEDDDEDDPE	4-day	4.0	DDPEDDPEDDDEDD	4-day	4.0	P PL	1
F02023	DPEDDPEEDDDEDD	4/5-day	4.5	PEDDPEDDPEDDPE	4-day	4.0	DDP PL	1
F02024	PEDDPEDDPEEDDD	4/5-day	4.5	PEDDPDDDDDDDDDD	irregular		DD PL	1
Mean			4.2			4.1		1.0
S.D.			0.3			0.3		0.0
(N)			(12)			(11)		(11)

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 2-Methylvaleraldehyde by oral administration in rats

Appendix 35-3. Results of observations about estrous cycle

2-MV 250 mg/kg

Animal No.	Pre-mating period						Mating period	Times of vaginal estrus observed
	Pre-treatment period			Treatment period				
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)		
F03025	DDPEDDPEDDPEDD	4-day	4.0	PEDDPEDDDEDDPE	4-day	4.0	DDDPL	1
F03026	DDEDDPEDDPEDDP	4-day	4.0	EDDPEDDPEDDPED	4-day	4.0	DPPL	1
F03027	EDDPEDDPEDDPED	4-day	4.0	DPEDDPEDDPEDDP	4-day	4.0	PL	1
F03028	EDDPEDDDEDDDED	4-day	4.0	DDEDDPEDDDEDDD	4-day	4.0	PL	1
F03029	DDEDDDEDDDPEDD	4/5-day	4.5	DDEDDDEDDDPEDD	4/5-day	4.5	DPL	1
F03030	EDDPEDDPEDDPED	4-day	4.0	DPEDDPEDDPEDDP	4-day	4.0	PL	1
F03031	PEDDPEDDPEDDPE	4-day	4.0	DDPEDDPEDDPEDD	4-day	4.0	PPL	1
F03032	DDEDDDEDDPEDDP	4-day	4.0	EDDPEDDPEDDPED	4-day	4.0	DPPL	1
F03033	PEDDPEDDPEDDPE	4-day	4.0	DDPEDDPEDDPEDD	4-day	4.0	PPL	1
F03034	DDPEDDPPEDDPEED	4/5-day	4.5	DDPEDDPPEDDDEE	5-day	5.0	DDPPL	1
F03035	DEDDPEDDPEDDPE	4-day	4.0	DDPEDDPEDDPEDD	4-day	4.0	PPL	1
F03036	PEDDPEDDPEDDPE	4-day	4.0	DDPEDDPEDDPEDD	4-day	4.0	PPL	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 2-Methylvaleraldehyde by oral administration in rats

Appendix 35-4. Results of observations about estrous cycle

2-MV 1000 mg/kg

Animal No.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F04037	D P E D D P E D D D E D D D	4-day	4.0	P E E D D P E E D D D P E D	5-day	5.0	D D E PL	1	
F04038	P 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 P P PL	1	
F04039	D 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 D E D D P E	4-day	4.0	D D P PL	1	
F04040	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D D E D D P E D D	4-day	4.0	P PL	1	
F04041	D 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	
F04042	P E D D D P E D D D P E D D	5-day	5.0	P E D D P E D D D E D D P E	4-day	4.0	D D P PL	1	
F04043	D D P E D D D D E D D D D D	5-day	5.0	E D D P E D D D E D D D P E	4/5-day	4.3	PL	1	
F04044	D D D E E D D D P E D D D E	4/5-day	4.5	D D D E D D D E E D D D E D	4/5-day	4.5	D D P PL	1	
F04045	D D P E D D P E D D D P E D	4/5-day	4.5	D P E D D P E D D P E D D P	4-day	4.0	PL	1	
F04046	P 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	
F04047	D P E D D D D E D D P E D D	4/5-day	4.5	D P E D D D P E D D D E D D	4/5-day	4.5	P PL	1	
F04048	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D D E D D P E	4-day	4.0	D D P PL	1	
Mean			4.4			4.3		1.0	
S.D.			0.4			0.4		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 2-Methylvaleraldehyde by oral administration in rats

Appendix 36-1. Results of observations about reproductive performance

Control (vehicle: corn oil)

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M01001	F01001	+	+	4
M01002	F01002	+	+	3
M01003	F01003	+	+	3
M01004	F01004	+	+	3
M01005	F01005	+	+	2
M01006	F01006	+	+	2
M01007	F01007	+	+	5
M01008	F01008	+	+	4
M01009	F01009	-		
M01010	F01010	+	+	1
M01011	F01011	+	+	3
M01012	F01012	+	+	4
Total		+: 11, -: 1	+: 11, -: 0	
Mean				3.1
S.D.				1.1
(N)				(11)

+, confirmed

-, not confirmed

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

Appendix 36-2. Results of observations about reproductive performance

2-MV 62.5 mg/kg

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M02013	F02013	+	+	4
M02014	F02014	+	+	2
M02015	F02015	+	+	2
M02016	F02016	-		
M02017	F02017	+	+	2
M02018	F02018	+	+	4
M02019	F02019	+	+	4
M02020	F02020	+	+	3
M02021	F02021	+	+	5
M02022	F02022	+	+	2
M02023	F02023	+	+	4
M02024	F02024	+	+	3
Total		+: 11, -: 1	+: 11, -: 0	
Mean				3.2
S.D.				1.1
(N)				(11)

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 2-Methylvaleraldehyde by oral administration in rats

Appendix 36-3. Results of observations about reproductive performance

2-MV 250 mg/kg

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M03025	F03025	+	-	4
M03026	F03026	+	+	3
M03027	F03027	+	+	1
M03028	F03028	+	+	1
M03029	F03029	+	+	2
M03030	F03030	+	+	1
M03031	F03031	+	+	2
M03032	F03032	+	+	3
M03033	F03033	+	+	2
M03034	F03034	+	+	4
M03035	F03035	+	+	2
M03036	F03036	+	+	2
Total		+: 12, -: 0	+: 11, -: 1	
Mean				2.3
S.D.				1.1
(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 2-Methylvaleraldehyde by oral administration in rats

Appendix 36-4. Results of observations about reproductive performance

2-MV 1000 mg/kg

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M04037	F04037	+	+	4
M04038	F04038	+	+	4
M04039	F04039	+	+	4
M04040	F04040	+	+	2
M04041	F04041	+	+	1
M04042	F04042	+	+	4
M04043	F04043	+	-	1
M04044	F04044	+	+	4
M04045	F04045	+	+	1
M04046	F04046	+	+	2
M04047	F04047	+	+	2
M04048	F04048	+	+	4
Total		+: 12, -: 0	+: 11, -: 1	
Mean				2.8
S.D.				1.4
(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 2-Methylvaleraldehyde by oral administration in rats

Appendix 37-1. Observation of offspring (F₁)

Control (vehicle: corn oil)																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring			External abnormalities ^{b)}			
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio	Viability index (%)	(Number)	(%)	
							Male	Female	Total											
																				Male
F01001	22	16	16	100.0	+	15	8	7	15	0.53	0	93.8	93.8	100.0	8	7	0.53	100.0	0	0.0
F01002	22	15	15	100.0	+	13	6	7	13	0.46	0	86.7	86.7	100.0	6	7	0.46	100.0	0	0.0
F01003	22	16	16	100.0	+	13	6	7	13	0.46	0	81.3	81.3	100.0	6	7	0.46	100.0	0	0.0
F01004	23	15	15	100.0	+	15	4	5	9	0.44	6	100.0	60.0	60.0	4	5	0.44	100.0	0	0.0
F01005	22	15	15	100.0	+	15	8	3	11	0.73	4	100.0	73.3	73.3	8	3	0.73	100.0	0	0.0
F01006	22	15	15	100.0	+	15	7	6	13	0.54	2	100.0	86.7	86.7	7	6	0.54	100.0	0	0.0
F01007	22	19	19	100.0	+	17	8	9	17	0.47	0	89.5	89.5	100.0	8	8	0.50	94.1	0	0.0
F01008	22	15	13	86.7	+	11	7	4	11	0.64	0	84.6	84.6	100.0	7	4	0.64	100.0	0	0.0
F01009	Not copulated																			
F01010	21	17	16	94.1	+	16	5	10	15	0.33	1	100.0	93.8	93.8	5	9	0.36	93.3	0	0.0
F01011	22	15	14	93.3	+	13	5	8	13	0.38	0	92.9	92.9	100.0	5	8	0.38	100.0	0	0.0
F01012	22	15	12	80.0	+	11	7	4	11	0.64	0	91.7	91.7	100.0	7	4	0.64	100.0	0	0.0
Number of dams	11	11	11	11	11 ^{a)}	11			11	11	11	11	11	11			11	11	11	11
Total		173	166			154	71	70	141		13				71	68			0	
Mean	22.0	15.7	15.1	95.8		14.0	6.5	6.4	12.8	0.51	1.2	92.8	84.9	92.2	6.5	6.2	0.52	98.9		0.0
S.D.	0.4	1.3	1.8	6.8		1.9	1.4	2.2	2.3	0.12	2.0	6.8	10.3	13.6	1.4	1.9	0.12	2.6		0.0
%					100.0															

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

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

Appendix 37-2. Observation of offspring (F₁)

2-MV 62.5 mg/kg																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams)	Number of offspring at birth						Delivery index (offspring)	Birth index (%)	Live birth index (%)	Number of live offspring			External abnormalities ^{b)}		
						Number of offspring	Live			Sex ratio	Dead offspring				4 days	Sex ratio	Viability index (%)	Number		
							Male	Female	Total									Male	Female	
																				(%)
F02013	21	14	13	92.9	+	13	5	7	12	0.42	1	100.0	92.3	92.3	5	7	0.42	100.0	1	8.3
F02014	21	17	17	100.0	+	16	9	7	16	0.56	0	94.1	94.1	100.0	9	7	0.56	100.0	0	0.0
F02015	22	17	16	94.1	+	16	8	8	16	0.50	0	100.0	100.0	100.0	8	8	0.50	100.0	0	0.0
F02016	Not copulated																			
F02017	22	15	15	100.0	+	15	5	10	15	0.33	0	100.0	100.0	100.0	5	10	0.33	100.0	0	0.0
F02018	22	17	17	100.0	+	15	9	6	15	0.60	0	88.2	88.2	100.0	9	6	0.60	100.0	0	0.0
F02019	22	16	16	100.0	+	15	10	4	14	0.71	1	93.8	87.5	93.3	10	4	0.71	100.0	0	0.0
F02020	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
F02021	23	15	15	100.0	+	15	5	8	13	0.38	2	100.0	86.7	86.7	5	7	0.42	92.3	0	0.0
F02022	22	18	18	100.0	+	17	7	10	17	0.41	0	94.4	94.4	100.0	7	10	0.41	100.0	0	0.0
F02023	22	15	15	100.0	+	15	7	8	15	0.47	0	100.0	100.0	100.0	7	8	0.47	100.0	0	0.0
F02024	21	17	17	100.0	+	16	5	10	15	0.33	1	94.1	88.2	93.8	5	10	0.33	100.0	0	0.0
Number of dams	11	11	11	11	11 ^{a)}	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Total		175	173			167	74	88	162		5				74	87			1	
Mean	21.8	15.9	15.7	98.8		15.2	6.7	8.0	14.7	0.45	0.5	96.8	93.8	96.9	6.7	7.9	0.46	99.3		0.8
S.D.	0.6	1.4	1.5	2.6		1.1	2.1	1.9	1.4	0.13	0.7	4.1	5.6	4.6	2.1	2.0	0.13	2.3		2.5
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN	KW	AN	AN	KW	AN	KW	AN	DT	KW	AN	AN	AN	AN	AN	AN

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

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

NS: Not significantly different from the control group.

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

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 37-3. Observation of offspring (F₁)

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring			External abnormalities ^{b)}			
						Number of offspring	Sex ratio			Dead offspring				4 days	Sex ratio	Viability index (%)	(Number)	(%)		
							Live													
							Male	Female	Total											
F03025	Not pregnant																			
F03026	22	13	13	100.0	+	13	6	7	13	0.46	0	100.0	100.0	100.0	6	7	0.46	100.0	0	0.0
F03027	21	18	18	100.0	+	18	12	6	18	0.67	0	100.0	100.0	100.0	12	6	0.67	100.0	0	0.0
F03028	22	15	15	100.0	+	15	6	8	14	0.43	1	100.0	93.3	93.3	6	8	0.43	100.0	0	0.0
F03029	22	18	17	94.4	+	17	13	4	17	0.76	0	100.0	100.0	100.0	13	4	0.76	100.0	0	0.0
F03030	21	14	14	100.0	+	14	6	8	14	0.43	0	100.0	100.0	100.0	6	8	0.43	100.0	0	0.0
F03031	22	15	15	100.0	+	13	5	8	13	0.38	0	86.7	86.7	100.0	5	8	0.38	100.0	0	0.0
F03032	22	16	15	93.8	+	14	5	9	14	0.36	0	93.3	93.3	100.0	5	7	0.42	85.7	0	0.0
F03033	22	16	16	100.0	+	15	8	7	15	0.53	0	93.8	93.8	100.0	8	7	0.53	100.0	0	0.0
F03034	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
F03035	22	15	15	100.0	+	15	9	5	14	0.64	1	100.0	93.3	93.3	9	5	0.64	100.0	0	0.0
F03036	22	16	16	100.0	+	14	5	9	14	0.36	0	87.5	87.5	100.0	5	9	0.36	100.0	0	0.0
Number of dams	11	11	11	11	11 ^{a)}	11			11	11	11	11	11	11			11	11	11	11
Total		171	168			162	83	77	160		2				83	75				0
Mean	21.8	15.5	15.3	98.3		14.7	7.5	7.0	14.5	0.51	0.2	96.5	95.3	98.8	7.5	6.8	0.51	98.7		0.0
S.D.	0.4	1.5	1.4	2.9		1.6	2.8	1.6	1.6	0.14	0.4	5.3	5.1	2.7	2.8	1.5	0.13	4.3		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	AN	AN	AN	KW	AN	KW	AN	AN	KW	AN	KW	AN	DT	KW	AN	AN	AN	AN	AN	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.

Significantly different from control (vehicle: corn oil) (*: P<0.05).

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.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 37-4. Observation of offspring (F₁)

2-MV 1000 mg/kg																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring			External abnormalities ^{b)}			
						Number of offspring	Sex ratio			Dead offspring				4 days		Sex ratio	Viability index (%)	(Number)	(%)	
							Male	Female	Total					Male	Female					
F04037	22	18	18	100.0	+	16	11	5	16	0.69	0	88.9	88.9	100.0	11	4	0.73	93.8	0	0.0
F04038	22	19	19	100.0	+	18	10	8	18	0.56	0	94.7	94.7	100.0	9	7	0.56	88.9	0	0.0
F04039	22	16	15	93.8	+	12	5	6	11	0.45	1	80.0	73.3	91.7	5	6	0.45	100.0	0	0.0
F04040	22	14	14	100.0	+	14	6	8	14	0.43	0	100.0	100.0	100.0	6	7	0.46	92.9	0	0.0
F04041	21	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	16	15	93.8	+	13	3	6	9	0.33	4	86.7	60.0	69.2	3	6	0.33	100.0	0	0.0
F04043	Not pregnant																			
F04044	22	15	9	60.0	+	9	2	7	9	0.22	0	100.0	100.0	100.0	2	7	0.22	100.0	0	0.0
F04045	22	16	16	100.0	+	15	6	9	15	0.40	0	93.8	93.8	100.0	5	9	0.36	93.3	0	0.0
F04046	22	13	12	92.3	+	10	5	5	10	0.50	0	83.3	83.3	100.0	5	5	0.50	100.0	0	0.0
F04047	21	19	18	94.7	+	18	9	8	17	0.53	1	100.0	94.4	94.4	8	8	0.50	94.1	0	0.0
F04048	22	16	16	100.0	+	16	6	10	16	0.38	0	100.0	100.0	100.0	6	10	0.38	100.0	0	0.0
Number of dams	11	11	11	11	11 ^{a)}	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Total		176	166			155	67	82	149		6				64	79			0	
Mean	21.8	16.0	15.1	94.1		14.1	6.1	7.5	13.5	0.43	0.5	93.4	89.9	95.9	5.8	7.2	0.43	96.6		0.0
S.D.	0.4	2.0	2.9	11.7		2.9	2.8	1.8	3.3	0.13	1.2	7.5	13.0	9.3	2.6	1.9	0.14	4.1		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN	KW	AN	AN	KW	AN	KW	AN	DT	KW	AN	AN	AN	AN	AN	AN

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

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

NS: Not significantly different from the control group.

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

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

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 38-1. Body weights of offspring (F₁) before weaning

Control (vehicle: corn oil)

Dam No.	Days after birth			
	Male body weight		Female body weight	
	0	4	0	4
F01001	6.4 (8)	11.0 (8)	6.4 (7)	10.8 (7)
F01002	7.4 (6)	12.3 (6)	6.9 (7)	11.5 (7)
F01003	6.9 (6)	11.3 (6)	6.6 (7)	11.2 (7)
F01004	6.6 (4)	13.0 (4)	6.9 (5)	12.7 (5)
F01005	6.8 (8)	10.9 (8)	6.5 (3)	10.5 (3)
F01006	7.1 (7)	8.5 (7)	6.2 (6)	7.4 (6)
F01007	6.4 (8)	9.3 (8)	6.1 (9)	9.8 (8)
F01008	7.0 (7)	11.7 (7)	6.4 (4)	10.6 (4)
F01009	Not copulated			
F01010	6.3 (5)	9.7 (5)	6.1 (10)	9.5 (9)
F01011	6.1 (5)	10.3 (5)	5.8 (8)	9.5 (8)
F01012	7.6 (7)	13.3 (7)	7.4 (4)	13.0 (4)
Number of dams	11	11	11	11
Mean	6.8	11.0	6.5	10.6
S.D.	0.5	1.5	0.5	1.6

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

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

Appendix 38-2. Body weights of offspring (F₁) before weaning

2-MV 62.5 mg/kg

Dam No.	Days after birth			
	Male body weight		Female body weight	
	0	4	0	4
F02013	6.1 (5)	10.3 (5)	5.8 (7)	10.0 (7)
F02014	5.8 (9)	9.0 (9)	5.6 (7)	9.1 (7)
F02015	6.5 (8)	11.0 (8)	6.4 (8)	10.4 (8)
F02016	Not copulated			
F02017	6.7 (5)	8.9 (5)	6.6 (10)	8.9 (10)
F02018	6.8 (9)	11.7 (9)	6.6 (6)	11.3 (6)
F02019	6.8 (10)	10.9 (10)	6.7 (4)	10.5 (4)
F02020	6.1 (4)	10.8 (4)	6.4 (10)	11.2 (10)
F02021	7.3 (5)	13.4 (5)	6.4 (8)	11.9 (7)
F02022	5.9 (7)	10.1 (7)	5.5 (10)	9.3 (10)
F02023	6.2 (7)	9.4 (7)	5.8 (8)	8.8 (8)
F02024	6.0 (5)	9.1 (5)	5.9 (10)	9.4 (10)
Number of dams	11	11	11	11
Mean	6.4	10.4	6.2	10.1
S.D.	0.5	1.4	0.4	1.1
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

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

NS: Not significantly different from the control group.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 38-3. Body weights of offspring (F₁) before weaning

Dam No.	Days after birth			
	Male body weight		Female body weight	
	0	4	0	4
F03025	Not pregnant			
F03026	6.2 (6)	10.8 (6)	6.0 (7)	10.3 (7)
F03027	5.5 (12)	6.7 (12)	5.3 (6)	6.7 (6)
F03028	6.2 (6)	8.0 (6)	5.8 (8)	7.7 (8)
F03029	6.7 (13)	9.6 (13)	6.3 (4)	9.4 (4)
F03030	6.0 (6)	9.5 (6)	5.5 (8)	8.7 (8)
F03031	7.3 (5)	11.8 (5)	6.8 (8)	10.6 (8)
F03032	6.3 (5)	11.2 (5)	6.0 (9)	11.1 (7)
F03033	6.7 (8)	9.9 (8)	6.5 (7)	10.2 (7)
F03034	6.0 (8)	9.9 (8)	5.7 (6)	8.9 (6)
F03035	6.1 (9)	7.9 (9)	5.9 (5)	8.2 (5)
F03036	6.5 (5)	10.4 (5)	6.1 (9)	10.2 (9)
Number of dams	11	11	11	11
Mean	6.3	9.6	6.0	9.3
S.D.	0.5	1.5	0.4	1.4
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

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

NS: Not significantly different from the control group.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 38-4. Body weights of offspring (F₁) before weaning

2-MV 1000 mg/kg

Dam No.	Days after birth			
	Male body weight		Female body weight	
	0	4	0	4
F04037	6.2 (11)	8.7 (11)	5.8 (5)	8.2 (4)
F04038	5.8 (10)	10.7 (9)	5.4 (8)	9.5 (7)
F04039	6.4 (5)	12.1 (5)	7.0 (6)	11.9 (6)
F04040	6.3 (6)	9.8 (6)	5.9 (8)	9.2 (7)
F04041	6.0 (4)	10.2 (4)	5.9 (10)	9.6 (10)
F04042	6.7 (3)	12.7 (3)	6.4 (6)	12.2 (6)
F04043	Not pregnant			
F04044	7.4 (2)	12.8 (2)	6.9 (7)	11.8 (7)
F04045	6.2 (6)	9.5 (5)	5.8 (9)	9.8 (9)
F04046	7.6 (5)	12.9 (5)	6.9 (5)	12.5 (5)
F04047	5.4 (9)	7.7 (8)	5.1 (8)	7.7 (8)
F04048	5.9 (6)	9.7 (6)	5.7 (10)	9.2 (10)
Number of dams	11	11	11	11
Mean	6.4	10.6	6.1	10.1
S.D.	0.7	1.8	0.6	1.7
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

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

NS: Not significantly different from the control group.

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

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

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

Appendix 39-1. General conditions in offspring (F₁) before weaning

Control (vehicle: corn oil)						
Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F01001	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01002	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01003	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01004	Number of offspring	9	9	9	9	9
	General appearance, No abnormality	9	9	9	9	9
F01005	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F01006	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01007	Number of offspring	17	17	16	16	16
	General appearance, No abnormality	17	16	16	16	16
	General appearance, Death	0	1	0	0	0
F01008	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F01009	Not copulated					
F01010	Number of offspring	15	15	15	14	14
	General appearance, No abnormality	15	15	14	14	14
	General appearance, Death	0	0	1	0	0
F01011	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01012	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
Number of offspring		141	141	140	139	139
General appearance, No abnormality		141	140	139	139	139
General appearance, Death			1	1		

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

Appendix 39-2. General conditions in offspring (F₁) before weaning

2-MV 62.5 mg/kg						
Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F02013	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02014	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02015	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02016	Not copulated					
F02017	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02018	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02019	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02020	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02021	Number of offspring	13	13	12	12	12
	General appearance, No abnormality	13	12	12	12	12
	General appearance, Death	0	1	0	0	0
F02022	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F02023	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02024	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
	Number of offspring	162	162	161	161	161
	General appearance, No abnormality	162	161	161	161	161
	General appearance, Death		1			

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

Appendix 39-3. General conditions in offspring (F₁) before weaning

2-MV 250 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F03025	Not pregnant					
F03026	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03027	Number of offspring	18	18	18	18	18
	General appearance, No abnormality	18	18	18	18	18
F03028	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03029	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F03030	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03031	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03032	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	12
	General appearance, Death	0	0	0	0	2
F03033	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03034	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03035	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03036	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
	Number of offspring	160	160	160	160	160
	General appearance, No abnormality	160	160	160	160	158
	General appearance, Death					2

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

Appendix 39-4. General conditions in offspring (F₁) before weaning

2-MV 1000 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
		F04037	Number of offspring	16	16	16
	General appearance, No abnormality	16	16	15	15	15
	General appearance, Death	0	0	1	0	0
F04038	Number of offspring	18	18	16	16	16
	General appearance, No abnormality	18	16	16	16	16
	General appearance, Death	0	2	0	0	0
F04039	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F04040	Number of offspring	14	14	13	13	13
	General appearance, No abnormality	14	13	13	13	13
	General appearance, Death	0	1	0	0	0
F04041	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04042	Number of offspring	9	9	9	9	9
	General appearance, No abnormality	9	9	9	9	9
F04043	Not pregnant					
F04044	Number of offspring	9	9	9	9	9
	General appearance, No abnormality	9	9	9	9	9
F04045	Number of offspring	15	15	15	14	14
	General appearance, No abnormality	15	15	14	14	14
	General appearance, Death	0	0	1	0	0
F04046	Number of offspring	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10
F04047	Number of offspring	17	17	17	17	16
	General appearance, No abnormality	17	17	17	16	16
	General appearance, Death	0	0	0	1	0
F04048	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
	Number of offspring	149	149	146	144	143
	General appearance, No abnormality	149	146	144	143	143
	General appearance, Death		3	2	1	