

最終報告書

1-Ethoxy-2-(2-methoxyethoxy)ethane のラットを用いる 反復投与毒性・生殖発生毒性併合試験

厚生労働省医薬食品局審査管理課 化学物質安全対策室 委託

試験施設

一般財団法人食品薬品安全センター 秦野

〒257-8523 神奈川県秦野市落合 729 番地の5

TEL 0463-82-4751

試験委託者 厚生労働省医薬食品局審査管理課 化学物質安全対策室
(東京都千代田区霞が関 1-2-2)

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被験物質 1-Ethoxy-2-(2-methoxyethoxy)ethane

試験項目 反復投与毒性・生殖発生毒性併合試験

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試験資料保管場所 秦野研究所資料保存施設

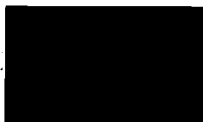
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保管期間 試験終了後 10 年間
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運営管理者 一般財団法人食品薬品安全センター 秦野研究所
所長 

本試験は、「新規化学物質等に係る試験の方法について」(平成 23 年 3 月 31 日付け、薬食発 0331 第 7 号厚生労働省医薬食品局長、平成 23・03・29 製局第 5 号経済産業省製造産業局長、環境省令第 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、環境省令第 110331010 号環境省総合環境政策局長通知)を遵守して実施した。

2014 年 3 月 26 日

試験責任者 

試験従事者

試験責任者

試験担当主任者

試験担当者

投与・観察

動物飼育管理

(検疫を含む)

尿検査

血液学的検査

(採血を含む)

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信頼性保証書

要約

1-Ethoxy-2-(2-methoxyethoxy)ethane の反復投与毒性・生殖発生毒性併合試験を化審法ガイドラインに従って実施した。被験物質を注射用水に希釈して 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 日までの 41～46 日間投与し、出生児は哺育 4 日、母動物は哺育 5 日に剖検した。また、0 および 1000 mg/kg の用量に非交配雌 (10 匹/群) を設け、42 日間投与した後に半数を剖検し、残りの半数と 0 および 1000 mg/kg 群の雄 5 匹は、42 日間投与した後に 14 日間飼育して剖検した。

1. 反復投与毒性および回復性

自発運動の低下が 1000 mg/kg 群の非交配雌を含む雌雄全例に、投与後の一過性の流涎が 1000 mg/kg 群の雄および交配雌の一部に観察された。また、体重増加抑制が 1000 mg/kg 群の妊娠雌に、摂餌量の低下が 1000 mg/kg 群の雄および非交配雌、さらには 250 mg/kg 群の分娩雌に認められた。血色素量およびヘマトクリット値の低下が 1000 mg/kg 群の雄および非交配雌に、網状赤血球比率の低下が 250 mg/kg 以上の雄および 1000 mg/kg 群の非交配雌に、MCHC および血小板数の低下が 1000 mg/kg 群の非交配雌に認められた。総蛋白濃度の低下と γ -GTP の増加が 1000 mg/kg 群の雄に認められ、尿中カリウムおよび塩素イオン濃度の低下が 1000 mg/kg 群の雄にみられた。胸腺重量の低下、肝臓および腎臓の相対重量の増加が 1000 mg/kg 群の雄および非交配雌にみられ、雄ではさらに精巣上体および前立腺の重量が低下した。胸腺髄質の萎縮、小葉中心性の肝細胞肥大および肝細胞の曇りガラス変性が 1000 mg/kg 群の雄および非交配雌に観察され、小葉中心性の肝細胞肥大は 250 mg/kg 群の雄にも認められた。また、1000 mg/kg 群の雄では、精巣の精細管内で精子細胞の脱落、生殖細胞層の空胞化および多核巨細胞が、精巣上体の管腔内で精子の減少および細胞残屑が、前立腺の管腔内で内容物の減少がそれぞれ観察された。

回復観察では上記の毒性所見に回復性はみられたが、1000 mg/kg 群の非交配雌に尿中電解質の変動が、同群の雄に肝臓の相対重量の増加と精巣および精巣上体の病理所見が依然として観察された。

2. 生殖発生毒性

性周期の延長が 1000 mg/kg 群の交配雌にみられ、同群では妊娠期間の延長、着床率 (着床数/妊娠黄体数)、出産率 (生児出産雌数/妊娠動物数)、産児数、出産生児数、分娩率 (産児数/着床痕数)、生児出産率 (出産生児数/着床痕数) および出生率 (出産生児数/産児数) の低下がみられた。

3. 無毒性量

250 mg/kg 群の雄に網状赤血球比率の低下と小葉中心性の肝細胞肥大が、250 mg/kg 群の分娩雌に摂餌量の低下が観察されたことから雌雄動物の反復投与毒性に対する無毒性量 (NOAEL) は 62.5 mg/kg/day と判断された。また、性周期および妊娠期間の延長、出産率、着床率、産児数、出産生児数、分娩率、生児出産率および出生率の低下が 1000 mg/kg 群で認められたことから、生殖発生毒性に対する無毒性量は 250 mg/kg/day と判断された。

試験目的

雌雄ラットの交配前(2週間)および交配期間中(最長2週間)、ならびに雄では交配期間終了後2週間、雌では妊娠期間を通して周産期(哺育4日まで)に1-ethoxy-2-(2-methoxyethoxy)ethaneを反復経口投与し、雌雄ラットに現れる一般毒性および回復性、ならびに生殖発生毒性を明らかにすることを目的とした。

試験ガイドラインと GLP

本試験は、「新規化学物質等に係る試験の方法について:以下、化審法ガイドライン」(平成23年3月31日付け、薬食発0331第7号厚生労働省医薬食品局長、平成23・03・29製局第5号経済産業省製造産業局長、環境企発第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、「一般財団法人食品薬品安全センター 動物実験に関する指針(機関内規程)」(平成2年10月1日、平成25年4月1日改定)に基づいて実施した。本試験における動物実験計画は、秦野研究所動物実験委員会の審査を受け、承認されている(動物実験承認番号:1130230A)。なお、承認された動物実験計画からの変更はなかった。

材料と方法

1. 被験物質

被験物質である1-ethoxy-2-(2-methoxyethoxy)ethane[化学名(別名):ジエチレングリコールエチルメチルエーテル、IUPAC名:1-エトキシ-2-(2-メトキシエトキシ)エタン、略称:EMEE、CAS番号:1002-67-1、分子式: $C_7H_{16}O_3$ 、分子量:148.20、ロット番号:AWM2005、含量:100.0%(キャピラリーカラムGC)、不純物:2,6-ジ-tert-ブチル-4-メチルフェノール(BHT):30 ppm(安定剤として)、水分:0.1%、Annex A)は、無色澄明な液体である。被験物質は和光純薬工業株式会社から購入し(被験物質入手:2013年6月

14 日および 2013 年 7 月 12 日)、使用時まで密閉容器で室温(実測値 15.8~24.6℃)、遮光条件下で保管した。1-Ethoxy-2-(2-methoxyethoxy)ethane の構造式を次に示す。



被験物質の安定性については、実験開始前および実験終了後に秦野研究所にて赤外吸収スペクトルを測定し、色調や性状、スペクトルに変化がなかったことが確認されている(試験番号:Q-13-009)。

2. 動物および飼育方法

日本チャールス・リバー厚木飼育センターより 8 週齢の Sprague-Dawley (SD) 系 [CrI:CD(SD)、SPF] ラット雄 55 匹、雌 83 匹を購入し、飼育室(5 号室)に収容した。入荷日も含めて 15 日間、検疫と飼育環境への馴化のため飼育した。その間毎日、動物の一般状態を観察し、入荷日(検疫 1 日)および検疫終了日に体重を測定した。検疫・馴化期間中は動物の尾に赤のフェルトペンで馴化番号を記し、飼育ケージに試験番号、性別および馴化番号を記入した動物カードを掛けて識別した。また、雌動物については、検疫 3 日から毎日、性周期を観察した。入荷動物の入荷時および検疫終了時の体重は下記の通りであった。

動物入荷日	:2013 年 10 月 7 日
入荷時体重	:雄 275.3~310.0 g、雌 187.7~222.3 g
検疫終了日	:2013 年 10 月 21 日
検疫終了時体重	:雄 343.1~449.6 g、雌 213.6~314.8 g

検疫・馴化期間中の一般状態、詳細な症状観察および体重推移に試験実施に影響を及ぼすと判断される異常は認められなかった。なお、雌動物では、規則的な性周期の回帰が認められない 13 匹を除外し、検疫終了時の体重を基に体重別層化無作為抽出法により群分けを行った。群分けした動物には一連の動物番号を割り当て、フェルトペンで尾に動物番号を標識し、色彩の異なった動物カードに試験番号および動物番号を記入して飼育ケージに掛けた。群分けから棄却した雄動物 7 匹、雌動物 15 匹(性周期の結果により除外した例を含む)は全て余剰動物とし、雌雄各 2 匹は採血練習に使用したが、残りの雌雄は、他の目的に転用予定がなかったため、安楽死させた。

動物は許容温度 21.0~25.0℃、許容湿度 40.0~75.0%、換気設定約 15 回/時間、明暗サイクル 12 時間(7 時~19 時)点灯、12 時間(19 時~7 時)消灯に設定された飼育室内で、金属製金網床ケージ(220w×270d×190h mm)に 1 匹ずつ(交配時は 2 匹)収容し、固型飼料(CE-2、日本クレア)と水道水(秦野市水道局給水)を自由に摂取させて飼育した(剖検前の絶食に関しては剖検の項を参照)。交配雌は、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 22.0~24.5℃、湿度は 50.0~73.5%であった。また、供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを確認した。

3. 投与検体

1) 調製

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

2) 安定性試験

注射用水を媒体とした 0.0100 mg/mL および 200 mg/mL 濃度の被験物質調製液については、冷蔵、遮光条件下における 8 日間の安定性が確認されている(試験番号:Q-13-009)。

3) 含量試験

初回に調製(調製日:2013 年 10 月 21 日)した投与検体(12.5、50 および 200 mg/mL)について、被験物質含量を測定した。その結果、平均含量は調製指示濃度の 98.5~100.0%であり、各測定値のばらつきはそれぞれ平均値の 97.0~105.6%で規定範囲内にあった(Annex B)。なお、投与検体中の被験物質含量測定は Annex C に従った。

4. 投与量の設定および投与方法

本試験の投与量は、「1-Ethoxy-2-(2-methoxyethoxy)ethane のラットを用いる反復投与毒性・生殖発生毒性併合試験(予備試験)」(試験番号:R-13-001)の結果をもとに設定した。なお、予備試験で使用した被験物質および媒体は本試験と同じロットを用いた。

予備試験では、0(媒体、注射用水)、250、500 および 1000 mg/kg の EMEE を 10 週齢の雌雄各 3 匹の SD 系ラットに 14 日間、反復強制経口投与した結果、肝臓重量の増加および MCHC の低下が 500 mg/kg 以上の群の雌で、自発運動の低下と血色素量の低下が 1000 mg/kg 群の雌雄で、ヘマトクリット値の低下と総蛋白濃度の低下が 1000 mg/kg 群の雄で認められたが、いずれも軽度な変化であったことから、限度量の 1000 mg/kg を本試験の高用量に設定し、以下公比 4 で中用量には 250 mg/kg を、低用量には 62.5 mg/kg を設定した。

本試験では、雄動物は交配前 2 週間、交配期間を通して剖検前日まで(総投与回数 42 回)、雌動物は交配前 2 週間、交配期間、妊娠期間を通して分娩後の哺育 4 日まで(総投与回数 41~46 回)、交尾が確認されなかった雌は剖検前日まで(総投与回数 52 回)、分娩しなかった雌は妊娠 25 日相当日まで、非交配雌の反復毒性を評価するために設定したサテライト群は投与 42 日まで、1 日 1 回、1 週 7 回、毎日 9 時~13 時の間(9 時 00 分~11 時 48 分)に投与した。投与容量は 5 mL/kg とし、雌雄とも最新の測定日の体重を基に投与液量を算出した。なお、対照群には媒体である日局注射用水を同様に投与した。投与経路は化審法ガイドラインに拠り、ラット用胃管による強制経口投与とした。

本試験の群構成および動物番号を以下に示した。

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

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

5. 検査法

1) 親動物 (F₀)

① 一般状態の観察

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

② 回復および遅発毒性の観察

雄動物は対照群および高用量群のうち動物番号の大きい各 5 例を、雌動物はサテライト群の動物番号の大きい各 5 例を最終投与翌日(回復 1 日)から 14 日間、毎日 1 回以上、一般状態を観察した。

③ 詳細な症状観察

全例について、検疫終了日、投与 8、15、24、30、36 および 42 日(分娩例は哺育 0 日から 4 日の間)、回復期間中は回復 7 および 14 日にスコアリング法による詳細な症状観察を行った。観察は、いずれも 13 時～17 時の間(13 時 04 分～14 時 40 分)に行った。

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

④ 機能検査

雄およびサテライト群の雌は、各群の動物番号の若い 5 例について、投与 39 日に自発運動量測定と握力測定を実施し、投与 42 日に詳細な症状観察に引き続いて刺激に対する感覚運動反応を検査した。分娩雌については投与期間が近接し、出来るだけ分娩から日数が経過した各群の 5 例(高用量群を除く)を選び、投与最終週に自発運動量測定、握力測定および刺激に対する感覚運動反応を検査した。

(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(Chatillon、Columbus Instruments)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) 自発運動量測定

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、速やかに自発運動量測定を開始した。

⑤体重測定

雄およびサテライト群の雌は、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。交配雌は投与 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、未交尾例は投与 21、28、35、42、49 日および剖検日に測定した。

⑥摂餌量測定

雄およびサテライト群の雌は、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、サテライト群の雌は投与 21～22 日にも測定した。交配雌は投与 1～2、7～8、14～15 日および妊娠 0～1、7～8、14～15、20～21 日ならびに哺育 3～4 日に測定し、未交尾例は投与 29～30、35～36、41～42、48～49 日に測定した。

⑦尿検査

雄およびサテライト群の雌を検査対象とし、投与 37 日の検査では各群の動物番号が若い 5 例、また、回復 13 日における検査では回復例全例を検査した。

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

項目	測定法	使用機器
色調・濁度	視診	
pH・潜血・蛋白・糖・ケトン体	試験紙法	オーションイレブン AE-4020(アークレイ)
ウロビリノーゲン・ビリルビン	同上	同上
沈渣	鏡検	光学顕微鏡
尿量	計量	メスシリンダー等
比重	屈折法	デジタル臨床屈折計 SU-202(エルマ販売)
ナトリウムイオン濃度	イオン電極法	自動分析装置 JCA-BM6010(日本電子)
カリウムイオン濃度	同上	同上
塩素イオン濃度	同上	同上

⑧性周期観察

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

⑨交配

投与 15 日の 16 時 00 分~16 時 07 分に同群内の雌雄を 1 対 1 で同居させた。翌朝より毎朝、膣栓を確認し、同居中の雌の膣スミア標本を作製して鏡検した。膣内に膣栓あるいは膣スミア標本中に精子が確認された動物を交尾成立動物とし、この日を妊娠 0 日と起算して個別飼育に戻した。交配結果および妊娠の成否により、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数、交尾率[(交尾動物数/交配に用いた動物数)×100, %]、妊娠率[(妊娠動物数/交尾した雌動物数)×100, %]を算出した。

⑩妊娠・分娩・哺育状態の観察

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

⑪採血

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

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

⑫血液学的検査

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

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

⑬血液生化学的検査

採血対象動物について以下の項目を検査した。抗凝固剤としてヘパリンを用いて採取した血液から血漿を分離して測定した。なお、得られた血漿の一部は甲状腺機能に関するホルモン(T3、T4 および TSH)測定用として凍結保存(-70℃以下)したが、甲状腺の病理学的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・GLODH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フェリナーゼ活性(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トランスフェラーゼ活性(AST)	IFCC法	同上
アラニンアミトランスフェラーゼ活性(ALT)	同上	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	同上
カリウムイオン濃度(K)	同上	同上
塩素イオン濃度(Cl)	同上	同上

⑭剖検および器官重量

以下の時期に、採血対象動物はペントバルビタールナトリウム麻酔下で採血した後、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、引き続き剖検した。

対象動物	解剖時期	屠殺前の絶食
雄		
投与終了時剖検例	投与 42 日の翌日	18～24 時間絶食
回復観察例	回復 15 日	18～24 時間絶食
雌		
分娩例	哺育 4 日の翌日	18～24 時間絶食
未分娩例	妊娠26日相当日	実施せず
交尾が確認されなかった例(未交尾)	投与52日の翌日	実施せず
全哺育児が死亡した例	全哺育児の死亡日	実施せず
非交配群(投与終了時剖検例)	投与42日の翌日	18～24 時間絶食
非交配群(回復観察例)	回復15日	18～24 時間絶食

全例について、脳、甲状腺および上皮小体、胸腺、心臓、肝臓、腎臓、脾臓、副腎、精巣、精巣上体、前立腺(腹側葉)および精嚢(凝固腺を含む)、卵巣、子宮の重量を測定した。また、全例の脳、脊髄、下垂体、眼球(ハーダー腺)、顎下腺および舌下腺、気管、甲状腺および上皮小体、胸腺、心臓、肺および気管支、肝臓、腎臓、脾臓、膵臓、副腎、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、下顎リンパ節、腸間膜リンパ節、精巣、精巣上体、前立腺、精嚢および凝固腺、卵巣、子宮、膣、膀胱、大腿骨および大腿骨骨髓、骨格筋、坐骨神経および病変部を採取し、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。精巣および精巣上体はブアン液に固定(長期保存は 10%中性緩衝ホルマリン溶液)し、その他の器官・組織は 10%中性緩衝ホルマリン溶液に固定した。

なお、未交尾例、未分娩例および全哺育児が死亡した例の器官重量値は評価対象から除外した。

⑮病理組織学的検査

剖検した動物のうち、雄およびサテライト群の雌の投与終了時剖検では対照群ならびに高用量群の動物番号が若い各 5 例、分娩雌の投与終了時剖検では哺育 5 日に採血した対照群ならびに中用量群の各 5 例、さらには高用量群の全哺育児が死亡した分娩雌のうち動物番号の若い 5 例については、組織学的検査対象器官のヘマトキシリン・エオジン(HE)標本作製し、病理組織学的検査を実施した。高用量群で被験物質によると考えられる変化が認められた器官・組織については、他の全ての用量群と回復観察例についても病理組織学的検査を実施し、剖検時に肉眼的異常がみられた器官・組織に関しても同様に HE 標本作製し、病理組織学的検査を実施した。

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, %]、生児出産率[(出産生児数/着床痕数)×100, %]、出産率[(生児

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

②剖検

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

6. データの解析法

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

その他のデータは、個体ごとに得られた値あるいは litter ごとの平均値を 1 標本とし、サテライト群内あるいはその他の群内で比較した。その際、解析の対象が 2 群の場合には、まず F 検定を行い、有意差が認められなければ Student's-t 検定を行った。F 検定において有意差が認められた場合は、Aspin-Welch 検定を行った。解析の対象が 3 群以上の場合には、まず、Bartlett の方法により各群の分散の一意性について検定(有意水準:5%)を行った。分散が一意であった場合には、一元配置型の分散分析(有意水準:5%)を行い、群間に有意性が認められた場合は、Dunnett 法により多重比較を行った(有意水準:5%)。一方、いずれかの群で分散が 0 となった場合および分散が一意でなかった場合には、Kruskal-Wallis の順位検定(有意水準:5%)を行い、群間に有意性が認められた場合には、Dunnett 型の検定法により多重比較を行った(有意水準:5%)。

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

2013 年 12 月 13 日 11:00～14:40 に受変電設備の定期点検のために停電し、それに伴い動物飼育室内の照明が消え、同日の 11:00～14:43 に空調が停止した。しかし、いずれの動物の一般状態にも上述事象に起因したと考えられる変化は認められず、飼育室の温湿度(21.5～23.0℃、57.0～63.0%)は許容範囲内であったことから、試験への影響はないと判断した。

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

試験成績

1. 親動物

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

雄では、1000 mg/kg 群の全例において投与 1 日から自発運動の低下が主として投与後に観察されたが、その頻度は投与回数が増すにつれて減少した。同群の雄では、投与 35 日から投与後に一過性の流涎が最大 6 例に観察された。250 mg/kg 以下の群の雄に一般状態の異常は観察されなかった。

雌でも雄と同様に、1000 mg/kg 群の交配雌および非交配雌の全例において投与 1 日から自発運動の低下が投与後に観察され、流涎も交配雌 1 例に認められた。250 mg/kg 群の交配雌 1 例においては、妊娠 8 日から立毛が観察され、哺育 1 日まで継続してみられた。その他、対照群の非交配雌 1 例に前肢の脱毛が投与 25 日から解剖日まで観察された。

回復観察中の雌雄に、一般状態の異常は観察されなかった。

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

投与 15 日のハンドリング時にやや抵抗し、接触に対してやや過敏に反応した例が 1000 mg/kg 群の交配雌 1 例に、投与 36 日にわずかな立毛が 250 mg/kg 群の交配雌 1 例に観察されたが、雄および非交配雌を含む雌とも、被験物質投与の影響を示す変化は認められなかった。

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

雄では、投与期間ならびに回復期間を通して、被験物質投与の影響を示す体重の変化は認められなかった。

交配雌の交配前の体重、ならびに非交配雌の投与期間および回復期間の体重には、被験物質投与の影響を示す変化は認められなかった。

妊娠雌では、1000 mg/kg 群の妊娠 20 日の体重が対照群と比較して有意に減少したが、哺育期間中の体重には被験物質投与の影響を示す変化は認められなかった。

4) 摂餌量 (Table 11-1~Table 14, Appendix 11-1-1~Appendix 14-3)

雄では、1000 mg/kg 群の投与 1~2 日および投与 41~42 日の摂餌量が対照群と比較して有意に低下した。回復期間の摂餌量に被験物質投与の影響を示す変化は認められなかった。

非交配雌では、1000 mg/kg 群の投与 7~8 日および投与 41~42 日の摂餌量が対照群と比較して有意に低下したが、回復期間の摂餌量に被験物質投与の影響を示す変化は認められなかった。

交配雌では、交配前および妊娠期間の摂餌量に被験物質投与の影響を示す変化は認められなかったが、250 mg/kg 群の哺育 3~4 日の摂餌量が対照群と比較して有意に低下した。

5)機能検査

①刺激に対する感覚運動反応 (Table 15～Table 16, Appendix 15-1～Appendix 16-5)

投与最終週に実施したプライエル反応、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、非交配雌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 17-1～Appendix 19-2)

雄では、投与最終週に測定した前肢および後肢の握力に、被験物質投与の影響を示す変化は認められなかった。

分娩雌の握力測定では、250 mg/kg 以下の群に被験物質投与の影響を示す変化はみられなかった。非交配雌の握力測定では、被験物質投与の影響を示す変化は認められなかった。

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

投与最終週に実施した雌雄の自発運動量測定では、区画移動数および立ち上がり回数ともに被験物質投与の影響を示す変化は認められなかった。

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

雄では、投与最終週において 1000 mg/kg 群のカリウムおよび塩素イオン濃度が対照群と比較して有意に低下したが、回復観察中の尿検査では被験物質投与の影響を示す変化は認められなかった。

非交配雌では、投与期間中の尿検査において被験物質投与の影響を示す変化は認められなかったが、回復 13 日の尿検査では 1000 mg/kg 群の尿比重、ナトリウム、カリウムおよび塩素イオン濃度が対照群と比較して有意に低下した。

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

①雄動物

投与終了時の雄では、1000 mg/kg 群の血色素量とヘマトクリット値が対照群と比較して有意に低下し、250 mg/kg 以上の群の網状赤血球比率が対照群と比較して有意に低下した。

回復終了時の雄では、1000 mg/kg 群の MCV(平均 48.4 fL)および MCH(平均 16.6 pg)が対照群の MCV(平均 51.6 fL)および MCH(平均 17.8 pg)と比較して有意に低下したが、その差はわずかであり、投与終了時に認められていない変化であることから、被験物質投与の影響ではないと判断した。

雄(回復終了時)	試験数*	サンプル数	平均	平均±2SD
MCV	4	20	50.9	47.9-53.8
MCH	4	20	17.7	16.9-18.4

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:注射用水)を使用

②雌動物

投与終了時の 250 mg/kg 以下の群の分娩雌では、いずれの検査項目についても対照群と比較して有意差は認められなかった。

投与終了時の非交配雌では、1000 mg/kg 群の血色素量、ヘマトクリット値、MCHC、血小板数および網状赤血球比率が対照群と比較して有意に低下した。

回復終了時の非交配雌では、いずれの検査項目についても対照群と 1000 mg/kg 群の間に有意差は認められなかった。

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

①雄動物

投与終了時の雄では、1000 mg/kg 群の総蛋白濃度およびナトリウムイオン濃度が対照群と比較して有意に低下し、同群の γ -GTP および BUN が対照群と比較して有意に増加した。その他、1000 mg/kg 群の APL が対照群と比較して有意に低下したが、増加とは逆の変化であることから、被験物質の影響ではないと判断した。また、62.5 mg/kg 群の胆汁酸濃度が対照群と比較して有意に低下したが、用量に依存した変化ではなかった。

回復終了時の雄では、1000 mg/kg 群のリン脂質濃度が対照群と比較して有意に増加したが、投与終了時にはみられていない変化であり、被験物質投与の影響ではないと判断した。

②雌動物

投与終了時の分娩雌では、62.5 および 250 mg/kg 群のクレアチニン濃度が対照群と比較して有意に低下したが、増加とは逆の変化であり、腎臓への影響を示すものではなかった。

投与終了時の非交配雌では、1000 mg/kg 群の AST が対照群と比較して有意に低下したが、異常を示す増加の変化ではなかった。その他に被験物質投与の影響を示す変化は認められなかった。

回復終了時の非交配雌では、いずれの検査項目についても対照群と 1000 mg/kg 群の間に有意差は認められなかった。

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

①雄動物

投与終了時の雄では、1000 mg/kg 群の胸腺、精巣上体および前立腺の絶対重量と相対重量が対照群と比較して有意に低下し、同群の肝臓および腎臓の相対重量が対照群と比較して有意に増加した。

回復終了時の雄では、1000 mg/kg 群の精巣上体(左)の絶対重量が対照群と比較して有意に低下し、同群の肝臓の相対重量が対照群と比較して有意に増加した。

②雌動物

投与終了時の分娩雌では、250 mg/kg 群の心臓および腎臓の絶対重量が対照群と比較して有意に低下した。

投与終了時の非交配雌では、1000 mg/kg 群の胸腺の絶対重量と相対重量が対照群と比較して有意

に低下し、同群の肝臓および腎臓の相対重量が対照群と比較して有意に増加した。

回復終了時の非交配雌では、対照群と 1000 mg/kg 群の器官重量に被験物質投与の影響を示す変化は認められなかった。

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

①雄の投与終了時剖検例

1000 mg/kg 群では 2 例に胸腺の小型化が認められたほか、両側の精巣に小型化あるいは水腫様、両側の精巣上体に水腫様および前立腺の小型化がそれぞれ 1 例観察された。また、62.5 mg/kg 群に脾臓の大型化が、250 mg/kg 群に両側の腎臓の大型化が各 1 例みられた。一方、対照群に肉眼的な異常所見は認められなかった。

②雄の回復観察例

1000 mg/kg 群では、両側の精巣に小型化および水腫様が 1 例みられ、精巣上体では両側の小型化が 1 例、両側の水腫様が 4 例に観察された。対照群では、精巣および精巣上体に片側の小型化が認められた。

③分娩雌の投与終了時剖検例

62.5 mg/kg 群の 1 例および 250 mg/kg 群の 2 例の腺胃粘膜に暗色域が観察された。また、62.5 mg/kg 群に両側の腎臓に腎盂の拡張が、250 mg/kg 群の胸腺に小型化、肝臓に散在した白色域あるいは横隔膜結節、脾臓の漿膜と癒着、縦隔リンパ節の大型化がそれぞれ 1 例みられた。なお、1000 mg/kg 群には、投与終了時(哺育 4 日)までに哺育児が生存した分娩例はなかった。

④全哺育児が死亡した例

全哺育児が死亡した 1000 mg/kg 群の 8 例のうち 2 例に脾臓の大型化が観察されたが、それ以外の異常所見は認められなかった。なお、対照群、62.5 および 250 mg/kg 群には、全哺育児が死亡した分娩雌はいなかった。

⑤未分娩例、不妊例および未交尾例

分娩しなかった 1000 mg/kg 群の 4 例および 250 mg/kg 群の 1 例のうち、1000 mg/kg 群の 3 例および 250 mg/kg 群の 1 例は不妊であったが、1000 mg/kg 群の 1 例は、子宮に着床跡が認められた。これらの動物のうち、1000 mg/kg 群の不妊 1 例では子宮に腔の拡張が観察された。

交尾しなかった 250 mg/kg 群の 1 例には、異常はなかった。

⑥非交配雌の投与終了時剖検例

対照群の 1 例に前肢の脱毛がみられたが、それ以外に肉眼的な異常所見は認められなかった。

⑦非交配雌の回復観察例

1000 mg/kg 群の 1 例の回腸から直腸までの腸管内(盲腸・結腸を含む)にガスが貯留していた。それ以外に肉眼的な異常所見は認められなかった。

11) 病理組織学的検査所見 (Table 33-1～Table 34-2, Appendix 33-1～Appendix 34-2)

①雄の投与終了時剖検例

投与終了時剖検例のうち、採血を行った対照群および 1000 mg/kg 群の 5 例について病理組織学的検査を実施した。さらに被験物質の影響が示唆された肝臓、胸腺、精巣、精巣上体および前立腺は、62.5 および 250 mg/kg 群の 5 例についても病理組織学的検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学的検査を実施した。病理組織所見は、以下の通りである。

胸腺では、1000 mg/kg 群の観察した全例に髄質の萎縮が観察された(Photo 1)。この変化は、62.5 および 250 mg/kg 群にはみられず、対照群と比較してその変化の程度および頻度は有意に増強していた。

肺では、1000 mg/kg 群の 2 例の肺泡に泡沫細胞の集簇が、対照群および 1000 mg/kg 群の各 1 例に小肉芽腫が観察されたが、両群間に程度および頻度の差は認められなかった。また、対照群に限局性の動脈壁への鉍質沈着、1000 mg/kg 群に限局性の出血あるいは限局性の骨化生がみられたが、いずれも軽微な変化であった。

肝臓では、1000 mg/kg 群の観察した全例および 250 mg/kg 群の 3 例に小葉中心性の肝細胞肥大が認められ、そのうち 1000 mg/kg 群では、全例の肝細胞に曇りガラス変性が観察された(Photo 2)。これらの変化は、対照群および 62.5 mg/kg 群ではみられず、1000 mg/kg 群の変化は、対照群と比較してその程度および頻度が増強していた。一方、対照群および 62.5 mg/kg 群の全例、250 mg/kg 群の 2 例、1000 mg/kg 群の 3 例に門脈周囲性の肝細胞の脂肪化が、対照群の 4 例、62.5、250 および 1000 mg/kg 群の各 1 例に小肉芽腫が観察されたが、対照群と各被験物質群との間に程度および頻度の差は認められなかった。

脾臓では、対照群および 1000 mg/kg 群の全例に髄外造血および褐色色素の沈着が観察されたが、両群間に程度の差は認められなかった。また、剖検時に肉眼的な異常所見が認められた 62.5 mg/kg 群の 1 例では、髄外造血および褐色色素の沈着が観察されたが、他の例と比較するとやや褐色色素の沈着が多かった。

腎臓では、対照群の 4 例および 1000 mg/kg 群の 3 例の皮質に好塩基性尿細管が、両群の各 1 例に好酸性小体が観察されたが、両群間に頻度および程度の差は認められなかった。その他、対照群の髄質に嚢胞がみられた。また、剖検時に肉眼的な異常所見が認められた 250 mg/kg 群の 1 例では、皮質に好塩基性尿細管および髄質に嚢胞がみられた。

精巣では、1000 mg/kg 群の全例の両側で、精細管内に円形の精子細胞や伸長した精子細胞の脱落が認められた(Photo 3)ほか、精細管内の生殖細胞層に空胞化ならびに多核巨細胞が観察され、そのうち変化の程度が強い例では、精母細胞が精細管内に脱落していた。これらの変化は、対照群、62.5 および 250 mg/kg 群ではみられず、1000 mg/kg 群の変化は、対照群と比較してその程度および頻度が増強していた。一方、62.5 あるいは 250 mg/kg 群のそれぞれ 1 例には、限局性の精細管萎縮が観察されたほか、精細管内に多核巨細胞を伴う例もみられた。

精巣上体では、1000 mg/kg 群の全例の両側で、管腔内に精子の減少および細胞残屑が観察され(Photo 4)、1000 mg/kg 群の変化は、対照群と比較してその程度および頻度が増強していた。一方、同

様の組織変化は、62.5 および 250 mg/kg 群でも各 1 例に観察されたが、いずれも精巣に限局性の精細管萎縮が観察された例であった。

前立腺では、1000 mg/kg 群の全例の管腔内に内容液の減少が観察された。これらの変化は、対照群、62.5 および 250 mg/kg 群ではみられず、1000 mg/kg 群の変化は、対照群と比較してその程度および頻度が増強していた。その他、対照群の 2 例、62.5 および 250 mg/kg 群の各 4 例、1000 mg/kg 群の 3 例の間質にリンパ球浸潤が観察されたが、対照群と各被験物質群との間に程度および頻度の差は認められなかった。

その他、対照群および 1000 mg/kg 群の膵臓に、膵管の増生を伴う腺房細胞の限局性の萎縮が、1000 mg/kg 群の下垂体に嚢胞あるいは甲状腺に鰓後体がみられたが、いずれも被験物質投与の影響を示す変化ではないと判断した。

その他の組織学的検査対象器官・組織には、組織学的な異常所見は認められなかった。

②雄の回復観察例

回復 15 日に剖検した対照群および 1000 mg/kg 群の 5 例については、投与終了時の剖検例で被験物質の影響が示唆された肝臓、胸腺、精巣、精巣上体および前立腺について病理組織学的検査を実施した。病理組織所見は、以下の通りである。

胸腺では、1000 mg/kg 群の 2 例に髄質の萎縮が観察されたが、対照群との間に頻度および程度の差は認められなかった。

肝臓では、1000 mg/kg 群の例には、投与終了時に観察された小葉中心性の肝細胞肥大は認められなかった。また、対照群の全例、1000 mg/kg 群の 2 例に門脈周囲性の肝細胞の脂肪化が観察されたが、対照群と 1000 mg/kg 群との間に程度および頻度の差は認められなかった。その他、1000 mg/kg 群に小肉芽腫が 1 例、対照群に限局性の壊死巣が 1 例にみられた。

精巣では、1000 mg/kg 群の全例の両側で、精細管内に精子細胞や精子の脱落ならびに生殖細胞層に空胞化が認められ、そのうち 4 例の精細管内には精母細胞の脱落が、3 例には限局性の精細管萎縮ならびに多核巨細胞が観察された。これら 1000 mg/kg 群の精子細胞および精母細胞ならびに生殖細胞層の組織変化は、対照群と比較して程度または頻度が増強していた。対照群にも片側あるいは両側で限局性の精細管萎縮が 2 例、多核巨細胞が 1 例に観察された。

精巣上体では、1000 mg/kg 群の全例の両側の管腔内に細胞残屑および精子の減少が観察され、対照群と比較して頻度が増強していた。これらの変化は、対照群の 1 例でも観察されたが、精巣に精細管萎縮がみられ、かつ片側の精巣上体に小型化が認められた例であった。

前立腺では、1000 mg/kg 群の例には、投与終了時に観察された管腔内の内容液の減少は認められなかった。その他、対照群の 3 例の間質にリンパ球浸潤が観察された。

③分娩雌の投与終了時剖検例

哺育 4 日の翌日に剖検した分娩雌のうち、採血を行った対照群および 250 mg/kg 群の 5 例について、病理組織学的検査を実施した。また、剖検時に異常が認められた器官についても病理組織学的検査を実施した。病理組織所見は、以下の通りである。

肺では、250 mg/kg 群の 3 例の肺胞に泡沫細胞の集簇が観察されたが、対照群との間に程度および頻度の差は認められなかった。

肝臓では、250 mg/kg 群の例には、雄の投与終了時に観察された小葉中心性の肝細胞肥大は認められなかった。また、対照群の 3 例および 250 mg/kg 群の 2 例に門脈周囲性の肝細胞の脂肪化が、対照群および 250 mg/kg 群の各 2 例に小肉芽腫が観察されたが、対照群との間に程度および頻度の差は認められなかった。その他、250 mg/kg 群の例には、被膜に線維化を伴う横隔膜結節あるいは限局性の壊死巣が認められたが、被験物質投与の影響を示す変化ではないと判断した。

胃では、250 mg/kg 群の 2 例の腺胃粘膜にびらんが観察され、そのうち 1 例には粘膜固有層に水腫を伴っていたが、対照群との間に程度および頻度の差は認められなかった。その他、250 mg/kg 群の 1 例に腺胃の粘膜固有層に固有胃腺の限局性の拡張がみられた。また、剖検時に肉眼的な異常所見が認められた 62.5 mg/kg 群の 1 例では、腺胃粘膜にびらんが観察された。

脾臓では、対照群および 250 mg/kg 群の全例に髄外造血および褐色色素の沈着が観察されたが、対照群との間に程度の差は認められなかった。その他、250 mg/kg 群の 1 例では、漿膜に炎症細胞の浸潤がみられた。

腎臓では、対照群の 2 例および 250 mg/kg 群の 1 例の皮質に好塩基性尿細管が観察されたが、対照群との間に頻度および程度の差は認められなかった。その他、250 mg/kg 群の 1 例の皮髄境界部に鉍質沈着がみられた。また、剖検時に肉眼的な異常所見が認められた 62.5 mg/kg 群の 1 例では、腎盂が拡張しており、皮質に好塩基性尿細管がみられた。

その他、対照群の下垂体に嚢胞が、250 mg/kg 群の甲状腺に異所性胸腺がみられたほか、剖検時に肉眼的な異常所見が認められた 250 mg/kg 群の 1 例の縦隔リンパ節では、炎症細胞を伴う水腫がみられたが、いずれも被験物質投与の影響を示す変化ではないと判断した。

その他の組織学的検査対象器官・組織には、組織学的な異常所見は認められなかった。

なお、対照群の 1 例の上皮小体がスライド標本上になかったため、観察することが出来なかったが、評価への影響はないと判断した。

④全哺育児が死亡した例

全哺育児が死亡した 1000 mg/kg 群の分娩雌のうち 5 例の組織学的検査対象器官・組織ならびに病変部を病理組織学的に検査した。

肺では、肺胞に泡沫細胞の集簇、限局性の炎症細胞浸潤、漿膜下に水腫および限局性の動脈壁への鉍質沈着が 1 例に観察されたが、この例以外に変化はみられなかった。

肝臓では、全例に小葉中心性の肝細胞肥大が認められ、そのうちの 4 例に肝細胞に曇りガラス変性が観察された。また、門脈周囲性の肝細胞の脂肪化が 3 例に、小肉芽腫あるいは限局性の壊死巣が各 1 例観察された。

脾臓では、全例に髄外造血および褐色色素の沈着が認められ、そのうち 1 例の漿膜には、炎症細胞の浸潤が観察された。

腎臓では、3 例の皮質に好塩基性尿細管が、1 例の皮質に硝子円柱が観察されたが、いずれも軽微

な変化であった。

卵巣では、4 例に性周期が回帰していると考えられる排卵直後の卵胞が認められた。

その他、下垂体の嚢胞あるいは甲状腺の鰓後体がみられた。

また、雄の 1000 mg/kg 群で変化の認められた胸腺には、組織学的な変化は観察されず、その他の組織学的検査対象器官・組織には、組織学的な異常所見は認められなかった。

⑤未分娩例、不妊例および未交尾例

1000 mg/kg 群の 3 例および 250 mg/kg 群の 2 例の雌動物には、病理組織学的な異常所見はみられなかったが、1000 mg/kg 群で剖検時子宮に肉眼的な異常所見が認められた不妊の 1 例では、粘膜および腔内に好中球浸潤が中等度に観察された。

⑥非交配雌の投与終了時剖検例

投与終了時に剖検した対照群および 1000 mg/kg 群の非交配雌各 5 例について、病理組織学的検査を実施した。また、剖検時に異常が認められた器官についても病理組織学的検査を実施した。病理組織所見は以下の通りである。

胸腺では、1000 mg/kg 群の 2 例の髄質に萎縮が認められた。

肺では、1000 mg/kg 群の 2 例の肺胞に泡沫細胞の集簇が、対照群の 1 例に限局性の骨化生が観察されたが、対照群との間に程度および頻度の差は認められなかった。

肝臓では、1000 mg/kg 群の全例に小葉中心性の肝細胞肥大が認められ、そのうちの 2 例の肝細胞に曇りガラス変性が観察された。これらの変化は対照群ではみられず、肝細胞肥大は対照群と比較して程度および頻度が増強していた。その他、1000 mg/kg 群の 5 例および対照群の 2 例に門脈周囲性の肝細胞の脂肪化が観察されたが、対照群との間に程度および頻度の差はなかった。

脾臓では、対照群および 1000 mg/kg 群の全例に髄外造血および褐色色素の沈着が観察されたが、対照群との間に程度の差は認められなかった。

腎臓では、対照群の皮質に好塩基性尿細管、髄質に嚢胞、漿膜下に限局性の線維化が、1000 mg/kg 群の皮髄境界部に鉍質沈着がそれぞれ 1 例みられた。

その他、対照群には心臓に限局性の心筋の変性／線維化、ハーダー腺の間質にリンパ球浸潤が、1000 mg/kg 群には下垂体の嚢胞、甲状腺に鰓後体、卵巣に卵胞嚢胞が各 1 例にみられたが、被験物質投与の影響を示す変化ではないと判断した。

その他の組織学的検査対象器官・組織には、組織学的な異常所見は認められなかった。

なお、対照群の 1 例の上皮小体がスライド標本上になかったため、観察することが出来なかったが、評価への影響はないと判断した。

⑦非交配雌の回復観察例

回復 15 日に剖検した対照群および 1000 mg/kg 群の 5 例については、投与終了時の剖検例で被験物質の影響が示唆された肝臓および胸腺について病理組織学的検査を実施した。病理組織所見は、以下の通りである。

肝臓では、対照群および 1000 mg/kg 群の全例に門脈周囲性の肝細胞の脂肪化が、1000 mg/kg 群

の 1 例に限局性の壊死巣が観察されたが、対照群と 1000 mg/kg 群との間に程度および頻度の差は認められず、胸腺の髄質の萎縮あるいは肝臓の肝細胞肥大も回復観察例には認められなかった。

2. 生殖能力

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

4 あるいは 5 日間隔の性周期が投与開始後にそれ以外の性周期に変化した動物が、1000 mg/kg 群で 12 例中 7 例にみられ、その頻度は対照群と比較して有意に増加し、同群の投与開始後の平均発情回帰日数が対照群と比較して有意に延長した。

1000 mg/kg 群では、全例で交尾が確認されたが、3 例は不妊であった。250 mg/kg 群では、交尾が確認されなかった例が 1 組みられ、さらに不妊例が 1 例みられた。同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数に被験物質投与の影響を示す変化は認められなかった。

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

1000 mg/kg 群の妊娠期間が対照群と比較して有意に延長した。また、同群の出産率は対照群と比較して有意に低下した。

3) 分娩および哺育状態

分娩状態の観察では、1000 mg/kg 群の 8 例中 6 例は生存児が確認されなかったことから分娩不良と判断され、残りの 2 例についても哺育 1 日には全哺育児が死亡した。250 mg/kg 以下の群においては、いずれの分娩雌とも分娩状態は良好で、哺育状態にも異常は観察されなかった。

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

1000 mg/kg 群の着床率が対照群と比較して有意に低下した。黄体数および着床数には、対照群と各被験物質群との間に有意差は認められなかった。

3. 出生児

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

1000 mg/kg 群の産児数、出生児数、分娩率、生児出産率および出生率が、対照群と比較して有意低下し、同群の哺育 4 日の生存率は 0%を示した。250 mg/kg 以下の群では、いずれの項目についても対照群と比較して有意差は認められなかった。哺育 0 日の生児に外表奇形は観察されなかった。

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

雌雄とも 250 mg/kg 以下の群の哺育 0 日または哺育 4 日の哺育児体重に被験物質投与の影響を示す変化は認められなかった。

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

出生児の一般状態観察では、1000 mg/kg 群の 2 腹中 1 腹で哺育 0 日に哺育不良が観察され、いずれも哺育 1 日に全哺育児が死亡した。250 mg/kg 以下の群の出生児には、被験物質投与の影響を示す一般状態の変化はみられなかった。

死亡児の剖検では、1000 mg/kg 群の雌 1 例に全身浮腫が観察された他、対照群の雄 1 例に外脳、二分脊椎、開眼および水腎の複合奇形が観察されたが、被験物質投与の影響を示す異常は認められなかった。哺育 4 日の生存児の剖検では、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、雌では妊娠期間を通して周産期(哺育4日まで)に1-ethoxy-2-(2-methoxyethoxy)ethaneを経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

1. 反復投与毒性および回復性

一般状態観察では、投与初期に1000 mg/kg群の非交配雌を含む雌雄の全例で自発運動の低下が観察された。したがって、被験物質は麻酔作用を示すと考えられるが、本被験物質と同じエーテル結合を有するジエチルエーテルに比べるとその作用は弱いものと推察される。その他、1000 mg/kg群の雄の数例に一過性の流涎が観察されたが、詳細な症状観察や機能検査で神経毒性を示す影響が観察されなかったことから被験物質の刺激による変化と推察された。

摂餌量の測定では、1000 mg/kg群の雄および非交配雌で被験物質投与の影響と考えられる摂餌量の低下が認められたが、体重推移には影響を示す変化はなかった。なお、1000 mg/kg群の妊娠雌では、胎児の子宮内死亡あるいは発育抑制に関連したと推察される体重増加抑制が妊娠末期にみられ、250 mg/kg群においては哺育3日の摂餌量が低下した。

尿検査では、カリウムおよび塩素イオン濃度の低下が1000 mg/kg群の雄にみられ、被験物質投与の影響が示唆されたが、腎臓の病理組織学的検査で関連する異常は認められていないことから、その原因は不明であった。なお、類似物質のエチレングリコールモノメチルエーテル(CAS番号:109-86-4)を投与したラットにおいても尿比重の低下が報告されているが、腎臓の病理組織検査では異常は認められない⁴⁾。

血液学的検査では、1000 mg/kg群の雄および非交配雌の血色素量とヘマトクリット値が低下し、さらに250 mg/kg以上の雄および1000 mg/kg群の非交配雌で網状赤血球比率が低下した。1000 mg/kg群の非交配雌ではMCHCと血小板数も低下したことから、被験物質投与による赤血球への影響が疑われたが、赤色尿や脾臓での髄外造血の亢進などは観察されなかった。なお、類似物質の2-(1-メチルエトキシ)エタノールでは、溶血性貧血が報告されている¹⁾。

器官重量測定では、1000 mg/kg群の雄および非交配雌の胸腺と雄の精巣上体および前立腺の重量が低下し、病理組織学的検査では1000 mg/kg群の雄と非交配雌に胸腺の萎縮が、同群の精巣では精細管内に精子細胞の脱落や生殖細胞層の空胞化が、精巣上体では管腔内に精子の減少および細胞残屑が観察され、前立腺では管腔内に内容物の減少が認められた。これらの変化は被験物質投与による影響と考えられる。類似物質のジエチレングリコールジメチルエーテル(CAS番号:111-96-6)を投与したCrI:CDラットでも精巣、精巣上体、精囊および前立腺重量の低下がみられ、精子形成サイクルの全ステージに影響が及んでいたことが報告されている²⁾。また、胸腺の萎縮についても類似物質のエチレングリコールモノメチルエーテル(CAS番号:109-86-4)を投与したマウス³⁾、ラット⁴⁾およびウサギ⁴⁾で報告され

ている。

1000 mg/kg 群の雄および非交配雌では、肝臓および腎臓の相対重量が増加した。肝臓の病理組織学的検査では、1000 mg/kg 群の雄および非交配雌、さらには同群の全哺育児が死亡した分娩雌に小葉中心性の肝細胞肥大が認められ、肝細胞に曇りガラス変性が観察された。これらの変化は、被験物質投与による薬物代謝酵素の誘導に関連した変化と考えられる。小葉中心性の肝細胞肥大は 250 mg/kg 群の雄でも認められたが、同群の分娩雌にはこれらの変化はなかった。なお、類似物質のジエチレングリコールジメチルエーテル(CAS 番号:111-96-6)では、反復投与により肝臓の P-450 酵素を誘導することが確認されている⁵⁾。

血液生化学的検査では、1000 mg/kg 群の雄に総蛋白濃度の低下と γ -GTP の増加が認められ、これらは肝機能の低下を示唆する変化と推察されるが、BUN(平均 17 mg/dL)の増加とナトリウムイオン濃度(平均 143.6 mEq/L)の低下は、いずれも背景データの範囲内(下表参照)であることから、偶発的な変化と判断した。

雄(投与終了時)	試験数*	サンプル数	平均	平均 $\pm$ 2SD
BUN	4	20	16	12-20
ナトリウムイオン濃度	4	20	143.6	142.2-145.0

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:注射用水)を使用

回復観察中の一般状態、詳細な症状観察、体重推移、摂餌量に被験物質投与の影響を示す変化は認められなかった。しかし、尿検査では尿比重、ナトリウム、カリウムおよび塩素イオン濃度の低下が 1000 mg/kg 群の非交配雌にみられた。尿中電解質の変動は、投与期間中の雄に観察されており、回復観察中の雄でも有意差はないが電解質濃度の低下傾向がみられていることから、被験物質投与の影響が考えられた。器官重量測定では、精巣上体の重量低下と肝臓の相対重量の増加が 1000 mg/kg 群の雄でみられ、病理組織学的検査では、精巣の精細管内に精子細胞の脱落、生殖細胞層の空胞化ならびに多核巨細胞が、精巣上体の管腔内に精子の減少および細胞残屑がそれぞれ観察された。これらはいずれも投与終了時にも認められていることから、回復性に乏しい変化と考えられるが、回復期間終了時の非交配雌では、胸腺の萎縮あるいは肝細胞肥大は観察されなかった。

2. 生殖発生毒性

1000 mg/kg 群において投与開始後の性周期が変動した動物が増加し、発情回帰日数が延長した。また、同群では全例で交尾が確認されたが、3 例は不妊であった。1000 mg/kg 群の妊娠例でも妊娠期間が延長し、着床率(着床数/妊娠黄体数)が低下した。また、同群では分娩不良が観察され、出産率(生児出産雌数/妊娠動物数)が低下した。これらの変化は、いずれも雌の内分泌系への被験物質の影響と考えられるが、不妊については雄の精巣および精巣上体に認められた異常が原因の可能性も考えられる。

1000 mg/kg 群では、産児数および出産生児数が減少して分娩率(産児数/着床痕数)、生児出産率(出産生児数/着床痕数)および出生率(出産生児数/産児数)が低下した。さらに、同群では哺育不良も観察され、新生児生存率(出産生児数/産児数)が 0%を示した。これらの変化も、雌の分娩および哺育に関連する内分泌系への被験物質の影響と考えられ、死亡児および哺育 4 日の生存児の剖検では、被験物質投与の影響を示す異常が認められていないことから、次世代への直接影響を示唆するものではないと考えられる。

3. 無毒性量

250 mg/kg 群の雄に網状赤血球比率の低下と小葉中心性の肝細胞肥大が、250 mg/kg 群の分娩雌に摂餌量の低下が観察されたことから雌雄動物の反復投与毒性に対する無毒性量(NOAE)は 62.5 mg/kg/day と判断された。また、1000 mg/kg 群では性周期および妊娠期間の延長、出産率、着床率、産児数、出産生児数、分娩率、生児出産率および出生率の低下が認められたことから、生殖発生毒性に対する無毒性量は 250 mg/kg/day と判断された。

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Photo 1 Thymus of a male rat (Animal No. M04037) orally administered with 1000 mg/kg of EMEE.
Atrophy of medulla is observed. (Hematoxylin-Eosin stain)



Photo 2 Liver of a male rat (Animal No. M04041) orally administered with 1000 mg/kg of EMEE.
Hypertrophy of hepatocyte and ground glass appearance are observed in the centrilobular zone.
(Hematoxylin-Eosin stain)

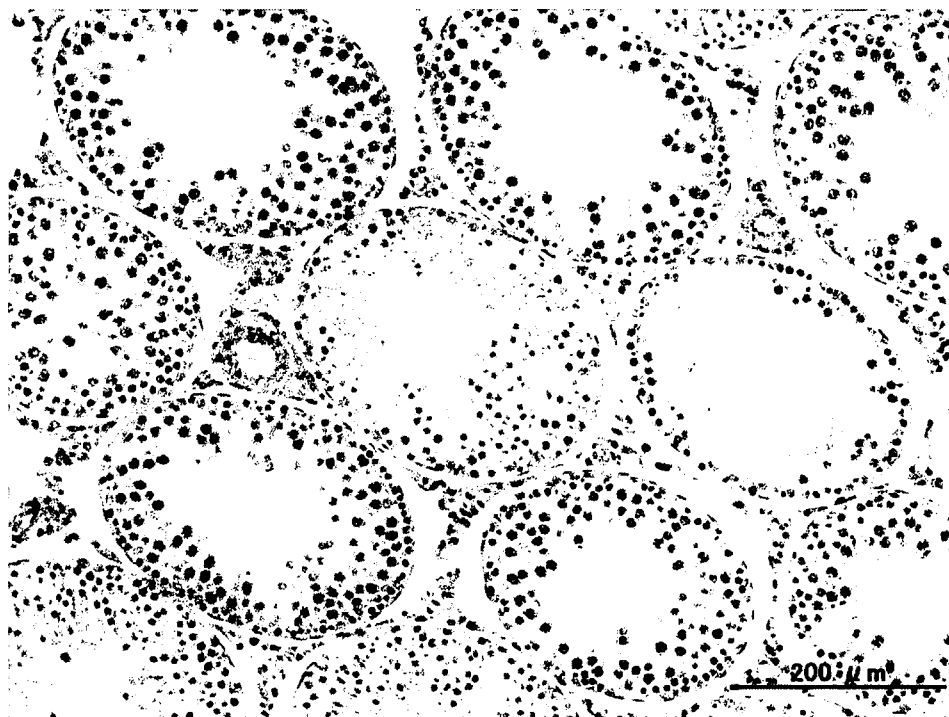


Photo 3 Testis of a male rat (Animal No. M04039) orally administered with 1000 mg/kg of EMEE.
Exfoliation of spermatocyte, spermatid and sperm into lumen of seminiferous tubules is observed.
(Hematoxylin-Eosin stain)

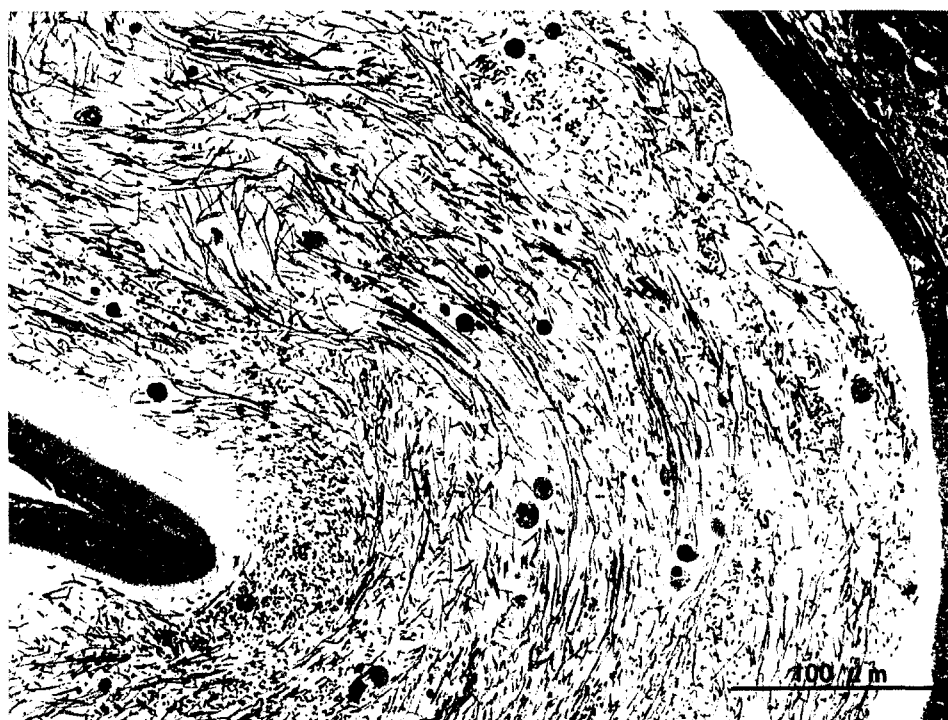


Photo 4 Epididymis of a male rat (Animal No. M04039) orally administered with 1000 mg/kg of EMEE.
Cell debris and decreased sperm cells are observed in the lumen. (Hematoxylin-Eosin stain)

Annex A

検 査 成 績 書

財団法人食品薬品安全センター 御中

2013年6月14日
和光純薬工業株式会社

Code No.044-32575

ジエチレングリコールエチルメチルエーテル

規格／等級	和光特級	
Lot No.	AWM2005	
数量	500ml × 2	
検査項目	検査成績	規格値
外観	無色、透明の液体	無色～ほとんど無色、透明の液体
密度(20℃)	0.923g/ml	0.918～0.928g/ml
屈折率n _{20/D}	1.410	(実測値報告)
水分	0.1%	0.1%以下
含量(キャピラリーカラムGC)	100.0%	98.0%以上
検査年月日	2013/06/04	

判 定	合 格	検査責任者	
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(1/1)

成績書発行番号

9031637

SOP/CHE/001

採用開始 2013年4月19日

試験番号: R-13-002

含 量 試 験 結 果

被験(対照)物質: 1-Ethoxy-2-(2-methoxyethoxy)ethane

調製年月日: 2013年10月21日

ロット番号: AWM2005

測定年月日: 2013年10月21日

媒体: 注射用水

試料 番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
1	12.5	12.5	12.5	100.0	100.0	100.0
2		12.8		102.4		102.4
3		12.2		97.6		97.6
4	50.0	49.3	49.8	98.6	99.5	99.0
5		49.4		98.8		99.2
6		50.6		101.2		101.6
7	200	208	197	104.0	98.5	105.6
8		191		95.5		97.0
9		192		96.0		97.5

含量の判定基準(溶液)

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

Annex C

投与検体中の被験物質濃度測定法

試験操作は特に規定する場合を除き室温下で行う。

1. 試薬

蒸留水 (HPLC 用、以下、水)
アセトン (HPLC 用)

和光純薬工業
和光純薬工業

2. 使用機器

電子天秤 (RC210D または R200D)
ガスクロマトグラフ

ザルトリウス
島津製作所

構成: GC-17A (ガスクロマトグラフ)、AOC-20i (オートインジェクタ)、C-R7A (データ処理装置)

3. 標準溶液の調製

被験物質約 50 mg を精密に量り取り、水に溶かし正確に 10 mL する。この液 1 mL を正確に採り、水を加えて正確に 50 mL として標準原液 (約 0.1 mg/mL) とする。標準原液を 1、1、2.5 及び 5 mL ずつ正確に採り、それぞれ水を加えて正確に 20、10、10 及び 10 mL として標準溶液 (約 5、10、25 及び 50 µg/mL、St 1~4) とする。標準原液及び標準溶液は測定日ごとに n=1 で調製する。

4. 試料溶液の調製

1) 投与検体約 12.5 mg/mL

投与検体 1 mL を正確に採り、水を加えて正確に 100 mL とする。この液 2 mL を正確に採り、水を加えて正確に 10 mL として試料溶液とする (約 0.025 mg/mL、希釈率 500)。試料溶液の調製は投与検体の採取から n=3 とする。

2) 投与検体約 50 mg/mL

投与検体 1 mL を正確に採り、水を加えて正確に 100 mL とする。この液 1 mL を正確に採り、水を加えて正確に 20 mL として試料溶液とする (約 0.025 mg/mL、希釈率 2000)。試料溶液の調製は投与検体の採取から n=3 とする。

3) 投与検体約 200 mg/mL

投与検体 1 mL を正確に採り、水を加えて正確に 100 mL とする。この液 1 mL を正確に採り、水を加えて正確に 100 mL として試料溶液とする (約 0.02 mg/mL、希釈率 10000)。試料溶液の調製は投与検体の採取から n=3 とする。

5. 投与検体中被験物質の濃度測定法

標準溶液 (St 1~4) 及び試料溶液をそれぞれ下記の試験条件でガスクロマトグラフィーにより試験を行う。標準溶液は各濃度 3 回ずつ、試料溶液はそれぞれ 1 回ずつ測定し、標準溶液から作成した検量線を用いて試料溶液中の被験物質濃度を求め、これに希釈率を乗じて投与検体中の被験物質濃度を算出する。また、投与検体の媒体 (n=1) を 1 回測定し、被験物質に相当するピークがないことを確認する。

試験条件

検出器	水素炎イオン化検出器 (FID)
	水素 60 kPa、空気 50 kPa、メイクアップガス (ヘリウム) 80 kPa
カラム	Rtx-1301 (内径 0.32 mm、長さ 30 m、膜厚 1.5 µm)、RESTEK
キャリアガス	ヘリウム (He、70 kPa)
カラム温度	70°C (0.5 分)、15°C/分、200°C
注入口温度	250°C
検出器温度	250°C
注入量	1 µL
注入方式	スプリット (スプリット比 1:25)
オートインジェクタ洗浄溶媒	アセトン

システム適合性

測定開始前に水を 1 回、測定開始前及び測定終了後にシステム適合性用溶液 (St 3) を 1 回ずつ、測定する。溶媒のクロマトグラム上の測定対象物質の保持時間付近に妨害ピークがないことを確認する。また、システム適合性用溶液において保持時間とピーク面積の変動(測定開始前に対する測定終了後の偏差%)を確認する。変動の許容基準は保持時間が $\pm 3.0\%$ 以内、ピーク面積が $\pm 5.0\%$ 以内を目安とする。

6. 数値の取り扱い

- 1) 投与検体の濃度は、四捨五入して、有効数字3桁目まで表示する。
- 2) 標準溶液の濃度は、切り捨てて、有効数字4桁目まで表示する。
- 3) 試験結果における測定濃度 (mg/mL) 及びその平均は四捨五入して有効数字3桁で表示する。
- 4) 含量(%), 平均含量(%), 及びばらつき(%)は四捨五入して、小数第1位まで表示する。
- 5) システム適合性における偏差%は四捨五入して、小数第1位まで表示する。

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 1-1. General conditions of male rats

[illegible]

PRE: Before administration. Post: after administration

Group	Number of males and general conditions	Days of administration																																									
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43							
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre							
Control (vehicle; water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7							
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7							
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0							
	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	0	0	0	0	0	0	0							
EMEE 62.5 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12							
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12								
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0								
	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	0	0	0	0	0	0								
EMEE 250 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12							
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12								
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0								
	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	0	0	0	0	0	0								
EMEE 1000 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7								
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	12	11	12	10	12	11	12	10	12	7	12	11	12	9	7								
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	2	0	1	0	2	0	5	0	1	0	2	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	0	0	0	0	1	0								

Pre: Before administration. Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Number of males and general conditions	Days of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: water for injection)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
EMEE 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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 2-1. General conditions of female rats

Group	Number of females and general conditions	Days of administration																																					
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control (vehicle: water for injection)	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	5	5	5	5	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	5	5	5	5	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	0	0	0	0	0	0	0	0	0	0
EMEE 62.5 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	4	4	1	1	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	4	4	1	1	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	0	0	0	0	0	0	0	0	0	0
EMEE 250 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	8	4	4	4	4	2	2
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	8	4	4	4	4	2	2
	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	0	0	0	0	0	0	0	0	0	0
EMEE 1000 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	4	4	2	2	1	1
	General appearance, No abnormality	12	0	12	0	12	12	12	12	12	12	12	12	11	12	11	12	11	12	11	12	11	12	12	12	12	12	12	12	12	12	9	9	4	4	2	2	1	1
	Behavior, Decrease in locomotor activity	0	12	0	12	0	0	0	0	0	0	0	0	1	0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Group	Number of females and general conditions	Days of administration																																									
		20		21		22		23		24		25		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
EM EE 250 mg/kg	Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	General appearance, No abnormality	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Pre: Before administration, Post: after administration.

Group	Number of females and general conditions	Days of administration																									
		41		42		43		44		45		46		47		48		49		50		51		52		53	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
EMEE 250 mg/kg	Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	General appearance, No abnormality	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Number of females and general conditions	Days of administration																																																	
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control (vehicle water for injection)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Forelimb, Alopecia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	EMEE 1000 mg/kg	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
General appearance, No abnormality		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Behavior, Decrease in locomotor activity		0	10	0	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Forelimb, Alopecia		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Group	Number of females and general conditions	Days of administration																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
Control (vehicle: water for injection)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Number of females and general conditions	Days of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: water for injection)	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
EMEE 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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 3. General conditions in dams during pregnancy

Group	Number of dams and general conditions	Days of pregnancy																											
		0		1		2		3		4		5		6		7		8		9		10		11		12		13	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EMEE 62.5 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EMEE 250 mg/kg	Number of dams	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	9
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
EMEE 1000 mg/kg	Number of dams	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
	General appearance, No abnormality	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Group	Number of dams and general conditions	Days of pregnancy																									
		14		15		16		17		18		19		20		21		22		23		24		25		26	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
Control (vehicle: water for injection)	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	0	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Piloerection	0	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	
	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	
EMEE 62.5 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	0	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Piloerection	0	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	
	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	
EMEE 250 mg/kg	Number of dams	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	0
	General appearance, No abnormality	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Piloerection	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	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	
	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
EMEE 1000 mg/kg	Number of dams	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	6	6	1	1	1	1	1	1
	General appearance, No abnormality	9	9	9	7	9	8	9	8	9	8	9	8	9	8	9	8	9	8	6	6	1	1	1	1	1	1
	Fur, Hair, Coat, Piloerection	0	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	1	0	1	0	1	0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0
	Behavior, Decrease in locomotor activity	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 4. General conditions in dams during lactation

Group	Number of dams and general conditions	Days of lactation											
		0		1		2		3		4		5	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of dams	6	6	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	6	6	12	12	12	12	12	12	12	12	12	12
	Fur, Hair, Coat, Piloerection	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
EMEE 62.5 mg/kg	Number of dams	7	7	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	7	7	12	12	12	12	12	12	12	12	12	12
	Fur, Hair, Coat, Piloerection	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
EMEE 250 mg/kg	Number of dams	2	2	10	10	10	10	10	10	10	10	10	10
	General appearance, No abnormality	2	2	9	9	10	10	10	10	10	10	10	10
	Fur, Hair, Coat, Piloerection	0	0	1	1	0	0	0	0	0	0	0	0
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0
EMEE 1000 mg/kg	Number of dams	8	2	2	0	0	0	0	0	0	0	0	0
	General appearance, No abnormality	8	1	2	0	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0
	Mouth, Salivation	0	1	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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
[Posture in home-cage] Crouching position	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Locomotor in home-cage] Decrease in locomotor activity	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Handling behavior] No resistance	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Heart beats] bradycardia	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Body temperature] hypothermia	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Fur] Moist fur	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Skin color/Mucous membrane] Abnormal	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Lacrimation] observed	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Piloerection] Slight	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Respiratory rate] hypopnea	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Stereotypy] observed	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Touch response] Sensitive	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0

^a the recovery test was performed in 5 animals for each of the 0 and 1000 mg/kg groups^b Values represent number of animals with the findings.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 5 (continued). 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
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	1	1	0	0	1	0	0		
	EMEE (250 mg/kg)	12	1	1	1	1	1	1	0		
	EMEE (1000 mg/kg)	12	1	0	1	0	1	0	1	0	0
[Defecation] (frequency/30sec)	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	EMEE (62.5 mg/kg)	12	1	1	0	0	0	0	0		
	EMEE (250 mg/kg)	12	0	1	1	0	0	0	0		
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	0	0

^a the recovery test was performed in 5 animals for each of the 0 and 1000 mg/kg groups

^b Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 6-1. Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						The lactation period	
				8	15	24	30	36	42	49	
[Posture in home-cage] Crouching position	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Locomotor in home-cage] Decrease in locomotor activity	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Handling behavior] Resistance	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	1	0	0	0	0 (1)		0 (4)
[Heart beats] bradycardia	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Body temperature] hypothermia	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Fur] Moist fur	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Skin color/Mucous membrane] Abnormal (pale skin)	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Lacrimation] observed	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Piloerection] slight	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	1	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Respiratory rate] Hypopnea	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Stereotypy] observed	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0 (1)		0 (4)
[Touch response] Sensitive	Control (vehicle: water for injection)	12	0 *	0	0	0	0	0			0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	0			0
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0 (2)	0 (1)	0 (10)
	EMEE (1000 mg/kg)	12	0	0	1	0	0	0	0 (1)		0 (4)

* Values represent number of animals with the findings.

Figures in parentheses indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 6-1 (continued). 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: water for injection)	12	2 ^a	1	1	0	0	2				0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	1				0
	EMEE (250 mg/kg)	12	0	0	0	0	0	1	0	(2)	0	(1) 5
	EMEE (1000 mg/kg)	12	0	0	0	0	0	1	1	(1)		(4) 0
[Defecation] (frequency/30sec)	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0				0
	EMEE (62.5 mg/kg)	12	0	0	0	0	0	1				1
	EMEE (250 mg/kg)	12	0	0	0	0	0	0	0	(2)	0	(1) 2
	EMEE (1000 mg/kg)	12	0	0	0	0	0	0	0	(1)		(4) 0

^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 1-Ethoxy-2-(2-methoxyethoxy)ethane 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
[Posture in home-cage] Crouching position	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Locomotor in home-cage] Decrease in locomotor activity	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Handling behavior] Resistance	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Heart beats] bradycardia	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Body temperature] hypothermia	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Fur] Moist fur	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Skin color/Mucous membrane] Abnormal	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Lacrimation] observed	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Piloerection] slight	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Respiratory rate] Hypopnea	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Stereotypy] observed	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Touch response] Sensitive	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 6-2 (continued). 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
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	10	1 ^b	0	0	0	0	0	0	0	0
	EMEE (1000 mg/kg)	10	1	1	0	1	0	0	0	0	0
[Defecation] (frequency/30sec)	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	EMEE (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 total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 7-1. Body weights of male rats

Group	Control (vehicle: water for injection)	EM EE 62.5 mg/kg	EM EE 250 mg/kg	EM EE 1000 mg/kg
Number of males	12	12	12	12
Days of administration				
1	412.0 ± 20.5	406.3 ± 19.1	411.1 ± 18.3	406.5 ± 19.6
4	422.7 ± 24.6	417.2 ± 21.3	424.2 ± 18.3	411.7 ± 22.0
7	433.6 ± 25.3	426.3 ± 21.2	436.4 ± 21.1	424.2 ± 23.9
14	456.0 ± 30.0	446.7 ± 23.6	461.8 ± 21.9	450.8 ± 25.6
21	473.2 ± 29.7	463.9 ± 24.9	479.2 ± 27.8	466.3 ± 26.4
28	496.0 ± 32.8	483.5 ± 29.1	500.8 ± 29.2	485.3 ± 29.1
35	514.8 ± 39.9	497.9 ± 31.0	519.2 ± 32.3	499.8 ± 32.6
42	525.5 ± 42.8	512.0 ± 35.8	532.0 ± 35.6	508.7 ± 34.7

Each value shows mean (g) ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)		EMEE 1000 mg/kg	
Number of males	5		5	
Days of recovery				
	1	527.8 ± 42.6	511.7 ± 42.6	
	7	547.2 ± 48.5	527.8 ± 41.3	
	14	549.7 ± 50.3	529.0 ± 43.8	

Each value shows mean (g) ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 8-1. Body weights of female rats

Group	Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg
Number of females	12	12	12	12
Days of administration				
1	259.1 ± 20.1	265.2 ± 16.4	255.7 ± 16.7	260.8 ± 16.2
4	264.1 ± 23.7	270.6 ± 17.5	266.4 ± 17.7	272.5 ± 16.4
7	268.0 ± 25.6	275.8 ± 16.9	269.8 ± 17.0	278.0 ± 17.3
14	279.3 ± 29.2	288.5 ± 18.5	279.6 ± 18.8	286.6 ± 17.4

Each value shows mean (g) ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)	EMEE 1000 mg/kg
Number of females	10	10
Days of administration		
1	259.8 ± 19.0	259.1 ± 20.3
4	268.1 ± 20.4	264.2 ± 20.4
7	274.1 ± 22.7	273.6 ± 23.0
14	282.3 ± 25.1	279.9 ± 29.6
21	288.7 ± 33.2	287.4 ± 25.0
28	303.5 ± 35.3	296.9 ± 24.7
35	310.2 ± 36.7	299.0 ± 23.2
42	313.1 ± 34.4	301.5 ± 25.2

Each value shows mean (g) ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)	EMEE 1000 mg/kg
Number of females	5	5
Days of recovery		
1	293.4 ± 15.7	296.5 ± 30.3
7	302.0 ± 22.3	307.2 ± 31.9
14	301.8 ± 17.2	302.1 ± 28.9

Each value shows mean (g) ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 9. Body weights of dams during pregnancy

Group	Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg
Number of dams	12	12	10	9
Days of pregnancy				
0	286.8 ± 28.7	292.4 ± 19.6	283.0 ± 15.3	289.8 ± 15.1
7	327.2 ± 26.8	336.7 ± 19.1	316.2 ± 27.5	326.9 ± 20.9
14	367.9 ± 27.8	379.3 ± 20.9	352.4 ± 34.5	354.0 ± 29.5
20	453.9 ± 30.2	463.8 ± 23.6	430.1 ± 54.9	401.5 ± 34.5 **
26	±	±	±	311.7 ± (1)

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 10. Body weights of dams during lactation

Group	Control (vehicle: water for injection)	EM EE 62.5 mg/kg	EM EE 250 mg/kg	EM EE 1000 mg/kg
Number of dams	12	12	10	8
Days of lactation				
0	345.3 ± 31.5	349.4 ± 28.5	335.6 ± 28.3	347.1 ± 19.0
4	362.5 ± 24.0	362.7 ± 27.8	338.0 ± 25.3	±

Each value shows mean ± S.D. (g).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 11-1. Food consumption of male rats

Group	Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg
Number of males	12	12	12	12
Days of administration				
1	31.2 ± 3.9	30.9 ± 3.4	30.4 ± 2.5	25.0 ± 3.3 **
7	28.1 ± 3.2	26.4 ± 2.2	29.1 ± 1.9	26.5 ± 2.2
14	28.3 ± 2.7	27.2 ± 2.7	29.1 ± 3.3	27.3 ± 2.7
29	30.6 ± 4.0	28.6 ± 2.9	28.0 ± 3.0	28.2 ± 2.7
35	28.7 ± 3.4	28.9 ± 3.4	28.3 ± 2.3	26.5 ± 3.1
41	29.7 ± 2.5	29.0 ± 3.3	29.0 ± 2.7	26.4 ± 3.2 *

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)			EMEE 1000 mg/kg		
Number of males	5			5		
Days of recovery						
	6	30.3	± 2.8	30.6	± 2.8	
	12	29.5	± 2.3	28.4	± 3.0	

Each value shows mean (g) ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 12-1. Food consumption of female rats

Group	Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg
Number of females	12	12	12	12
Days of administration				
1	22.7 ± 2.5	20.7 ± 3.8	21.5 ± 2.7	20.7 ± 3.0
7	20.1 ± 4.9	21.0 ± 3.4	20.5 ± 2.6	22.7 ± 2.8
14	19.8 ± 3.5	22.9 ± 2.9	20.4 ± 2.7	20.4 ± 4.0

Each value shows mean (g) ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)			EMEE 1000 mg/kg		
Number of females	10			10		
Days of administration						
1	21.2	±	4.1	18.0	±	4.0
7	21.0	±	3.6	17.2	±	3.3 *
14	21.5	±	3.4	19.9	±	3.3
21	22.3	±	2.9	20.5	±	4.9
29	21.2	±	3.9	21.1	±	2.8
35	21.8	±	3.7	21.3	±	2.4
41	20.4	±	2.7	17.3	±	3.1 *

Each value shows mean (g) ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)			EMEE 1000 mg/kg		
Number of females	5			5		
Days of recovery						
	6	18.6 ±	5.2	19.6 ±	3.9	
	12	21.0 ±	5.0	20.4 ±	3.9	

Each value shows mean (g) ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 13. Food consumption in dams during pregnancy

Group	Control (vehicle: water for injection)		EMEE 62.5 mg/kg		EMEE 250 mg/kg		EMEE 1000 mg/kg	
Number of dams	12		12		10		9	
Days of pregnancy								
0	23.9 ±	3.0	22.8 ±	3.3	22.7 ±	3.3	22.1 ±	3.2
7	28.6 ±	3.6	29.5 ±	4.1	26.3 ±	4.3	27.6 ±	3.0
14	29.3 ±	4.6	29.2 ±	3.1	26.0 ±	3.2	25.9 ±	7.2
20	27.4 ±	4.4	23.8 ±	5.7	24.9 ±	4.5	25.7 ±	4.1

Each value shows mean ± S.D. (g).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 14. Food consumption in dams during lactation

Group	Control (vehicle: water for injection)	EM EE 62.5 mg/kg	EM EE 250 mg/kg
Number of dams	12	12	10
Days of lactation	3		
	45.9 ± 5.0	43.4 ± 8.1	36.1 ± 7.0 **

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)	EMEE (62.5 mg/kg)	EMEE (250 mg/kg)	EMEE (1000 mg/kg)
Male, Administration period				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)	EMEE (62.5 mg/kg)	EMEE (250 mg/kg)	EMEE (1000 mg/kg)
Female, dam				
Number of animals	5	5	5	0
Righting reflex	100	100	100	
Visual placing	100	100	100	
Pupillary reflex	100	100	100	
Startle reaction	100	100	100	
Preyer's reaction	100	100	100	
Withdrawal reflex	100	100	100	
Eyelid reflex	100	100	100	
Female, satellite groups				
Number of animals	5			5
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Preyer's reaction	100			100
Withdrawal reflex	100			100
Eyelid reflex	100			100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 17. Assessment of grip strength of male rats at the last week of the dosing period

Group	Control (vehicle: water for injection)	EMEE (62.5 mg/kg)	EMEE (250 mg/kg)	EMEE (1000 mg/kg)
Number of males	5	5	5	5
Administration period				
Forelimb	0.982 ± 0.069	0.941 ± 0.050	0.983 ± 0.027	1.012 ± 0.045
Hindlimb	0.722 ± 0.085	0.681 ± 0.106	0.652 ± 0.022	0.676 ± 0.105

Each value shows mean (kg) ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)	EMEE (62.5 mg/kg)	EMEE (250 mg/kg)
Number of females	5	5	5
Administration period			
Forelimb	0.716 ± 0.035	0.731 ± 0.039	0.706 ± 0.043
Hindlimb	0.596 ± 0.048	0.603 ± 0.037	0.570 ± 0.036

Each value shows mean (kg) ±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)			EMEE (1000 mg/kg)		
Number of females	5			5		
Administration period						
Forelimb	0.761	±	0.064	0.735	±	0.027
Hindlimb	0.608	±	0.025	0.642	±	0.062

Each value shows mean (kg) ±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 20. Motor activity of male rats at the last week of the dosing period

Group	Control (vehicle: water for injection)		EMEE (62.5 mg/kg)		EMEE (250 mg/kg)		EMEE (1000 mg/kg)	
Number of males	5		5		5		5	
Administration period								
Ambulation (counts)								
5min	1076	± 217	1231	± 136	1385	± 345	1129	± 119
10min	1016	± 205	1007	± 165	1344	± 347	1050	± 230
15min	875	± 326	912	± 144	1256	± 335	890	± 298
20min	715	± 394	816	± 188	1031	± 335	606	± 249
Total	3683	± 1082	3967	± 524	5016	± 1337	3674	± 804
Rearing (counts)								
5min	29	± 10	32	± 4	32	± 9	25	± 10
10min	24	± 10	21	± 9	33	± 12	25	± 14
15min	17	± 9	15	± 7	25	± 6	15	± 8
20min	12	± 7	13	± 6	13	± 5	10	± 8
Total	82	± 22	80	± 22	102	± 25	75	± 36

Each value shows mean±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)		EMEE (62.5 mg/kg)		EMEE (250 mg/kg)	
Number of females	5		5		5	
Administration period						
Ambulation (counts)						
5min	1100	± 153	1159	± 141	1202	± 379
10min	1054	± 204	782	± 119	994	± 429
15min	772	± 176	593	± 250	694	± 379
20min	574	± 313	468	± 432	746	± 403
Total	3501	± 783	3002	± 705	3636	± 1507
Rearing (counts)						
5min	31	± 21	30	± 7	29	± 19
10min	25	± 19	11	± 4	22	± 13
15min	8	± 7	3	± 2	8	± 5
20min	4	± 7	3	± 7	12	± 9
Total	69	± 49	48	± 14	71	± 37

Each value shows mean±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)			EMEE (1000 mg/kg)		
Number of females	5			5		
Administration period						
Ambulation (counts)						
5min	1263	±	117	1334	±	130
10min	1073	±	136	1228	±	135
15min	1068	±	153	930	±	182
20min	1026	±	107	648	±	572
Total	4430	±	384	4139	±	958
Rearing (counts)						
5min	35	±	6	40	±	13
10min	30	±	11	34	±	8
15min	23	±	9	22	±	7
20min	25	±	14	17	±	23
Total	112	±	32	113	±	45

Each value shows mean±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 23-1. Urinalysis in male rats

Group	Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg
Number of males	5	5	5	5
pH				
6.5	1	2	1	3
7.0	2	2	3	2
7.5	0	0	0	0
8.0	2	1	1	0
Protein				
- (negative)	0	0	0	0
± (10 ≤ and < 30 mg/dL)	0	1	1	1
+ (30 ≤ and < 100 mg/dL)	5	3	4	4
2+ (100 ≤ and < 300 mg/dL)	0	1	0	0
Glucose				
- (negative)	5	5	5	5
Ketone				
- (negative)	1	2	2	4
± (5 ≤ and < 10 mg/dL)	4	2	3	1
+ (10 ≤ and < 40 mg/dL)	0	1	0	0
Bilirubin				
- (negative)	5	5	5	5
Occult blood				
- (negative)	5	5	5	5
Urobilinogen				
± (normal)	5	4	5	5
+ (2.0 ≤ and < 4.0 mg/dL)	0	1	0	0
Color				
light yellow	5	5	5	5
Turbidity				
- (negative)	5	5	5	5
Red Blood cells				
- (not observed)	5	5	5	5
White Blood cells				
- (not observed)	5	5	5	5
Casts				
- (not observed)	5	5	5	5
Cristals				
- (not observed)	0	1	0	1
± (a few)	5	4	4	4
+ (abundant)	0	0	1	0
Epithelial cells				
- (not observed)	5	5	5	5
± (a few)	0	0	0	0
+ (abundant)	0	0	0	0

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)		EMEE 62.5 mg/kg		EMEE 250 mg/kg		EMEE 1000 mg/kg	
Number of males	5		5		5		5	
Urine volume (mL/24hr)	15.9	± 3.3	17.6	± 4.4	18.9	± 4.3	22.4	± 4.3
Specific gravity	1.063	± 0.007	1.056	± 0.009	1.056	± 0.012	1.054	± 0.008
Electrolyte, density								
Na(mEq/L)	119.5	± 21.7	102.4	± 10.6	95.5	± 27.4	92.0	± 14.8
K(mEq/L)	281.2	± 31.0	240.9	± 27.9	220.0	± 60.0	175.4	± 44.7 **
Cl(mEq/L)	159.1	± 27.3	130.2	± 10.7	121.3	± 37.7	104.7	± 29.8 *
Electrolyte, gross volume								
Na(mEq/24hr)	1.88	± 0.42	1.78	± 0.35	1.73	± 0.35	2.01	± 0.20
K(mEq/24hr)	4.43	± 0.88	4.15	± 0.63	4.00	± 0.75	3.80	± 0.55
Cl(mEq/24hr)	2.52	± 0.61	2.26	± 0.41	2.20	± 0.51	2.27	± 0.36

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)	EM EE 1000 mg/kg
Number of males	5	5
pH		
7.0	0	1
7.5	1	1
8.0	4	3
Protein		
- (negative)	0	0
$\pm$ ($10 \leq$ and < 30 mg/dL)	1	3
+ ($30 \leq$ and < 100 mg/dL)	4	2
Glucose		
- (negative)	5	5
Ketone		
- (negative)	4	4
$\pm$ ($5 \leq$ and < 10 mg/dL)	1	1
Bilirubin		
- (negative)	5	5
Occult blood		
- (negative)	5	5
Urobilinogen		
$\pm$ (normal)	5	5
Color		
light yellow	5	5
Turbidity		
- (negative)	5	5
Red Blood cells		
- (not observed)	5	5
White Blood cells		
- (not observed)	5	5
Casts		
- (not observed)	5	5
Cristals		
- (not observed)	0	0
$\pm$ (a few)	5	5
Epithelial cells		
- (not observed)	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)			EM EE 1000 mg/kg		
Number of males	5			5		
Urine volume (mL/24hr)	17.3	±	2.8	22.7	±	5.6
Specific gravity	1.054	±	0.011	1.045	±	0.011
Electrolyte, density						
Na(mEq/L)	106.4	±	27.8	89.3	±	23.5
K(mEq/L)	242.1	±	48.3	197.6	±	45.7
Cl(mEq/L)	133.9	±	29.7	112.7	±	31.2
Electrolyte, gross volume						
Na(mEq/24hr)	1.81	±	0.45	1.95	±	0.38
K(mEq/24hr)	4.11	±	0.56	4.31	±	0.50
Cl(mEq/24hr)	2.28	±	0.46	2.44	±	0.30

Each value shows mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)	EMEE 1000 mg/kg
Number of females	5	5
pH		
6.0	0	2
6.5	0	2
7.0	4	1
7.5	0	0
8.0	1	0
Protein		
- (negative)	3	1
± (10 ≤ and < 30 mg/dL)	1	3
+ (30 ≤ and < 100 mg/dL)	1	1
Glucose		
- (negative)	5	5
Ketone		
- (negative)	5	3
± (5 ≤ and < 10 mg/dL)	0	2
Bilirubin		
- (negative)	5	5
Occult blood		
- (negative)	5	5
Urobilinogen		
± (normal)	5	5
Color		
light yellow	5	5
Turbidity		
- (negative)	5	5
Red Blood cells		
- (not observed)	5	5
White Blood cells		
- (not observed)	5	5
Casts		
- (not observed)	5	5
Cristals		
- (not observed)	1	1
± (a few)	4	4
Epithelial cells		
- (not observed)	5	4
± (a few)	0	1

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)			EMEE 1000 mg/kg		
Number of females	5			5		
Urine volume (mL/24hr)	13.8	±	7.4	14.2	±	2.1
Specific gravity	1.050	±	0.014	1.059	±	0.005
Electrolyte, density						
Na(mEq/L)	80.0	±	28.5	102.8	±	16.1
K(mEq/L)	188.2	±	52.7	215.5	±	28.2
Cl(mEq/L)	94.6	±	35.5	118.2	±	22.2
Electrolyte, gross volume						
Na(mEq/24hr)	1.06	±	0.53	1.44	±	0.13
K(mEq/24hr)	2.56	±	1.30	3.04	±	0.46
Cl(mEq/24hr)	1.31	±	0.77	1.67	±	0.37

Each value shows mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)	EMEE 1000 mg/kg
Number of females	5	5
pH		
6.0	0	1
6.5	0	1
7.0	0	2
7.5	2	0
8.0	3	1
Protein		
- (negative)	5	5
Glucose		
- (negative)	5	5
Ketone		
- (negative)	5	5
Bilirubin		
- (negative)	5	5
Occult blood		
- (negative)	5	4
± (0.03 ≤ and < 0.06 mg/dL)	0	0
+ (0.06 ≤ and < 0.20 mg/dL)	0	0
2+ (0.20 ≤ and < 1.00 mg/dL)	0	1
Urobilinogen		
± (normal)	5	5
Color		
light yellow	5	5
Turbidity		
- (negative)	5	5
Red Blood cells		
- (not observed)	5	5
White Blood cells		
- (not observed)	5	5
Casts		
- (not observed)	5	5
Cristals		
- (not observed)	2	2
± (a few)	3	3
Epithelial cells		
- (not observed)	5	4
± (a few)	0	1

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)			EMEE 1000 mg/kg		
Number of females	5			5		
Urine volume (mL/24hr)	13.0	±	3.2	15.3	±	2.7
Specific gravity	1.055	±	0.007	1.039	±	0.009 *
Electrolyte, density						
Na(mEq/L)	110.1	±	10.5	80.3	±	23.5 *
K(mEq/L)	256.3	±	28.5	154.6	±	52.9 **
Cl(mEq/L)	148.2	±	16.2	85.4	±	28.7 **
Electrolyte, gross volume						
Na(mEq/24hr)	1.44	±	0.38	1.22	±	0.39
K(mEq/24hr)	3.27	±	0.57	2.36	±	0.87
Cl(mEq/24hr)	1.89	±	0.30	1.30	±	0.49

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg	
Number of males		5	5	5	5	
RBC	10000/ μ L	856 $\pm$ 55	869 $\pm$ 35	837 $\pm$ 20	807 $\pm$ 23	
HGB	g/dL	15.2 $\pm$ 0.4	15.2 $\pm$ 0.7	14.8 $\pm$ 0.2	13.9 $\pm$ 0.3	**
Hematocrit	%	43.6 $\pm$ 1.0	43.1 $\pm$ 2.2	42.8 $\pm$ 0.9	40.8 $\pm$ 0.8	*
MCV	fL	51.1 $\pm$ 3.3	49.6 $\pm$ 2.3	51.2 $\pm$ 2.0	50.6 $\pm$ 1.9	
MCH	pg	17.8 $\pm$ 0.9	17.5 $\pm$ 0.7	17.7 $\pm$ 0.4	17.2 $\pm$ 0.6	
MCHC	g/dL	34.7 $\pm$ 0.7	35.3 $\pm$ 0.3	34.5 $\pm$ 0.6	34.0 $\pm$ 0.4	
Platelet	10000/ μ L	104.3 $\pm$ 11.5	104.8 $\pm$ 14.6	99.6 $\pm$ 13.0	84.3 $\pm$ 19.2	
PT	sec.	22.0 $\pm$ 3.0	23.9 $\pm$ 6.9	27.8 $\pm$ 6.3	19.7 $\pm$ 4.4	
APTT	sec.	27.0 $\pm$ 2.4	28.7 $\pm$ 3.2	29.2 $\pm$ 3.4	23.6 $\pm$ 2.8	
WBC	100/ μ L	84.8 $\pm$ 20.4	82.1 $\pm$ 23.3	84.8 $\pm$ 10.5	71.5 $\pm$ 33.7	
Neutrophil	%	18.4 $\pm$ 3.7	19.1 $\pm$ 6.3	14.6 $\pm$ 3.7	18.2 $\pm$ 9.9	
Eosinophil	%	1.8 $\pm$ 0.8	1.9 $\pm$ 0.2	1.5 $\pm$ 0.1	0.7 $\pm$ 0.9	
Basophil	%	0.0 $\pm$ 0.1	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	
Monocyte	%	4.3 $\pm$ 0.5	4.5 $\pm$ 1.0	4.9 $\pm$ 0.9	5.3 $\pm$ 0.6	
Lymphocyte	%	75.5 $\pm$ 4.3	74.5 $\pm$ 6.8	79.0 $\pm$ 3.4	75.8 $\pm$ 10.0	
Reticulocyte	%	3.40 $\pm$ 0.39	2.84 $\pm$ 0.31	2.59 $\pm$ 0.32	1.91 $\pm$ 0.41	**

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EMEE 1000 mg/kg	
Number of males		5	5	
RBC	10000/ μ L	829 $\pm$ 11	849 $\pm$ 36	
HGB	g/dL	14.8 $\pm$ 0.4	14.1 $\pm$ 0.7	
Hematocrit	%	42.8 $\pm$ 0.9	41.1 $\pm$ 2.1	
MCV	fL	51.6 $\pm$ 1.4	48.4 $\pm$ 1.9	*
MCH	pg	17.8 $\pm$ 0.6	16.6 $\pm$ 0.6	*
MCHC	g/dL	34.5 $\pm$ 0.5	34.4 $\pm$ 0.7	
Platelet	10000/ μ L	100.1 $\pm$ 11.4	102.0 $\pm$ 16.5	
PT	sec.	22.5 $\pm$ 2.2	24.4 $\pm$ 9.0	
APTT	sec.	24.2 $\pm$ 1.9	24.9 $\pm$ 4.1	
WBC	100/ μ L	67.4 $\pm$ 14.9	59.5 $\pm$ 13.2	
Neutrophil	%	16.4 $\pm$ 4.1	25.8 $\pm$ 13.2	
Eosinophil	%	1.6 $\pm$ 0.7	2.2 $\pm$ 0.8	
Basophil	%	0.0 $\pm$ 0.1	0.0 $\pm$ 0.1	
Monocyte	%	3.2 $\pm$ 0.8	2.9 $\pm$ 0.7	
Lymphocyte	%	78.8 $\pm$ 4.8	69.0 $\pm$ 13.3	
Reticulocyte	%	3.42 $\pm$ 0.52	3.37 $\pm$ 0.42	

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg
Number of females		5	5	5
RBC	10000/ μ L	672 $\pm$ 36	684 $\pm$ 18	665 $\pm$ 43
HGB	g/dL	12.9 $\pm$ 0.5	13.2 $\pm$ 0.4	12.4 $\pm$ 0.6
Hematocrit	%	39.0 $\pm$ 1.8	39.3 $\pm$ 1.7	37.5 $\pm$ 1.8
MCV	fL	58.0 $\pm$ 3.2	57.4 $\pm$ 2.4	56.3 $\pm$ 1.3
MCH	pg	19.3 $\pm$ 0.8	19.3 $\pm$ 0.8	18.7 $\pm$ 0.4
MCHC	g/dL	33.2 $\pm$ 0.6	33.7 $\pm$ 0.6	33.1 $\pm$ 0.3
Platelet	10000/ μ L	118.5 $\pm$ 7.1	128.6 $\pm$ 19.7	127.0 $\pm$ 4.7
PT	sec.	13.8 $\pm$ 0.8	13.6 $\pm$ 0.9	14.1 $\pm$ 0.6
APTT	sec.	18.5 $\pm$ 1.3	19.1 $\pm$ 1.4	18.1 $\pm$ 0.3
WBC	100/ μ L	120.2 $\pm$ 8.2	114.3 $\pm$ 40.8	109.3 $\pm$ 13.5
Neutrophil	%	34.7 $\pm$ 5.3	33.9 $\pm$ 15.4	33.4 $\pm$ 4.9
Eosinophil	%	0.7 $\pm$ 0.2	0.8 $\pm$ 0.4	1.1 $\pm$ 1.2
Basophil	%	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Monocyte	%	4.3 $\pm$ 1.5	4.7 $\pm$ 1.1	3.9 $\pm$ 0.6
Lymphocyte	%	60.2 $\pm$ 6.6	60.6 $\pm$ 15.9	61.6 $\pm$ 5.5
Reticulocyte	%	8.60 $\pm$ 2.52	8.21 $\pm$ 1.92	7.97 $\pm$ 2.11

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EM EE 1000 mg/kg	
Number of females		5	5	
RBC	10000/ μ L	785 $\pm$ 38	768 $\pm$ 47	
HGB	g/dL	14.8 $\pm$ 0.5	13.7 $\pm$ 0.7	*
Hematocrit	%	41.7 $\pm$ 1.0	39.7 $\pm$ 1.6	*
MCV	fL	53.2 $\pm$ 2.5	51.8 $\pm$ 2.2	
MCH	pg	18.8 $\pm$ 0.9	17.8 $\pm$ 0.6	
MCHC	g/dL	35.4 $\pm$ 0.4	34.4 $\pm$ 0.5	**
Platelet	10000/ μ L	100.6 $\pm$ 13.3	71.6 $\pm$ 14.9	*
PT	sec.	12.8 $\pm$ 0.7	13.4 $\pm$ 0.2	
APTT	sec.	18.3 $\pm$ 1.6	18.2 $\pm$ 2.1	
WBC	100/ μ L	69.0 $\pm$ 28.1	69.0 $\pm$ 16.2	
Neutrophil	%	12.0 $\pm$ 3.7	10.9 $\pm$ 1.7	
Eosinophil	%	1.8 $\pm$ 0.8	1.3 $\pm$ 0.5	
Basophil	%	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	
Monocyte	%	2.8 $\pm$ 0.9	3.6 $\pm$ 1.0	
Lymphocyte	%	83.4 $\pm$ 4.3	84.2 $\pm$ 2.3	
Reticulocyte	%	2.98 $\pm$ 0.91	1.54 $\pm$ 0.22	*

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EM EE 1000 mg/kg
Number of females		5	5
RBC	10000/ μ L	792 $\pm$ 20	812 $\pm$ 22
HGB	g/dL	14.5 $\pm$ 0.5	14.6 $\pm$ 0.3
Hematocrit	%	41.5 $\pm$ 1.9	41.9 $\pm$ 0.8
MCV	fL	52.3 $\pm$ 1.8	51.6 $\pm$ 0.8
MCH	pg	18.3 $\pm$ 0.4	18.0 $\pm$ 0.4
MCHC	g/dL	35.0 $\pm$ 0.5	34.9 $\pm$ 0.4
Platelet	10000/ μ L	98.5 $\pm$ 7.4	101.9 $\pm$ 15.5
PT	sec.	12.6 $\pm$ 0.7	13.0 $\pm$ 0.3
APTT	sec.	17.8 $\pm$ 1.5	18.8 $\pm$ 2.0
WBC	100/ μ L	40.0 $\pm$ 8.0	34.7 $\pm$ 8.5
Neutrophil	%	14.9 $\pm$ 4.0	17.8 $\pm$ 4.8
Eosinophil	%	2.3 $\pm$ 0.7	2.3 $\pm$ 0.5
Basophil	%	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Monocyte	%	4.6 $\pm$ 1.6	2.9 $\pm$ 0.7
Lymphocyte	%	78.2 $\pm$ 5.8	77.0 $\pm$ 4.6
Reticulocyte	%	2.96 $\pm$ 0.62	2.45 $\pm$ 0.96

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg	
Number of males		5	5	5	5	
Total protein	g/dL	5.8 ± 0.1	5.4 ± 0.4	5.4 ± 0.1	5.3 ± 0.2	*
Albumin	g/dL	3.6 ± 0.1	3.5 ± 0.2	3.6 ± 0.1	3.5 ± 0.3	
A/G		1.70 ± 0.14	1.81 ± 0.13	1.96 ± 0.09	1.89 ± 0.31	
Glucose	mg/dL	132 ± 12	136 ± 9	147 ± 7	136 ± 16	
Total cholesterol	mg/dL	37 ± 6	41 ± 6	39 ± 3	43 ± 8	
Triglyceride	mg/dL	41 ± 11	46 ± 18	38 ± 12	26 ± 17	
Phospholipid	mg/dL	70 ± 5	76 ± 6	74 ± 6	78 ± 12	
AST	U/L	62 ± 8	63 ± 8	60 ± 9	79 ± 19	
ALT	U/L	29 ± 7	30 ± 4	30 ± 6	65 ± 40	
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	1 ± 1	**
LDH	U/L	114 ± 66	171 ± 128	111 ± 67	102 ± 57	
Bile acid	μmol/L	11.3 ± 4.2	5.7 ± 0.8 *	11.6 ± 3.6	10.4 ± 3.7	
BUN	mg/dL	14 ± 1	15 ± 2	14 ± 1	17 ± 2	*
Creatinine	mg/dL	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	
Total bilirubin	mg/dL	0.06 ± 0.01	0.05 ± 0.00	0.06 ± 0.02	0.07 ± 0.02	
ALP	U/L	564 ± 83	516 ± 114	495 ± 96	358 ± 101	*
Inorganic phosphorus	mg/dL	5.6 ± 0.3	6.3 ± 0.5	5.7 ± 0.4	5.7 ± 0.6	
Ca	mg/dL	9.3 ± 0.2	9.3 ± 0.1	9.2 ± 0.2	9.2 ± 0.3	
Na	mEq/L	145.4 ± 1.1	145.9 ± 0.7	145.0 ± 0.6	143.6 ± 1.3	*
K	mEq/L	3.90 ± 0.15	3.87 ± 0.19	3.93 ± 0.12	4.90 ± 2.18	
Cl	mEq/L	106.3 ± 1.0	107.2 ± 0.9	106.7 ± 1.0	105.3 ± 0.9	

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EMEE 1000 mg/kg
Number of males		5	5
Total protein	g/dL	5.4 ± 0.2	5.7 ± 0.3
Albumin	g/dL	3.5 ± 0.1	3.6 ± 0.1
A/G		1.87 ± 0.17	1.76 ± 0.17
Glucose	mg/dL	137 ± 9	143 ± 28
Total cholesterol	mg/dL	37 ± 7	49 ± 11
Triglyceride	mg/dL	19 ± 6	22 ± 7
Phospholipid	mg/dL	64 ± 4	75 ± 9 *
AST	U/L	68 ± 5	70 ± 9
ALT	U/L	30 ± 9	29 ± 3
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	120 ± 57	128 ± 96
Bile acid	μmol/L	8.7 ± 1.7	9.7 ± 2.4
BUN	mg/dL	15 ± 2	15 ± 1
Creatinine	mg/dL	0.6 ± 0.1	0.6 ± 0.0
Total bilirubin	mg/dL	0.06 ± 0.01	0.06 ± 0.01
ALP	U/L	464 ± 98	453 ± 33
Inorganic phosphorus	mg/dL	5.7 ± 0.4	5.2 ± 0.6
Ca	mg/dL	8.4 ± 0.2	8.5 ± 0.4
Na	mEq/L	144.9 ± 1.4	145.0 ± 1.2
K	mEq/L	3.84 ± 0.09	3.95 ± 0.25
Cl	mEq/L	109.0 ± 1.8	108.3 ± 1.1

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg
Number of females		5	5	5
Total protein	g/dL	6.0 ± 0.5	6.0 ± 0.4	5.8 ± 0.1
Albumin	g/dL	4.1 ± 0.3	4.0 ± 0.3	3.9 ± 0.1
A/G		2.18 ± 0.19	1.99 ± 0.15	2.01 ± 0.11
Glucose	mg/dL	120 ± 8	126 ± 13	124 ± 6
Total cholesterol	mg/dL	54 ± 13	57 ± 14	54 ± 11
Triglyceride	mg/dL	37 ± 16	41 ± 12	31 ± 4
Phospholipid	mg/dL	113 ± 24	114 ± 18	100 ± 12
AST	U/L	105 ± 30	102 ± 38	86 ± 13
ALT	U/L	49 ± 16	57 ± 18	37 ± 7
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0
LDH	U/L	133 ± 66	103 ± 25	122 ± 81
Bile acid	μmol/L	14.6 ± 4.3	23.0 ± 16.2	10.0 ± 1.8
BUN	mg/dL	17 ± 3	16 ± 3	14 ± 3
Creatinine	mg/dL	0.6 ± 0.1	0.5 ± 0.0 *	0.5 ± 0.0 *
Total bilirubin	mg/dL	0.09 ± 0.03	0.09 ± 0.01	0.08 ± 0.01
ALP	U/L	230 ± 35	241 ± 87	229 ± 44
Inorganic phosphorus	mg/dL	6.7 ± 0.8	6.1 ± 0.7	5.9 ± 0.5
Ca	mg/dL	9.1 ± 0.4	9.1 ± 0.3	9.0 ± 0.2
Na	mEq/L	142.9 ± 1.0	142.6 ± 1.2	143.7 ± 1.8
K	mEq/L	3.93 ± 0.29	3.60 ± 0.26	3.59 ± 0.18
Cl	mEq/L	107.9 ± 1.9	107.3 ± 2.3	108.9 ± 1.3

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EMEE 1000 mg/kg
Number of females		5	5
Total protein	g/dL	5.9 ± 0.5	5.5 ± 0.2
Albumin	g/dL	4.1 ± 0.5	3.8 ± 0.1
A/G		2.26 ± 0.25	2.38 ± 0.14
Glucose	mg/dL	120 ± 17	116 ± 9
Total cholesterol	mg/dL	67 ± 18	63 ± 5
Triglyceride	mg/dL	22 ± 13	23 ± 6
Phospholipid	mg/dL	118 ± 28	119 ± 7
AST	U/L	69 ± 14	53 ± 4 *
ALT	U/L	27 ± 6	22 ± 2
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	66 ± 21	49 ± 10
Bile acid	μmol/L	11.7 ± 2.8	8.6 ± 2.2
BUN	mg/dL	19 ± 7	16 ± 3
Creatinine	mg/dL	0.7 ± 0.1	0.6 ± 0.0
Total bilirubin	mg/dL	0.10 ± 0.03	0.11 ± 0.03
ALP	U/L	238 ± 57	199 ± 65
Inorganic phosphorus	mg/dL	5.2 ± 0.8	4.8 ± 1.0
Ca	mg/dL	9.4 ± 0.4	9.1 ± 0.0
Na	mEq/L	144.8 ± 0.9	144.8 ± 0.7
K	mEq/L	3.80 ± 0.24	3.63 ± 0.36
Cl	mEq/L	106.2 ± 1.5	107.6 ± 0.8

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EMEE 1000 mg/kg
Number of females		5	5
Total protein	g/dL	5.8 ± 0.1	5.8 ± 0.4
Albumin	g/dL	4.0 ± 0.2	3.9 ± 0.3
A/G		2.29 ± 0.22	2.06 ± 0.18
Glucose	mg/dL	117 ± 19	107 ± 2
Total cholesterol	mg/dL	59 ± 14	49 ± 4
Triglyceride	mg/dL	15 ± 3	14 ± 4
Phospholipid	mg/dL	109 ± 20	90 ± 6
AST	U/L	67 ± 5	78 ± 24
ALT	U/L	29 ± 10	26 ± 12
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	62 ± 22	89 ± 45
Bile acid	μmol/L	11.2 ± 1.1	11.8 ± 4.3
BUN	mg/dL	17 ± 2	17 ± 2
Creatinine	mg/dL	0.6 ± 0.1	0.6 ± 0.1
Total bilirubin	mg/dL	0.09 ± 0.02	0.09 ± 0.03
ALP	U/L	233 ± 47	297 ± 68
Inorganic phosphorus	mg/dL	4.2 ± 0.4	3.9 ± 0.7
Ca	mg/dL	8.6 ± 0.2	8.6 ± 0.1
Na	mEq/L	145.4 ± 0.7	145.5 ± 0.6
K	mEq/L	3.72 ± 0.57	3.26 ± 0.23
Cl	mEq/L	109.6 ± 1.8	110.4 ± 1.5

Each value shows mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)		EMEE 62.5 mg/kg		EMEE 250 mg/kg		EMEE 1000 mg/kg	
Number of males		7		12		12		7	
Body weight	(g)	491.2 ± 42.3		482.7 ± 33.0		499.5 ± 32.4		474.6 ± 29.5	
Brain	(mg)	2042.2 ± 61.6		2041.1 ± 40.9		2024.8 ± 82.2		1991.7 ± 60.7	
	(mg/g)	4.187 ± 0.419		4.246 ± 0.294		4.068 ± 0.288		4.211 ± 0.300	
Thymus	(mg)	301.4 ± 53.4		277.8 ± 56.9		312.9 ± 46.0		156.8 ± 57.4 **	
	(mg/g)	0.623 ± 0.150		0.578 ± 0.124		0.629 ± 0.102		0.331 ± 0.120 **	
Heart	(mg)	1417.9 ± 133.4		1478.9 ± 164.8		1477.3 ± 86.5		1472.4 ± 104.8	
	(mg/g)	2.890 ± 0.188		3.067 ± 0.306		2.962 ± 0.153		3.106 ± 0.187	
Liver	(mg)	13320.2 ± 1580.6		12804.6 ± 1459.2		13996.5 ± 947.7		15020.7 ± 1854.2	
	(mg/g)	27.050 ± 1.020		26.488 ± 1.888		28.044 ± 1.326		31.589 ± 2.672 **	
Kidney (R)	(mg)	1621.4 ± 128.9		1623.5 ± 139.8		1702.4 ± 151.0		1679.8 ± 68.7	
	(mg/g)	3.305 ± 0.135		3.363 ± 0.156		3.412 ± 0.261		3.547 ± 0.178	
Kidney (L)	(mg)	1569.8 ± 97.8		1595.4 ± 126.8		1712.6 ± 145.2		1676.9 ± 123.9	
	(mg/g)	3.206 ± 0.195		3.307 ± 0.159		3.432 ± 0.242		3.538 ± 0.238 *	
Kidneys	(mg)	3191.1 ± 220.7		3218.9 ± 264.5		3415.0 ± 280.8		3356.7 ± 190.9	
	(mg/g)	6.511 ± 0.311		6.670 ± 0.306		6.843 ± 0.465		7.086 ± 0.402 *	
Spleen	(mg)	866.8 ± 145.5		870.8 ± 108.3		847.9 ± 98.3		817.0 ± 91.9	
	(mg/g)	1.756 ± 0.180		1.812 ± 0.256		1.702 ± 0.200		1.722 ± 0.158	
Testis (R)	(mg)	1715.8 ± 147.5		1614.5 ± 187.9		1629.8 ± 185.0		1439.7 ± 273.0	
	(mg/g)	3.505 ± 0.317		3.343 ± 0.297		3.275 ± 0.430		3.022 ± 0.456	
Testis (L)	(mg)	1698.3 ± 168.1		1616.2 ± 151.8		1628.3 ± 196.9		1426.1 ± 272.5	
	(mg/g)	3.466 ± 0.307		3.349 ± 0.234		3.269 ± 0.427		2.993 ± 0.464	
Testes	(mg)	3414.1 ± 312.9		3230.7 ± 337.7		3258.1 ± 380.0		2865.8 ± 543.7	
	(mg/g)	6.971 ± 0.617		6.692 ± 0.524		6.545 ± 0.853		6.015 ± 0.915	
Epididymis (R)	(mg)	643.9 ± 33.2		614.8 ± 57.5		610.2 ± 64.8		494.0 ± 35.7 **	
	(mg/g)	1.317 ± 0.109		1.274 ± 0.093		1.222 ± 0.111		1.039 ± 0.157 **	
Epididymis (L)	(mg)	633.4 ± 34.7		607.6 ± 57.5		594.2 ± 52.6		492.6 ± 74.7 **	
	(mg/g)	1.294 ± 0.083		1.260 ± 0.094		1.191 ± 0.103		1.037 ± 0.136 **	
Epididymides	(mg)	1277.2 ± 65.5		1222.4 ± 110.8		1204.4 ± 114.8		986.6 ± 159.6 **	
	(mg/g)	2.612 ± 0.190		2.534 ± 0.176		2.414 ± 0.208		2.077 ± 0.291 **	

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg
Number of males		7	12	12	7
Prostate, ventral	(mg)	665.2 ± 163.4	577.5 ± 135.8	610.8 ± 161.5	421.2 ± 108.2 **
	(mg/g)	1.361 ± 0.332	1.203 ± 0.299	1.231 ± 0.349	0.887 ± 0.215 *
Seminal vesicles	(mg)	1638.6 ± 338.0	1555.6 ± 218.3	1845.5 ± 333.7	1495.9 ± 178.9
	(mg/g)	3.341 ± 0.661	3.222 ± 0.392	3.697 ± 0.627	3.158 ± 0.374
Thyroid gland	(mg)	22.2 ± 4.1	21.2 ± 4.6	24.7 ± 3.7	19.7 ± 2.9
	(mg/g)	0.046 ± 0.010	0.044 ± 0.010	0.050 ± 0.007	0.042 ± 0.007
Adrenal gland (R)	(mg)	25.4 ± 5.1	25.1 ± 3.1	24.6 ± 3.0	23.0 ± 2.7
	(mg/g)	0.052 ± 0.013	0.052 ± 0.007	0.049 ± 0.006	0.049 ± 0.005
Adrenal gland (L)	(mg)	27.1 ± 4.7	26.4 ± 4.3	25.8 ± 3.8	24.2 ± 2.2
	(mg/g)	0.056 ± 0.013	0.055 ± 0.010	0.052 ± 0.007	0.051 ± 0.003
Adrenal glands	(mg)	52.5 ± 9.6	51.6 ± 7.1	50.4 ± 6.7	47.2 ± 4.4
	(mg/g)	0.108 ± 0.025	0.107 ± 0.017	0.101 ± 0.012	0.099 ± 0.007

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)		EMEE 1000 mg/kg	
Number of males		5		5	
Body weight	(g)	525.9	± 48.9	504.9	± 42.0
Brain	(mg)	2058.6	± 51.8	2058.2	± 59.6
	(mg/g)	3.945	± 0.423	4.096	± 0.322
Thymus	(mg)	283.3	± 75.6	203.8	± 71.1
	(mg/g)	0.535	± 0.111	0.399	± 0.122
Heart	(mg)	1443.8	± 100.3	1452.9	± 159.9
	(mg/g)	2.756	± 0.211	2.877	± 0.188
Liver	(mg)	12432.9	± 1395.9	13401.0	± 1433.5
	(mg/g)	23.617	± 0.780	26.511	± 0.978 **
Kidney (R)	(mg)	1627.1	± 119.3	1568.0	± 180.6
	(mg/g)	3.102	± 0.168	3.101	± 0.158
Kidney (L)	(mg)	1668.1	± 104.5	1565.9	± 191.2
	(mg/g)	3.180	± 0.151	3.102	± 0.287
Kidneys	(mg)	3295.2	± 200.7	3133.9	± 362.4
	(mg/g)	6.282	± 0.253	6.203	± 0.430
Spleen	(mg)	808.1	± 148.7	717.2	± 110.3
	(mg/g)	1.534	± 0.202	1.415	± 0.128
Testis (R)	(mg)	1478.4	± 479.8	1285.3	± 438.7
	(mg/g)	2.829	± 0.964	2.529	± 0.801
Testis (L)	(mg)	1613.6	± 170.6	1293.4	± 360.3
	(mg/g)	3.086	± 0.413	2.551	± 0.650
Testes	(mg)	3092.0	± 647.8	2578.7	± 798.5
	(mg/g)	5.915	± 1.353	5.079	± 1.450
Epididymis (R)	(mg)	518.5	± 243.7	481.4	± 79.3
	(mg/g)	0.989	± 0.469	0.954	± 0.137
Epididymis (L)	(mg)	588.2	± 69.0	469.2	± 83.4 *
	(mg/g)	1.128	± 0.188	0.928	± 0.139
Epididymides	(mg)	1106.7	± 302.1	950.6	± 162.3
	(mg/g)	2.117	± 0.613	1.882	± 0.275

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)		EM EE 1000 mg/kg	
Number of males		5		5	
Prostate, ventral	(mg)	598.2	± 172.3	730.2	± 80.9
	(mg/g)	1.133	± 0.290	1.448	± 0.139
Seminal vesicles	(mg)	1854.7	± 433.3	1779.3	± 121.6
	(mg/g)	3.512	± 0.628	3.529	± 0.112
Thyroid gland	(mg)	20.5	± 5.9	23.8	± 2.3
	(mg/g)	0.039	± 0.010	0.048	± 0.007
Adrenal gland (R)	(mg)	21.2	± 2.4	22.4	± 5.5
	(mg/g)	0.041	± 0.006	0.044	± 0.008
Adrenal gland (L)	(mg)	22.1	± 1.9	21.9	± 5.1
	(mg/g)	0.042	± 0.005	0.043	± 0.007
Adrenal glands	(mg)	43.3	± 4.0	44.3	± 10.5
	(mg/g)	0.083	± 0.010	0.087	± 0.015

Each value shows mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)		EMEE 62.5 mg/kg		EMEE 250 mg/kg	
Number of females		12		12		10	
Body weight	(g)	326.4 ±	24.6	324.0 ±	22.8	306.6 ±	25.1
Brain	(mg)	1910.4 ±	80.1	1969.4 ±	47.2	1896.9 ±	55.7
	(mg/g)	5.877 ±	0.405	6.105 ±	0.425	6.225 ±	0.569
Thymus	(mg)	220.8 ±	55.0	232.9 ±	78.0	179.0 ±	41.0
	(mg/g)	0.679 ±	0.165	0.718 ±	0.235	0.583 ±	0.118
Heart	(mg)	1098.2 ±	63.9	1040.6 ±	79.8	1007.1 ±	77.6 *
	(mg/g)	3.378 ±	0.265	3.215 ±	0.176	3.293 ±	0.210
Liver	(mg)	10374.4 ±	614.1	10317.3 ±	768.8	9742.8 ±	928.7
	(mg/g)	31.860 ±	1.722	31.873 ±	1.558	31.794 ±	1.754
Kidney (R)	(mg)	1121.9 ±	106.2	1133.8 ±	109.3	999.7 ±	113.9 *
	(mg/g)	3.441 ±	0.272	3.501 ±	0.263	3.269 ±	0.361
Kidney (L)	(mg)	1096.8 ±	82.2	1097.0 ±	112.1	990.5 ±	120.8 *
	(mg/g)	3.370 ±	0.266	3.388 ±	0.277	3.240 ±	0.393
Kidneys	(mg)	2218.7 ±	185.5	2230.8 ±	218.0	1990.1 ±	233.0 *
	(mg/g)	6.811 ±	0.523	6.888 ±	0.527	6.510 ±	0.749
Spleen	(mg)	794.7 ±	99.5	737.5 ±	94.4	780.7 ±	141.7
	(mg/g)	2.446 ±	0.351	2.286 ±	0.341	2.572 ±	0.594
Ovary (R)	(mg)	53.5 ±	7.1	52.3 ±	11.7	57.7 ±	8.6
	(mg/g)	0.165 ±	0.027	0.162 ±	0.038	0.190 ±	0.037
Ovary (L)	(mg)	55.5 ±	8.4	53.9 ±	8.7	51.0 ±	7.0
	(mg/g)	0.170 ±	0.022	0.167 ±	0.028	0.167 ±	0.021
Ovaries	(mg)	109.0 ±	8.6	106.2 ±	12.4	108.6 ±	10.6
	(mg/g)	0.335 ±	0.028	0.329 ±	0.043	0.356 ±	0.043
Uterus	(mg)	654.7 ±	110.8	657.5 ±	79.1	737.8 ±	229.8
	(mg/g)	2.008 ±	0.315	2.035 ±	0.250	2.392 ±	0.677
Thyroid gland	(mg)	19.2 ±	2.9	18.8 ±	4.9	17.8 ±	5.0
	(mg/g)	0.059 ±	0.011	0.058 ±	0.015	0.059 ±	0.021
Adrenal gland (R)	(mg)	37.3 ±	4.4	37.9 ±	4.2	34.2 ±	8.8
	(mg/g)	0.114 ±	0.011	0.117 ±	0.010	0.113 ±	0.034
Adrenal gland (L)	(mg)	39.0 ±	4.4	39.9 ±	4.4	36.3 ±	9.4
	(mg/g)	0.120 ±	0.016	0.123 ±	0.012	0.119 ±	0.036
Adrenal glands	(mg)	76.3 ±	7.7	77.9 ±	8.1	70.5 ±	18.0
	(mg/g)	0.235 ±	0.024	0.241 ±	0.020	0.232 ±	0.070

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)		EMEE 1000 mg/kg	
Number of females		5		5	
Body weight	(g)	315.6	± 39.7	285.4	± 23.8
Brain	(mg)	1923.2	± 87.3	1904.4	± 51.3
	(mg/g)	6.148	± 0.569	6.715	± 0.660
Thymus	(mg)	345.9	± 38.5	230.3	± 46.0 **
	(mg/g)	1.102	± 0.116	0.814	± 0.181 *
Heart	(mg)	992.5	± 53.7	943.2	± 84.8
	(mg/g)	3.169	± 0.248	3.306	± 0.149
Liver	(mg)	7598.7	± 713.3	8136.8	± 899.6
	(mg/g)	24.174	± 1.390	28.506	± 1.993 **
Kidney (R)	(mg)	953.7	± 54.0	968.4	± 60.7
	(mg/g)	3.046	± 0.259	3.401	± 0.184 *
Kidney (L)	(mg)	936.8	± 79.8	945.3	± 52.2
	(mg/g)	2.982	± 0.181	3.320	± 0.145 *
Kidneys	(mg)	1890.6	± 132.1	1913.7	± 107.6
	(mg/g)	6.028	± 0.430	6.722	± 0.310 *
Spleen	(mg)	572.9	± 114.6	578.2	± 103.1
	(mg/g)	1.828	± 0.385	2.018	± 0.254
Ovary (R)	(mg)	48.2	± 14.7	39.3	± 5.6
	(mg/g)	0.152	± 0.045	0.138	± 0.022
Ovary (L)	(mg)	45.3	± 9.9	39.0	± 7.5
	(mg/g)	0.144	± 0.028	0.137	± 0.022
Ovaries	(mg)	93.5	± 24.5	78.3	± 12.1
	(mg/g)	0.296	± 0.073	0.275	± 0.041
Uterus	(mg)	654.7	± 318.6	570.9	± 197.1
	(mg/g)	2.104	± 1.037	2.057	± 0.934
Thyroid gland	(mg)	17.4	± 4.7	17.9	± 4.1
	(mg/g)	0.056	± 0.014	0.063	± 0.015
Adrenal gland (R)	(mg)	31.2	± 1.1	32.2	± 5.5
	(mg/g)	0.100	± 0.014	0.115	± 0.029
Adrenal gland (L)	(mg)	32.9	± 4.3	34.6	± 6.9
	(mg/g)	0.106	± 0.019	0.123	± 0.035
Adrenal glands	(mg)	64.1	± 4.9	66.8	± 12.3
	(mg/g)	0.206	± 0.030	0.238	± 0.063

Each value shows mean ± S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group		Control (vehicle: water for injection)		EMEE 1000 mg/kg	
Number of females		5		5	
Body weight	(g)	285.3	± 15.5	292.3	± 28.5
Brain	(mg)	1986.7	± 73.3	1935.5	± 26.0
	(mg/g)	6.982	± 0.459	6.669	± 0.609
Thymus	(mg)	207.4	± 45.5	272.3	± 91.6
	(mg/g)	0.725	± 0.149	0.926	± 0.287
Heart	(mg)	883.9	± 34.1	924.1	± 93.6
	(mg/g)	3.101	± 0.080	3.164	± 0.135
Liver	(mg)	7421.0	± 447.4	7111.9	± 458.9
	(mg/g)	26.034	± 1.360	24.426	± 1.699
Kidney (R)	(mg)	953.3	± 60.6	957.0	± 90.7
	(mg/g)	3.348	± 0.250	3.286	± 0.291
Kidney (L)	(mg)	941.2	± 72.8	948.4	± 66.5
	(mg/g)	3.304	± 0.270	3.255	± 0.187
Kidneys	(mg)	1894.5	± 132.8	1905.5	± 152.9
	(mg/g)	6.652	± 0.517	6.540	± 0.466
Spleen	(mg)	531.2	± 43.9	526.9	± 105.7
	(mg/g)	1.867	± 0.190	1.801	± 0.321
Ovary (R)	(mg)	46.5	± 14.5	58.2	± 4.4
	(mg/g)	0.165	± 0.058	0.200	± 0.016
Ovary (L)	(mg)	47.6	± 15.2	55.5	± 6.1
	(mg/g)	0.169	± 0.058	0.190	± 0.019
Ovaries	(mg)	94.1	± 29.1	113.8	± 10.3
	(mg/g)	0.334	± 0.114	0.391	± 0.033
Uterus	(mg)	543.4	± 116.9	588.8	± 227.1
	(mg/g)	1.896	± 0.334	1.999	± 0.649
Thyroid gland	(mg)	21.1	± 3.7	18.1	± 3.9
	(mg/g)	0.075	± 0.015	0.061	± 0.007
Adrenal gland (R)	(mg)	30.6	± 5.1	30.8	± 4.5
	(mg/g)	0.108	± 0.021	0.106	± 0.019
Adrenal gland (L)	(mg)	33.3	± 3.8	32.6	± 3.6
	(mg/g)	0.117	± 0.018	0.112	± 0.015
Adrenal glands	(mg)	63.9	± 8.6	63.4	± 8.0
	(mg/g)	0.225	± 0.039	0.218	± 0.035

Each value shows mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Findings	Dose Grade	Control (vehicle: water for injection)		EMEE 62.5 mg/kg		EMEE 250 mg/kg		EMEE 1000 mg/kg	
		-	P	-	P	-	P	-	P
Epididymis									
Edematous, bilateral		7	0	12	0	12	0	6	1
Kidney									
Enlargement, bilateral		7	0	12	0	11	1	7	0
Prostate									
Small		7	0	12	0	12	0	6	1
Spleen									
Enlargement		7	0	11	1	12	0	7	0
Testis									
Edematous, bilateral		7	0	12	0	12	0	6	1
Small, bilateral		7	0	12	0	12	0	6	1
Thymus									
Small		7	0	12	0	12	0	5	2

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

	Group	Control (vehicle: water for injection)		EMEE 1000 mg/kg	
Findings	Grade	-	P	-	P
Epididymis					
Edematous, bilateral		5	0	1	4
Small, unilateral/bilateral		4	1 ^{a)}	4	1 ^{b)}
Testis					
Edematous, bilateral		5	0	4	1
Small, unilateral/bilateral		4	1 ^{a)}	4	1 ^{b)}

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

Numerals represent the number of animals.

a): Unilateral b): Bilateral

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Findings	Dose Grade	Control(vehicle:water for injection)		EM EE 62.5 mg/kg		EM EE 250 mg/kg	
		-	P	-	P	-	P
Kidney							
Dilatatio, pelvis, bilateral		12	0	11	1	10	0
Liver							
Diaphragmatic nodule		12	0	12	0	9	1
Whitish spot, scattered		12	0	12	0	9	1
Lymph node							
Enlargement, mediastinal		12	0	12	0	9	1
Spleen							
Adhesion, with serosa		12	0	12	0	9	1
Stomach							
Dark colored area, glandular stomach		12	0	11	1	8	2
Thymus							
Small		12	0	12	0	9	1

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Findings	Dose Grade	Control (vehicle: water for injection)		EMEE 1000 mg/kg	
		-	P	-	P
Hair					
Alepecia, forelimb		4	1	5	0

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Findings	Dose Grade	Control(vehicle:water for injection)		EMEE 1000 mg/kg	
		-	P	-	P
Ileum					
Retention, gas, lumen		5	0	4	1
Cecum					
Retention, gas, lumen		5	0	4	1
Colon					
Retention, gas, lumen		5	0	4	1
Rectum					
Retention, gas, lumen		5	0	4	1

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)														EMEE							EMEE						
	Dose(mg/kg)	0							62.5							250							1000						
	Grade	-	±	+	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																													
Cyst		5					0	2	0					0	12	0					0	12	3				2	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																													
Ultimobranchial body		5					0	2	0					0	12	0					0	12	2				3	2	
Parathyroid gland		5						2	0						12	0						12	5						2
Thymus																													
Atrophy, medulla		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	0	2	4	0	0	1	** ##
Heart		5						2	0						12	0						12	5						2
Trachea		5						2	0						12	0						12	5						2
Lung																													
Accumulation, foam cell, alveolus		5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	3	2	0	0	0		2
Hemorrhage, focal		5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Metaplasia, osseous, focal		5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Microgranuloma		4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Mineralization, focal, arterial wall		4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		2
Bronchus		5						2	0						12	0						12	5						2

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

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

P<0.01: Significantly different from control (One-tailed Fisher exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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 Dose(mg/kg) Grade	Control (vehicle: water for injection)							EMEE 62.5							EMEE 250							EMEE 1000						
		0							62.5							250							1000						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver																													
Fatty change, hepatocyte, periportal		0	3	2	0	0		2	0	4	1	0	0		7	3	2	0	0	0		7	2	3	0	0	0		2
Ground glass appearance, hepatocyte		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	0	3	2	0	0		2
Hypertrophy, hepatocyte, centrilobular		5	0	0	0	0		2	5	0	0	0	0		7	2	3	0	0	0		7	0	2	3	0	0		2
Microgranuloma		1	4	0	0	0		2	4	1	0	0	0		7	4	1	0	0	0		7	4	1	0	0	0		2
Pancreas																													
Atrophy, acinar cell, focal, replacing ductal proliferation		4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	0	1	0	0		2
Stomach		5						2	0						12	0						12	5						2
Duodenum		5						2	0						12	0						12	5						2
Jejunum		5						2	0						12	0						12	5						2
Ileum		5						2	0						12	0						12	5						2
Cecum		5						2	0						12	0						12	5						2
Colon		5						2	0						12	0						12	5						2
Rectum		5						2	0						12	0						12	5						2
Lymph node, mesenteric		5						2	0						12	0						12	5						2
Spleen																													
Deposit, pigment, brown		0	5	0	0	0		2	0	0	0	1	0		11	0	0	0	0	0		12	0	4	1	0	0		2
Hematopoiesis, extramedullary		0	0	5	0	0		2	0	0	1	0	0		11	0	0	0	0	0		12	0	0	5	0	0		2
Kidney																													
Basophilic tubule, cortex		1	4	0	0	0		2	0	0	0	0	0		12	0	1	0	0	0		11	2	3	0	0	0		2
Cyst, medulla		4					1	2	0					0	12	0					1	11	5				0		2
Eosinophilic body		4	1	0	0	0		2	0	0	0	0	0		12	1	0	0	0	0		11	4	0	1	0	0		2
Urinary bladder		5						2	0						12	0						12	5						2

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

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

P<0.01: Significantly different from control (One-tailed Fisher exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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 Dose(mg/kg) Grade	Control (vehicle: water for injection)							EMEE 62.5							EMEE 250							EMEE 1000						
		0																											
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Adrenal gland		5						2	0						12	0							12	5					2
Testis																													
Atrophy, seminiferous tubule, focal, bilateral		5	0	0	0	0		2	4	1	0	0	0		7	4	0	1	0	0		7	5	0	0	0	0		2
Exfoliation, spermatid & sperm, seminiferous tubule, bilateral		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	0	3	2	0	0		2 ** #
Exfoliation, spermatocyte, seminiferous tubule, bilateral		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	4	0	1	0	0		2
Multinucleated giant cell, seminiferous tubule, bilateral		5	0	0	0	0		2	5	0	0	0	0		7	4	1	0	0	0		7	0	5	0	0	0		2 ** #
Vacuolation, germ cell layer, seminiferous tubule, bilateral		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	0	4	1	0	0		2 ** #
Epididymis																													
Cell debris, lumen, bilateral		5	0	0	0	0		2	4	1	0	0	0		7	4	0	1	0	0		7	0	1	4	0	0		2 ** #
Decrease, sperm, lumen, bilateral		5	0	0	0	0		2	5	0	0	0	0		7	4	1	0	0	0		7	0	1	4	0	0		2 ** #
Prostate																													
Cellular infiltration, lymphocyte, interstitial		3	2	0	0	0		2	1	3	1	0	0		7	1	4	0	0	0		7	2	1	2	0	0		2
Decrease, liquid content, lumen, bilateral		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	0	5	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		5						2	0						12	0							12	5					2
Sciatic nerve		5						2	0						12	0							12	5					2
Skeletal muscle		5						2	0						12	0							12	5					2
Femur		5						2	0						12	0							12	5					2
Marrow, femur		5						2	0						12	0							12	5					2

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

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

P<0.01: Significantly different from control (One-tailed Fisher exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)							EM EE						
	Dose(mg/kg)	0							1000						
	Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Thymus															
Atrophy, medulla		5	0	0	0	0			3	1	1	0	0		
Liver															
Fatty change, hepatocyte, periportal		0	5	0	0	0			3	2	0	0	0		
Microgranuloma		5	0	0	0	0			4	1	0	0	0		
Necrosis, focal		4	1	0	0	0			5	0	0	0	0		
Testis															
Atrophy, seminiferous tubule, focal															
focal, unilateral/bilateral		3	1	1	0	0			2	2	0	1	0		
Exfoliation, spermatid & sperm,															
seminiferous tubule, bilateral		5	0	0	0	0			0	3	1	1	0	..	##
Exfoliation, spermatocyte,															
seminiferous tubule, bilateral		5	0	0	0	0			1	2	1	1	0		#
Multinucleated giant cell,															
seminiferous tubule, bilateral		4	0	1	0	0			2	2	1	0	0		
Vacuolation, germ cell layer,															
seminiferous tubule, bilateral		5	0	0	0	0			0	3	1	1	0	..	##
Epididymis															
Cell debris, lumen, unilateral/bilateral		4	0	1	0	0			0	1	4	0	0		#
Decrease, sperm, lumen, unilateral/bilateral		4	0	1	0	0			0	1	3	1	0		#
Defect, unilateral		4					1		5					0	
Prostate															
Cellular infiltration, lymphocyte, interstitial		2	2	1	0	0			5	0	0	0	0		

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

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

P<0.01: Significantly different from control (One-tailed Fisher exact test).

P<0.05: Significantly different from control (One-tailed Fisher exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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 Dose(mg/kg) Grade	Control (vehicle: water for injection)							EMEE 62.5							EMEE 250						
		0																				
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5						7	0						12	5						5
Spinal cord		5						7	0						12	5						5
Pituitary gland																						
Cyst		4					1	7	0					0	12	5					0	5
Submandibular gland		5						7	0						12	5						5
Sublingual gland		5						7	0						12	5						5
Lymph node, submandibular		5						7	0						12	5						5
Thyroid gland																						
Ectopic thymic tissue		5					0	7	0					0	12	4					1	5
Parathyroid gland		4						8	0						12	5						5
Thymus		5						7	0						12	6						4
Heart		5						7	0						12	5						5
Trachea		5						7	0						12	5						5
Lung																						
Accumulation, foam cell, alveolus		5	0	0	0	0		7	0	0	0	0	0		12	2	3	0	0	0		5
Bronchus		5						7	0						12	5						5

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)							EMEE							EMEE						
	Dose(mg/kg)	0							62.5							250						
	Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver																						
Fatty change, hepatocyte, periportal		2	3	0	0	0		7	0	0	0	0	0		12	4	2	0	0	0		4
Fibrosis, focal, capsule		5	0	0	0	0		7	0	0	0	0	0		12	5	0	1	0	0		4
Microgranuloma		3	1	1	0	0		7	0	0	0	0	0		12	4	1	1	0	0		4
Necrosis, focal		5	0	0	0	0		7	0	0	0	0	0		12	4	2	0	0	0		4
Nodule, hepatodiaphragmatic		5					0	7	0					0	12	5					1	4
Pancreas																						
		5						7	0						12	5						5
Stomach																						
Dilatation, fundic gland,																						
focal, glandular stomach		5	0	0	0	0		7	1	0	0	0	0		11	6	1	0	0	0		3
Edema, lamina propria, glandular stomach		5	0	0	0	0		7	1	0	0	0	0		11	6	1	0	0	0		3
Erosion, mucosa, glandular stomach		5	0	0	0	0		7	0	0	1	0	0		11	5	1	1	0	0		3
Duodenum																						
		5						7	0						12	5						5
Jejunum																						
		5						7	0						12	5						5
Ileum																						
		5						7	0						12	5						5
Cecum																						
		5						7	0						12	5						5
Colon																						
		5						7	0						12	5						5
Rectum																						
		5						7	0						12	5						5
Lymph node, mesenteric																						
		5						7	0						12	5						5
Spleen																						
Cellular infiltration, inflammatory, serosa		5	0	0	0	0		7	0	0	0	0	0		12	5	1	0	0	0		4
Deposit, pigment, brown		0	0	4	1	0		7	0	0	0	0	0		12	0	0	4	2	0		4
Hematopoiesis, extramedullary		0	0	4	1	0		7	0	0	0	0	0		12	0	0	2	4	0		4

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)								EMEE						EMEE						
	Dose(mg/kg)	0								62.5						250						
	Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney																						
Basophilic tubule, cortex		3	2	0	0	0		7	0	0	1	0	0		11	4	1	0	0	0		5
Dilatation, pelvis, bilateral		5	0	0	0	0		7	0	0	0	1	0		11	5	0	0	0	0		5
Mineralization, Cortico-medullary junction		5	0	0	0	0		7	1	0	0	0	0		11	4	1	0	0	0		5
Urinary bladder		5						7	0						12	5						5
Adrenal gland		5						7	0						12	5						5
Ovary		5						7	0						12	5						5
Uterus		5						7	0						12	5						5
Vagina		5						7	0						12	5						5
Eyeball		5						7	0						12	5						5
Harderian gland		5						7	0						12	5						5
Sciatic nerve		5						7	0						12	5						5
Skeletal muscle		5						7	0						12	5						5
Femur		5						7	0						12	5						5
Marrow, femur		5						7	0						12	5						5
Lymph node																						
Mediastinum																						
Edema, with inflonmatory cell																0	1	0	0	0		

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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 Dose(mg/kg) Grade	Control (vehicle: water for injection)							EMEE 1000						
		0													
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5							5						
Spinal cord		5							5						
Pituitary gland Cyst		5					0		4					1	
Submandibular gland		5							5						
Sublingual gland		5							5						
Lymph node, submandibular		5							5						
Thyroid gland Ultimobranchial body		5					0		4					1	
Parathyroid gland		4						1	5						
Thymus Atrophy, medulla		5	0	0	0	0			3	2	0	0	0		
Heart Degeneration/fibrosis, myocardial, focal		4	1	0	0	0			5	0	0	0	0		
Trachea		5							5						
Lung Accumulation, foam cell, alveolus		5	0	0	0	0			3	2	0	0	0		
Metaplasia, osseous, focal		4	1	0	0	0			5	0	0	0	0		
Bronchus		5							5						

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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 Dose(mg/kg) Grade	Control (vehicle: water for injection)							EMEE						
		0							1000						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Fatty change, hepatocyte, periportal		3	2	0	0	0			0	5	0	0	0		
Ground glass appearance, hepatocyte		5	0	0	0	0			3	2	0	0	0		
Hypertrophy, hepatocyte, centrilobular		5	0	0	0	0			0	4	1	0	0	**	##
Pancreas		5							5						
Stomach		5							5						
Duodenum		5							5						
Jejunum		5							5						
Ileum		5							5						
Cecum		5							5						
Colon		5							5						
Rectum		5							5						
Lymph node, mesenteric		5							5						
Spleen															
Deposit, pigment, brown		0	0	1	4	0			0	0	3	2	0		
Hematopoiesis, extramedullary		0	1	4	0	0			0	1	4	0	0		

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

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

P<0.01 : Significantly different from control (One-tailed Fisher exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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 Dose(mg/kg) Grade	Control (vehicle: water for injection)							EMEE						
		0							1000						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney															
Basophilic tubule, cortex		4	1	0	0	0			5	0	0	0	0		
Cyst, medulla		4					1		5					0	
Fibrosis, focal, subserosa		4	1	0	0	0			5	0	0	0	0		
Mineralization, Cortico-medullary junction		5	0	0	0	0			4	1	0	0	0		
Urinary bladder		5							5						
Adrenal gland		5							5						
Ovary															
Cyst, follicular		5					0		4					1	
Uterus		5							5						
Vagina		5							5						
Eyeball		5							5						
Harderian gland															
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0			5	0	0	0	0		
Sciatic nerve		5							5						
Skeletal muscle		5							5						
Femur		5							5						
Marrow, femur		5							5						

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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 Dose(mg/kg) Grade	Control (vehicle: water for injection)							EMEE						
		0							1000						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Thymus		5							5						
Liver															
Fatty change, hepatocyte, periportal		0	5	0	0	0			0	5	0	0	0		
Necrosis, focal		5	0	0	0	0			4	1	0	0	0		

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 35. Results of observations about estrous cycle

Dose	Control (vehicle: water for injection)				EM EE (62.5 mg/kg)				EM EE (250 mg/kg)				EM EE (1000 mg/kg)			
Number of animals examined	12				12				12				12			
Pre-treatment period																
Number of animals showing type of cycle																
4-day cycle	7				8				7				8			
4/5-day cycle	1				2				3				1			
5-day cycle	4				2				2				3			
Mean length of estrous cycle in days; Mean±S.D. (N)	4.4 ± 0.5 (12)				4.2 ± 0.4 (12)				4.3 ± 0.4 (12)				4.3 ± 0.5 (12)			
Treatment period																
Number of animals showing each type of cycle																
4-day cycle	10				10				4				0			
4/5-day cycle	1				0				7				1			
5-day cycle	1				2				1				4			
uncycle	0				0				0				1			
irregular	0				0				0				6			
Mean length of estrous cycle in days; Mean±S.D. (N)	4.1 ± 0.3 (12)				4.2 ± 0.4 (12)				4.4 ± 0.3 (12)				5.4 ± 0.5 (10) **			
Frequency of animals that show abnormal estrous cycles after the treatment	0 / 12				0 / 12				0 / 12				7 / 12 **			
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.0 ± 0.0 (12)				1.0 ± 0.0 (12)				1.0 ± 0.0 (11)				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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 36. Results of observations about reproductive performance

Dose	Control (vehicle: water for injection)	EMEE (62.5 mg/kg)	EMEE (250 mg/kg)	EMEE (1000 mg/kg)
Number of mated pares [A]	12	12	12	12
Number of copulated pares [B]	12	12	11	12
Copulation index [(B/A)×100, %]	100.0	100.0	91.7	100.0
Number of fertile males [C]	12	12	10	9
Fertility index [(C/B)×100, %]	100.0	100.0	90.9	75.0
Paring days until copulation ; Mean±S.D. (N)	2.5 ± 1.4 (12)	2.1 ± 1.0 (12)	2.3 ± 1.4 (11)	2.3 ± 1.2 (12)

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 37. Observation of offspring (F₁)

Group	Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg
Number of dams	12	12	10	6
Gestation length (days)				
Mean ± S.D. per dam	21.9 ± 0.3	22.3 ± 0.5	22.2 ± 0.4	23.5 ± 0.5 **
Number of corpora lutea				
Total	204	206	162	137
Mean ± S.D. per dam	17.0 ± 1.8	17.2 ± 1.5	16.2 ± 2.4	15.2 ± 2.1 (9)
Number of implantation scars				
Total	199	206	152	118
Mean ± S.D. per dam	16.6 ± 1.4	17.2 ± 1.5	15.2 ± 3.6	13.1 ± 3.5 (9)
Implantation index (%) ^{a)}	97.8 ± 3.5	100.0 ± 0.0	92.5 ± 14.0	85.5 ± 15.8 * (9)
Delivery index (dams,%) ^{b)}	100.0	100.0	100.0	22.2 **
Number of offspring at birth				
Total	180	188	134	31
Mean ± S.D. per dam	15.0 ± 1.0	15.7 ± 1.4	13.4 ± 3.8	5.2 ± 4.1 **
Number of live offspring at birth				
Male	90	100	64	9
Female	86	86	67	6
Total	176	186	131	15
Mean ± S.D. per dam	14.7 ± 1.3	15.5 ± 1.4	13.1 ± 3.7	2.5 ± 4.5 **
Sex ratio ^{c)}				
Mean ± S.D. per dam	0.51 ± 0.13	0.54 ± 0.10	0.46 ± 0.14	0.57 ± (2)
Number of dead offspring				
Total	4	2	3	16
Mean ± S.D. per dam	0.3 ± 0.7	0.2 ± 0.6	0.3 ± 0.5	2.7 ± 1.6 **
Delivery index (offspring) ^{d)}				
Mean% ± S.D. per dam	90.8 ± 7.4	91.4 ± 5.1	87.5 ± 9.2	39.1 ± 29.6 **
Birth index ^{e)}				
Mean% ± S.D. per dam	88.8 ± 8.8	90.4 ± 5.6	85.7 ± 8.9	20.6 ± 32.7 **
Live birth index ^{f)}				
Mean% ± S.D. per dam	97.7 ± 4.4	99.0 ± 3.6	98.1 ± 3.1	27.4 ± 42.5 **
Number of offspring on day 4				
Male	90	99	63	0
Female	84	85	64	0
Sex ratio ^{g)}				
Mean ± S.D. per dam	0.51 ± 0.13	0.54 ± 0.11	0.47 ± 0.15	±
Viability index ^{h)}				
Mean% ± S.D. per dam	99.0 ± 2.4	99.0 ± 2.3	96.7 ± 8.6	0.0 ± (2)
Number of external abnormalities ^{b)}	0	0	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± (2)

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

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

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

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

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

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

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

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

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

Figures in parentheses indicate number of dams.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Group	Control (vehicle: water for injection)	EMEE 62.5 mg/kg	EMEE 250 mg/kg	EMEE 1000 mg/kg
Number of dams	12	12	10	2
Male				
Days after birth				
0	6.7 ± 0.5	6.7 ± 0.4	7.0 ± 0.3	6.4 ±
4	10.9 ± 0.8	10.4 ± 1.4	10.8 ± 1.6	±
Female				
Days after birth				
0	6.3 ± 0.4	6.3 ± 0.3	6.6 ± 0.3	5.7 ±
4	10.6 ± 0.8	9.8 ± 1.5	10.2 ± 1.7	±

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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: water for injection)	Number of offspring	176	176	176	174	174
	General appearance, No abnormality	176	176	174	174	174
	General appearance, Death			2		
	Abnormal findings of offspring, Lack of nursing					
EMEE 62.5 mg/kg	Number of offspring	186	186	185	184	184
	General appearance, No abnormality	186	185	184	184	184
	General appearance, Death		1	1		
	Abnormal findings of offspring, Lack of nursing					
EMEE 250 mg/kg	Number of offspring	131	131	129	128	128
	General appearance, No abnormality	131	129	128	128	127
	General appearance, Death		2	1		1
	Abnormal findings of offspring, Lack of nursing					
EMEE 1000 mg/kg	Number of offspring	15	15			
	General appearance, No abnormality	4				
	General appearance, Death		15			
	Abnormal findings of offspring, Lack of nursing	11				

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Table 40. Morphological observations of offspring (F₁)

Dose	Control (vehicle: water for injection)	EMEE (62.5 mg/kg)	EMEE (250 mg/kg)	EMEE (1000 mg/kg)
Dead offspring				
Number of dead offspring ^{a)}	6	4	7	31
Number of missing offspring	1	1	1	8
Number of dead offspring examined	5 (0) ^{b)}	3 (0) ^{b)}	6 (2) ^{b)}	23 (12) ^{b)}
Number of dead offspring with external changes	1	0	0	1
Exencephaly	1			0
Spina bifida	1			0
Open eye (bilateral)	1			0
Anasarca	0			1
Number of dead offspring with visceral changes	1	0	0	0
Hydronephrosis (bilateral)	1			
Live offspring				
Number of live offspring examined (postnatal day 0)	176	186	131	15
Number of live offspring with external changes	0	0	0	0
Number of live offspring examined (postnatal day 4)	174	184	127	0
Number of live offspring with external changes	0	0	0	0
Number of live offspring with visceral changes	0	0	0	0

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible][illegible]

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

b: Mouth, Salivation.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible]

Pre: Before administration, Post: after administration.

∴ General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

[illegible]

Pre: Before administration. Post: after administration.

-: General appearance. No abnormality.

b: Mouth, Salivation.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible]

Pre: Before administration, Post: after administration.

-: General appearance. No abnormality.

a: Behavior, Decrease in locomotor activity.

[illegible]

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

b; Mouth, Salivation.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

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

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of administration																																					
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18			
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	5	5	5	5	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	5	5	5	5	5	5
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 mg/kg

Female No.	Days of administration																																						
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18				
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post			
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	4	4	1	1
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	4	4	1	1	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible]

Pre: Before administration, Post: after administration.

-; General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

[illegible]

Pre: Before administration, Post: after administration.

+: General appearance, No abnormality.

[illegible]

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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		19			
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post				
F04037	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04038	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04039	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04040	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04041	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04042	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04043	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04044	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04045	-	a	-	a	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04046	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04047	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04048	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
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	9	9	4	4	2	2	1	1
-	12	0	12	0	12	12	12	12	12	12	12	12	12	11	12	11	12	11	12	11	12	11	12	12	12	12	12	12	12	12	12	9	9	4	4	2	2	1	1	
a	0	12	0	12	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0	1	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: Behavior, Decrease in locomotor activity.

[illegible]

EMEE 1000 mg/kg

Pre: Before administration, Post: after administration.
-: General appearance. No abnormality.
a: Behavior. Decrease in locomotor activity.
c: Forelimb, Alopecia.

Female No.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

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

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 3-1. General conditions in dams during pregnancy

Control (vehicle: water for injection)

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

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Dam No.	Days of pregnancy																									
	14		15		16		17		18		19		20		21		22		23		24		25		26	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	0	0	0	0	0	0	0	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	0	0	0	0	0	0	0	
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	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

b: Mouth, Salivation.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 3-2. General conditions in dams during pregnancy

EMEE 62.5 mg/kg

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

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 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	
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	0	0	0	0	0	0	0	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	0	0	0	0	0	0	0	
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

b: Mouth, Salivation.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 3-3. General conditions in dams during pregnancy

EMEE 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	c	c	c	c	c	c	c	c	c	c	c	c	c	
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03033	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of dams	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	9	
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 250 mg/kg

Dam No.	Days of pregnancy																									
	14		15		16		17		18		19		20		21		22		23		24		25		26	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03028	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03033	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of dams	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	0	0	0	0	0	0	0	
-	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	
c	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

b: Mouth, Salivation.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 3-4. General conditions in dams during pregnancy

EMEE 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04040	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04043	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04046	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of dams	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
-	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
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	

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04040	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04043	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-
F04044	-	-	-	a	-	b	-	b	-	b	-	b	-	b	-	b	-	b	-	b	-	b	-	b	-	b
F04045	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04046	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of dams	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	6	6	1	1	1	1	1	
-	9	9	9	7	9	8	9	8	9	8	9	8	9	8	9	8	9	8	6	6	1	1	1	1	1	
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	
b	0	0	0	0	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	
a	0	0	0	2	0	0	0	0	0	0	0	0	0	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.

c: Fur, Hair, Coat, Piloerection.

b: Mouth, Salivation.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 4-1. General conditions in dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F01001	-	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-	-
F01003	#	#	-	-	-	-	-	-	-	-	-
F01004	#	#	-	-	-	-	-	-	-	-	-
F01005	#	#	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-
F01010	#	#	-	-	-	-	-	-	-	-	-
F01011	#	#	-	-	-	-	-	-	-	-	-
F01012	#	#	-	-	-	-	-	-	-	-	-
Number of dams	6	6	12	12	12	12	12	12	12	12	12
-	6	6	12	12	12	12	12	12	12	12	12
c	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

b: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 4-2. General conditions in dams during lactation

EMEE 62.5 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F02013	-	-	-	-	-	-	-	-	-	-	-
F02014	-	-	-	-	-	-	-	-	-	-	-
F02015	#	#	-	-	-	-	-	-	-	-	-
F02016	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-
F02020	#	#	-	-	-	-	-	-	-	-	-
F02021	#	#	-	-	-	-	-	-	-	-	-
F02022	#	#	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-
F02024	#	#	-	-	-	-	-	-	-	-	-
Number of dams	7	7	12	12	12	12	12	12	12	12	12
-	7	7	12	12	12	12	12	12	12	12	12
c	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

b: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 4-3. General conditions in dams during lactation

EMEE 250 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F03025	-	-	-	-	-	-	-	-	-	-	-
F03026	-	-	-	-	-	-	-	-	-	-	-
F03027	#	#	-	-	-	-	-	-	-	-	-
F03028	#	#	c	c	-	-	-	-	-	-	-
F03029	#	#	-	-	-	-	-	-	-	-	-
F03030	#	#	-	-	-	-	-	-	-	-	-
F03031	#	#	-	-	-	-	-	-	-	-	-
F03032	#	#	-	-	-	-	-	-	-	-	-
F03034	#	#	-	-	-	-	-	-	-	-	-
F03035	#	#	-	-	-	-	-	-	-	-	-
Number of dams	2	2	10	10	10	10	10	10	10	10	10
-	2	2	9	9	10	10	10	10	10	10	10
c	0	0	1	1	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

b: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 4-4. General conditions in dams during lactation

EMEE 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	-	Total litter loss									
F04039	-	-	-								
F04041	-	Total litter loss									
F04042	-	Total litter loss									
F04044	-	b	-	Total litter loss							
F04045	-	Total litter loss									
F04047	-	Total litter loss									
F04048	-	Total litter loss									
Number of dams	8	2	2	0	0	0	0	0	0	0	0
-	8	1	2	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0
b	0	1	0	0	0	0	0	0	0	0	0

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Fur, Hair, Coat, Piloerection.

b: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}										Body temperature										Fur																													
	Posture in home-cage										Locomotor in home-cage										Handling behavior										Heart beats										Body temperature										Fur									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14															
M01001	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2												
M01002	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2												
M01003	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2												
M01004	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2												
M01005	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2												
M01006	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2												
M01007	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2													
M01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2										
M01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2										
M01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2										
M01011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2										
M01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2										
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0										
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)								

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

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

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

Handling behavior [2, normal; 1, no resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed (rearing)]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, snout tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

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

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

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

Handling behavior [2, normal; 1, no resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur (2, normal; 1, Moist fur)

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2: normal; 3: slight]

respiratory rate 2: normal; 1: hypopneal

stereotypy(? not observed: 3 observed (rearing))

tough response: 2. normal: 3. sensitive 1

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, pait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

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

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (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, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (62.5 mg/kg)

Male No.	Cage-side observations ^{a)}							Removing from cage / Observations made while handling ^{b)}														Body temperature							Fur						
	Posture in home-cage							Locomotor in home-cage							Handling behavior							Heart beats							Pre ^a T8 ^b T15 T24 T30 T36 T42						
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8 ^b	T15	T24	T30	T36	T42
M02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02014	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02015	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02016	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02017	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02018	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02019	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02020	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02021	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02022	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02023	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02024	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

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

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

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

Handling behavior [2, normal; 1, no resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed (rearing)]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion); b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation); and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (62.5mg/kg)

Male No.	Removing from cage / Observations made while handling ^{a)}														Open-field observations ^{b)}																											
	Skin color / Mucous membranes							Lacrimation							Piloerection							Respiratory rate							Stereotypy							touch response						
	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42							
M02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M02014	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M03015	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M03016	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M03017	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M02018	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M03019	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M02020	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M02021	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M03022	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M02023	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
M03024	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0						
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)						

^{a)} pre-treatment; ^{b)} day 8 of treatment

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

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

Handling behavior [2, normal; 1, no resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed (rearing)]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals: a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (62.5 mg/kg)

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

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (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, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (250 mg/kg)

Male No.	Cage-side observations ^{a)}							Removing from cage / Observations made while handling ^{b)}														Body temperature							Fur						
	Posture in home-cage							Locomotor in home-cage							Handling behavior							Heart beats							Pre ^a T8 ^b T15 T24 T30 T36 T42						
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre ^a	T8 ^b	T15	T24	T30	T36	T42
M03025	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03026	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03027	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03028	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03029	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03030	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03031	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03032	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03033	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03034	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03035	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03036	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

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

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

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

Handling behavior [2, normal; 1, no resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed (rearing)]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (250 mg/kg)

Male No.	Removing from cage / Observations made while handling ^{b)}								Open-field observations ^{c)}																																				
	Skin color / Mucous membranes							Lacrimation							Piloerection							Respiratory rate							Stereotypy							touch response									
	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42			
M03025	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03026	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03027	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03028	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03029	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03030	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03031	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03032	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03033	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03034	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03035	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M03036	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

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

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

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

Handling behavior [2, normal; 1, no resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed (rearing)]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion); b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation); and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex)

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (250 mg/kg)

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

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (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, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible]

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

Posture in home-cage [2, sitting or standing; 1, crouching position]
Locomotor in home-cage [2, normal; 1, decrease in locomotor activity]
Handling behavior [2, normal; 1, no resistance]
Heart beats [2, normal; 1, bradycardia]
Body temperature [2, normal; 1, hypothermia]
Fur [2, normal; 1, Moist fur]
Skin color / Mucous membranes [2, normal; 1, abnormal]
Lacrimation [2, not observed; 1, observed]
Paloerection [2, normal; 3, slight]
respiratory rate [2, normal; 1, hypopnea]
stereotypy [2, not observed; 3, observed (rearing)]
touch respons [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cageside observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, Straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

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

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

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

Handling behavior [2, normal; 1, no resistance]

Heart beats { 2, normal; 1, bradycardia }

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal: 1, Moist fur 1

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

Lacrimation [2, not observed; 1, observed]

Piloerection (1, not observed; 2, normal; 3, slight)

respiratory rate[? normal: 1 hypotension]

stereotypy[2, not observed; 3, observed (rearing)]

touch response[2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals: a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, ear, bizarre behavior, Straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (1000 mg/kg)

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

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (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, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible]

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate[2, normal; 1, hypopnea]

stereotypy[2, not observed; 3, observed]

touch response[2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebra opening, tremor, convulsion, rail, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle; water for injection)

Female No.	Removing from cage / Observations made while handling ^{a)}																Open-field observations ^{c)}																touch response																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	Skin color / Mucous membranes										Lactation						Piloerection						respiratory rate						Stereotypy																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
F01001	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, . tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

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
F01001	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01002	1	0	0	0	0	1			0	0	0	0	0	0	0			0
F01003	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01004	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01005	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01006	0	0	0	0	0	0			0	0	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
F01010	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01011	1	1	1	0	0	1			0	0	0	0	0	0	0			0
F01012	0	0	0	0	0	0			0	0	0	0	0	0	0			0
Total score	2	1	1	0	0	2			0	0	0	0	0	0	0			0
(N)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (62.5 mg/kg)																																																												
Female No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}																																																	
	Posture in home-cage										Locomotor in home-cage										Handling behavior										Heart beats										body temperature										Fur									
	Pre	T ^a	T ^b	T15	T24	T30	T36	T42	T49	L ^c	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L					
F02013	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02014	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02015	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02016	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02017	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02018	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02019	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02020	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02021	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02022	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02023	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
F02024	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2		
Totalscore	1:0	1:0	1:0	1:0	1:0	1:0			1:0	1:0	1:0	1:0	1:0	1:0	1:0			1:0	1:0	1:0	1:0	1:0	1:0			1:0	1:0	1:0	1:0	1:0			1:0	1:0	1:0	1:0	1:0	1:0			1:0	1:0	1:0	1:0	1:0	1:0			1:0	1:0	1:0	1:0	1:0	1:0			1:0			
(N)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)			(12)			

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

Posture in home-cage { 2, sitting or standing; 1, crouching position }

Locomotor in home-cage { 2, normal; 1, decrease in locomotor activity }

Handling behavior { 2, normal; 3, resistance }

Heart beats { 2, normal; 1, bradycardia }

Body temperature { 2, normal; 1, hypothermia }

Fur { 2, normal; 1, moist fur }

Skin color/ Mucous membranes { 2, normal; 1, abnormal (pale skin) }

Lacrimation { 2, not observed; 1, observed }

Piloerection { 2, normal; 3, slight; 4, severe }

respiratory rate { 2, normal; 1, hypopnea }

stereotypy { 2, not observed; 3, observed }

touch response { 2, normal; 3, sensitive }

Except the above findings, there were no changes in all animals: a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, Straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMDE (62.5 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{a)}										respiratory rate										Stereotypy										touch response																			
	Skin color / Mucous membranes										Lacrimation										Piloerection																																							
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L						
F02013	2	2	2	2	2	2		2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2								
F02014	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02015	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02016	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02017	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02018	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02019	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02020	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02021	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02022	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02023	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
F02024	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2							
Totalscore	1:0	1:0	1:0	1:0	1:0	1:0		1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0			1:0	3:0	3:0	3:0	3:0	3:0	3:0			3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0			1:0	3:0	3:0	3:0	3:0	3:0	3:0			3:0	3:0	3:0	3:0	3:0	3:0			3:0						
(N)	(12)	(12)	(12)	(12)	(12)	(12)		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)			(12)						

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals: a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (62.5 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
F02013	0	0	0	0	0	0			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	0	0			0
F02016	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	0	0	0	0	1			0	0	0	0	0	0	1			1
Total score	0	0	0	0	0	1			0	0	0	0	0	0	1			1
(N)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

BMFE (250 mg/kg)

Female No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}																																																	
	Posture in home-cage										Locomotor in home-cage										Handling behavior										Heart beats										body temperature										Fur									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c		Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L														
F03025	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2										
F03026	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2										
F03027	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2			2						
F03028	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2	2	2	2	2	2			2											
F03029	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2										
F03030	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2										
F03031	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2	2	2	2	2	2			2											
F03032	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2										
F03033	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2	2	2	2	2	2			2											
F03034	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2	2	2	2	2	2			2											
F03035	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2										
F03036	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2							
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0								
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)						

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, snub tail, vocalization, touch response, withdrawal reflex, pinna reflex)

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (250 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{a)}																																																	
	Skin color / Mucous membranes										Lacrimation										Piloerection										respiratory rate										Stereotypy										touch response									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L						
F03025	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2											
F03026	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2											
F03027	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2	2	2	2	2	2			2										
F03028	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	3			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2										
F03029	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2										
F03030	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2											
F03031	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2											
F03032	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2											
F03033	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2											
F03034	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2											
F03035	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2			2											
F03036	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2	2	2			2									
Totalscore	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:1	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0									
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)							

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Pulveration [2, normal; 3, slight; 4, severe]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals. a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bladder behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (250 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
F03025	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F03026	0	0	0	0	0	0			1	0	0	0	0	0	0			2
F03027	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0		0
F03028	0	0	0	0	0	1			2	0	0	0	0	0	0			0
F03029	0	0	0	0	0	0			1	0	0	0	0	0	0			0
F03030	0	0	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			1	0	0	0	0	0	0			0
F03033	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	0	0	
Total score	0	0	0	0	0	1	0	0	5	0	0	0	0	0	0	0	0	2
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)	(12)	(12)	(12)	(12)	(12)	(12)	(2)	(1)	(10)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (1000 mg/kg)

Female No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}										body temperature										Fur																													
	Posture in home-cage										Locomotor in home-cage										Handling behavior										Heart beats										body temperature										Fur									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	T49	L ^c		Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L														
F04037	2	2	2	2	2	2				2	2	2	2	2	2					2	2	2	2	2	2	2			2	2	2	2	2	2			2	2	2	2	2	2																		
F04038	2	2	2	2	2	2		2		2	2	2	2	2	2			2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2								2										
F04039	2	2	2	2	2	2		2		2	2	2	2	2	2			2		2	2	3	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2								2										
F04040	2	2	2	2	2	2				2	2	2	2	2	2					2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2																	
F04041	2	2	2	2	2	2	2		2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2			2	2	2	2	2	2	2					2											
F04042	2	2	2	2	2	2	2			2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2																	
F04043	2	2	2	2	2	2		2		2	2	2	2	2	2	2		2		2	2	2	2	2	2	2		2	2	2	2	2	2	2			2	2	2	2	2	2	2						2											
F04044	2	2	2	2	2	2	2			2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2																	
F04045	2	2	2	2	2	2	2			2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2																	
F04046	2	2	2	2	2	2	2		2		2	2	2	2	2	2		2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2						2										
F04047	2	2	2	2	2	2	2			2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2																
F04048	2	2	2	2	2	2	2			2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2																
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:1	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0									
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)									

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (1000 mg/kg)																																																															
Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}																																																				
	Skin color / Mucous membranes										Lacrimation											Piloerection											respiratory rate									Stereotypy											touch response										
	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L									
	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L	Pre	T8	T15	T24	T30	T36	T42	T49	L									
F04037	2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2												
F04038	2	2	2	2	2	2		2		2	2	2	2	2	2		2		2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2				2	2	2	2	2	2			2										
F04039	2	2	2	2	2	2		2		2	2	2	2	2	2		2		2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2				2	2	2	2	2	2			2										
F04040	2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2			2									
F04041	2	2	2	2	2	2	2			2	2	2	2	2	2	2		2		2	2	2	2	2	2			2	2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2			2								
F04042	2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2			2									
F04043	2	2	2	2	2	2		2		2	2	2	2	2	2		2		2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2				2	2	2	2	2	2			2										
F04044	2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2			2									
F04045	2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2			2									
F04046	2	2	2	2	2	2		2		2	2	2	2	2	2		2		2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2				2	2	2	2	2	2			2										
F04047	2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2			2									
F04048	2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2				2	2	2	2	2	2			2									
Totalscore	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0							
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(4)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(4)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(4)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(4)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(4)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(4)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(4)	

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals: a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex)

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (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			
F04038	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04039	0	0	0	0	0	1			0	0	0	0	0	0	0			0
F04040	0	0	0	0	0	0				0	0	0	0	0	0			
F04041	0	0	0	0	0	0	1			0	0	0	0	0	0	0		
F04042	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	0			0
F04044	0	0	0	0	0	0				0	0	0	0	0	0			
F04045	0	0	0	0	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			
F04048	0	0	0	0	0	0				0	0	0	0	0	0			
Total score	0	0	0	0	0	1	1		0	0	0	0	0	0	0	0		0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)		(4)	(12)	(12)	(12)	(12)	(12)	(12)	(1)		(4)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}																																																									
	Posture in home-cage										Locomotor in home-cage										Handling behavior										Heart beats										body temperature										Fur																	
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T21	T30	T36	T42	R7	R14	Pre	T8	T15	T21	T30	T36	T42	R7	R14	Pre	T8	T15	T21	T30	T36	T42	R7	R14	Pre	T8	T15	T21	T30	T36	T42	R7	R14	Pre	T8	T15	T21	T30	T36	T42	R7	R14														
F05049	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2		
F05050	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2		
F05051	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2		
F05052	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2		
F05053	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2		
F05054	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2										
F05055	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2										
F05056	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2										
F05057	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2										
F05058	2	2	2																																																																	

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate[2, normal; 1, hypopnea]

stereotypy[$\geq$ not observed; 3, observed

touch response[2: normal; 3: sensitive]

Except the above findings, there were no changes in all animals: a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																																																
Female No.	Removing from cage / Observations made while handling ^{b)}																Open-field observations ^{c)}																															
	Skin color / Mucous membranes								Lacrimation								Piloerection								respiratory rate								Stereotypy								touch response							
	Pre ^a	T8 ^a	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14			
F05049	2	2	2	2	2	2	2		2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2						
F05050	2	2	2	2	2	2	2		2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2						
F05051	2	2	2	2	2	2	2		2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2						
F05052	2	2	2	2	2	2	2		2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2						
F05053	2	2	2	2	2	2	2		2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2						
F05054	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F05055	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F05056	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F05057	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F05058	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
Totalscore	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	

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

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

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

Handling behavior (2 normal; 3, resistance)

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate [2, normal; 1, hypopneal]

stereotypy: 2, not observed; 3, observed 1

tough response: 2, normal; 3, sensitive; 1

Except the above findings, there were no changes in all animals: a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

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

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (1000 mg/kg)

Female No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}																																																	
	Posture in home-cage										Locomotor in home-cage										Handling behavior										Heart beats										body temperature										Fur									
	Pre ^c	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14															
F06059	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2																
F06060	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2																
F06061	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2																
F06062	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2																
F06063	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2																
F06064	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2														
F06065	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2														
F06066	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2														
F06067	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2														
F06068	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2														
Totalscore	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0												
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)											

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (1000 mg/kg)																																																		
Female No.	Removing from cage / Observations made while handling ^{b)}																Open-field observations ^{c)}																																	
	Skin color / Mucous membranes								Lacrimation								Piloerection								respiratory rate								Stereotypy								touch response									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14					
F06059	2	2	2	2	2	2	2		2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2							
F06060	2	2	2	2	2	2	2		2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2							
F06061	2	2	2	2	2	2	2		2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2							
F06062	2	2	2	2	2	2	2		2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2							
F06063	2	2	2	2	2	2	2		2	2	2	2	2	2	2				2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2							
F06064	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
F06065	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
F06066	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
F06067	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
F06068	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
Total score (N)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (5)	1:0 (5)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (5)	1:0 (5)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (5)	3:0 (5)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (10)	1:0 (5)	1:0 (5)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (5)	3:0 (5)	3:0 (10)	3:0 (10)	3:0 (10)	3:0 (5)	3:0 (5)

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

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

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

Handling behavior [2, normal; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight; 4, severe]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed]

touch response [2, normal; 3, sensitive]

Except the above findings, there were no changes in all animals: a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, gait, bizarre behavior, snub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (1000 mg/kg)

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

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, gait, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M01001	408.3	422.3	431.6	453.6	470.6	494.1	518.1	521.8
M01002	427.6	439.2	447.4	465.3	478.9	501.0	518.8	524.4
M01003	388.3	397.3	413.3	437.7	449.7	467.4	476.4	483.7
M01004	449.2	469.7	479.2	496.4	507.6	524.1	553.5	560.2
M01005	381.6	387.5	395.3	407.7	427.3	443.8	447.4	456.5
M01006	402.4	404.2	418.1	444.4	468.6	490.6	511.7	523.9
M01007	416.8	431.9	447.9	478.8	507.1	532.6	554.7	577.1
M01008	384.6	392.8	399.3	411.6	423.5	442.1	457.4	463.3
M01009	413.8	426.7	435.7	463.5	492.9	529.6	551.0	549.5
M01010	435.0	452.7	466.6	505.6	511.3	533.4	569.3	593.8
M01011	414.7	419.1	425.1	440.1	457.1	478.4	490.3	508.0
M01012	422.0	428.9	443.8	467.7	483.4	515.1	528.5	543.4
Number of males	12	12	12	12	12	12	12	12
Mean	412.0	422.7	433.6	456.0	473.2	496.0	514.8	525.5
S.D.	20.5	24.6	25.3	30.0	29.7	32.8	39.9	42.8

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M02013	398.1	411.5	423.7	445.0	469.1	486.5	501.6	516.1
M02014	415.0	428.6	448.3	467.8	488.7	516.6	531.3	540.4
M02015	426.6	440.2	441.2	454.2	464.8	477.7	491.9	502.8
M02016	397.6	399.8	411.6	429.0	443.9	464.7	477.9	489.5
M02017	396.4	414.7	422.6	442.8	458.9	475.3	494.8	502.6
M02018	437.3	452.9	462.2	488.5	504.7	529.5	547.7	566.0
M02019	438.5	450.2	452.8	473.9	493.4	523.4	538.8	569.0
M02020	400.4	410.8	419.0	452.2	464.6	480.8	496.5	518.3
M02021	394.8	397.8	407.6	428.9	457.8	473.9	482.5	489.2
M02022	383.0	394.4	403.3	415.3	427.0	446.9	456.6	462.4
M02023	405.9	413.6	429.2	454.0	471.6	492.8	509.6	530.6
M02024	382.3	391.3	393.8	409.0	421.9	433.3	445.4	456.8
Number of males	12	12	12	12	12	12	12	12
Mean	406.3	417.2	426.3	446.7	463.9	483.5	497.9	512.0
S.D.	19.1	21.3	21.2	23.6	24.9	29.1	31.0	35.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 250 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M03025	438.9	447.8	458.4	477.2	495.9	520.7	550.9	559.8
M03026	415.3	429.1	441.1	465.8	476.3	497.0	509.6	516.3
M03027	393.8	401.9	414.1	438.3	442.7	463.3	480.2	485.4
M03028	410.3	422.9	434.8	455.2	477.7	496.7	517.7	533.0
M03029	432.4	446.4	462.4	485.2	502.3	519.4	529.3	536.4
M03030	380.2	397.7	397.8	422.0	433.4	452.5	464.3	475.4
M03031	430.7	449.9	464.0	500.6	527.9	548.7	571.4	596.9
M03032	383.7	397.0	406.7	437.5	449.4	465.6	482.1	495.9
M03033	414.7	426.7	442.1	456.4	477.2	501.5	523.1	530.8
M03034	407.7	420.1	438.6	470.2	503.2	529.1	559.1	573.4
M03035	410.8	425.9	441.9	463.3	468.3	492.8	519.4	531.8
M03036	414.2	424.8	434.7	470.4	496.4	522.3	523.8	549.4
Number of males	12	12	12	12	12	12	12	12
Mean	411.1	424.2	436.4	461.8	479.2	500.8	519.2	532.0
S.D.	18.3	18.3	21.1	21.9	27.8	29.2	32.3	35.6
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M04037	408.3	400.2	412.7	447.3	471.4	504.9	523.2	517.4
M04038	386.1	379.2	386.2	398.4	413.2	434.1	444.1	448.8
M04039	414.4	424.2	429.5	450.9	461.6	469.9	480.8	475.1
M04040	422.4	432.5	449.5	467.6	490.8	499.7	525.7	541.2
M04041	428.7	432.3	450.6	480.5	481.4	511.9	534.8	529.6
M04042	422.2	425.5	429.8	456.3	473.1	495.7	511.8	531.2
M04043	410.5	426.7	434.0	462.4	481.9	493.0	503.3	519.0
M04044	376.3	382.1	394.9	423.7	430.7	443.1	448.2	461.9
M04045	404.4	412.4	431.6	460.6	474.7	497.7	512.0	522.3
M04046	435.3	441.3	460.8	491.7	509.3	531.6	542.0	559.7
M04047	381.3	382.6	393.9	426.5	444.4	454.8	467.9	474.9
M04048	387.6	400.8	416.6	444.2	463.4	487.4	503.5	523.4
Number of males	12	12	12	12	12	12	12	12
Mean	406.5	411.7	424.2	450.8	466.3	485.3	499.8	508.7
S.D.	19.6	22.0	23.9	25.6	26.4	29.1	32.6	34.7
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of recovery		
	1	7	14
M01008	469.0	481.8	484.9
M01009	539.3	573.8	578.1
M01010	581.2	608.0	617.1
M01011	504.8	520.6	527.7
M01012	544.6	552.0	540.9
Number of males	5	5	5
Mean	527.8	547.2	549.7
S.D.	42.6	48.5	50.3

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Male No.	Days of recovery		
	1	7	14
M04044	459.9	473.3	472.6
M04045	525.5	545.6	544.0
M04046	566.6	577.4	584.8
M04047	478.4	498.9	498.7
M04048	528.2	543.7	544.9
Number of males	5	5	5
Mean	511.7	527.8	529.0
S.D.	42.6	41.3	43.8
Significance	NS	NS	NS
Statistical method	TT	TT	TT

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of administration			
	1	4	7	14
F01001	274.2	270.7	280.5	297.5
F01002	269.4	273.9	274.4	288.6
F01003	262.2	269.3	267.5	280.6
F01004	263.3	276.9	278.2	306.9
F01005	243.3	238.6	243.5	245.0
F01006	285.0	290.8	295.7	306.2
F01007	247.7	259.6	268.9	273.5
F01008	217.0	211.0	217.2	225.8
F01009	280.0	280.0	290.4	304.6
F01010	241.2	246.6	238.7	244.4
F01011	278.4	296.1	305.8	315.4
F01012	247.9	255.1	254.9	263.4
Number of females	12	12	12	12
Mean	259.1	264.1	268.0	279.3
S.D.	20.1	23.7	25.6	29.2

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 mg/kg

Female No.	Days of administration			
	1	4	7	14
F02013	255.6	258.6	259.1	259.6
F02014	244.4	260.1	264.0	276.5
F02015	285.5	288.2	289.1	299.9
F02016	258.6	263.1	277.3	297.5
F02017	269.3	277.2	276.3	281.8
F02018	262.1	271.8	269.7	293.8
F02019	262.7	273.1	268.9	296.3
F02020	275.2	280.8	277.7	280.3
F02021	245.2	245.9	259.5	269.3
F02022	289.3	287.2	302.5	315.3
F02023	287.6	299.5	309.0	320.4
F02024	246.6	241.1	256.6	271.5
Number of females	12	12	12	12
Mean	265.2	270.6	275.8	288.5
S.D.	16.4	17.5	16.9	18.5
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 250 mg/kg

Female No.	Days of administration								
	1	4	7	14	21	28	35	42	49
F03025	272.3	265.8	287.1	291.6					
F03026	271.0	290.6	289.5	304.1					
F03027	267.7	287.6	287.5	286.2					
F03028	243.1	247.8	249.6	267.3					
F03029	262.8	266.3	260.3	274.4					
F03030	220.2	239.6	246.5	245.4					
F03031	248.4	260.1	263.7	270.3					
F03032	251.7	253.4	263.1	274.8					
F03033	256.1	268.6	262.5	276.7					
F03034	258.8	275.2	272.3	286.8					
F03035	237.4	248.7	256.4	261.9					
F03036	278.5	293.3	298.5	315.3	357.8	395.7	353.6	359.6	368.5
Number of females	12	12	12	12					
Mean	255.7	266.4	269.8	279.6					
S.D.	16.7	17.7	17.0	18.8					
Significance	NS	NS	NS	NS	---	---	---	---	---
Statistical method	AN	AN	AN	AN	NA	NA	NA	NA	NA

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Female No.	Days of administration			
	1	4	7	14
F04037	275.6	285.6	279.4	297.9
F04038	235.6	247.5	240.2	255.7
F04039	252.2	272.0	297.2	276.0
F04040	252.0	255.4	269.2	272.9
F04041	255.7	270.6	278.5	281.5
F04042	287.6	294.5	292.1	318.3
F04043	284.7	296.2	288.7	312.9
F04044	252.7	261.4	268.1	285.3
F04045	275.2	291.5	305.2	293.6
F04046	259.5	266.9	280.1	279.7
F04047	253.8	273.5	275.1	290.0
F04048	245.3	254.6	261.8	275.1
Number of females	12	12	12	12
Mean	260.8	272.5	278.0	286.6
S.D.	16.2	16.4	17.3	17.4
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F05049	292.9	305.8	311.3	328.1	362.7	386.1	387.9	389.9
F05050	263.2	281.4	288.0	302.9	304.1	323.9	340.2	335.2
F05051	280.5	280.5	299.3	310.4	312.2	314.4	326.7	337.9
F05052	244.7	247.4	253.6	269.4	270.3	290.1	287.6	290.8
F05053	279.3	285.8	292.9	292.7	305.3	322.3	327.1	321.5
F05054	263.4	266.3	264.6	264.3	266.1	284.1	290.9	289.5
F05055	246.1	263.5	269.4	273.9	269.6	280.9	286.8	285.8
F05056	240.1	248.5	244.0	249.3	246.6	260.3	257.1	275.2
F05057	246.1	262.3	268.1	271.6	270.9	288.4	291.3	295.6
F05058	241.3	239.9	249.8	260.3	278.8	284.5	306.1	309.8
Number of females	10	10	10	10	10	10	10	10
Mean	259.8	268.1	274.1	282.3	288.7	303.5	310.2	313.1
S.D.	19.0	20.4	22.7	25.1	33.2	35.3	36.7	34.4

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F06059	256.7	259.2	271.7	268.0	284.5	289.9	299.6	297.6
F06060	220.6	229.2	232.2	232.9	258.3	257.1	270.8	271.7
F06061	287.5	288.4	298.1	308.3	320.4	320.9	327.6	330.8
F06062	270.3	271.0	287.7	281.3	301.8	315.4	319.3	316.8
F06063	286.4	295.9	298.3	307.4	307.2	313.3	312.3	314.5
F06064	262.5	268.2	281.1	294.6	310.3	322.2	322.5	339.6
F06065	256.8	256.7	270.6	266.4	277.0	298.4	284.7	299.6
F06066	263.8	278.2	294.4	328.9	305.2	315.3	313.0	305.2
F06067	241.5	252.4	258.0	256.3	254.5	271.9	273.9	273.8
F06068	245.2	242.7	243.4	254.8	255.2	264.4	266.5	265.2
Number of females	10	10	10	10	10	10	10	10
Mean	259.1	264.2	273.6	279.9	287.4	296.9	299.0	301.5
S.D.	20.3	20.4	23.0	29.6	25.0	24.7	23.2	25.2
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of recovery		
	1	7	14
F05054	286.8	303.4	300.9
F05055	290.5	292.2	298.6
F05056	273.2	275.8	276.7
F05057	301.3	302.1	308.7
F05058	315.0	336.6	323.9
Number of females	5	5	5
Mean	293.4	302.0	301.8
S.D.	15.7	22.3	17.2

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EM EE 1000 mg/kg

Female No.	Days of recovery		
	1	7	14
F06064	343.9	356.5	346.0
F06065	286.6	301.4	294.2
F06066	307.0	317.9	314.7
F06067	278.4	283.5	274.9
F06068	266.8	276.7	280.9
Number of females	5	5	5
Mean	296.5	307.2	302.1
S.D.	30.3	31.9	28.9
Significance	NS	NS	NS
Statistical method	TT	TT	TT

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 9-1. Body weights of dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	293.7	327.7	350.8	434.2
F01002	300.1	345.3	388.3	478.8
F01003	284.4	324.7	358.6	430.3
F01004	305.0	347.9	395.5	466.6
F01005	249.3	294.1	344.5	442.9
F01006	314.6	349.6	388.4	477.3
F01007	286.9	320.6	366.5	449.6
F01008	230.2	286.1	337.6	423.5
F01009	309.1	345.9	381.8	467.3
F01010	258.4	299.8	330.0	412.6
F01011	329.1	375.7	423.6	522.0
F01012	280.7	308.9	349.7	441.9
Number of dams	12	12	12	12
Mean	286.8	327.2	367.9	453.9
S.D.	28.7	26.8	27.8	30.2

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 9-2. Body weights of dams during pregnancy

EMEE 62.5 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	260.8	309.6	363.0	439.8
F02014	277.9	316.4	357.7	445.3
F02015	312.9	353.8	398.3	478.0
F02016	295.7	349.2	399.7	486.6
F02017	291.8	326.3	367.9	451.7
F02018	294.2	327.9	358.5	440.7
F02019	293.5	346.6	386.4	468.2
F02020	296.2	331.7	379.6	482.7
F02021	278.2	322.8	357.4	444.4
F02022	315.5	366.3	407.0	492.7
F02023	326.3	366.4	413.7	500.9
F02024	266.1	323.5	362.8	434.5
Number of dams	12	12	12	12
Mean	292.4	336.7	379.3	463.8
S.D.	19.6	19.1	20.9	23.6
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 9-3. Body weights of dams during pregnancy

EMEE 250 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F03025	298.3	324.7	355.1	437.3	
F03026	297.2	331.4	372.5	479.8	
F03027	306.3	352.6	392.8	477.2	
F03028	267.3	256.7	274.2	302.0	
F03029	292.8	341.6	373.1	465.8	
F03030	261.7	297.2	332.8	405.1	
F03031	272.6	305.6	342.3	418.2	
F03032	276.3	305.3	344.3	405.9	
F03033	> 279.7 >	331.5 >	368.7 >	336.8 >	332.2 >
F03034	287.6	335.8	391.8	487.8	
F03035	270.0	311.2	345.2	421.8	
Number of dams	10	10	10	10	
Mean	283.0	316.2	352.4	430.1	
S.D.	15.3	27.5	34.5	54.9	
Significance	NS	NS	NS	NS	---
Statistical method	AN	AN	AN	DU	NA

>: Excluded from analysis (not pregnant)

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 9-4. Body weights of dams during pregnancy

EMEE 1000 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F04037	297.6	341.4	371.0	428.8	
F04038	259.9	286.9	299.3	327.0	311.7
F04039	288.2	328.9	362.7	420.4	
F04040	> 270.0 >	311.1 >	310.3 >	291.1 >	336.6 >
F04041	296.3	343.0	369.0	385.3	
F04042	315.3	353.6	396.0	445.0	
F04043	> 309.8 >	359.6 >	355.0 >	342.3 >	338.9 >
F04044	287.8	336.7	372.7	411.2	
F04045	290.4	328.3	346.8	394.1	
F04046	> 297.7 >	332.9 >	325.5 >	301.3 >	310.5 >
F04047	294.9	321.0	348.8	417.8	
F04048	278.2	302.7	319.3	383.5	
Number of dams	9	9	9	9	1
Mean	289.8	326.9	354.0	401.5	311.7
S.D.	15.1	20.9	29.5	34.5	
Significance	NS	NS	NS	**	---
Statistical method	AN	AN	AN	DU	NA

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 10-1. Body weights of dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation	
	0	4
F01001	311.1	349.7
F01002	338.9	366.8
F01003	344.5	363.6
F01004	376.3	380.1
F01005	318.9	334.2
F01006	360.2	385.1
F01007	336.5	365.0
F01008	310.2	325.8
F01009	372.8	394.9
F01010	309.2	332.3
F01011	411.2	396.8
F01012	354.1	355.9
Number of dams	12	12
Mean	345.3	362.5
S.D.	31.5	24.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 10-2. Body weights of dams during lactation

EMEE 62.5 mg/kg

Dam No.	Days of lactation	
	0	4
F02013	313.9	333.1
F02014	340.1	360.9
F02015	354.0	341.0
F02016	378.1	404.2
F02017	333.5	366.6
F02018	313.1	344.5
F02019	358.5	364.4
F02020	363.2	381.2
F02021	339.1	335.5
F02022	415.9	421.2
F02023	331.1	360.9
F02024	351.7	339.3
Number of dams	12	12
Mean	349.4	362.7
S.D.	28.5	27.8
Significance	NS	NS
Statistical method	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 10-3. Body weights of dams during lactation

EMEE 250 mg/kg

Dam No.	Days of lactation	
	0	4
F03025	358.0	338.0
F03026	325.7	352.6
F03027	365.3	378.4
F03028	274.4	286.0
F03029	355.9	344.6
F03030	308.0	337.6
F03031	320.5	310.3
F03032	349.2	336.5
F03034	353.0	358.2
F03035	345.8	337.8
Number of dams	10	10
Mean	335.6	338.0
S.D.	28.3	25.3
Significance	NS	NS
Statistical method	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 10-4. Body weights of dams during lactation

EMEE 1000 mg/kg

Dam No.	Days of lactation	
	0	4
F04037	368.2	Total litter loss
F04039	334.7	Total litter loss
F04041	342.4	Total litter loss
F04042	373.6	Total litter loss
F04044	365.3	Total litter loss
F04045	324.5	Total litter loss
F04047	337.6	Total litter loss
F04048	330.6	Total litter loss
Number of dams	8	
Mean	347.1	
S.D.	19.0	
Significance	NS	---
Statistical method	AN	NA

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of administration					
	1	7	14	29	35	41
M01001	30.1	29.3	28.0	29.1	27.1	30.6
M01002	32.3	30.0	29.6	34.7	28.4	30.5
M01003	31.9	29.8	26.7	28.0	25.2	25.7
M01004	42.2	30.5	31.0	31.1	32.5	31.5
M01005	30.6	25.5	26.9	22.0	25.1	28.5
M01006	27.4	24.5	27.9	34.6	32.2	29.2
M01007	29.6	32.1	30.1	31.9	31.1	31.4
M01008	29.6	24.9	23.0	28.3	22.9	26.6
M01009	32.6	32.0	31.0	33.6	27.8	30.6
M01010	32.1	29.6	32.5	34.3	34.0	35.2
M01011	27.4	22.1	25.9	26.3	28.0	27.7
M01012	28.7	27.0	26.8	33.7	30.1	29.3
Number of males	12	12	12	12	12	12
Mean	31.2	28.1	28.3	30.6	28.7	29.7
S.D.	3.9	3.2	2.7	4.0	3.4	2.5

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02013	28.9	26.5	27.0	27.5	30.4	29.0
M02014	29.1	25.7	28.2	29.3	27.6	26.9
M02015	28.7	23.2	26.3	24.4	27.3	27.8
M02016	30.7	29.7	28.2	29.3	26.6	27.2
M02017	37.3	28.9	30.4	30.4	31.7	28.6
M02018	36.1	30.0	32.2	28.0	31.8	29.6
M02019	32.3	25.7	28.6	34.9	35.3	36.7
M02020	28.9	23.8	22.2	27.7	29.3	28.7
M02021	29.6	25.1	24.8	28.2	26.6	27.2
M02022	28.0	25.9	24.6	27.2	24.8	25.9
M02023	34.4	27.0	28.0	31.6	31.5	34.5
M02024	27.0	25.3	26.3	24.5	23.5	26.3
Number of males	12	12	12	12	12	12
Mean	30.9	26.4	27.2	28.6	28.9	29.0
S.D.	3.4	2.2	2.7	2.9	3.4	3.3
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	AN	AN	AN	DU

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 250 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03025	31.4	29.2	34.6	34.5	33.1	32.2
M03026	32.2	33.6	29.7	28.0	30.8	29.9
M03027	28.8	28.3	23.2	27.0	28.0	24.4
M03028	32.6	29.4	31.6	27.8	29.3	31.8
M03029	32.2	28.9	28.1	25.1	29.1	28.2
M03030	29.3	27.5	28.7	27.1	26.1	24.9
M03031	30.3	29.0	28.1	29.5	29.9	31.3
M03032	27.5	30.1	23.5	27.3	26.8	28.7
M03033	28.4	26.6	29.9	30.5	28.7	26.6
M03034	30.0	29.8	32.9	29.3	27.2	30.5
M03035	35.5	30.3	29.0	28.2	26.3	27.8
M03036	27.0	26.4	29.4	21.8	24.7	31.4
Number of males	12	12	12	12	12	12
Mean	30.4	29.1	29.1	28.0	28.3	29.0
S.D.	2.5	1.9	3.3	3.0	2.3	2.7
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	AN	AN	AN	DU

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04037	24.1	22.8	24.3	27.0	25.7	22.6
M04038	21.6	25.5	25.3	27.6	24.8	21.1
M04039	28.2	23.7	25.2	27.0	29.6	27.5
M04040	29.1	24.9	27.8	31.2	28.4	31.0
M04041	25.0	28.5	29.5	28.5	27.5	28.1
M04042	23.8	26.9	26.4	29.5	24.9	28.2
M04043	24.5	29.9	30.5	26.7	26.0	26.5
M04044	22.1	25.3	24.6	24.5	22.7	23.5
M04045	29.6	29.2	26.1	27.6	26.5	27.0
M04046	28.8	28.3	33.2	34.0	32.7	30.9
M04047	19.2	27.1	26.5	24.6	21.2	22.8
M04048	24.0	25.6	27.6	30.7	27.5	28.1
Number of males	12	12	12	12	12	12
Mean	25.0	26.5	27.3	28.2	26.5	26.4
S.D.	3.3	2.2	2.7	2.7	3.1	3.2
Significance	**	NS	NS	NS	NS	*
Statistical method	DU	DU	AN	AN	AN	DU

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

NS: Not significantly different from the control group.

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of recovery	
	6	12
M01008	30.6	28.7
M01009	34.0	30.9
M01010	31.5	32.7
M01011	28.7	27.6
M01012	26.7	27.5
Number of males	5	5
Mean	30.3	29.5
S.D.	2.8	2.3

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Male No.	Days of recovery	
	6	12
M04044	26.5	25.1
M04045	31.5	29.5
M04046	32.8	32.8
M04047	29.0	26.4
M04048	33.1	28.2
Number of males	5	5
Mean	30.6	28.4
S.D.	2.8	3.0
Significance	NS	NS
Statistical method	TT	TT

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of administration		
	1	7	14
F01001	25.8	18.9	22.3
F01002	23.4	22.3	16.2
F01003	20.2	21.3	15.1
F01004	23.5	28.1	21.8
F01005	22.0	15.1	21.7
F01006	23.3	15.5	21.7
F01007	20.5	21.2	23.0
F01008	17.5	9.7	16.9
F01009	24.5	19.7	22.0
F01010	26.3	22.9	16.4
F01011	24.0	24.9	25.1
F01012	21.4	21.0	15.7
Number of females	12	12	12
Mean	22.7	20.1	19.8
S.D.	2.5	4.9	3.5

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 mg/kg

Female No.	Days of administration		
	1	7	14
F02013	16.1	24.0	18.8
F02014	19.6	21.5	21.7
F02015	21.7	22.5	17.0
F02016	26.8	20.7	25.7
F02017	19.8	22.9	21.6
F02018	17.7	21.9	23.7
F02019	16.5	20.0	25.7
F02020	16.3	21.6	22.9
F02021	23.9	15.8	23.4
F02022	25.9	20.3	27.2
F02023	24.2	27.0	23.2
F02024	19.7	14.1	23.9
Number of females	12	12	12
Mean	20.7	21.0	22.9
S.D.	3.8	3.4	2.9
Significance	NS	NS	NS
Statistical method	AN	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 250 mg/kg

Female No.	Days of administration						
	1	7	14	29	35	41	48
F03025	21.7	18.4	23.4				
F03026	23.4	22.6	24.0				
F03027	25.4	23.1	15.2				
F03028	18.4	17.5	21.0				
F03029	23.2	19.3	17.8				
F03030	18.7	20.4	18.5				
F03031	21.9	18.5	20.7				
F03032	20.4	16.3	19.1				
F03033	16.1	23.0	21.6				
F03034	22.0	22.3	23.9				
F03035	22.5	19.9	21.2				
F03036	24.7	24.3	17.9	22.3	15.9	21.1	22.9
Number of females	12	12	12				
Mean	21.5	20.5	20.4				
S.D.	2.7	2.6	2.7				
Significance	NS	NS	NS	---	---	---	---
Statistical method	AN	AN	AN	NA	NA	NA	NA

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Female No.	Days of administration		
	1	7	14
F04037	17.8	23.5	25.4
F04038	15.6	22.1	19.9
F04039	27.4	27.8	19.7
F04040	22.1	22.1	13.8
F04041	20.7	19.6	16.8
F04042	21.7	18.4	25.3
F04043	17.5	24.8	24.9
F04044	22.4	21.9	18.5
F04045	20.0	26.6	14.3
F04046	22.8	23.5	23.2
F04047	20.7	21.4	20.7
F04048	19.9	20.3	21.8
Number of females	12	12	12
Mean	20.7	22.7	20.4
S.D.	3.0	2.8	4.0
Significance	NS	NS	NS
Statistical method	AN	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of administration						
	1	7	14	21	29	35	41
F05049	22.0	28.4	27.9	24.8	24.2	27.6	19.9
F05050	25.2	24.4	22.2	25.2	25.7	25.7	21.5
F05051	25.8	16.4	22.4	25.7	24.5	16.6	21.8
F05052	17.6	20.0	22.2	22.0	20.0	17.3	18.4
F05053	21.7	21.4	23.3	19.1	19.6	25.9	19.0
F05054	11.9	20.3	17.6	21.0	15.8	21.4	17.6
F05055	20.8	20.6	20.7	17.7	20.5	20.2	18.6
F05056	20.8	19.0	15.1	19.3	14.1	18.9	27.0
F05057	25.2	22.7	21.3	23.8	23.2	21.6	18.9
F05058	20.6	16.5	22.0	24.8	24.1	22.8	21.7
Number of females	10	10	10	10	10	10	10
Mean	21.2	21.0	21.5	22.3	21.2	21.8	20.4
S.D.	4.1	3.6	3.4	2.9	3.9	3.7	2.7

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06059	21.7	18.8	15.2	24.4	21.0	23.4	17.7
F06060	14.1	12.8	20.7	22.5	23.1	22.9	19.1
F06061	18.9	16.9	20.3	22.1	22.3	23.2	18.6
F06062	21.5	21.4	15.5	21.9	20.1	24.6	14.5
F06063	20.3	20.1	18.6	13.0	22.5	18.8	17.8
F06064	23.1	18.1	26.6	27.2	16.3	22.2	19.9
F06065	12.0	13.9	18.9	24.6	23.1	21.4	22.2
F06066	19.2	21.5	22.8	13.8	18.1	18.1	11.1
F06067	12.9	14.7	20.5	20.3	18.8	17.5	14.8
F06068	16.0	13.8	20.1	14.7	25.6	20.5	16.9
Number of females	10	10	10	10	10	10	10
Mean	18.0	17.2	19.9	20.5	21.1	21.3	17.3
S.D.	4.0	3.3	3.3	4.9	2.8	2.4	3.1
Significance	NS	*	NS	NS	NS	NS	*
Statistical method	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of recovery	
	6	12
F05054	20.2	15.0
F05055	15.4	25.8
F05056	14.7	16.3
F05057	15.8	23.1
F05058	27.0	24.6
Number of females	5	5
Mean	18.6	21.0
S.D.	5.2	5.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Female No.	Days of recovery	
	6	12
F06064	25.5	22.0
F06065	20.9	24.5
F06066	18.7	14.0
F06067	17.9	20.7
F06068	15.2	20.8
Number of females	5	5
Mean	19.6	20.4
S.D.	3.9	3.9
Significance	NS	NS
Statistical method	TT	TT

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 13-1. Food consumption in dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	21.9	23.1	22.1	25.6
F01002	25.8	31.6	32.2	19.1
F01003	25.5	24.7	27.0	25.4
F01004	23.4	34.5	32.4	32.8
F01005	21.7	31.6	28.8	25.4
F01006	20.1	25.9	29.0	23.6
F01007	22.9	29.0	24.4	25.2
F01008	20.6	28.6	37.5	34.4
F01009	28.1	30.9	24.0	29.3
F01010	29.2	25.1	31.4	32.5
F01011	21.5	32.3	34.7	26.0
F01012	25.8	26.0	28.0	29.9
Number of dams	12	12	12	12
Mean	23.9	28.6	29.3	27.4
S.D.	3.0	3.6	4.6	4.4

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 13-2. Food consumption in dams during pregnancy

EMEE 62.5 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	16.4	31.0	29.1	22.9
F02014	23.0	27.2	29.2	25.2
F02015	22.5	23.9	32.9	17.1
F02016	26.3	35.9	35.2	32.8
F02017	20.2	23.7	26.2	23.1
F02018	19.3	24.6	25.8	24.7
F02019	21.3	32.2	26.6	23.5
F02020	21.8	30.5	30.6	26.4
F02021	24.6	28.4	27.4	22.7
F02022	26.0	32.1	29.0	31.6
F02023	23.9	35.1	32.2	11.2
F02024	28.1	29.4	25.7	24.4
Number of dams	12	12	12	12
Mean	22.8	29.5	29.2	23.8
S.D.	3.3	4.1	3.1	5.7
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 13-3. Food consumption in dams during pregnancy

EMEE 250 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03025	22.8	26.9	26.5	22.4
F03026	20.8	25.7	27.6	23.2
F03027	27.3	34.0	31.6	29.1
F03028	20.9	18.3	20.3	20.0
F03029	28.7	29.6	27.7	30.0
F03030	21.6	26.3	26.5	23.7
F03031	21.4	21.7	23.3	19.5
F03032	17.6	24.6	23.0	27.5
F03033	> 16.3	> 28.7	> 25.7	> 15.8
F03034	23.9	29.6	26.0	32.1
F03035	21.8	25.9	27.8	21.0
Number of dams	10	10	10	10
Mean	22.7	26.3	26.0	24.9
S.D.	3.3	4.3	3.2	4.5
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN

>: Excluded from analysis (not pregnant)

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 13-4. Food consumption in dams during pregnancy

EMEE 1000 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	23.2	32.4	30.5	27.2
F04038	16.8	24.6	24.1	21.6
F04039	21.7	24.7	29.3	29.8
F04040	> 18.4 >	> 25.7 >	> 12.9 >	> 18.1 >
F04041	26.0	26.7	34.0	22.2
F04042	21.3	30.0	31.1	22.5
F04043	> 23.0 >	> 31.7 >	> 16.1 >	> 8.6 >
F04044	25.6	31.6	14.9	33.1
F04045	25.5	25.5	14.6	27.1
F04046	> 22.4 >	> 26.2 >	> 24.7 >	> 16.9 >
F04047	19.4	27.3	23.2	26.1
F04048	19.6	25.9	31.3	21.5
Number of dams	9	9	9	9
Mean	22.1	27.6	25.9	25.7
S.D.	3.2	3.0	7.2	4.1
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN

>: Excluded from analysis (not pregnant)

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 14-1. Food consumption in dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation
	3
F01001	47.8
F01002	50.0
F01003	45.5
F01004	50.7
F01005	37.7
F01006	41.0
F01007	53.2
F01008	42.5
F01009	43.6
F01010	48.4
F01011	39.6
F01012	51.2
Number of dams	12
Mean	45.9
S.D.	5.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 14-2. Food consumption in dams during lactation

EMEE 62.5 mg/kg

Dam No.	Days of lactation
	3
F02013	45.8
F02014	47.7
F02015	27.4
F02016	61.0
F02017	42.9
F02018	47.9
F02019	36.9
F02020	44.8
F02021	35.8
F02022	42.5
F02023	42.0
F02024	45.6
Number of dams	12
Mean	43.4
S.D.	8.1
Significance	NS
Statistical method	DU

NS: Not significantly different from the control group.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 14-3. Food consumption in dams during lactation

EMEE 250 mg/kg

Dam No.	Days of lactation
	3
F03025	26.4
F03026	41.8
F03027	44.9
F03028	31.7
F03029	28.6
F03030	46.2
F03031	31.3
F03032	37.1
F03034	40.9
F03035	31.8
Number of dams	10
Mean	36.1
S.D.	7.0
Significance	**
Statistical method	DU

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.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male, Administration period

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

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (62.5 mg/kg)

Male, Administration period

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

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (250 mg/kg)

Male, Administration period

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

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (1000 mg/kg)

Male, Administration period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M04037	2	2	2	2	+	+	+
M04038	2	2	2	2	+	+	+
M04039	2	2	2	2	+	+	+
M04040	2	2	2	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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F01001	2	2	2	2	+	+	+
F01005	2	2	2	2	+	+	+
F01006	2	2	2	2	+	+	+
F01008	2	2	2	2	+	+	+
F01009	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (62.5 mg/kg)

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F02014	2	2	2	2	+	+	+
F02016	2	2	2	2	+	+	+
F02021	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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (250 mg/kg)

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F03026	2	2	2	2	+	+	+
F03031	2	2	2	2	+	+	+
F03032	2	2	2	2	+	+	+
F03034	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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 16-4. Functional findings of female rats at the last week of the dosing period

Control (vehicle: water for injection)

Female, satellite groups

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

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE (1000 mg/kg)

Female, satellite groups

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F06059	2	2	2	2	+	+	+
F06060	2	2	2	2	+	+	+
F06061	2	2	2	2	+	+	+
F06062	2	2	2	2	+	+	+
F06063	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 17-1. Assessment of grip strength of male rats at the last week of the dosing period

Control (vehicle: water for injection)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M01001	0.908	0.752
M01002	1.089	0.773
M01003	0.936	0.816
M01004	0.986	0.613
M01005	0.992	0.656
Number of males	5	5
Mean	0.982	0.722
S.D.	0.069	0.085

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 17-2. Assessment of grip strength of male rats at the last week of the dosing period

EMEE (62.5 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M02013	0.987	0.731
M02014	0.905	0.623
M02015	0.985	0.842
M02016	0.874	0.633
M02017	0.956	0.576
Number of males	5	5
Mean	0.941	0.681
S.D.	0.050	0.106

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 17-3. Assessment of grip strength of male rats at the last week of the dosing period

EMEE (250 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M03025	0.951	0.634
M03026	1.002	0.638
M03027	0.993	0.647
M03028	0.959	0.688
M03029	1.011	0.655
Number of males	5	5
Mean	0.983	0.652
S.D.	0.027	0.022

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 17-4. Assessment of grip strength of male rats at the last week of the dosing period

EMEE (1000 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M04037	1.063	0.732
M04038	1.035	0.613
M04039	0.978	0.567
M04040	0.952	0.637
M04041	1.030	0.830
Number of males	5	5
Mean	1.012	0.676
S.D.	0.045	0.105

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 18-1. Assessment of grip strength of female rats at the last week of the dosing period

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F01001	0.689	0.516
F01005	0.775	0.583
F01006	0.698	0.623
F01008	0.696	0.629
F01009	0.724	0.627
Number of females	5	5
Mean	0.716	0.596
S.D.	0.035	0.048

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 18-2. Assessment of grip strength of female rats at the last week of the dosing period

EMEE (62.5 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F02014	0.699	0.578
F02016	0.731	0.665
F02021	0.769	0.598
F02022	0.685	0.573
F02024	0.770	0.602
Number of females	5	5
Mean	0.731	0.603
S.D.	0.039	0.037

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 18-3. Assessment of grip strength of female rats at the last week of the dosing period

EMEE (250 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F03026	0.742	0.535
F03031	0.698	0.587
F03032	0.748	0.613
F03034	0.700	0.529
F03035	0.642	0.584
Number of females	5	5
Mean	0.706	0.570
S.D.	0.043	0.036

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 19-1. Assessment of grip strength of female rats at the last week of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F05049	0.750	0.625
F05050	0.870	0.589
F05051	0.754	0.605
F05052	0.728	0.581
F05053	0.702	0.641
Number of females	5	5
Mean	0.761	0.608
S.D.	0.064	0.025

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 19-2. Assessment of grip strength of female rats at the last week of the dosing period, satellite group

EMEE (1000 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F06059	0.723	0.565
F06060	0.765	0.656
F06061	0.724	0.726
F06062	0.703	0.599
F06063	0.760	0.663
Number of females	5	5
Mean	0.735	0.642
S.D.	0.027	0.062

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 20-1. Motor activity of male rats at the last week of the dosing period

Control (vehicle: water for injection)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1374	1334	1330	1081	5119	28	16	12	16	72
M01002	967	981	821	1027	3796	19	21	13	17	70
M01003	1174	1041	998	697	3910	36	40	32	12	120
M01004	1067	958	791	678	3494	21	27	18	14	80
M01005	798	768	437	93	2096	43	18	8	0	69
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1076	1016	875	715	3683	29	24	17	12	82
S.D.	217	205	326	394	1082	10	10	9	7	22

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 20-2. Motor activity of male rats at the last week of the dosing period

EMEE (62.5 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02013	1301	1079	993	864	4237	35	25	12	10	82
M02014	1219	956	731	655	3561	34	21	24	19	98
M02015	1331	1219	1102	1107	4759	36	28	18	16	98
M02016	1304	771	828	647	3550	28	5	5	5	43
M02017	1000	1011	907	808	3726	26	24	14	15	79
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1231	1007	912	816	3967	32	21	15	13	80
S.D.	136	165	144	188	524	4	9	7	6	22

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 20-3. Motor activity of male rats at the last week of the dosing period

EMEE (250 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03025	1928	1865	1783	1611	7187	37	48	27	8	120
M03026	1174	1104	1051	824	4153	35	23	23	12	93
M03027	1145	1007	920	781	3853	22	20	15	10	67
M03028	1145	1232	1178	982	4537	22	30	29	21	102
M03029	1531	1510	1350	958	5349	43	44	30	13	130
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1385	1344	1256	1031	5016	32	33	25	13	102
S.D.	345	347	335	335	1337	9	12	6	5	25

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 20-4. Motor activity of male rats at the last week of the dosing period

EMEE (1000 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04037	1162	1334	1191	632	4319	22	39	23	15	99
M04038	1102	874	694	745	3415	28	15	16	14	73
M04039	1003	845	730	231	2809	10	10	7	1	28
M04040	1314	1262	1233	893	4702	38	41	22	19	120
M04041	1063	934	600	529	3126	28	18	8	2	56
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1129	1050	890	606	3674	25	25	15	10	75
S.D.	119	230	298	249	804	10	14	8	8	36

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 21-1. Motor activity of female rats at the last week of the dosing period

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01001	1090	846	732	355	3023	29	21	18	3	71
F01005	1131	1037	801	473	3442	31	11	10	0	52
F01006	917	1120	640	361	3038	11	13	1	0	25
F01008	1031	903	627	571	3132	20	22	3	0	45
F01009	1333	1364	1060	1111	4868	66	59	10	17	152
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1100	1054	772	574	3501	31	25	8	4	69
S.D.	153	204	176	313	783	21	19	7	7	49

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 21-2. Motor activity of female rats at the last week of the dosing period

EMEE (62.5 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02014	1300	795	979	1147	4221	36	10	3	16	65
F02016	1159	697	567	0	2423	29	16	6	0	51
F02021	926	666	600	567	2759	24	7	4	1	36
F02022	1180	971	282	252	2685	24	7	1	0	32
F02024	1232	779	536	373	2920	39	14	2	0	55
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1159	782	593	468	3002	30	11	3	3	48
S.D.	141	119	250	432	705	7	4	2	7	14

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 21-3. Motor activity of female rats at the last week of the dosing period

EMEE (250 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03026	711	566	561	410	2248	16	9	10	4	39
F03031	1751	1687	1159	1392	5989	26	20	7	18	71
F03032	1215	1069	607	624	3515	25	43	10	18	96
F03034	1047	750	183	442	2422	17	14	0	0	31
F03035	1285	900	960	860	4005	62	24	13	18	117
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1202	994	694	746	3636	29	22	8	12	71
S.D.	379	429	379	403	1507	19	13	5	9	37

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 22-1. Motor activity of female rats at the last week of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05049	1297	995	1131	1089	4512	34	35	33	28	130
F05050	1334	1033	1116	865	4348	38	15	14	4	71
F05051	1242	1100	1199	1147	4688	36	24	15	19	94
F05052	1073	942	803	995	3813	24	32	21	33	110
F05053	1371	1294	1089	1034	4788	41	44	30	39	154
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1263	1073	1068	1026	4430	35	30	23	25	112
S.D.	117	136	153	107	384	6	11	9	14	32

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 22-2. Motor activity of female rats at the last week of the dosing period, satellite group

EMEE (1000 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06059	1196	1145	667	100	3108	21	22	14	1	58
F06060	1318	1282	869	286	3755	46	38	20	3	107
F06061	1297	1222	926	720	4165	31	33	17	17	98
F06062	1549	1421	1152	1577	5699	52	44	28	57	181
F06063	1308	1069	1034	557	3968	49	35	29	9	122
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1334	1228	930	648	4139	40	34	22	17	113
S.D.	130	135	182	572	958	13	8	7	23	45

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 23-1-1. Urinalysis in male rats

Control (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	7.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01002	8.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M01003	7.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01004	8.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01005	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
Protein,	-: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤													
Glucose,	-: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤													
Ketone,	-: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤													
Bilirubin,	-: negative; +: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤													
Occult blood,	-: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤													
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤													
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked													
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Crystals,	-: not observed; ±: a few; +: abundant													
Epithelial cells,	-: not observed; ±: a few; +: abundant													

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M01001	18.0	1.055	105.7	245.1	133.7	1.90	4.41	2.41
M01002	14.7	1.073	158.1	330.7 §	203.8	2.32	4.86	3.00
M01003	13.6	1.064	110.7	273.1	141.5	1.51	3.71	1.92
M01004	20.4	1.060	110.9	278.3	161.2	2.26	5.68	3.29
M01005	12.6	1.064	111.9	278.6	155.4	1.41	3.51	1.96
Number of males	5	5	5	5	5	5	5	5
Mean	15.9	1.063	119.5	281.2	159.1	1.88	4.43	2.52
S.D.	3.3	0.007	21.7	31.0	27.3	0.42	0.88	0.61

S.G.: Specific gravity

§, Remeasurement

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 23-1-2. Urinalysis in male rats

EMEE 62.5 mg/kg

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02013	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M02014	7.0	2+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M02015	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
M02016	7.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M02017	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	-	-
Protein,	-: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤													
Glucose,	-: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤													
Ketone,	-: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤													
Bilirubin,	-: negative; +: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤													
Occult blood,	-: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤													
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤													
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked													
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Crystals,	-: not observed; ±: a few; +: abundant													
Epithelial cells,	-: not observed; ±: a few; +: abundant													

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 23-1-2(continued). Urinalysis in male rats

EMEE 62.5 mg/kg

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M02013	14.1	1.065	107.8	280.2	134.9	1.52	3.95	1.90
M02014	13.6	1.063	97.4	257.5	146.1	1.32	3.50	1.99
M02015	24.1	1.044	86.6	214.0 §	118.3	2.09	5.16	2.85
M02016	19.7	1.051	106.6	217.6	127.2	2.10	4.29	2.51
M02017	16.4	1.056	113.6	235.1	124.5	1.86	3.86	2.04
Number of males	5	5	5	5	5	5	5	5
Mean	17.6	1.056	102.4	240.9	130.2	1.78	4.15	2.26
S.D.	4.4	0.009	10.6	27.9	10.7	0.35	0.63	0.41
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	AN	AN

S.G.: Specific gravity

§, Remeasurement

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 23-1-3. Urinalysis in male rats

EMEE 250 mg/kg

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03025	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
M03026	7.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M03027	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M03028	7.0	+	-	±	-	-	±	light yellow	-	-	-	-	+	-
M03029	7.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
Protein,	-: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤													
Glucose,	-: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤													
Ketone,	-: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤													
Bilirubin,	-: negative; +: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤													
Occult blood,	-: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤													
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤													
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked													
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Crystals,	-: not observed; ±: a few; +: abundant													
Epithelial cells,	-: not observed; ±: a few; +: abundant													

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 23-1-3(continued). Urinalysis in male rats

EMEE 250 mg/kg

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M03025	23.7	1.050	88.7	195.7	111.5	2.10	4.64	2.64
M03026	14.5	1.072	137.4	313.7 §	175.6	1.99	4.55	2.55
M03027	20.8	1.042	62.7	150.5	71.2	1.30	3.13	1.48
M03028	14.1	1.064	102.2	230.4	131.7	1.44	3.25	1.86
M03029	21.2	1.053	86.7	209.6	116.7	1.84	4.44	2.47
Number of males	5	5	5	5	5	5	5	5
Mean	18.9	1.056	95.5	220.0	121.3	1.73	4.00	2.20
S.D.	4.3	0.012	27.4	60.0	37.7	0.35	0.75	0.51
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	AN	AN

S.G.: Specific gravity

§, Remeasurement

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 23-1-4. Urinalysis in male rats

EMEE 1000 mg/kg

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04037	6.5	±	-	-	-	-	±	light yellow	-	-	-	-	-	-
M04038	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M04039	7.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M04040	6.5	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M04041	7.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
Protein,	-: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤													
Glucose,	-: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤													
Ketone,	-: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤													
Bilirubin,	-: negative; +: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤													
Occult blood,	-: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤													
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤													
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked													
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Crystals,	-: not observed; ±: a few; +: abundant													
Epithelial cells,	-: not observed; ±: a few; +: abundant													

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 23-1-4(continued). Urinalysis in male rats

EMEE 1000 mg/kg

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M04037	23.2	1.052	94.4	179.0	110.6	2.19	4.15	2.57
M04038	16.3	1.068	112.8	251.0	154.3	1.84	4.09	2.52
M04039	27.2	1.048	83.3	157.8	90.0	2.27	4.29	2.45
M04040	25.1	1.047	73.4	139.3	82.1	1.84	3.50	2.06
M04041	20.0	1.054	96.2	149.7	86.6	1.92	2.99	1.73
Number of males	5	5	5	5	5	5	5	5
Mean	22.4	1.054	92.0	175.4	104.7	2.01	3.80	2.27
S.D.	4.3	0.008	14.8	44.7	29.8	0.20	0.55	0.36
Significance	NS	NS	NS	**	*	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	AN	AN

S.G.: Specific gravity

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01008	8.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M01009	8.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M01010	8.0	±	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01011	7.5	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M01012	8.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
Protein,	-: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤													
Glucose,	-: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤													
Ketone,	-: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤													
Bilirubin,	-: negative; ±: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤													
Occult blood,	-: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤													
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤													
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked													
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Crystals,	-: not observed; ±: a few; +: abundant													
Epithelial cells,	-: not observed; ±: a few; +: abundant													

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M01008	13.3	1.062	106.5	272.9	134.4	1.42	3.63	1.79
M01009	16.3	1.063	127.7	289.8	163.8	2.08	4.72	2.67
M01010	17.4	1.062	139.3	268.0	163.1	2.42	4.66	2.84
M01011	21.0	1.042	85.1	189.1	104.5	1.79	3.97	2.19
M01012	18.6	1.043	73.2	190.7	103.5	1.36	3.55	1.93
Number of males	5	5	5	5	5	5	5	5
Mean	17.3	1.054	106.4	242.1	133.9	1.81	4.11	2.28
S.D.	2.8	0.011	27.8	48.3	29.7	0.45	0.56	0.46

S.G.: Specific gravity

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

URINE 1000 mg/eg														
Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04044	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
M04045	7.5	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
M04046	8.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M04047	7.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M04048	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
Protein,	-: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤													
Glucose,	-: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤													
Ketone,	-: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤													
Bilirubin,	-: negative; +: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤													
Occult blood,	-: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤													
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤													
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked													
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Crystals,	-: not observed; ±: a few; +: abundant													
Epithelial cells,	-: not observed; ±: a few; +: abundant													

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M04044	21.6	1.035	78.9	169.3	102.1	1.70	3.66	2.21
M04045	21.8	1.050	113.6	218.1	130.5	2.48	4.75	2.84
M04046	27.1	1.040	61.8	167.7	80.0	1.67	4.55	2.17
M04047	14.5	1.062	114.2	269.2	157.5	1.66	3.90	2.28
M04048	28.7	1.037	78.0	164.0	93.3	2.24	4.71	2.68
Number of males	5	5	5	5	5	5	5	5
Mean	22.7	1.045	89.3	197.6	112.7	1.95	4.31	2.44
S.D.	5.6	0.011	23.5	45.7	31.2	0.38	0.50	0.30
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

S.G.: Specific gravity

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Control (vehicle, water for injection)														
Female No.	pH	Protein	Glucose	Ketone	Quality					Urinary sediments				
					Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05049	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
F05050	7.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
F05051	7.0	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F05052	7.0	-	-	-	-	-	±	light yellow	-	-	-	-	±	-
F05053	7.0	-	-	-	-	-	±	light yellow	-	-	-	-	±	-

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
F05049	12.9	1.064	129.7	281.4	157.7	1.67	3.63	2.03
F05050	6.9	1.059	73.4	162.3	75.0	0.51	1.12	0.52
F05051	25.8	1.034	60.5	160.1	85.3	1.56	4.13	2.20
F05052	14.8	1.035	62.2	159.1	77.6	0.92	2.35	1.15
F05053	8.7	1.056	74.4	177.9	77.4	0.65	1.55	0.67
Number of females	5	5	5	5	5	5	5	5
Mean	13.8	1.050	80.0	188.2	94.6	1.06	2.56	1.31
S.D.	7.4	0.014	28.5	52.7	35.5	0.53	1.30	0.77

S.G.: Specific gravity

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Urine 1000 mg/kg														
Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06059	7.0	-	-	-	-	-	±	light yellow	-	-	-	-	±	-
F06060	6.5	±	-	±	-	-	±	light yellow	-	-	-	-	±	-
F06061	6.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	±
F06062	6.5	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
F06063	6.0	+	-	±	-	-	±	light yellow	-	-	-	-	-	-
Protein,	-: negative, ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤													
Glucose,	-: negative, ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤													
Ketone,	-: negative, ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤													
Bilirubin,	-: negative, ±: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤													
Occult blood,	-: negative, ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤													
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤													
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked													
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Crystals,	-: not observed; ±: a few; +: abundant													
Epithelial cells,	-: not observed; ±: a few; +: abundant													

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Female No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
F06059	14.0	1.054	92.2	171.2	81.8	1.29	2.40	1.15
F06060	11.0	1.068	127.2	247.3	130.1	1.40	2.72	1.43
F06061	14.7	1.058	111.4	222.4	136.1	1.64	3.27	2.00
F06062	16.7	1.057	89.3	209.7	112.6	1.49	3.50	1.88
F06063	14.6	1.060	94.0	226.8	130.6	1.37	3.31	1.91
Number of females	5	5	5	5	5	5	5	5
Mean	14.2	1.059	102.8	215.5	118.2	1.44	3.04	1.67
S.D.	2.1	0.005	16.1	28.2	22.2	0.13	0.46	0.37
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AW	TT	TT	TT	TT	AW	TT	TT

S.G.: Specific gravity

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05054	8.0	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F05055	8.0	-	-	-	-	-	±	light yellow	-	-	-	-	±	-
F05056	7.5	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F05057	7.5	-	-	-	-	-	±	light yellow	-	-	-	-	±	-
F05058	8.0	-	-	-	-	-	±	light yellow	-	-	-	-	±	-
Protein,	-: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤													
Glucose,	-: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤													
Ketone,	-: negative; ±(5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤													
Bilirubin,	-: negative; +: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤													
Occult blood,	-: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤													
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤													
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked													
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Crystals,	-: not observed; ±: a few; +: abundant													
Epithelial cells,	-: not observed; ±: a few; +: abundant													

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
F05054	9.3	1.064	94.1	271.1	155.7	0.88	2.52	1.45
F05055	16.4	1.045	108.9	212.3	124.6	1.79	3.48	2.04
F05056	11.0	1.059	123.1	289.1	166.2	1.35	3.18	1.83
F05057	16.2	1.052	110.5	251.2	139.7	1.79	4.07	2.26
F05058	12.0	1.054	114.1	257.8	155.0	1.37	3.09	1.86
Number of females	5	5	5	5	5	5	5	5
Mean	13.0	1.055	110.1	256.3	148.2	1.44	3.27	1.89
S.D.	3.2	0.007	10.5	28.5	16.2	0.38	0.57	0.30

S.G.: Specific gravity

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Urinalysis														
Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06064	8.0	-	-	-	-	-	±	light yellow	-	-	-	-	±	-
F06065	7.0	-	-	-	-	-	±	light yellow	-	-	-	-	±	-
F06066	6.5	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F06067	7.0	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F06068	6.0	-	-	-	-	2+	±	light yellow	-	-	-	-	±	±
Protein,	-: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤													
Glucose,	-: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤													
Ketone,	-: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤													
Bilirubin,	-: negative; +: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤													
Occult blood,	-: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤													
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤													
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked													
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field													
Crystals,	-: not observed; ±: a few; +: abundant													
Epithelial cells,	-: not observed; ±: a few; +: abundant													

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Female No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
F06064	12.7	1.044	93.1	153.8	90.5	1.18	1.95	1.15
F06065	12.9	1.049	96.1	199.9	105.6	1.24	2.58	1.36
F06066	19.2	1.035	87.2	160.7	95.4	1.67	3.09	1.83
F06067	15.7	1.026	39.0	66.8	35.0	0.61	1.05	0.55
F06068	16.2	1.041	86.3	191.9	100.4	1.40	3.11	1.63
Number of females	5	5	5	5	5	5	5	5
Mean	15.3	1.039	80.3	154.6	85.4	1.22	2.36	1.30
S.D.	2.7	0.009	23.5	52.9	28.7	0.39	0.87	0.49
Significance	NS	*	*	**	**	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

S.G.: Specific gravity

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																
Male No.	RBC	HGB	Hematocrit	MCV	MCH	MCHC	Platelet	PT	APTT	WBC	Neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte	Reticulocyte
	10000/ μ L	g/dL	%	fL	pg	g/dL	10000/ μ L	sec.	sec.	100/ μ L	%	%	%	%	%	%
M01001	831	15.3	43.6	52.5	18.4	35.1	106.5	19.4	27.8	97.1	14.2	1.5	0.1	4.0	80.2	3.73
M01002	936	15.7	43.8	46.8	16.8	35.8	99.8	20.1	23.8	114.2	23.2	1.1	0.0	5.0	70.7	2.88
M01003	787	14.7	43.2	54.9	18.7	34.0	91.0	20.1	27.0	72.0	17.6	1.8	0.1	3.6	76.9	3.52
M01004	872	14.7	42.4	48.6	16.9	34.7	122.3	26.1	26.1	64.8	21.2	3.2	0.0	4.3	71.3	3.75
M01005	855	15.4	45.1	52.7	18.0	34.1	102.1	24.4	30.5	75.8	15.8	1.3	0.0	4.4	78.5	3.12
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	856	15.2	43.6	51.1	17.8	34.7	104.3	22.0	27.0	84.8	18.4	1.8	0.0	4.3	75.5	3.40
S.D.	55	0.4	1.0	3.3	0.9	0.7	11.5	3.0	2.4	20.4	3.7	0.8	0.1	0.5	4.3	0.39

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 mg/kg

Male No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M02013	832	14.4	40.9	49.2	17.3	35.2	114.5	17.7	25.7	112.6	26.7	1.8	0.0	4.6	66.9	3.19
M02014	870	14.6	40.9	47.0	16.8	35.7	114.1	21.8	27.2	101.3	22.2	2.2	0.0	3.9	71.7	2.55
M02015	847	15.3	43.6	51.5	18.1	35.1	99.8	19.2	28.1	70.4	10.8	1.7	0.0	4.1	83.4	3.06
M02016	874	16.1	45.8	52.4	18.4	35.2	81.2	26.0	28.6	60.8	14.6	2.0	0.0	3.8	79.6	2.50
M02017	924	15.6	44.4	48.1	16.9	35.1	114.5	35.0	34.1	65.5	21.2	1.8	0.0	6.3	70.7	2.92
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	869	15.2	43.1	49.6	17.5	35.3	104.8	23.9	28.7	82.1	19.1	1.9	0.0	4.5	74.5	2.84
S.D.	35	0.7	2.2	2.3	0.7	0.3	14.6	6.9	3.2	23.3	6.3	0.2	0.0	1.0	6.8	0.31
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	DU	AN	AN	DU	AN	AN	DU	AN	AN	KW	AN	AN	AN	DU

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 250 mg/kg

Male No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M03025	845	15.0	43.2	51.1	17.8	34.7	93.9	31.9	32.9	66.4	10.4	1.7	0.0	6.0	81.9	3.12
M03026	821	14.9	43.3	52.7	18.1	34.4	82.5	18.4	23.9	88.8	19.8	1.4	0.0	4.4	74.4	2.51
M03027	811	14.6	43.4	53.5	18.0	33.6	96.7	24.2	30.5	92.4	11.7	1.6	0.0	4.0	82.7	2.30
M03028	854	14.5	41.3	48.4	17.0	35.1	114.3	31.2	30.6	90.1	14.9	1.4	0.0	5.7	78.0	2.63
M03029	853	14.9	42.8	50.2	17.5	34.8	110.8	33.2	27.9	86.3	16.1	1.5	0.0	4.5	77.9	2.38
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	837	14.8	42.8	51.2	17.7	34.5	99.6	27.8	29.2	84.8	14.6	1.5	0.0	4.9	79.0	2.59
S.D.	20	0.2	0.9	2.0	0.4	0.6	13.0	6.3	3.4	10.5	3.7	0.1	0.0	0.9	3.4	0.32
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**
Statistical method	AN	DU	DU	AN	AN	DU	AN	AN	DU	AN	AN	KW	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.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Male No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M04037	789	13.9	41.4	52.5	17.6	33.6	72.2	19.6	25.9	60.4	31.6	0.2	0.0	5.5	62.7	1.76
M04038	790	13.5	39.7	50.3	17.1	34.0	99.5	19.1	21.8	39.4	22.3	0.3	0.0	5.8	71.6	2.55
M04039	792	14.2	41.7	52.7	17.9	34.1	70.0	15.1	20.2	67.9	10.4	2.4	0.0	5.0	82.2	1.57
M04040	828	14.0	40.6	49.0	16.9	34.5	69.5	26.9	26.9	60.9	20.0	0.5	0.0	5.9	73.6	2.07
M04041	836	13.7	40.7	48.7	16.4	33.7	110.2	17.7	23.1	128.7	6.6	0.2	0.1	4.4	88.7	1.61
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	807	13.9	40.8	50.6	17.2	34.0	84.3	19.7	23.6	71.5	18.2	0.7	0.0	5.3	75.8	1.91
S.D.	23	0.3	0.8	1.9	0.6	0.4	19.2	4.4	2.8	33.7	9.9	0.9	0.0	0.6	10.0	0.41
Significance	NS	**	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**
Statistical method	AN	DU	DU	AN	AN	DU	AN	AN	DU	AN	AN	KW	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.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																
Male No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M01008	831	15.0	42.7	51.4	18.1	35.1	92.8	20.5	22.2	79.0	15.3	0.6	0.0	3.0	81.1	3.73
M01009	846	14.6	43.0	50.8	17.3	34.0	99.5	20.7	23.0	83.5	15.0	1.7	0.0	1.9	81.4	3.36
M01010	819	15.0	43.7	53.4	18.3	34.3	87.2	22.4	24.0	70.8	23.6	2.4	0.0	3.7	70.3	4.14
M01011	819	15.1	43.2	52.7	18.4	35.0	116.9	26.1	24.5	51.3	13.7	2.1	0.2	3.9	80.1	2.89
M01012	832	14.2	41.4	49.8	17.1	34.3	104.2	22.6	27.2	52.3	14.2	1.3	0.0	3.4	81.1	2.97
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	829	14.8	42.8	51.6	17.8	34.5	100.1	22.5	24.2	67.4	16.4	1.6	0.0	3.2	78.8	3.42
S.D.	11	0.4	0.9	1.4	0.6	0.5	11.4	2.2	1.9	14.9	4.1	0.7	0.1	0.8	4.8	0.52

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Male No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M04044	838	14.7	42.8	51.1	17.5	34.3	100.3	28.6	26.1	53.6	14.4	3.0	0.2	2.2	80.2	3.75
M04045	802	13.0	38.5	48.0	16.2	33.8	115.3	13.1	19.5	78.3	19.7	1.5	0.0	2.7	76.1	3.60
M04046	837	14.1	40.1	47.9	16.8	35.2	121.0	18.5	22.1	60.2	15.0	1.7	0.0	3.7	79.6	2.85
M04047	878	14.1	40.3	45.9	16.1	35.0	93.5	25.5	27.5 §	63.0	37.5	1.7	0.0	3.7	57.1	3.67
M04048	892	14.7	43.7	49.0	16.5	33.6	80.1	36.2	29.5 §	42.3	42.3	3.1	0.0	2.4	52.2	2.99
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	849	14.1	41.1	48.4	16.6	34.4	102.0	24.4	24.9	59.5	25.8	2.2	0.0	2.9	69.0	3.37
S.D.	36	0.7	2.1	1.9	0.6	0.7	16.5	9.0	4.1	13.2	13.2	0.8	0.1	0.7	13.3	0.42
Significance	NS	NS	NS	*	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AW	TT	TT	TT	TT	TT	TT	AW	TT	TT	AW	TT	TT	TT	TT	TT

§. Remeasurement

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

NS: Not significantly different from the control group.

AW: Analysis by Aspin-Welch t-test.

TT: Analysis by Student's t-test.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																
Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F01001	686	12.8	38.5	56.1	18.7	33.2	119.7	14.1	19.9	120.4	32.7	0.9	0.0	2.5	63.9	7.39
F01005	723	13.6	40.8	56.4	18.8	33.3	127.3	14.1	17.4	117.5	42.9	0.9	0.0	6.7	49.5	8.42
F01006	675	12.9	38.4	56.9	19.1	33.6	109.0	14.8	19.9	108.1	29.0	0.7	0.0	3.8	66.5	7.43
F01008	637	13.1	40.6	63.7	20.6	32.3	122.3	13.0	18.1	130.1	36.5	0.4	0.0	4.4	58.7	12.99
F01009	639	12.3	36.5	57.1	19.2	33.7	114.2	13.1	17.4	124.7	32.5	0.8	0.1	4.1	62.5	6.77
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	672	12.9	39.0	58.0	19.3	33.2	118.5	13.8	18.5	120.2	34.7	0.7	0.0	4.3	60.2	8.60
S.D.	36	0.5	1.8	3.2	0.8	0.6	7.1	0.8	1.3	8.2	5.3	0.2	0.0	1.5	6.6	2.52

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 mg/kg

Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F02014	670	13.6	40.0	59.7	20.3	34.0	97.4	14.2	16.7	97.3	21.6	0.9	0.0	3.1	74.4	7.77
F02016	707	13.5	40.3	57.0	19.1	33.5	122.5	14.3	19.3	125.4	19.0	1.4	0.0	4.4	75.2	7.58
F02021	698	12.8	38.1	54.6	18.3	33.6	136.4	13.6	20.3	178.0	41.6	0.9	0.1	4.4	53.0	6.10
F02022	663	12.7	36.9	55.7	19.2	34.4	147.8	12.2	19.1	101.3	56.4	0.5	0.0	5.9	37.2	8.26
F02024	683	13.5	41.0	60.0	19.8	32.9	139.0	13.9	20.0	69.4	31.0	0.3	0.0	5.6	63.1	11.33
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	684	13.2	39.3	57.4	19.3	33.7	128.6	13.6	19.1	114.3	33.9	0.8	0.0	4.7	60.6	8.21
S.D.	18	0.4	1.7	2.4	0.8	0.6	19.7	0.9	1.4	40.8	15.4	0.4	0.0	1.1	15.9	1.92
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	KW	AN	KW	KW	KW	KW	AN	AN	AN	AN

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 250 mg/kg

Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F03026	637	12.1	36.9	57.9	19.0	32.8	129.6	14.1	17.7	123.5	26.7	0.6	0.0	3.1	69.6	9.81
F03031	630	11.7	35.3	56.0	18.6	33.1	130.1	13.5	18.1	112.6	39.6	0.4	0.0	3.3	56.7	7.91
F03032	738	13.4	40.3	54.6	18.2	33.3	118.7	13.6	18.1	120.0	35.2	3.2	0.0	4.4	57.2	5.20
F03034	660	12.6	37.7	57.1	19.1	33.4	127.9	14.1	17.9	95.4	35.0	0.9	0.1	4.4	59.6	10.24
F03035	662	12.2	37.1	56.0	18.4	32.9	128.8	15.1	18.5	94.9	30.5	0.5	0.0	4.1	64.9	6.70
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	665	12.4	37.5	56.3	18.7	33.1	127.0	14.1	18.1	109.3	33.4	1.1	0.0	3.9	61.6	7.97
S.D.	43	0.6	1.8	1.3	0.4	0.3	4.7	0.6	0.3	13.5	4.9	1.2	0.0	0.6	5.5	2.11
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	KW	AN	KW	KW	KW	KW	AN	AN	AN	AN

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																
Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F05049	791	15.6	43.4	54.9	19.7	35.9	81.4	11.9	16.6	89.4	11.3	1.1	0.1	2.8	84.7	3.29
F05050	795	14.7	41.4	52.1	18.5	35.5	101.9	13.3	17.2	81.1	14.1	1.6	0.0	4.3	80.0	2.01
F05051	742	14.2	40.7	54.9	19.1	34.9	112.8	12.5	18.4	96.7	10.5	1.2	0.0	2.3	86.0	3.55
F05052	839	14.7	41.4	49.3	17.5	35.5	112.8	12.4	20.8	42.2	7.3	1.9	0.0	2.4	88.4	2.05
F05053	758	14.6	41.6	54.9	19.3	35.1	94.0	13.7	18.5	35.8	17.0	3.1	0.0	2.0	77.9	4.02
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	785	14.8	41.7	53.2	18.8	35.4	100.6	12.8	18.3	69.0	12.0	1.8	0.0	2.8	83.4	2.98
S.D.	38	0.5	1.0	2.5	0.9	0.4	13.3	0.7	1.6	28.1	3.7	0.8	0.0	0.9	4.3	0.91

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F06059	781	14.4	41.8	53.5	18.4	34.4	65.8	13.6	17.0	80.6	10.0	1.0	0.0	3.8	85.2	1.48
F06060	837	14.4	40.9	48.9	17.2	35.2	50.5	13.6	18.0	43.1	10.0	2.1	0.0	3.7	84.2	1.94
F06061	772	13.2	38.6	50.0	17.1	34.2	90.3	13.3	16.7	67.0	13.0	0.7	0.0	3.0	83.3	1.47
F06062	730	13.2	38.9	53.3	18.1	33.9	72.6	13.3	21.8	84.4	9.0	1.4	0.0	2.3	87.3	1.42
F06063	719	13.2	38.3	53.3	18.4	34.5	78.9	13.3	17.6	69.8	12.5	1.3	0.0	5.0	81.2	1.40
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	768	13.7	39.7	51.8	17.8	34.4	71.6	13.4	18.2	69.0	10.9	1.3	0.0	3.6	84.2	1.54
S.D.	47	0.7	1.6	2.2	0.6	0.5	14.9	0.2	2.1	16.2	1.7	0.5	0.0	1.0	2.3	0.22
Significance	NS	*	*	NS	NS	**	*	NS	NS	NS	NS	NS	NS	NS	NS	*
Statistical method	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	AW

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																
Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F05054	771	14.0	39.9	51.8	18.2	35.1	97.0	13.4	16.6	35.2	16.4	2.6	0.0	5.7	75.3	2.93
F05055	804	15.2	44.6	55.5	18.9	34.1	97.6	12.1	18.3	33.7	10.9	1.8	0.0	4.2	83.1	3.82
F05056	813	14.5	41.4	50.9	17.8	35.0	88.4	12.9	17.3	37.2	10.4	1.9	0.0	1.9	85.8	2.42
F05057	802	14.6	41.4	51.6	18.2	35.3	108.8	13.0	20.2	53.6	17.3	3.4	0.0	5.8	73.5	3.29
F05058	771	14.1	40.0	51.9	18.3	35.3	100.8	11.7	16.6	40.1	19.5	2.0	0.0	5.2	73.3	2.32
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	792	14.5	41.5	52.3	18.3	35.0	98.5	12.6	17.8	40.0	14.9	2.3	0.0	4.6	78.2	2.96
S.D.	20	0.5	1.9	1.8	0.4	0.5	7.4	0.7	1.5	8.0	4.0	0.7	0.0	1.6	5.8	0.62

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F06064	815	15.0	42.4	52.0	18.4	35.4	108.7	13.0	18.4	43.7	22.4	2.1	0.0	3.2	72.3	2.73
F06065	846	14.9	42.9	50.7	17.6	34.7	78.7	13.2	18.0	40.3	11.9	3.0	0.0	3.5	81.6	1.09
F06066	796	14.3	40.8	51.3	18.0	35.0	101.2	13.2	22.2	29.2	13.6	2.1	0.0	2.1	82.2	2.25
F06067	813	14.3	41.7	51.3	17.6	34.3	99.5	12.4	16.9	23.0	21.7	2.6	0.0	2.2	73.5	2.43
F06068	790	14.5	41.6	52.7	18.4	34.9	121.2	13.2	18.4	37.2	19.4	1.6	0.0	3.5	75.5	3.76
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	812	14.6	41.9	51.6	18.0	34.9	101.9	13.0	18.8	34.7	17.8	2.3	0.0	2.9	77.0	2.45
S.D.	22	0.3	0.8	0.8	0.4	0.4	15.5	0.3	2.0	8.5	4.8	0.5	0.0	0.7	4.6	0.96
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

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01001	5.7	3.6	1.71	152	37	34	70	70	36	0	183	9.8	16	0.5	0.06	539
M01002	5.8	3.8	1.90	125	40	45	79	70	35	0	58	14.4	14	0.4	0.07	465
M01003	5.9	3.6	1.57	129	44	27	69	54	22	0	115	8.1	14	0.5	0.06	613
M01004	5.8	3.7	1.76	124	34	56	65	56	30	0	175	17.0	13	0.4	0.05	523
M01005	5.6	3.4	1.55	128	29	42	67	60	21	0	38	7.4	14	0.5	0.05	679
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.6	1.70	132	37	41	70	62	29	0	114	11.3	14	0.5	0.06	564
S.D.	0.1	0.1	0.14	12	6	11	5	8	7	0	66	4.2	1	0.1	0.01	83

Control (vehicle: water for injection)					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01001	6.0	9.2	144.2	4.08	105.6
M01002	5.2	9.5	144.5	3.71	106.3
M01003	5.6	9.1	146.7	3.99	106.1
M01004	5.6	9.5	146.4	3.79	108.1
M01005	5.8	9.3	145.3	3.95	105.6
Number of males	5	5	5	5	5
Mean	5.6	9.3	145.4	3.90	106.3
S.D.	0.3	0.2	1.1	0.15	1.0

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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	5.8	3.6	1.64	141	47	55	84	64	33	0	110	6.7	16	0.5	0.05	466
M02014	5.5	3.5	1.75	142	34	38	66	67	29	0	355	5.7	14	0.5	0.05	503
M02015	5.6	3.6	1.80	120	48	19	77	54	25	0	85	4.9	17	0.5	0.05	713
M02016	5.4	3.5	1.84	140	37	68	75	56	29	0	252	4.9	12	0.4	0.04	477
M02017	4.8	3.2	2.00	139	41	49	76	74	36	0	51	6.2	14	0.4	0.05	421
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.5	1.81	136	41	46	76	63	30	0	171	5.7	15	0.5	0.05	516
S.D.	0.4	0.2	0.13	9	6	18	6	8	4	0	128	0.8	2	0.1	0.00	114
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN	AN	AN	KW	DU	AN	DU	DU	AN	AN	DU

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).

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.

EMEE 62.5 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M02013	6.1	9.5	145.2	4.16	105.8
M02014	5.7	9.3	145.6	3.67	107.2
M02015	6.3	9.2	145.8	3.86	108.4
M02016	6.4	9.4	147.0	3.94	107.4
M02017	7.1	9.2	146.0	3.73	107.0
Number of males	5	5	5	5	5
Mean	6.3	9.3	145.9	3.87	107.2
S.D.	0.5	0.1	0.7	0.19	0.9
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	KW	DU

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).

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 250 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M03025	5.4	3.5	1.84	158	36	30	68	66	34	0	65	10.1	16	0.5	0.07	415
M03026	5.4	3.6	2.00	148	43	55	83	52	24	0	49	16.5	14	0.4	0.06	662
M03027	5.5	3.7	2.06	147	39	26	71	49	23	0	219	11.9	14	0.4	0.04	471
M03028	5.2	3.4	1.89	142	39	32	72	70	34	0	103	13.0	14	0.4	0.09	460
M03029	5.4	3.6	2.00	140	37	45	75	61	33	0	118	6.7	13	0.5	0.05	465
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.6	1.96	147	39	38	74	60	30	0	111	11.6	14	0.4	0.06	495
S.D.	0.1	0.1	0.09	7	3	12	6	9	6	0	67	3.6	1	0.1	0.02	96
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN	AN	AN	KW	DU	AN	DU	DU	AN	AN	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

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

EMEE 250 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M03025	6.0	8.9	144.1	3.87	105.8
M03026	5.1	9.4	144.8	4.06	107.2
M03027	6.0	9.2	145.6	3.83	105.4
M03028	5.9	9.1	145.1	4.06	107.7
M03029	5.7	9.2	145.2	3.84	107.2
Number of males	5	5	5	5	5
Mean	5.7	9.2	145.0	3.93	106.7
S.D.	0.4	0.2	0.6	0.12	1.0
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	KW	DU

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 27-1-4. Biochemical findings of male rats at the end of the dosing period

EMEE 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	5.7	3.8	2.00	144	52	14	86	73	45	2	76	7.9	19	0.6	0.07	253
M04038	5.4	3.8	2.38	152	33	30	69	90	71	1	71	16.6	15	0.6	0.07	499
M04039	5.2	3.2	1.60	109	41	17	70	57	29	1	57	7.3	16	0.5	0.06	324
M04040	5.1	3.2	1.68	134	40	16	71	105	132	2	109	10.1	19	0.4	0.06	290
M04041	5.3	3.4	1.79	141	51	55	96	68	47	0	198	9.9	16	0.5	0.10	424
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.3	3.5	1.89	136	43	26	78	79	65	1	102	10.4	17	0.5	0.07	358
S.D.	0.2	0.3	0.31	16	8	17	12	19	40	1	57	3.7	2	0.1	0.02	101
Significance	*	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	NS	*	NS	NS	*
Statistical method	DU	AN	AN	AN	AN	AN	AN	AN	KW	DU	AN	DU	DU	AN	AN	DU

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).

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.

EMEE 1000 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04037	4.8	9.2	143.0	4.08	104.5
M04038	6.3	9.5	141.7	8.80 §	104.4
M04039	5.5	9.2	144.6	3.82	105.3 §
M04040	6.2	8.8	144.7	3.88	106.4
M04041	5.9	9.4	144.2	3.91	105.9
Number of males	5	5	5	5	5
Mean	5.7	9.2	143.6	4.90	105.3
S.D.	0.6	0.3	1.3	2.18	0.9
Significance	NS	NS	*	NS	NS
Statistical method	AN	AN	DU	KW	DU

§. Remeasurement

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).

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01008	5.6	3.6	1.80	147	33	14	59	75	45	0	139	8.5	17	0.7	0.06	412
M01009	5.5	3.6	1.89	141	28	28	60	64	25	0	65	6.3	14	0.5	0.07	592
M01010	5.2	3.5	2.06	140	38	20	64	73	27	0	194	8.5	15	0.5	0.05	334
M01011	5.4	3.6	2.00	123	43	18	67	65	27	0	61	9.3	13	0.5	0.06	517
M01012	5.5	3.4	1.62	133	44	13	69	64	25	0	143	10.9	14	0.6	0.04	464
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.5	1.87	137	37	19	64	68	30	0	120	8.7	15	0.6	0.06	464
S.D.	0.2	0.1	0.17	9	7	6	4	5	9	0	57	1.7	2	0.1	0.01	98

Control (vehicle: water for injection)					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01008	6.3	8.6	143.7	3.92	105.8
M01009	5.9	8.3	143.3	3.88	110.0
M01010	5.7	8.5	146.0	3.89	109.5
M01011	5.5	8.2	145.0	3.83	109.4
M01012	5.2	8.3	146.6	3.69	110.1
Number of males	5	5	5	5	5
Mean	5.7	8.4	144.9	3.84	109.0
S.D.	0.4	0.2	1.4	0.09	1.8

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04044	5.4	3.6	2.00	192	41	19	69	59	26	0	82	11.4	13	0.6	0.06	507
M04045	6.1	3.7	1.54	141	51	19	73	63	30	0	107	11.5	15	0.6	0.05	447
M04046	5.6	3.6	1.80	121	65	35	90	74	25	0	62	5.7	14	0.5	0.07	438
M04047	5.3	3.4	1.79	132	38	19	66	81	32	0	91	10.0	16	0.6	0.05	455
M04048	5.9	3.7	1.68	130	52	18	77	75	31	0	298	9.8	16	0.6	0.07	419
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.6	1.76	143	49	22	75	70	29	0	128	9.7	15	0.6	0.06	453
S.D.	0.3	0.1	0.17	28	11	7	9	9	3	0	96	2.4	1	0.0	0.01	33
Significance	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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.

EMEE 1000 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04044	5.7	8.6	146.2	4.29	108.1
M04045	5.9	8.8	143.1	4.11	107.6
M04046	5.1	8.9	144.6	3.91	107.1 §
M04047	5.0	8.0	145.1	3.66	108.8
M04048	4.5	8.3	145.8	3.77	109.8
Number of males	5	5	5	5	5
Mean	5.2	8.5	145.0	3.95	108.3
S.D.	0.6	0.4	1.2	0.25	1.1
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

§, Remeasurement

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F01001	5.8	4.1	2.41	121	45	50	97	85	38	0	107	11.9	18	0.6	0.10	242
F01005	6.0	4.1	2.16	109	56	20	113	103	43	0	76	20.0	14	0.5	0.12	255
F01006	5.4	3.6	2.00	124	36	43	83	72	35	0	94	17.6	18	0.5	0.09	170
F01008	6.6	4.4	2.00	129	67	53	141	114	53	0	143	14.5	14	0.6	0.10	230
F01009	6.3	4.4	2.32	117	66	20	133	150	75	0	243	9.2	20	0.6	0.05	255
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.0	4.1	2.18	120	54	37	113	105	49	0	133	14.6	17	0.6	0.09	230
S.D.	0.5	0.3	0.19	8	13	16	24	30	16	0	66	4.3	3	0.1	0.03	35

Control (vehicle: water for injection)					
Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F01001	6.6	9.0	143.8	3.66	108.1
F01005	6.8	9.4	143.1	4.21	111.0
F01006	6.3	8.5	141.3	4.26	107.5
F01008	8.0	9.5	142.5	3.88	106.0
F01009	6.0	9.0	143.7	3.65	107.1
Number of females	5	5	5	5	5
Mean	6.7	9.1	142.9	3.93	107.9
S.D.	0.8	0.4	1.0	0.29	1.9

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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	5.4	3.6	2.00	114	42	47	92	100	52	0	90	13.3	19	0.5	0.11	387
F02016	5.9	3.9	1.95	126	55	52	114	78	49	0	122	19.5	18	0.5	0.08	236
F02021	6.1	3.9	1.77	131	76	31	130	94	49	0	77	5.8	12	0.5	0.08	180
F02022	6.3	4.3	2.15	114	65	27	133	167	88	0	137	28.5	16	0.5	0.08	230
F02024	6.2	4.2	2.10	146	48	50	100	72	45	0	89	47.9	15	0.5	0.08	170
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.0	4.0	1.99	126	57	41	114	102	57	0	103	23.0	16	0.5	0.09	241
S.D.	0.4	0.3	0.15	13	14	12	18	38	18	0	25	16.2	3	0.0	0.01	87
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	DU	AN	AN

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

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

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

EMEE 62.5 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F02014	6.9	8.9	141.2	3.80	107.2
F02016	5.3	8.8	142.2	3.72	108.5
F02021	6.8	9.5	144.1	3.66	109.0
F02022	5.8	8.8	141.9	3.14	103.4
F02024	5.7	9.3	143.4	3.69	108.4
Number of females	5	5	5	5	5
Mean	6.1	9.1	142.6	3.60	107.3
S.D.	0.7	0.3	1.2	0.26	2.3
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 28-1-3. Biochemical findings of female rats at the end of the dosing period

EMEE 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	Direct bilirubin mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F03026	5.9	3.9	1.95	120	53	34	99	71	37	0	58	12.2	15	0.5	0.08	215
F03031	5.6	3.8	2.11	133	64	37	108	72	45	0	160	8.2	10	0.5	0.08	300
F03032	5.8	3.9	2.05	129	54	29	107	94	43	0	61	11.0	17	0.5	0.08	235
F03034	5.9	4.0	2.11	122	36	30	80	93	28	0	84	10.4	13	0.5	0.09	213
F03035	5.7	3.7	1.85	118	61	27	105	99	34	0	247	8.0	13	0.5	0.07	181
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.9	2.01	124	54	31	100	86	37	0	122	10.0	14	0.5	0.08	229
S.D.	0.1	0.1	0.11	6	11	4	12	13	7	0	81	1.8	3	0.0	0.01	44
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	DU	AN	AN

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

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

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

EMEE 250 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F03026	5.7	9.0	141.7	3.69	107.5
F03031	6.3	8.9	146.0	3.77	110.8
F03032	6.0	9.1	143.5	3.69	108.7
F03034	6.5	9.3	145.0	3.35	107.9
F03035	5.2	8.9	142.4	3.46	109.5
Number of females	5	5	5	5	5
Mean	5.9	9.0	143.7	3.59	108.9
S.D.	0.5	0.2	1.8	0.18	1.3
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05049	5.9	4.1	2.28	132	73	20	120	66	20	0	62	9.4	13	0.7	0.09	289
F05050	6.0	4.2	2.33	130	64	27	124	63	27	0	57	14.8	16	0.6	0.14	229
F05051	6.2	4.4	2.44	102	79	17	134	94	31	0	102	14.8	22	0.7	0.10	198
F05052	6.5	4.6	2.42	135	81	42	141	60	35	0	48	10.0	16	0.7	0.10	170
F05053	5.1	3.3	1.83	101	36	6	69	61	21	1	60	9.5	30	0.8	0.07	303
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.1	2.26	120	67	22	118	69	27	0	66	11.7	19	0.7	0.10	238
S.D.	0.5	0.5	0.25	17	18	13	28	14	6	0	21	2.8	7	0.1	0.03	57

Control (vehicle: water for injection)					
Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05049	5.8	9.2	143.9	4.10	103.6
F05050	5.3	9.6	144.4	3.85	107.1
F05051	4.7	9.5	144.7	3.92	107.5
F05052	4.0	9.9	146.3	3.49	106.5
F05053	6.1	8.8	144.8	3.64	106.1
Number of females	5	5	5	5	5
Mean	5.2	9.4	144.8	3.80	106.2
S.D.	0.8	0.4	0.9	0.24	1.5

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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	5.3	3.8	2.53	113	62	25	119	51	23	0	41	9.0	13	0.6	0.13	200
F06060	5.6	3.9	2.29	117	68	17	124	55	20	0	59	11.7	19	0.6	0.11	283
F06061	5.3	3.8	2.53	125	54	23	107	47	21	0	40	9.0	15	0.6	0.13	233
F06062	5.6	3.9	2.29	103	65	17	117	54	21	0	46	5.9	19	0.7	0.06	168
F06063	5.5	3.8	2.24	124	64	31	126	56	25	0	61	7.3	15	0.6	0.11	111
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.8	2.38	116	63	23	119	53	22	0	49	8.6	16	0.6	0.11	199
S.D.	0.2	0.1	0.14	9	5	6	7	4	2	0	10	2.2	3	0.0	0.03	65
Significance	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AW	AW	TT	TT	AW	TT	AW	AW	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.

AW: Analysis by Aspin-Welch t-test.

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.

EMEE 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06059	5.2	9.1	144.1	3.93 §	106.3
F06060	6.0	9.1	145.1	4.07	107.6
F06061	3.6	9.1	144.0	3.41	107.9
F06062	5.1	9.2	145.7	3.55	107.6
F06063	4.0	9.1	145.1	3.20	108.5
Number of females	5	5	5	5	5
Mean	4.8	9.1	144.8	3.63	107.6
S.D.	1.0	0.0	0.7	0.36	0.8
Significance	NS	NS	NS	NS	NS
Statistical method	TT	AW	TT	TT	TT

§, Remeasurement

NS: Not significantly different from the control group.

AW: Analysis by Aspin-Welch t-test.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 28-3-1. Biochemical findings of female rats at the end of the recovery period

Control (vehicle: water for injection)																
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05054	5.7	3.9	2.17	102	45	15	88	71	30	0	49	11.9	19	0.7	0.08	303
F05055	5.8	4.2	2.63	129	66	20	124	67	20	0	52	10.8	15	0.6	0.07	205
F05056	5.6	3.9	2.29	109	45	11	87	59	21	0	100	12.6	18	0.6	0.07	253
F05057	5.8	3.9	2.05	100	78	14	130	69	28	0	45	10.8	16	0.6	0.10	226
F05058	6.0	4.2	2.33	144	60	17	114	70	46	0	65	9.7	16	0.7	0.11	180
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	4.0	2.29	117	59	15	109	67	29	0	62	11.2	17	0.6	0.09	233
S.D.	0.1	0.2	0.22	19	14	3	20	5	10	0	22	1.1	2	0.1	0.02	47

Control (vehicle: water for injection)					
Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05054	4.1	8.6	145.0	4.64	109.3
F05055	4.2	8.6	144.7	3.35	108.1
F05056	4.7	8.6	146.4	3.87	112.5
F05057	4.2	8.8	145.9	3.22	108.4
F05058	3.7	8.3	144.9	3.50	109.9
Number of females	5	5	5	5	5
Mean	4.2	8.6	145.4	3.72	109.6
S.D.	0.4	0.2	0.7	0.57	1.8

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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	6.2	4.2	2.10	106	47	16	85	51	19	0	40	15.6	14	0.6	0.12	234
F06065	5.4	3.5	1.84	109	50	17	87	87	47	0	125	12.7	18	0.7	0.05	395
F06066	5.9	4.1	2.28	107	43	15	89	65	18	0	51	7.8	16	0.7	0.09	264
F06067	6.0	4.1	2.16	105	53	8	100	75	23	0	89	16.1	18	0.6	0.08	340
F06068	5.3	3.5	1.94	110	52	13	90	113	24	0	142	7.0	18	0.6	0.10	254
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.9	2.06	107	49	14	90	78	26	0	89	11.8	17	0.6	0.09	297
S.D.	0.4	0.3	0.18	2	4	4	6	24	12	0	45	4.3	2	0.1	0.03	68
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	AW	AW	TT	AW	AW	TT	TT	TT	AW	TT	TT	TT	TT

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.

EMEE 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06064	3.7	8.7	144.7	3.61	108.2
F06065	4.6	8.4	145.3	3.22	110.5
F06066	3.5	8.7	145.3	3.20	109.7
F06067	3.1	8.5	146.0	2.96	111.7
F06068	4.6	8.5	146.1	3.31	111.9
Number of females	5	5	5	5	5
Mean	3.9	8.6	145.5	3.26	110.4
S.D.	0.7	0.1	0.6	0.23	1.5
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)																	
Male No.	Body weight (g)	Brain		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)
M01001	494.8	2042.4	4.128	355.9	0.719	1331.5	2.691	13359.6	27.000	1681.2	3.398	1579.1	3.191	3260.3	6.589	934.4	1.888
M01002	487.0	2076.2	4.263	356.8	0.733	1426.8	2.930	13216.8	27.139	1640.6	3.369	1578.2	3.241	3218.8	6.609	881.4	1.810
M01003	457.0	2099.0	4.593	296.0	0.648	1475.8	3.229	12434.2	27.208	1525.2	3.337	1544.3	3.379	3069.5	6.717	819.5	1.793
M01004	532.5	2074.4	3.896	237.8	0.447	1439.7	2.704	15047.0	28.257	1620.1	3.042	1582.2	2.971	3202.3	6.014	946.0	1.777
M01005	422.0	2053.3	4.866	352.9	0.836	1207.0	2.860	10623.1	25.173	1435.0	3.400	1468.5	3.480	2903.5	6.880	635.8	1.507
M01006	499.5	1911.0	3.826	259.5	0.520	1401.5	2.806	13257.3	26.541	1599.7	3.203	1474.1	2.951	3073.8	6.154	761.4	1.524
M01007	545.9	2039.1	3.735	250.6	0.459	1643.1	3.010	15303.1	28.033	1847.7	3.385	1762.1	3.228	3609.8	6.613	1088.8	1.995
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	491.2	2042.2	4.187	301.4	0.623	1417.9	2.890	13320.2	27.050	1621.4	3.305	1569.8	3.206	3191.1	6.511	866.8	1.756
S.D.	42.3	61.6	0.419	53.4	0.150	133.4	0.188	1580.6	1.020	128.9	0.135	97.8	0.195	220.7	0.311	145.5	0.180

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	1783.6	3.605	1759.1	3.555	3542.7	7.160	704.7	1.424	668.4	1.351	1373.1	2.775
M01002	1468.9	3.016	1477.8	3.034	2946.7	6.051	638.0	1.310	625.0	1.283	1263.0	2.593
M01003	1580.0	3.457	1522.1	3.331	3102.1	6.788	637.2	1.394	620.7	1.358	1257.9	2.753
M01004	1910.7	3.588	1978.3	3.715	3889.0	7.303	670.4	1.259	685.5	1.287	1355.9	2.546
M01005	1707.0	4.045	1652.3	3.915	3359.3	7.960	611.2	1.448	591.4	1.401	1202.6	2.850
M01006	1770.5	3.545	1765.5	3.535	3536.0	7.079	613.3	1.228	599.1	1.199	1212.4	2.427
M01007	1789.9	3.279	1733.0	3.175	3522.9	6.453	632.3	1.158	643.4	1.179	1275.7	2.337
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1715.8	3.505	1698.3	3.466	3414.1	6.971	643.9	1.317	633.4	1.294	1277.2	2.612
S.D.	147.5	0.317	168.1	0.307	312.9	0.617	33.2	0.109	34.7	0.083	65.5	0.190

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	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	797.7	1.612	2014.6	4.072	28.0	0.057	18.8	0.038	23.0	0.046	41.8	0.084
M01002	448.7	0.921	1001.4	2.056	24.3	0.050	21.4	0.044	24.8	0.051	46.2	0.095
M01003	605.8	1.326	1799.1	3.937	21.1	0.046	28.1	0.061	30.5	0.067	58.6	0.128
M01004	888.4	1.668	1648.8	3.096	22.1	0.042	27.5	0.052	27.6	0.052	55.1	0.103
M01005	675.8	1.601	1421.2	3.368	21.8	0.052	31.4	0.074	32.5	0.077	63.9	0.151
M01006	758.3	1.518	1699.2	3.402	23.4	0.047	20.2	0.040	20.1	0.040	40.3	0.081
M01007	481.8	0.883	1885.8	3.454	14.4	0.026	30.1	0.055	31.4	0.058	61.5	0.113
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	665.2	1.361	1638.6	3.341	22.2	0.046	25.4	0.052	27.1	0.056	52.5	0.108
S.D.	163.4	0.332	338.0	0.661	4.1	0.010	5.1	0.013	4.7	0.013	9.6	0.025

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M02013	490.5	2069.3	4.219	317.1	0.646	1353.2	2.759	13769.6	28.073	1583.4	3.228	1536.5	3.133	3119.9	6.361	981.6	2.001
M02014	517.6	2083.5	4.025	242.0	0.468	1420.8	2.745	15032.2	29.042	1639.3	3.167	1587.4	3.067	3226.7	6.234	900.3	1.739
M02015	478.3	2010.8	4.204	368.8	0.771	1424.9	2.979	12827.8	26.820	1670.7	3.493	1563.6	3.269	3234.3	6.762	873.2	1.826
M02016	454.7	2045.3	4.498	266.8	0.587	1337.0	2.940	12428.6	27.334	1438.4	3.163	1457.0	3.204	2895.4	6.368	890.4	1.958
M02017	469.4	1971.0	4.199	265.0	0.565	1277.7	2.722	12275.8	26.152	1598.1	3.405	1585.7	3.378	3183.8	6.783	744.7	1.586
M02018	536.4	2099.0	3.913	332.0	0.619	1778.2	3.315	13137.6	24.492	1948.6	3.633	1899.3	3.541	3847.9	7.174	1033.6	1.927
M02019	528.9	2025.9	3.830	231.2	0.437	1551.9	2.934	14930.2	28.229	1683.2	3.182	1653.0	3.125	3336.2	6.308	742.0	1.403
M02020	487.8	2005.0	4.110	218.6	0.448	1443.9	2.960	11888.3	24.371	1646.6	3.376	1622.6	3.326	3269.2	6.702	858.0	1.759
M02021	459.7	2083.3	4.532	372.9	0.811	1436.2	3.124	11182.8	24.326	1603.2	3.487	1584.9	3.448	3188.1	6.935	972.9	2.116
M02022	438.3	2038.6	4.651	276.6	0.631	1583.5	3.613	11782.7	26.883	1483.0	3.384	1514.6	3.456	2997.6	6.839	945.8	2.158
M02023	493.5	1991.7	4.036	232.3	0.471	1782.6	3.612	14101.3	28.574	1742.6	3.531	1726.4	3.498	3469.0	7.029	673.8	1.365
M02024	437.0	2069.7	4.736	210.8	0.482	1356.4	3.104	10298.1	23.565	1445.2	3.307	1413.9	3.235	2859.1	6.543	833.7	1.908
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	482.7	2041.1	4.246	277.8	0.578	1478.9	3.067	12804.6	26.488	1623.5	3.363	1595.4	3.307	3218.9	6.670	870.8	1.812
S.D.	33.0	40.9	0.294	56.9	0.124	164.8	0.306	1459.2	1.888	139.8	0.156	126.8	0.159	264.5	0.306	108.3	0.256
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	AN	DU	DU	AN	AN	AN	DU	AN	DU	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EM EE 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	1554.3	3.169	1537.1	3.134	3091.4	6.303	563.8	1.149	518.8	1.058	1082.6	2.207
M02014	1737.9	3.358	1754.3	3.389	3492.2	6.747	656.7	1.269	697.3	1.347	1354.0	2.616
M02015	1261.5	2.637	1393.8	2.914	2655.3	5.552	529.6	1.107	575.3	1.203	1104.9	2.310
M02016	1531.9	3.369	1554.0	3.418	3085.9	6.787	584.0	1.284	598.3	1.316	1182.3	2.600
M02017	1637.6	3.489	1648.7	3.512	3286.3	7.001	600.1	1.278	577.1	1.229	1177.2	2.508
M02018	1886.2	3.516	1846.5	3.442	3732.7	6.959	692.3	1.291	665.4	1.240	1357.7	2.531
M02019	1808.6	3.420	1716.0	3.244	3524.6	6.664	670.7	1.268	627.7	1.187	1298.4	2.455
M02020	1665.6	3.415	1672.5	3.429	3338.1	6.843	646.6	1.326	650.6	1.334	1297.2	2.659
M02021	1754.9	3.817	1740.3	3.786	3495.2	7.603	678.0	1.475	636.1	1.384	1314.1	2.859
M02022	1541.8	3.518	1530.8	3.493	3072.6	7.010	579.9	1.323	577.9	1.319	1157.8	2.642
M02023	1685.4	3.415	1670.3	3.385	3355.7	6.800	646.4	1.310	653.4	1.324	1299.8	2.634
M02024	1308.7	2.995	1329.8	3.043	2638.5	6.038	529.4	1.211	513.1	1.174	1042.5	2.386
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1614.5	3.343	1616.2	3.349	3230.7	6.692	614.8	1.274	607.6	1.260	1222.4	2.534
S.D.	187.9	0.297	151.8	0.234	337.7	0.524	57.5	0.093	57.5	0.094	110.8	0.176
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	DU	DU	DU	DU	DU	DU

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 62.5 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	693.6	1.414	1634.5	3.332	19.0	0.039	25.2	0.051	20.8	0.042	46.0	0.094
M02014	529.6	1.023	1694.7	3.274	20.8	0.040	25.5	0.049	25.2	0.049	50.7	0.098
M02015	698.4	1.460	1527.6	3.194	29.6	0.062	25.8	0.054	29.2	0.061	55.0	0.115
M02016	590.5	1.299	1234.1	2.714	24.8	0.055	29.4	0.065	33.1	0.073	62.5	0.137
M02017	563.9	1.201	1448.5	3.086	23.4	0.050	29.2	0.062	32.1	0.068	61.3	0.131
M02018	329.1	0.614	1637.0	3.052	21.5	0.040	26.2	0.049	26.4	0.049	52.6	0.098
M02019	710.8	1.344	1570.0	2.968	21.6	0.041	23.1	0.044	25.0	0.047	48.1	0.091
M02020	623.5	1.278	2080.9	4.266	25.1	0.051	25.5	0.052	25.6	0.052	51.1	0.105
M02021	671.4	1.461	1556.9	3.387	22.2	0.048	26.9	0.059	29.6	0.064	56.5	0.123
M02022	328.0	0.748	1245.7	2.842	11.8	0.027	17.8	0.041	18.3	0.042	36.1	0.082
M02023	499.1	1.011	1547.1	3.135	17.2	0.035	24.2	0.049	27.7	0.056	51.9	0.105
M02024	692.3	1.584	1490.6	3.411	16.9	0.039	22.9	0.052	24.2	0.055	47.1	0.108
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	577.5	1.203	1555.6	3.222	21.2	0.044	25.1	0.052	26.4	0.055	51.6	0.107
S.D.	135.8	0.299	218.3	0.392	4.6	0.010	3.1	0.007	4.3	0.010	7.1	0.017
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	AN	AN	AN	AN	AN	AN	KW	AN	KW

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 29-1-3. Organ weights of male rats at the end of the dosing period

EMEE 250 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)
M03025	524.4	1995.4	3.805	255.7	0.488	1550.7	2.957	14536.4	27.720	1719.1	3.278	1740.9	3.320	3460.0	6.598	799.0	1.524
M03026	486.2	2023.3	4.161	276.7	0.569	1553.4	3.195	14669.3	30.171	1863.4	3.833	1638.8	3.371	3502.2	7.203	720.3	1.481
M03027	456.4	2104.7	4.612	378.5	0.829	1489.9	3.264	13657.3	29.924	1621.2	3.552	1684.7	3.691	3305.9	7.243	819.5	1.796
M03028	500.7	2074.0	4.142	311.1	0.621	1391.1	2.778	14194.5	28.349	1933.3	3.861	1956.3	3.907	3889.6	7.768	905.2	1.808
M03029	505.5	1845.7	3.651	372.1	0.736	1423.0	2.815	13643.2	26.990	1657.5	3.279	1671.9	3.307	3329.4	6.586	708.6	1.402
M03030	449.4	1883.8	4.192	296.9	0.661	1346.8	2.997	11663.6	25.954	1432.6	3.188	1412.5	3.143	2845.1	6.331	815.3	1.814
M03031	561.4	2036.4	3.627	285.6	0.509	1580.2	2.815	15656.6	27.888	1920.0	3.420	1940.8	3.457	3860.8	6.877	1029.7	1.834
M03032	466.6	2029.3	4.349	246.1	0.527	1324.1	2.838	13698.4	29.358	1705.7	3.656	1751.9	3.755	3457.6	7.410	929.6	1.992
M03033	498.0	2110.0	4.237	285.0	0.572	1495.6	3.003	14282.3	28.679	1516.1	3.044	1707.5	3.429	3223.6	6.473	942.2	1.892
M03034	534.1	2074.7	3.884	339.2	0.635	1525.5	2.856	14539.3	27.222	1710.0	3.202	1680.4	3.146	3390.4	6.348	844.7	1.582
M03035	495.6	2048.5	4.133	336.2	0.678	1488.6	3.004	13825.1	27.896	1619.4	3.268	1589.8	3.208	3209.2	6.475	913.6	1.843
M03036	515.2	2071.9	4.022	371.1	0.720	1558.9	3.026	13591.6	26.381	1730.9	3.360	1775.7	3.447	3506.6	6.806	747.4	1.451
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	499.5	2024.8	4.068	312.9	0.629	1477.3	2.962	13996.5	28.044	1702.4	3.412	1712.6	3.432	3415.0	6.843	847.9	1.702
S.D.	32.4	82.2	0.288	46.0	0.102	86.5	0.153	947.7	1.326	151.0	0.261	145.2	0.242	280.8	0.465	98.3	0.200
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	AN	DU	DU	AN	AN	AN	DU	AN	DU	AN	AN

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

EMEE 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	1553.4	2.962	1570.3	2.994	3123.7	5.957	667.8	1.273	627.2	1.196	1295.0	2.469
M03026	1153.6	2.373	1097.5	2.257	2251.1	4.630	464.1	0.955	455.8	0.937	919.9	1.892
M03027	1841.4	4.035	1778.1	3.896	3619.5	7.931	604.2	1.324	615.8	1.349	1220.0	2.673
M03028	1740.9	3.477	1750.3	3.496	3491.2	6.973	640.3	1.279	628.5	1.255	1268.8	2.534
M03029	1714.4	3.391	1770.9	3.503	3485.3	6.895	617.2	1.221	605.5	1.198	1222.7	2.419
M03030	1539.6	3.426	1486.3	3.307	3025.9	6.733	529.3	1.178	524.7	1.168	1054.0	2.345
M03031	1599.7	2.849	1638.1	2.918	3237.8	5.767	684.8	1.220	619.9	1.104	1304.7	2.324
M03032	1555.6	3.334	1595.3	3.419	3150.9	6.753	621.2	1.331	592.2	1.269	1213.4	2.601
M03033	1681.2	3.376	1681.6	3.377	3362.8	6.753	578.1	1.161	587.9	1.181	1166.0	2.341
M03034	1575.3	2.949	1585.3	2.968	3160.6	5.918	652.7	1.222	620.3	1.161	1273.0	2.383
M03035	1780.8	3.593	1752.1	3.535	3532.9	7.129	679.5	1.371	635.0	1.281	1314.5	2.652
M03036	1821.7	3.536	1834.2	3.560	3655.9	7.096	583.5	1.133	617.2	1.198	1200.7	2.331
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1629.8	3.275	1628.3	3.269	3258.1	6.545	610.2	1.222	594.2	1.191	1204.4	2.414
S.D.	185.0	0.430	196.9	0.427	380.0	0.853	64.8	0.111	52.6	0.103	114.8	0.208
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	DU	DU	DU	DU	DU	DU

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

EMEE 250 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	502.9	0.959	1591.8	3.035	27.1	0.052	18.9	0.036	19.7	0.038	38.6	0.074
M03026	541.4	1.114	2058.4	4.234	23.9	0.049	25.3	0.052	26.4	0.054	51.7	0.106
M03027	449.1	0.984	1304.4	2.858	27.3	0.060	22.0	0.048	22.9	0.050	44.9	0.098
M03028	856.1	1.710	2037.7	4.070	29.7	0.059	24.5	0.049	26.0	0.052	50.5	0.101
M03029	508.0	1.005	2042.1	4.040	28.2	0.056	21.5	0.043	21.8	0.043	43.3	0.086
M03030	679.1	1.511	1960.5	4.362	20.3	0.045	24.5	0.055	25.1	0.056	49.6	0.110
M03031	722.1	1.286	2493.7	4.442	26.4	0.047	30.0	0.053	35.0	0.062	65.0	0.116
M03032	868.8	1.862	1831.4	3.925	20.6	0.044	25.8	0.055	26.2	0.056	52.0	0.111
M03033	548.8	1.102	1542.7	3.098	23.0	0.046	26.5	0.053	27.6	0.055	54.1	0.109
M03034	344.7	0.645	1712.6	3.207	20.1	0.038	22.6	0.042	24.9	0.047	47.5	0.089
M03035	730.4	1.474	2099.0	4.235	20.8	0.042	27.4	0.055	27.7	0.056	55.1	0.111
M03036	577.6	1.121	1471.7	2.857	29.1	0.056	26.7	0.052	25.8	0.050	52.5	0.102
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	610.8	1.231	1845.5	3.697	24.7	0.050	24.6	0.049	25.8	0.052	50.4	0.101
S.D.	161.5	0.349	333.7	0.627	3.7	0.007	3.0	0.006	3.8	0.007	6.7	0.012
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	AN	AN	AN	AN	AN	AN	KW	AN	KW

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 29-1-4. Organ weights of male rats at the end of the dosing period

EMEE 1000 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M04037	488.8	1918.0	3.924	126.3	0.258	1463.8	2.995	16817.6	34.406	1668.3	3.413	1655.4	3.387	3323.7	6.800	741.7	1.517
M04038	421.5	1993.1	4.729	184.9	0.439	1334.1	3.165	13547.1	32.140	1609.3	3.818	1595.1	3.784	3204.4	7.602	752.9	1.786
M04039	445.0	1984.3	4.459	137.6	0.309	1423.7	3.199	11879.5	26.696	1647.7	3.703	1601.3	3.598	3249.0	7.301	725.0	1.629
M04040	500.6	1972.5	3.940	258.8	0.517	1441.9	2.880	17161.0	34.281	1744.3	3.484	1757.4	3.511	3501.7	6.995	866.3	1.731
M04041	489.1	1956.4	4.000	161.8	0.331	1421.3	2.906	15872.4	32.452	1646.4	3.366	1649.0	3.371	3295.4	6.738	990.2	2.025
M04042	492.8	2113.7	4.289	156.9	0.318	1576.2	3.198	14792.6	30.017	1803.3	3.659	1918.9	3.894	3722.2	7.553	824.3	1.673
M04043	484.2	2004.0	4.139	71.5	0.148	1645.6	3.399	15074.6	31.133	1639.6	3.386	1560.9	3.224	3200.5	6.610	818.7	1.691
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	474.6	1991.7	4.211	156.8	0.331	1472.4	3.106	15020.7	31.589	1679.8	3.547	1676.9	3.538	3356.7	7.086	817.0	1.722
S.D.	29.5	60.7	0.300	57.4	0.120	104.8	0.187	1854.2	2.672	68.7	0.178	123.9	0.238	190.9	0.402	91.9	0.158
Significance	NS	NS	NS	**	**	NS	NS	NS	**	NS	NS	NS	*	NS	*	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	AN	DU	DU	AN	AN	AN	DU	AN	DU	AN	AN

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

NS: Not significantly different from the control group.

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

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 29-1-4 (continued). Organ weights of male rats at the end of the dosing period

EMEE 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	1192.6	2.440	1206.1	2.467	2398.7	4.907	371.7	0.760	401.1	0.821	772.8	1.581
M04038	1207.0	2.864	1253.6	2.974	2460.6	5.838	465.9	1.105	474.8	1.126	940.7	2.232
M04039	1111.2	2.497	1029.1	2.313	2140.3	4.810	387.3	0.870	384.3	0.864	771.6	1.734
M04040	1718.1	3.432	1721.7	3.439	3439.8	6.871	572.5	1.144	575.1	1.149	1147.6	2.292
M04041	1474.5	3.015	1486.9	3.040	2961.4	6.055	563.0	1.151	529.5	1.083	1092.5	2.234
M04042	1794.2	3.641	1754.6	3.560	3548.8	7.201	552.1	1.120	535.4	1.086	1087.5	2.207
M04043	1580.3	3.264	1530.5	3.161	3110.8	6.425	545.4	1.126	548.2	1.132	1093.6	2.259
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1439.7	3.022	1426.1	2.993	2865.8	6.015	494.0	1.039	492.6	1.037	986.6	2.077
S.D.	273.0	0.456	272.5	0.464	543.7	0.915	85.7	0.157	74.7	0.136	159.6	0.291
Significance	NS	NS	NS	NS	NS	NS	**	**	**	**	**	**
Statistical method	AN	AN	AN	AN	AN	AN	DU	DU	DU	DU	DU	DU

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 29-1-4 (continued). Organ weights of male rats at the end of the dosing period

EMEE 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	322.9	0.661	1397.8	2.860	15.2	0.031	21.5	0.044	24.4	0.050	45.9	0.094
M04038	437.3	1.037	1364.6	3.237	20.9	0.050	22.7	0.054	21.3	0.051	44.0	0.104
M04039	324.1	0.728	1501.3	3.374	18.1	0.041	18.3	0.041	21.2	0.048	39.5	0.089
M04040	605.4	1.209	1341.7	2.680	20.2	0.040	25.6	0.051	23.9	0.048	49.5	0.099
M04041	519.6	1.062	1374.5	2.810	21.5	0.044	26.3	0.054	26.4	0.054	52.7	0.108
M04042	338.3	0.686	1775.1	3.602	24.3	0.049	23.2	0.047	25.1	0.051	48.3	0.098
M04043	400.5	0.827	1716.4	3.545	17.9	0.037	23.5	0.049	26.8	0.055	50.3	0.104
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	421.2	0.887	1495.9	3.158	19.7	0.042	23.0	0.049	24.2	0.051	47.2	0.099
S.D.	108.2	0.215	178.9	0.374	2.9	0.007	2.7	0.005	2.2	0.003	4.4	0.007
Significance	**	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	AN	AN	AN	AN	AN	AN	KW	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).

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle; water for injection)

Male No.	Body 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	465.8	2048.1	4.397	188.9	0.406	1388.3	2.980	11228.9	24.107	1575.7	3.383	1509.8	3.241	3085.5	6.624	705.1	1.514
M01009	552.7	2040.6	3.692	258.5	0.468	1433.4	2.593	12968.0	23.463	1628.6	2.947	1672.1	3.025	3300.7	5.972	672.3	1.216
M01010	592.8	1986.5	3.351	389.9	0.658	1530.8	2.582	14632.5	24.684	1832.2	3.091	1785.4	3.012	3617.6	6.103	1050.3	1.772
M01011	498.9	2111.5	4.232	320.2	0.642	1312.4	2.631	11511.8	23.074	1539.7	3.086	1641.1	3.289	3180.8	6.376	787.7	1.579
M01012	519.5	2106.4	4.055	259.1	0.499	1554.3	2.992	11823.5	22.759	1559.3	3.002	1732.1	3.334	3291.4	6.336	825.0	1.588
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	525.9	2058.6	3.945	283.3	0.535	1443.8	2.756	12432.9	23.617	1627.1	3.102	1668.1	3.180	3295.2	6.282	808.1	1.534
S.D.	48.9	51.8	0.423	75.6	0.111	100.3	0.211	1395.9	0.780	119.3	0.168	104.5	0.151	200.7	0.253	148.7	0.202

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	1611.7	3.460	1602.7	3.441	3214.4	6.901	560.7	1.204	621.8	1.335	1182.5	2.539
M01009	1714.6	3.102	1697.8	3.072	3412.4	6.174	616.0	1.115	541.4	0.980	1157.4	2.094
M01010	1623.2	2.738	1675.2	2.826	3298.4	5.564	644.5	1.087	623.8	1.052	1268.3	2.140
M01011	1810.2	3.628	1765.6	3.539	3575.8	7.167	681.5	1.366	661.3	1.326	1342.8	2.692
M01012	632.1	1.217	1326.7	2.554	1958.8	3.771	89.7	0.173	492.8	0.949	582.5	1.121
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1478.4	2.829	1613.6	3.086	3092.0	5.915	518.5	0.989	588.2	1.128	1106.7	2.117
S.D.	479.8	0.964	170.6	0.413	647.8	1.353	243.7	0.469	69.0	0.188	302.1	0.613

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	660.5	1.418	1782.7	3.827	14.7	0.032	19.0	0.041	21.2	0.046	40.2	0.086
M01009	691.4	1.251	1984.9	3.591	16.1	0.029	18.5	0.033	19.3	0.035	37.8	0.068
M01010	801.6	1.352	2494.5	4.208	23.0	0.039	22.2	0.037	23.8	0.040	46.0	0.078
M01011	404.3	0.810	1700.6	3.409	19.3	0.039	23.9	0.048	22.3	0.045	46.2	0.093
M01012	433.2	0.834	1311.0	2.524	29.3	0.056	22.6	0.044	23.8	0.046	46.4	0.089
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	598.2	1.133	1854.7	3.512	20.5	0.039	21.2	0.041	22.1	0.042	43.3	0.083
S.D.	172.3	0.290	433.3	0.628	5.9	0.010	2.4	0.006	1.9	0.005	4.0	0.010

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 1000 mg/kg

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)
M04044	448.5	2057.3	4.587	119.5	0.266	1303.7	2.907	12037.9	26.840	1377.3	3.071	1479.2	3.298	2856.5	6.369	559.1	1.247
M04045	528.6	2001.5	3.786	208.4	0.394	1658.0	3.137	13989.7	26.466	1775.3	3.358	1850.0	3.500	3625.3	6.858	770.4	1.457
M04046	552.5	2119.1	3.835	219.2	0.397	1491.6	2.700	15410.2	27.892	1726.4	3.125	1660.5	3.005	3386.9	6.130	857.6	1.552
M04047	476.0	1996.4	4.194	162.7	0.342	1279.1	2.687	12004.0	25.218	1407.1	2.956	1363.5	2.864	2770.6	5.821	714.8	1.502
M04048	518.9	2116.9	4.080	309.4	0.596	1532.1	2.953	13563.3	26.139	1553.8	2.994	1476.2	2.845	3030.0	5.839	684.0	1.318
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	504.9	2058.2	4.096	203.8	0.399	1452.9	2.877	13401.0	26.511	1568.0	3.101	1565.9	3.102	3133.9	6.203	717.2	1.415
S.D.	42.0	59.6	0.322	71.1	0.122	159.9	0.188	1433.5	0.978	180.6	0.158	191.2	0.287	362.4	0.430	110.3	0.128
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	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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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	1269.2	2.830	1287.6	2.871	2556.8	5.701	481.4	1.073	464.5	1.036	945.9	2.109
M04045	1310.6	2.479	1355.6	2.565	2666.2	5.044	432.3	0.818	437.3	0.827	869.6	1.645
M04046	1529.3	2.768	1475.8	2.671	3005.1	5.439	566.7	1.026	556.7	1.008	1123.4	2.033
M04047	576.7	1.212	697.7	1.466	1274.4	2.677	377.2	0.792	349.4	0.734	726.6	1.526
M04048	1740.5	3.354	1650.3	3.180	3390.8	6.535	549.4	1.059	538.3	1.037	1087.7	2.096
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1285.3	2.529	1293.4	2.551	2578.7	5.079	481.4	0.954	469.2	0.928	950.6	1.882
S.D.	438.7	0.801	360.3	0.650	798.5	1.450	79.3	0.137	83.4	0.139	162.3	0.275
Significance	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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	604.4	1.348	1635.3	3.646	23.1	0.052	18.7	0.042	16.8	0.037	35.5	0.079
M04045	785.4	1.486	1778.2	3.364	23.4	0.044	17.9	0.034	19.1	0.036	37.0	0.070
M04046	770.1	1.394	1963.3	3.553	23.1	0.042	31.1	0.056	29.8	0.054	60.9	0.110
M04047	796.7	1.674	1716.2	3.605	27.8	0.058	20.1	0.042	20.1	0.042	40.2	0.084
M04048	694.3	1.338	1803.6	3.476	21.7	0.042	24.4	0.047	23.7	0.046	48.1	0.093
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	730.2	1.448	1779.3	3.529	23.8	0.048	22.4	0.044	21.9	0.043	44.3	0.087
S.D.	80.9	0.139	121.6	0.112	2.3	0.007	5.5	0.008	5.1	0.007	10.5	0.015
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	AW	AW	TT	TT	TT	TT	TT	TT	TT	TT

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	305.0	1775.2	5.820	275.5	0.903	1033.4	3.388	9429.2	30.915	969.2	3.178	988.6	3.241	1957.8	6.419	538.8	1.767
F01002	328.8	1982.6	6.030	251.6	0.765	1111.9	3.382	10105.7	30.735	1172.6	3.566	1118.6	3.402	2291.2	6.968	814.3	2.477
F01003	327.4	1817.9	5.553	209.1	0.639	996.2	3.043	10412.2	31.803	1242.0	3.794	1176.6	3.594	2418.6	7.387	800.4	2.445
F01004	349.0	2033.7	5.827	178.3	0.511	1099.1	3.149	11060.3	31.691	1235.7	3.541	1191.1	3.413	2426.8	6.954	916.1	2.625
F01005	296.5	1970.1	6.645	167.7	0.566	1056.2	3.562	9597.3	32.369	948.0	3.197	956.7	3.227	1904.7	6.424	839.0	2.830
F01006	350.9	1914.2	5.455	232.1	0.661	1147.8	3.271	10296.1	29.342	1170.4	3.335	1153.6	3.288	2324.0	6.623	819.4	2.335
F01007	329.9	1891.3	5.733	268.4	0.814	1189.8	3.607	11112.3	33.684	1077.1	3.265	1011.5	3.066	2088.6	6.331	839.0	2.543
F01008	299.9	1859.3	6.200	156.4	0.522	1086.1	3.622	10332.9	34.454	963.3	3.212	1020.4	3.402	1983.7	6.615	759.0	2.531
F01009	354.6	2025.0	5.711	329.7	0.930	1031.0	2.908	10861.5	30.630	1144.2	3.227	1083.2	3.055	2227.4	6.281	684.8	1.931
F01010	296.6	1901.5	6.411	240.4	0.811	1138.4	3.838	10393.0	35.040	1161.8	3.917	1177.4	3.970	2339.2	7.887	886.9	2.990
F01011	366.1	1902.8	5.197	152.0	0.415	1203.1	3.286	11254.1	30.741	1190.8	3.253	1148.7	3.138	2339.5	6.390	802.1	2.191
F01012	311.8	1851.0	5.936	188.9	0.606	1085.6	3.482	9637.6	30.910	1187.5	3.809	1135.5	3.642	2323.0	7.450	836.7	2.683
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	326.4	1910.4	5.877	220.8	0.679	1098.2	3.378	10374.4	31.860	1121.9	3.441	1096.8	3.370	2218.7	6.811	794.7	2.446
S.D.	24.6	80.1	0.405	55.0	0.165	63.9	0.265	614.1	1.722	106.2	0.272	82.2	0.266	185.5	0.523	99.5	0.351

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-1-1 (continued). Organ weights of female rats at the end of the dosing period

Control (vehicle: water for injection)																
Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	51.3	0.168	55.8	0.183	107.1	0.351	617.6	2.025	23.4	0.077	39.6	0.130	47.6	0.156	87.2	0.286
F01002	39.8	0.121	62.0	0.189	101.8	0.310	597.7	1.818	17.0	0.052	35.8	0.109	35.2	0.107	71.0	0.216
F01003	53.8	0.164	56.6	0.173	110.4	0.337	611.6	1.868	15.6	0.048	34.9	0.107	34.7	0.106	69.6	0.213
F01004	48.9	0.140	76.9	0.220	125.8	0.360	669.2	1.917	22.2	0.064	35.6	0.102	42.2	0.121	77.8	0.223
F01005	62.5	0.211	47.0	0.159	109.5	0.369	746.7	2.518	19.5	0.066	32.7	0.110	38.6	0.130	71.3	0.240
F01006	51.7	0.147	48.9	0.139	100.6	0.287	620.3	1.768	21.6	0.062	48.4	0.138	42.4	0.121	90.8	0.259
F01007	55.0	0.167	49.3	0.149	104.3	0.316	603.2	1.828	21.8	0.066	39.4	0.119	38.5	0.117	77.9	0.236
F01008	53.9	0.180	53.9	0.180	107.8	0.359	482.2	1.608	17.1	0.057	37.0	0.123	42.9	0.143	79.9	0.266
F01009	51.7	0.146	52.5	0.148	104.2	0.294	605.5	1.708	14.6	0.041	40.5	0.114	37.2	0.105	77.7	0.219
F01010	61.9	0.209	46.7	0.157	108.6	0.366	641.1	2.161	21.8	0.073	31.8	0.107	30.8	0.104	62.6	0.211
F01011	64.8	0.177	61.5	0.168	126.3	0.345	934.9	2.554	19.2	0.052	37.2	0.102	39.9	0.109	77.1	0.211
F01012	46.6	0.149	55.0	0.176	101.6	0.326	725.9	2.328	16.7	0.054	34.6	0.111	38.3	0.123	72.9	0.234
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	53.5	0.165	55.5	0.170	109.0	0.335	654.7	2.008	19.2	0.059	37.3	0.114	39.0	0.120	76.3	0.235
S.D.	7.1	0.027	8.4	0.022	8.6	0.028	110.8	0.315	2.9	0.011	4.4	0.011	4.4	0.016	7.7	0.024

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-1-2. Organ weights of female rats at the end of the dosing period

EMEE 62.5 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)
F02013	303.2	2012.6	6.638	171.2	0.565	875.3	2.887	9224.3	30.423	940.1	3.101	945.4	3.118	1885.5	6.219	755.1	2.490
F02014	324.4	2040.6	6.290	273.5	0.843	1034.1	3.188	10166.8	31.340	1112.8	3.430	975.2	3.006	2088.0	6.436	751.4	2.316
F02015	308.0	1984.1	6.442	122.8	0.399	978.8	3.178	9078.2	29.475	1164.7	3.781	1121.3	3.641	2286.0	7.422	550.5	1.787
F02016	360.2	1964.4	5.454	221.7	0.615	1118.3	3.105	11906.1	33.054	1281.3	3.557	1236.8	3.434	2518.1	6.991	788.8	2.190
F02017	326.4	2029.9	6.219	341.0	1.045	1112.4	3.408	10115.7	30.992	1171.3	3.589	1089.5	3.338	2260.8	6.926	825.8	2.530
F02018	300.8	1906.4	6.338	214.3	0.712	978.7	3.254	9926.4	33.000	1164.3	3.871	1153.5	3.835	2317.8	7.705	915.7	3.044
F02019	322.6	1991.0	6.172	204.7	0.635	1052.1	3.261	10815.7	33.527	1096.6	3.399	1076.1	3.336	2172.7	6.735	718.6	2.228
F02020	340.7	1970.2	5.783	217.0	0.637	1124.5	3.301	10614.5	31.155	1218.3	3.576	1198.2	3.517	2416.5	7.093	678.3	1.991
F02021	306.0	1902.4	6.217	223.4	0.730	969.3	3.168	9952.8	32.525	921.9	3.013	893.8	2.921	1815.7	5.934	642.9	2.101
F02022	371.4	1930.4	5.198	318.7	0.858	1126.2	3.032	11025.4	29.686	1248.0	3.360	1246.2	3.355	2494.2	6.716	710.6	1.913
F02023	316.1	1914.7	6.057	124.1	0.393	1016.5	3.216	10498.9	33.214	1113.7	3.523	1080.5	3.418	2194.2	6.941	812.1	2.569
F02024	307.6	1985.6	6.455	362.7	1.179	1101.3	3.580	10483.0	34.080	1172.2	3.811	1147.9	3.732	2320.1	7.543	700.5	2.277
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	324.0	1969.4	6.105	232.9	0.718	1040.6	3.215	10317.3	31.873	1133.8	3.501	1097.0	3.388	2230.8	6.888	737.5	2.286
S.D.	22.8	47.2	0.425	78.0	0.235	79.8	0.176	768.8	1.558	109.3	0.263	112.1	0.277	218.0	0.527	94.4	0.341
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	AN	AN	AN	DU	AN	AN	AN	DU	AN	DU	AN	DU	AN	AN	AN

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-1-2 (continued). Organ weights of female rats at the end of the dosing period

EMEE 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	50.1	0.165	57.5	0.190	107.6	0.355	619.6	2.044	11.5	0.038	35.6	0.117	40.6	0.134	76.2	0.251
F02014	55.5	0.171	48.6	0.150	104.1	0.321	610.2	1.881	13.9	0.043	32.6	0.100	37.3	0.115	69.9	0.215
F02015	48.0	0.156	56.9	0.185	104.9	0.341	623.2	2.023	14.2	0.046	36.8	0.119	37.4	0.121	74.2	0.241
F02016	41.9	0.116	66.2	0.184	108.1	0.300	645.5	1.792	20.4	0.057	41.2	0.114	42.2	0.117	83.4	0.232
F02017	49.7	0.152	37.5	0.115	87.2	0.267	600.3	1.839	25.2	0.077	35.2	0.108	38.0	0.116	73.2	0.224
F02018	56.1	0.187	44.1	0.147	100.2	0.333	624.4	2.076	14.9	0.050	35.3	0.117	42.3	0.141	77.6	0.258
F02019	78.1	0.242	54.7	0.170	132.8	0.412	739.7	2.293	21.6	0.067	33.0	0.102	34.6	0.107	67.6	0.210
F02020	64.5	0.189	56.5	0.166	121.0	0.355	823.3	2.416	25.0	0.073	38.7	0.114	36.4	0.107	75.1	0.220
F02021	54.8	0.179	46.5	0.152	101.3	0.331	646.4	2.112	22.0	0.072	41.2	0.135	42.0	0.137	83.2	0.272
F02022	43.3	0.117	51.4	0.138	94.7	0.255	671.3	1.807	18.3	0.049	47.6	0.128	51.4	0.138	99.0	0.267
F02023	54.3	0.172	62.4	0.197	116.7	0.369	532.2	1.684	14.6	0.046	38.9	0.123	40.1	0.127	79.0	0.250
F02024	31.2	0.101	65.0	0.211	96.2	0.313	753.4	2.449	24.4	0.079	39.1	0.127	36.7	0.119	75.8	0.246
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	52.3	0.162	53.9	0.167	106.2	0.329	657.5	2.035	18.8	0.058	37.9	0.117	39.9	0.123	77.9	0.241
S.D.	11.7	0.038	8.7	0.028	12.4	0.043	79.1	0.250	4.9	0.015	4.2	0.010	4.4	0.012	8.1	0.020
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	KW	KW	AN	AN	KW	KW	KW	KW	KW	KW

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-1-3. Organ weights of female rats at the end of the dosing period

EMEE 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	311.5	1856.9	5.961	182.2	0.585	983.1	3.156	8779.1	28.183	1101.3	3.535	1085.3	3.484	2186.6	7.020	788.9	2.533
F03026	322.2	1914.6	5.942	207.6	0.644	1041.5	3.232	10729.0	33.299	957.7	2.972	927.1	2.877	1884.8	5.850	799.4	2.481
F03027	339.8	1985.0	5.842	150.5	0.443	1125.5	3.312	11150.8	32.816	1142.1	3.361	1101.8	3.242	2243.9	6.604	703.2	2.069
F03028	249.2	1934.2	7.762	151.0	0.606	933.2	3.745	8319.8	33.386	986.1	3.957	978.6	3.927	1964.7	7.884	963.0	3.864
F03029	318.6	1948.7	6.116	218.2	0.685	1076.3	3.378	9981.8	31.330	1180.3	3.705	1226.0	3.848	2406.3	7.553	896.1	2.813
F03030	285.6	1814.8	6.354	145.2	0.508	939.2	3.289	9383.3	32.855	840.0	2.941	866.9	3.035	1706.9	5.977	680.7	2.383
F03031	294.4	1836.4	6.238	122.8	0.417	941.0	3.196	8903.0	30.241	874.2	2.969	834.4	2.834	1708.6	5.804	556.2	1.889
F03032	315.4	1846.7	5.855	161.2	0.511	1049.5	3.328	9527.2	30.207	991.7	3.144	957.5	3.036	1949.2	6.180	597.7	1.895
F03034	320.4	1900.0	5.930	258.6	0.807	1082.6	3.379	10668.7	33.298	1022.6	3.192	1027.3	3.206	2049.9	6.398	904.9	2.824
F03035	308.9	1931.5	6.253	193.0	0.625	899.1	2.911	9985.3	32.325	900.5	2.915	899.7	2.913	1800.2	5.828	916.5	2.967
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	306.6	1896.9	6.225	179.0	0.583	1007.1	3.293	9742.8	31.794	999.7	3.269	990.5	3.240	1990.1	6.510	780.7	2.572
S.D.	25.1	55.7	0.569	41.0	0.118	77.6	0.210	928.7	1.754	113.9	0.361	120.8	0.393	233.0	0.749	141.7	0.594
Significance	NS	NS	NS	NS	NS	*	NS	NS	NS	*	NS	*	NS	*	NS	NS	NS
Statistical method	AN	DU	AN	AN	AN	DU	AN	AN	AN	DU	AN	DU	AN	DU	AN	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-1-3 (continued). Organ weights of female rats at the end of the dosing period

EMEE 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	47.9	0.154	48.9	0.157	96.8	0.311	1286.8	4.131	14.2	0.046	30.9	0.099	30.3	0.097	61.2	0.196
F03026	61.6	0.191	56.6	0.176	118.2	0.367	607.5	1.885	17.0	0.053	32.9	0.102	32.7	0.101	65.6	0.204
F03027	60.4	0.178	53.1	0.156	113.5	0.334	844.6	2.486	18.4	0.054	30.5	0.090	33.4	0.098	63.9	0.188
F03028	68.6	0.275	42.7	0.171	111.3	0.447	444.2	1.783	26.7	0.107	46.0	0.185	48.2	0.193	94.2	0.378
F03029	57.9	0.182	44.5	0.140	102.4	0.321	861.5	2.704	16.6	0.052	35.6	0.112	44.0	0.138	79.6	0.250
F03030	42.0	0.147	58.2	0.204	100.2	0.351	583.5	2.043	15.8	0.055	24.6	0.086	26.6	0.093	51.2	0.179
F03031	56.0	0.190	45.1	0.153	101.1	0.343	660.1	2.242	14.1	0.048	31.3	0.106	31.5	0.107	62.8	0.213
F03032	50.7	0.161	47.0	0.149	97.7	0.310	727.8	2.308	15.0	0.048	30.2	0.096	31.3	0.099	61.5	0.195
F03034	64.4	0.201	64.5	0.201	128.9	0.402	618.9	1.932	13.2	0.041	52.9	0.165	55.2	0.172	108.1	0.337
F03035	67.1	0.217	49.2	0.159	116.3	0.376	743.4	2.407	27.1	0.088	26.7	0.086	29.8	0.096	56.5	0.183
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	57.7	0.190	51.0	0.167	108.6	0.356	737.8	2.392	17.8	0.059	34.2	0.113	36.3	0.119	70.5	0.232
S.D.	8.6	0.037	7.0	0.021	10.6	0.043	229.8	0.677	5.0	0.021	8.8	0.034	9.4	0.036	18.0	0.070
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	KW	KW	AN	AN	KW	KW	KW	KW	KW	KW

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)																	
Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	375.6	1993.5	5.308	406.4	1.082	1045.9	2.785	8636.6	22.994	1009.8	2.688	1021.1	2.719	2030.9	5.407	593.4	1.580
F05050	320.2	1906.5	5.954	349.9	1.093	1036.1	3.236	7405.7	23.128	923.4	2.884	935.9	2.923	1859.3	5.807	500.0	1.562
F05051	314.3	1928.5	6.136	323.9	1.031	1006.8	3.203	7983.6	25.401	972.5	3.094	948.3	3.017	1920.8	6.111	560.8	1.784
F05052	265.7	1785.5	6.720	345.4	1.300	923.1	3.474	6893.5	25.945	875.5	3.295	806.6	3.036	1682.1	6.331	455.9	1.716
F05053	302.3	2002.2	6.623	303.8	1.005	950.7	3.145	7074.2	23.401	987.5	3.267	972.2	3.216	1959.7	6.483	754.4	2.496
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	315.6	1923.2	6.148	345.9	1.102	992.5	3.169	7598.7	24.174	953.7	3.046	936.8	2.982	1890.6	6.028	572.9	1.828
S.D.	39.7	87.3	0.569	38.5	0.116	53.7	0.248	713.3	1.390	54.0	0.259	79.8	0.181	132.1	0.430	114.6	0.385

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-2-1 (continued). Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)																
Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	50.0	0.133	48.5	0.129	98.5	0.262	476.0	1.267	21.0	0.056	30.6	0.081	28.3	0.075	58.9	0.157
F05050	40.7	0.127	41.0	0.128	81.7	0.255	457.7	1.429	10.2	0.032	30.1	0.094	33.9	0.106	64.0	0.200
F05051	60.9	0.194	52.5	0.167	113.4	0.361	1215.8	3.868	20.0	0.064	32.8	0.104	39.2	0.125	72.0	0.229
F05052	27.2	0.102	30.2	0.114	57.4	0.216	521.8	1.964	15.1	0.057	31.8	0.120	29.7	0.112	61.5	0.231
F05053	62.3	0.206	54.4	0.180	116.7	0.386	602.2	1.992	20.9	0.069	30.7	0.102	33.5	0.111	64.2	0.212
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	48.2	0.152	45.3	0.144	93.5	0.296	654.7	2.104	17.4	0.056	31.2	0.100	32.9	0.106	64.1	0.206
S.D.	14.7	0.045	9.9	0.028	24.5	0.073	318.6	1.037	4.7	0.014	1.1	0.014	4.3	0.019	4.9	0.030

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

EMEE 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	279.6	1990.6	7.119	255.4	0.913	866.5	3.099	7923.8	28.340	953.2	3.409	912.6	3.264	1865.8	6.673	481.6	1.722
F06060	246.7	1890.6	7.664	228.4	0.926	839.1	3.401	6924.2	28.067	888.5	3.602	878.6	3.561	1767.1	7.163	472.5	1.915
F06061	307.1	1866.0	6.076	156.3	0.509	990.8	3.226	8152.2	26.546	976.9	3.181	1003.8	3.269	1980.7	6.450	633.3	2.062
F06062	297.2	1866.5	6.280	278.7	0.938	988.0	3.324	8239.2	27.723	1058.1	3.560	989.6	3.330	2047.7	6.890	587.8	1.978
F06063	296.5	1908.1	6.435	232.5	0.784	1031.5	3.479	9444.8	31.854	965.1	3.255	942.0	3.177	1907.1	6.432	715.7	2.414
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	285.4	1904.4	6.715	230.3	0.814	943.2	3.306	8136.8	28.506	968.4	3.401	945.3	3.320	1913.7	6.722	578.2	2.018
S.D.	23.8	51.3	0.660	46.0	0.181	84.8	0.149	899.6	1.993	60.7	0.184	52.2	0.145	107.6	0.310	103.1	0.254
Significance	NS	NS	NS	**	*	NS	NS	NS	**	NS	*	NS	*	NS	*	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-2-2 (continued). Organ weights of female rats at the end of the dosing period, satellite group

EMEE 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	45.2	0.162	42.5	0.152	87.7	0.314	503.9	1.802	21.2	0.076	30.0	0.107	31.2	0.112	61.2	0.219
F06060	36.1	0.146	31.8	0.129	67.9	0.275	913.1	3.701	15.5	0.063	39.4	0.160	44.1	0.179	83.5	0.338
F06061	34.2	0.111	42.3	0.138	76.5	0.249	534.8	1.741	13.0	0.042	27.2	0.089	26.1	0.085	53.3	0.174
F06062	45.6	0.153	47.9	0.161	93.5	0.315	407.0	1.369	16.7	0.056	27.6	0.093	33.1	0.111	60.7	0.204
F06063	35.2	0.119	30.6	0.103	65.8	0.222	495.8	1.672	23.0	0.078	36.7	0.124	38.5	0.130	75.2	0.254
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	39.3	0.138	39.0	0.137	78.3	0.275	570.9	2.057	17.9	0.063	32.2	0.115	34.6	0.123	66.8	0.238
S.D.	5.6	0.022	7.5	0.022	12.1	0.041	197.1	0.934	4.1	0.015	5.5	0.029	6.9	0.035	12.3	0.063
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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Weich 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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-3-1. Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Body 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	280.3	1963.3	7.004	177.4	0.633	864.4	3.084	7636.1	27.243	935.0	3.336	900.3	3.212	1835.3	6.548	502.8	1.794
F05055	280.2	2057.3	7.342	256.3	0.915	897.7	3.204	7781.5	27.771	1043.0	3.722	1052.2	3.755	2095.2	7.478	476.9	1.702
F05056	266.4	1935.2	7.264	147.3	0.553	834.5	3.133	6704.8	25.168	911.9	3.423	885.3	3.323	1797.2	6.746	584.5	2.194
F05057	291.5	2070.4	7.103	244.3	0.838	903.9	3.101	7266.0	24.926	892.7	3.062	889.5	3.051	1782.2	6.114	527.5	1.810
F05058	307.9	1907.4	6.195	211.7	0.688	919.2	2.985	7716.7	25.062	983.9	3.196	978.8	3.179	1962.7	6.374	564.3	1.833
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	285.3	1986.7	6.982	207.4	0.725	883.9	3.101	7421.0	26.034	953.3	3.348	941.2	3.304	1894.5	6.652	531.2	1.867
S.D.	15.5	73.3	0.459	45.5	0.149	34.1	0.080	447.4	1.360	60.6	0.250	72.8	0.270	132.8	0.517	43.9	0.190

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-3-1 (continued). Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	56.4	0.201	64.2	0.229	120.6	0.430	455.4	1.625	18.7	0.067	34.5	0.123	34.2	0.122	68.7	0.245
F05055	50.8	0.181	49.9	0.178	100.7	0.359	614.6	2.193	21.9	0.078	34.9	0.125	35.1	0.125	70.0	0.250
F05056	60.1	0.226	53.5	0.201	113.6	0.426	451.6	1.695	23.1	0.087	30.3	0.114	35.4	0.133	65.7	0.247
F05057	41.1	0.141	47.4	0.163	88.5	0.304	480.2	1.647	25.6	0.088	31.1	0.107	35.2	0.121	66.3	0.227
F05058	23.9	0.078	23.0	0.075	46.9	0.152	715.0	2.322	16.3	0.053	22.3	0.072	26.5	0.086	48.8	0.158
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	46.5	0.165	47.6	0.169	94.1	0.334	543.4	1.896	21.1	0.075	30.6	0.108	33.3	0.117	63.9	0.225
S.D.	14.5	0.058	15.2	0.058	29.1	0.114	116.9	0.334	3.7	0.015	5.1	0.021	3.8	0.018	8.6	0.039

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-3-2. Organ weights of female rats at the end of the recovery period

EMEE 1000 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06064	335.9	1931.5	5.750	276.4	0.823	1090.2	3.246	7512.7	22.366	1095.6	3.262	1049.7	3.125	2145.3	6.387	593.7	1.767
F06065	284.6	1925.3	6.765	339.0	1.191	876.8	3.081	7470.1	26.248	971.0	3.412	970.5	3.410	1941.5	6.822	667.4	2.345
F06066	304.3	1958.1	6.435	378.4	1.244	902.4	2.965	7206.9	23.684	853.1	2.803	917.5	3.015	1770.6	5.819	510.1	1.676
F06067	269.4	1963.2	7.287	150.8	0.560	880.3	3.268	6385.0	23.701	960.4	3.565	931.7	3.458	1892.1	7.023	463.1	1.719
F06068	267.3	1899.4	7.106	216.7	0.811	870.9	3.258	6984.9	26.131	905.1	3.386	872.7	3.265	1777.8	6.651	400.0	1.496
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	292.3	1935.5	6.669	272.3	0.926	924.1	3.164	7111.9	24.426	957.0	3.286	948.4	3.255	1905.5	6.540	526.9	1.801
S.D.	28.5	26.0	0.609	91.6	0.287	93.6	0.135	458.9	1.699	90.7	0.291	66.5	0.187	152.9	0.466	105.7	0.321
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

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 30-3-2 (continued). Organ weights of female rats at the end of the recovery period

EMEE 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	62.0	0.185	62.5	0.186	124.5	0.371	945.7	2.815	24.4	0.073	28.6	0.085	32.6	0.097	61.2	0.182
F06065	61.1	0.215	57.2	0.201	118.3	0.416	406.7	1.429	15.3	0.054	31.1	0.109	32.2	0.113	63.3	0.222
F06066	58.5	0.192	54.0	0.177	112.5	0.370	401.6	1.320	19.2	0.063	34.3	0.113	35.0	0.115	69.3	0.228
F06067	50.9	0.189	46.1	0.171	97.0	0.360	668.0	2.480	15.4	0.057	24.4	0.091	26.9	0.100	51.3	0.190
F06068	58.7	0.220	57.9	0.217	116.6	0.436	522.0	1.953	16.0	0.060	35.6	0.133	36.3	0.136	71.9	0.269
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	58.2	0.200	55.5	0.190	113.8	0.391	588.8	1.999	18.1	0.061	30.8	0.106	32.6	0.112	63.4	0.218
S.D.	4.4	0.016	6.1	0.019	10.3	0.033	227.1	0.649	3.9	0.007	4.5	0.019	3.6	0.015	8.0	0.035
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AW	AW	TT	AW	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Findings	Dose	Control (vehicle: water for injection)								EM EE 62.5 mg/kg								EM EE 250 mg/kg								EM EE 1000 mg/kg																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
	Animal No.	M01	M01	M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Findings	Dose	Control (vehicle: water for injection)					EMEE 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
Epididymis											
Edematous,bilateral		-	-	-	-	-	P	P	P	P	-
Small, unilateral/bilateral		-	-	-	-	p ^{a)}	-	-	-	p ^{b)}	-
Testis											
Edematous, bilateral		-	-	-	-	-	-	-	-	p	-
Small, unilateral/bilateral		-	-	-	-	p ^{a)}	-	-	-	p ^{b)}	-

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

a): Unilateral b): Bilateral

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible]

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

Fate: blanks; Subjected to autopsy on day 5 of lactation; ND, Not delivery; NP, Not pregnant; TL, Total litter loss; NC, Not copulated

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Findings	Dose Animal No.	Control (vehicle: water for injection)					EM EE 1000 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		049	050	051	052	053	059	060	061	062	063
Hair											
Alepecia, forelimb		-	-	P	-	-	-	-	-	-	-
Notes) - : No abnormal changes P : Non-graded change											

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Findings	Dose Animal No.	Control (vehicle: water for injection)					EM EE 1000 mg/kg				
		F05	F05	F06	F06	F06	F06	F06	F06	F06	F06
		054	055	056	057	058	064	065	066	067	068
Ileum											
Retention, gas, lumen		-	-	-	-	-	-	P	-	-	-
Cecum											
Retention, gas, lumen		-	-	-	-	-	-	P	-	-	-
Colon											
Retention, gas, lumen		-	-	-	-	-	-	P	-	-	-
Rectum											
Retention, gas, lumen		-	-	-	-	-	-	P	-	-	-
Notes) - : No abnormal changes P : Non-graded change											

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible]

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

[illegible][illegible]

Notes) -: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible]

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

Findings	Group	Control (vehicle: water for injection)					EMEE				
	Dose(mg/kg)	0					1000				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
Thymus											
Atrophy, medulla		-	-	-	-	-	+	-	±	-	-
Liver											
Fatty change, hepatocyte, periportal		±	±	±	±	±	±	-	-	±	-
Microgranuloma		-	-	-	-	-	-	-	-	±	-
Necrosis, focal		-	-	-	-	±	-	-	-	-	-
Testis											
Atrophy, seminiferous tubule		±	-	-	-	+	±	±	-	2+	-
focal, unilateral/bilateral											
Exfoliation, spermatid & sperm,											
seminiferous tubule, bilateral		-	-	-	-	-	±	+	±	2+	±
Exfoliation, spermatocyte, seminiferous tubule											
bilateral		-	-	-	-	-	±	+	±	2+	-
Multinucleated giant cell, seminiferous tubule											
bilateral		-	-	-	-	+	±	±	-	+	-
Vacuolation, germ cell layer, seminiferous tubule											
bilateral		-	-	-	-	-	±	+	±	2+	±
Epididymis											
Cell debris, lumen, unilateral/bilateral		-	-	-	-	+	+	+	+	+	±
Decrease, sperm, lumen, unilateral/bilateral		-	-	-	-	+	+	+	+	2+	±
Defect, unilateral		-	-	-	-	P	-	-	-	-	-
Prostate											
Cellular infiltration, lymphocyte, interstitial		-	±	-	+	±	-	-	-	-	-

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

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

[illegible]

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blanks. Subjected to autopsy on day 5 of lactation; ND, Not delivery; NP, Not pregnant; TL, Total litter loss; NC, Not copulated

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)												EMEE												EMEE												EMEE																						
	Dose(mg/kg)	0												62.5												250												1000																						
		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	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	048											
Face																																																												
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												
Fatty change, hepatocyte, periportal	-					*		*																		-	-		-	*		*	*		-	*		*	*		*																			
Fibrosis, focal, capsule	-					-		-																		-	-		-			*	*		-	-		-																						
Ground glass appearance, hepatocyte	-					-		-																		-	-		-	-		-	-		*	-		*	*		*																			
Hypertrophy, hepatocyte, centrilobular	-					-		-																		-	-		-	-		-	-		+	*		+	+		+																			
Microgranuloma	-					+		-		*																-	+		-	*		-	-		-	*																								
Necrosis, focal	-					-		-		-																-		*		*	-		-	-		-	*		-	*		-																		
Nodule, hepatodysplastic	-					-		-		-																-	-		-	*		-	*	P		-	-		-	-		-																		
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												
	-					-		-		-																-									-		-		-		-																			
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												
Dilatation, fundic gland,																																																												
focal, glandular stomach	-					-		-		-																-	-		-	-		*	-		-		-		-		-																			
Edema, lamina propria, glandular stomach	-					-		-		-																-	-		*		-	-	-	-		-		-		-																				
Erosion, mucosa, glandular stomach	-					-		-		-																*		+		-	-	-	-		-		-		-		-																			
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	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	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	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																					

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate : blanks. Subjected to autopsy on day 5 of lactation: ND, Not delivery; NP, Not pregnant; TL, Total litter loss; NC, Not copulated

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)												EMEE												EMEE												EMEE												
	Dose(mg/kg)	0												62.5												250												1000												
	Animal No.	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	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	NP	NC	TL	ND	TL	NP	TL	NP	TL	NP	TL	NP	TL
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	NE	NE	NE	NE	NE	NE	NE	NE	
Basophilic tubule, cortex		±			-	-	-	±								+													-	-	*	-					±	±	-	-	*									
Cast, lumen, cortex		-			-	-	-	-								-														-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Dilatation, pelvis, bilateral		-			-	-	-	-	-							2+													-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Mineralization, Cortico-medullary junction		-			-	-	-	-	-							-													-	-	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
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	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	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	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ovulatory follicle		-			-	-	-	-	-																				-																					
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	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, neutrophil, mucosa & lumen		-			-	-	-	-	-																				-																					
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	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	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	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	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	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	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	NE	NE	NE	NE
Lymph node																																																		
Mediastinum																																																		
Edema, with inflammatory cell																																																		

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blanks, Subjected to autopsy on day 5 of lactation; ND, Not delivery; NP, Not pregnant; TL, Total litter loss; NC, Not copulated

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)					EMEE				
	Dose(mg/kg)	0					1000				
	Animal No.	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 Cyst		-	-	-	-	-	-	-	-	P	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-
Thyroid gland Ultimobranchial body		-	-	-	-	-	-	-	-	P	-
Parathyroid gland		M	-	-	-	-	-	-	-	-	-
Thymus Atrophy, medulla		-	-	-	-	-	-	±	±	-	-
Heart Degeneration/fibrosis, myocardial, focal		-	-	-	±	-	-	-	-	-	-
Trachea		-	-	-	-	-	-	-	-	-	-
Lung Accumulation, foam cell, alveolus		-	-	-	-	-	±	±	-	-	-
Metaplasia, osseous, focal		-	-	±	-	-	-	-	-	-	-
Bronchus		-	-	-	-	-	-	-	-	-	-

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)					EMEE				
	Dose(mg/kg)	0					1000				
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063
Liver											
Fatty change, hepatocyte, periportal		-	±	-	±	-	±	±	±	±	±
Ground glass appearance, hepatocyte		-	-	-	-	-	-	-	±	-	±
Hypertrophy, hepatocyte, centrilobular		-	-	-	-	-	±	±	±	±	+
Pancreas		-	-	-	-	-	-	-	-	-	-
Stomach		-	-	-	-	-	-	-	-	-	-
Duodenum		-	-	-	-	-	-	-	-	-	-
Jejunum		-	-	-	-	-	-	-	-	-	-
Ileum		-	-	-	-	-	-	-	-	-	-
Cecum		-	-	-	-	-	-	-	-	-	-
Colon		-	-	-	-	-	-	-	-	-	-
Rectum		-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric		-	-	-	-	-	-	-	-	-	-
Spleen											
Deposit, pigment, brown		+	2+	2+	2+	2+	2+	+	+	2+	+
Hematopoiesis, extramedullary		±	+	+	+	+	+	+	±	+	+

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)					EMEE				
	Dose(mg/kg)	0					1000				
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063
Kidney											
Basophilic tubule, cortex		-	-	±	-	-	-	-	-	-	-
Cyst, medulla		-	-	P	-	-	-	-	-	-	-
Fibrosis, focal, subserosa		-	-	±	-	-	-	-	-	-	-
Mineralization, Cortico-medullary junction		-	-	-	-	-	±	-	-	-	-
Urinary bladder		-	-	-	-	-	-	-	-	-	-
Adrenal gland		-	-	-	-	-	-	-	-	-	-
Ovary											
Cyst, follicular		-	-	-	-	-	-	-	P	-	-
Uterus		-	-	-	-	-	-	-	-	-	-
Vagina		-	-	-	-	-	-	-	-	-	-
Eyeball		-	-	-	-	-	-	-	-	-	-
Harderian gland											
Cellular infiltration, lymphocyte, interstitial		±	-	-	-	-	-	-	-	-	-
Sciatic nerve		-	-	-	-	-	-	-	-	-	-
Skeletal muscle		-	-	-	-	-	-	-	-	-	-
Femur		-	-	-	-	-	-	-	-	-	-
Marrow, femur		-	-	-	-	-	-	-	-	-	-

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane 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	Control (vehicle: water for injection)					EMEE				
	Dose(mg/kg)	0					1000				
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 064	F06 065	F06 066	F06 067	F06 068
Thymus		-	-	-	-	-	-	-	-	-	-
Liver											
Fatty change, hepatocyte, periportal		±	±	±	±	±	±	±	±	±	±
Necrosis, focal		-	-	-	-	-	-	-	±	-	-

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
Appendix 35-1. Results of observations about estrous cycle

Control (vehicle: water for injection)

Control (vehicle; water for injection)									
Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F01001	D D 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	SP	1	
F01002	D D D E D D D E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1	
F01003	D E D D D P E D D D P E D D	5-day	5.0	D E D D P E D D D E D D P E	4-day	4.0	D D P SP	1	
F01004	D D D P E D D D P E D D D P	5-day	5.0	E D D D E D D D D E D D D E	4/5-day	4.3	D D D PL	1	
F01005	E D D D E D D P E D D P E D	4-day	4.0	D P E D D P E D D D E D D D	4-day	4.0	SP	1	
F01006	E D D P E E D D D P E D D D	5-day	5.0	P E D D D P E D D D D E D D	5-day	5.0	D SP	1	
F01007	D D D E D D D P E D D P E E	5-day	5.0	D D P E D D P E D D P E D D	4-day	4.0	D SP	1	
F01008	E D D P E D D P E D D P E D	4-day	4.0	D D E D D D E D D P E D D P	4-day	4.0	SP	1	
F01009	E D D P E D D D E D D D E D	4-day	4.0	D D E D D P E D D P E D D P	4-day	4.0	SP	1	
F01010	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 P E D D P E	4-day	4.0	D D D PL	1	
F01011	E D D P E E D D P E D D P E	4/5-day	4.3	D D P E D D P E D D D E D D	4-day	4.0	D SP	1	
F01012	D D D E D D D E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P SP	1	
Mean			4.4			4.1		1.0	
S.D.			0.5			0.3		0.0	
(N)			(12)			(12)		(12)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 35-2. Results of observations about estrous cycle

EMEE (62.5 mg/kg)

Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F02013	D D E D D D E D D D E D D D	4-day	4.0	E D D P E D D D E D D D E D	4-day	4.0	D D SP	1	
F02014	D E D D D E D D P E D D D E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P SP	1	
F02015	D D P E D D P E D D P E D D	4-day	4.0	P E D D D E D D P E D D D E	4-day	4.0	D D P SP	1	
F02016	D P E D D D P E D D D P E D	5-day	5.0	D D E D D D E D D D E D D D	4-day	4.0	SP	1	
F02017	D D E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D D E D	4-day	4.0	D P SP	1	
F02018	D D D P E D D D P E D D P E	4/5-day	4.5	E D D D P E D D D P E D D D	5-day	5.0	P SP	1	
F02019	D D D D E D D D P E D D D P	5-day	5.0	E D D D P E D D D P E D D D	5-day	5.0	P SP	1	
F02020	D P E D D D E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1	
F02021	E D D D E D D P E D D P E D	4-day	4.0	D D E D D D E D D D E D D D	4-day	4.0	SP	1	
F02022	E D D D E D D D E D D D E D	4-day	4.0	D D E D D D E D D D E D D D	4-day	4.0	SP	1	
F02023	E D D P E E D D P E D D P E	4/5-day	4.3	D D P E D D P E D D D E D D	4-day	4.0	P SP	1	
F02024	E D D D E D D D E D D D E D	4-day	4.0	D P E D D D E D D D E D D D	4-day	4.0	PL	1	
Mean			4.2			4.2		1.0	
S.D.			0.4			0.4		0.0	
(N)			(12)			(12)		(12)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 35-3. Results of observations about estrous cycle

EMEE (250 mg/kg)

Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F03025	D E D D D D E D D D P E D D	5-day	5.0	D P E D D D D P E D D D E D D	4/5-day	4.5	D SP	1	
F03026	D P E E D D P E E D D P E E	5-day	5.0	D D D D E D D D D E D D D E	4/5-day	4.5	SP	1	
F03027	E D D P E E D D P E D D P E	4/5-day	4.3	D D P E D D D D E D D P E D	4/5-day	4.5	D D P E SP	1	
F03028	D D D E D D D E D D D E D D	4-day	4.0	D E D D D E D D D D E D D D	4/5-day	4.5	D SP	1	
F03029	D D P E D D D E D D P E D D	4-day	4.0	P E D D P E D D P E D D D E	4-day	4.0	D D P SP	1	
F03030	P E D D D E D D D E D D D E	4-day	4.0	D D D E D D D E E D D D E D	4/5-day	4.5	D D P SP	1	
F03031	P E D D P E D D P E D D P E	4-day	4.0	D D D E D D D E D D D E D D	4-day	4.0	P PL	1	
F03032	E D D D E D D D E D D P E D	4-day	4.0	D P E D D D E D D P E D D P	4-day	4.0	SP	1	
F03033	D D D E E D D D E E D D D E	4/5-day	4.5	E D D D P E D D D E E D D D	5-day	5.0	SP	1	
F03034	D D D D E D D P E D D P E E	4/5-day	4.5	D D D D E D D D D E D D P E	4/5-day	4.5	SP	1	
F03035	D E D D D E D D P E D D P E	4-day	4.0	D D P E D D D E D D D E D D	4-day	4.0	P SP	1	
F03036	D E D D P E D D P E D D P E	4-day	4.0	D D D E E D D D P E D D D E	4/5-day	4.5	D D D D D D D D D D D D		
Mean			4.3			4.4		1.0	
S.D.			0.4			0.3		0.0	
(N)			(12)			(12)		(11)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
Appendix 35-4. Results of observations about estrous cycle

EMEE (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 D E D D P E D D P E D D P	4-day	4.0	E D D D D E D D D D P E D D	Irregular	5.5	D D SP	1	
F04038	D P E D D D E D D D E D D P	4-day	4.0	E D D D P E D D D D E D D D	5-day	5.0	D PL	1	
F04039	D D P E D D D E D D D P E D	4/5-day	4.5	D D D D D D D D D D D D E D	Uncycle		D D E SP	1	
F04040	D D E D D D P E D D D P E D	5-day	5.0	D D D E D D D P E D D D D E	5-day	5.0	PL	1	
F04041	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 E D D P E E	5-day	5.0	D D P E SP	1	
F04042	D D P E D D P E D D P E D D	4-day	4.0	P E D D D P E D D P E D D D	4/5-day	4.5	E SP	1	
F04043	D P E D D P E D D P E D D P	4-day	4.0	E D D D P E D D D D E D D D	Irregular	5.5	P SP	1	
F04044	D P E D D D P E D D D P E D	5-day	5.0	D D D E D D D D P E D D D D	Irregular	6.0	SP	1	
F04045	E D D P E D D D E D D D D D	4-day	4.0	D D D D D D D D D E D D D E	Irregular		SP	1	
F04046	E D D P E D D P E D D P E D	4-day	4.0	D P E D D D P E D D D P E D	5-day	5.0	D D PL	1	
F04047	P E D D P E D D P E D D P E	4-day	4.0	D D D P E D D D D P E D D P	Irregular	6.0	E SP	1	
F04048	D D D E D D P E E D D D P E	5-day	5.0	D D D D E D D D D E E D D D	Irregular	6.0	D PL	1	
Mean			4.3			5.4	**	1.0	
S.D.			0.5			0.5		0.0	
(N)			(12)			(10)		(12)	

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 36-1. Results of observations about reproductive performance

Control (vehicle: water for injection)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M01001	F01001	+	+	1
M01002	F01002	+	+	4
M01003	F01003	+	+	4
M01004	F01004	+	+	4
M01005	F01005	+	+	1
M01006	F01006	+	+	2
M01007	F01007	+	+	2
M01008	F01008	+	+	1
M01009	F01009	+	+	1
M01010	F01010	+	+	4
M01011	F01011	+	+	2
M01012	F01012	+	+	4
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.5
S.D.				1.4
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 36-2. Results of observations about reproductive performance

EMEE (62.5 mg/kg)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M02013	F02013	+	+	3
M02014	F02014	+	+	2
M02015	F02015	+	+	4
M02016	F02016	+	+	1
M02017	F02017	+	+	3
M02018	F02018	+	+	2
M02019	F02019	+	+	2
M02020	F02020	+	+	3
M02021	F02021	+	+	1
M02022	F02022	+	+	1
M02023	F02023	+	+	2
M02024	F02024	+	+	1
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.1
S.D.				1.0
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 36-3. Results of observations about reproductive performance

EMEE (250 mg/kg)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M03025	F03025	+	+	2
M03026	F03026	+	+	1
M03027	F03027	+	+	5
M03028	F03028	+	+	2
M03029	F03029	+	+	4
M03030	F03030	+	+	4
M03031	F03031	+	+	2
M03032	F03032	+	+	1
M03033	F03033	+	-	1
M03034	F03034	+	+	1
M03035	F03035	+	+	2
M03036	F03036	-		
Total		+: 11, -: 1	+: 10, -: 1	
Mean				2.3
S.D.				1.4
(N)				(11)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
Appendix 36-4. Results of observations about reproductive performance

EMEE (1000 mg/kg)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M04037	F04037	+	+	3
M04038	F04038	+	+	2
M04039	F04039	+	+	4
M04040	F04040	+	-	1
M04041	F04041	+	+	5
M04042	F04042	+	+	2
M04043	F04043	+	-	2
M04044	F04044	+	+	1
M04045	F04045	+	+	1
M04046	F04046	+	-	3
M04047	F04047	+	+	2
M04048	F04048	+	+	2
Total		+: 12, -: 0	+: 9, -: 3	
Mean				2.3
S.D.				1.2
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 37-1. Observation of offspring (F₁)

Control (vehicle: water for injection)

Control (vehicle, water for injection)																				
Dam No.	Gestation length	Number of corpora lutea	Number of implantation scars	Implan- tation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring			External abnormalities ^{b)}			
						Number of offspring	Sex ratio			Dead offspring				4 days	Sex ratio	Viability index (%)	(Number)	(%)		
							Male	Female	Total											
	(days)														Male	Female				
F01001	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
F01002	22	17	17	100.0	+	16	12	4	16	0.75	0	94.1	94.1	100.0	12	4	0.75	100.0	0	0.0
F01003	22	15	15	100.0	+	14	7	7	14	0.50	0	93.3	93.3	100.0	7	7	0.50	100.0	0	0.0
F01004	22	20	18	90.0	+	14	6	7	13	0.46	1	77.8	72.2	92.9	6	7	0.46	100.0	0	0.0
F01005	22	17	17	100.0	+	15	8	7	15	0.53	0	88.2	88.2	100.0	8	7	0.53	100.0	0	0.0
F01006	22	17	17	100.0	+	17	11	6	17	0.65	0	100.0	100.0	100.0	11	5	0.69	94.1	0	0.0
F01007	22	15	15	100.0	+	14	5	9	14	0.36	0	93.3	93.3	100.0	5	9	0.36	100.0	0	0.0
F01008	22	17	17	100.0	+	15	7	6	13	0.54	2	88.2	76.5	86.7	7	6	0.54	100.0	0	0.0
F01009	22	17	16	94.1	+	14	4	10	14	0.29	0	87.5	87.5	100.0	4	10	0.29	100.0	0	0.0
F01010	22	16	15	93.8	+	15	8	6	14	0.57	1	100.0	93.3	93.3	8	6	0.57	100.0	0	0.0
F01011	22	21	20	95.2	+	16	8	8	16	0.50	0	80.0	80.0	100.0	8	8	0.50	100.0	0	0.0
F01012	21	16	16	100.0	+	16	9	7	16	0.56	0	100.0	100.0	100.0	9	6	0.60	93.8	0	0.0
Number of dams	12	12	12	12	12 ^{a)}	12			12	12	12	12	12	12			12	12	12	12
Total		204	199			180	90	86	176		4				90	84			0	
Mean	21.9	17.0	16.6	97.8		15.0	7.5	7.2	14.7	0.51	0.3	90.8	88.8	97.7	7.5	7.0	0.51	99.0		0.0
S.D.	0.3	1.8	1.4	3.5		1.0	2.4	1.6	1.3	0.13	0.7	7.4	8.8	4.4	2.4	1.8	0.13	2.4		0.0
%					100.0															

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
Appendix 37-2. Observation of offspring (F₁)

EMEE 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	23	18	18	100.0	+	16	8	8	16	0.50	0	88.9	88.9	100.0	8	8	0.50	100.0	0	0.0
F02014	22	17	17	100.0	+	16	7	7	14	0.50	2	94.1	82.4	87.5	7	7	0.50	100.0	0	0.0
F02015	22	18	18	100.0	+	16	9	7	16	0.56	0	88.9	88.9	100.0	9	7	0.56	100.0	0	0.0
F02016	23	17	17	100.0	+	16	12	4	16	0.75	0	94.1	94.1	100.0	12	3	0.80	93.8	0	0.0
F02017	22	15	15	100.0	+	14	8	6	14	0.57	0	93.3	93.3	100.0	8	6	0.57	100.0	0	0.0
F02018	22	19	19	100.0	+	16	8	8	16	0.50	0	84.2	84.2	100.0	8	8	0.50	100.0	0	0.0
F02019	22	19	19	100.0	+	17	8	9	17	0.47	0	89.5	89.5	100.0	8	9	0.47	100.0	0	0.0
F02020	22	17	17	100.0	+	16	10	6	16	0.63	0	94.1	94.1	100.0	10	6	0.63	100.0	0	0.0
F02021	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
F02022	22	15	15	100.0	+	14	6	8	14	0.43	0	93.3	93.3	100.0	6	8	0.43	100.0	0	0.0
F02023	23	19	19	100.0	+	18	11	7	18	0.61	0	94.7	94.7	100.0	10	7	0.59	94.4	0	0.0
F02024	22	16	16	100.0	+	13	7	6	13	0.54	0	81.3	81.3	100.0	7	6	0.54	100.0	0	0.0
Number of dams	12	12	12	12	12 ^{a)}	12	100	86	186	12	12	12	12	12	12	12	12	12	12	12
Total		206	206			188	8.3	86	186		2			99	85			0		
Mean	22.3	17.2	17.2	100.0		15.7	8.3	7.2	15.5	0.54	0.2	91.4	90.4	99.0	8.3	7.1	0.54	99.0		0.0
S.D.	0.5	1.5	1.5	0.0		1.4	1.9	1.6	1.4	0.10	0.6	5.1	5.6	3.6	1.8	1.8	0.11	2.3		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	DT	DT	DT	DT	DU	DU	DT	AN	DT	DT	DT	DT	AN	AN	AN	KW		AN

+: Dams with live offspring, -: dams without live offspring

a): Number of dams with live offspring.

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

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

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
Appendix 37-3. Observation of offspring (F₁)

EMEE 250 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implan- tation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring				External abnormalities ^{b)}		
						Number of offspring	Sex ratio			Dead offspring				4 days		Sex ratio	Viability index (%)	(Number)	(%)	
							Male	Female	Total					Male	Female					
F03025	23	15	15	100.0	+	11	5	6	11	0.45	0	73.3	73.3	100.0	4	4	0.50	72.7	0	0.0
F03026	23	18	18	100.0	+	18	11	7	18	0.61	0	100.0	100.0	100.0	11	6	0.65	94.4	0	0.0
F03027	22	17	16	94.1	+	16	9	6	15	0.60	1	100.0	93.8	93.8	9	6	0.60	100.0	0	0.0
F03028	22	11	6	54.5	+	5	1	4	5	0.20	0	83.3	83.3	100.0	1	4	0.20	100.0	0	0.0
F03029	22	20	19	95.0	+	16	5	10	15	0.33	1	84.2	78.9	93.8	5	10	0.33	100.0	0	0.0
F03030	22	15	15	100.0	+	14	7	7	14	0.50	0	93.3	93.3	100.0	7	7	0.50	100.0	0	0.0
F03031	22	16	16	100.0	+	14	4	9	13	0.31	1	87.5	81.3	92.9	4	9	0.31	100.0	0	0.0
F03032	22	16	14	87.5	+	11	5	6	11	0.45	0	78.6	78.6	100.0	5	6	0.45	100.0	0	0.0
F03033	Not pregnant																			
F03034	22	18	18	100.0	+	17	10	7	17	0.59	0	94.4	94.4	100.0	10	7	0.59	100.0	0	0.0
F03035	22	16	15	93.8	+	12	7	5	12	0.58	0	80.0	80.0	100.0	7	5	0.58	100.0	0	0.0
F03036	Not copulated																			
Number of dams	10	10	10	10	10 ^{a)}	10			10	10	10	10	10	10			10	10	10	10
Total		162	152			134	64	67	131		3				63	64			0	
Mean	22.2	16.2	15.2	92.5		13.4	6.4	6.7	13.1	0.46	0.3	87.5	85.7	98.1	6.3	6.4	0.47	96.7		0.0
S.D.	0.4	2.4	3.6	14.0		3.8	3.0	1.8	3.7	0.14	0.5	9.2	8.9	3.1	3.1	2.0	0.15	8.6		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	DU	AN	DT	DT	DT	DT	DU	DU	DT	AN	DT	DT	DT	DT	AN	AN	AN	KW		AN

+: Dams with live offspring, -: dams without live offspring

a): Number of dams with live offspring

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

DT: Analysis by Dunnett type mean rank test.

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

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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 37-4. Observation of offspring (F₁)

EMEE 1000 mg/kg																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan- tation scars	Implan- tation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring				External abnormalities ^{b)}		
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio	Viability index	Viability index (%)	(Number)	(%)
							Male	Female	Total											
F04037	24	16	16	100.0	-	3	0	0	0		3	18.8	0.0	0.0	Total litter loss on day 0					
F04038	-	11	8	72.7	-	Total litter loss in utero														
F04039	23	17	15	88.2	+	13	7	4	11	0.64	2	86.7	73.3	84.6	0	0		0.0	0 0.0	
F04040	Not pregnant					Total litter loss in utero														
F04041	-	17	17	100.0	-	Total litter loss in utero														
F04042	24	16	15	93.8	-	4	0	0	0		4	26.7	0.0	0.0	Total litter loss on day 0					
F04043	Not pregnant					Total litter loss in utero														
F04044	23	16	8	50.0	+	5	2	2	4	0.50	1	62.5	50.0	80.0	0	0		0.0	0 0.0	
F04045	-	13	11	84.6	-	Total litter loss in utero														
F04046	Not pregnant					Total litter loss in utero														
F04047	24	17	16	94.1	-	5	0	0	0		5	31.3	0.0	0.0	Total litter loss on day 0					
F04048	23	14	12	85.7	-	1	0	0	0		1	8.3	0.0	0.0	Total litter loss on day 0					
Number of dams	6	9	9	9	2 ^{a)}	6			6	2	6	6	6	6			2	2	2	
Total		137	118			31	9	6	15		16				0	0		0		
Mean	23.5	15.2	13.1	85.5		5.2	1.5	1.0	2.5	0.57	2.7	39.1	20.6	27.4	0.0	0.0	0.0		0.0	
S.D.	0.5	2.1	3.5	15.8		4.1	2.8	1.7	4.5		1.6	29.6	32.7	42.5						
%					22.2															
Significance	**	NS	NS	*	**	**	**	**	**	---	**	**	**	**	---	---	---	---	---	
Statistical method	DU	AN	DT	DT	FT	DT	DU	DU	DT	NA	DT	DT	DT	DT	NA	NA	NA	NA	NA	

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: water for injection) (**: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

DT: Analysis by Dunnett type mean rank test.

FT: Analysis by Fisher's exact 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 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 38-1. Body weights of offspring (F₁) before weaning

Control (vehicle: water for injection)

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F01001	6.9	(5)	11.1	(5)	6.5	(9)	10.7	(9)
F01002	6.4	(12)	10.7	(12)	5.4	(4)	9.7	(4)
F01003	6.4	(7)	10.8	(7)	6.1	(7)	10.5	(7)
F01004	6.6	(6)	11.0	(6)	6.3	(7)	10.3	(7)
F01005	7.3	(8)	10.8	(8)	6.6	(7)	10.5	(7)
F01006	6.2	(11)	10.0	(11)	6.0	(6)	10.2	(5)
F01007	7.1	(5)	12.0	(5)	6.7	(9)	11.5	(9)
F01008	6.6	(7)	11.4	(7)	6.3	(6)	12.0	(6)
F01009	7.1	(4)	11.6	(4)	6.6	(10)	11.8	(10)
F01010	7.3	(8)	12.2	(8)	6.8	(6)	10.8	(6)
F01011	6.4	(8)	9.9	(8)	6.3	(8)	10.0	(8)
F01012	5.8	(9)	9.5	(9)	5.6	(7)	9.3	(6)
Number of dams	12		12		12		12	
Mean	6.7		10.9		6.3		10.6	
S.D.	0.5		0.8		0.4		0.8	

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 38-2. Body weights of offspring (F₁) before weaning

EMEE 62.5 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F02013	6.6	(8)	9.5	(8)	6.4	(8)	9.1	(8)
F02014	6.4	(7)	10.3	(7)	5.8	(7)	9.5	(7)
F02015	6.5	(9)	8.1	(9)	5.9	(7)	7.2	(7)
F02016	7.5	(12)	12.9	(12)	6.7	(4)	12.5	(3)
F02017	6.9	(8)	11.3	(8)	6.7	(6)	10.8	(6)
F02018	6.6	(8)	10.4	(8)	5.9	(8)	9.6	(8)
F02019	6.2	(8)	10.1	(8)	6.0	(9)	10.1	(9)
F02020	7.0	(10)	10.4	(10)	6.4	(6)	9.2	(6)
F02021	6.8	(6)	9.4	(6)	6.5	(10)	8.6	(10)
F02022	6.7	(6)	11.8	(6)	6.4	(8)	11.3	(8)
F02023	6.2	(11)	8.4	(10)	6.0	(7)	8.5	(7)
F02024	6.9	(7)	11.6	(7)	6.6	(6)	11.7	(6)
Number of dams	12		12		12		12	
Mean	6.7		10.4		6.3		9.8	
S.D.	0.4		1.4		0.3		1.5	
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.

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
Appendix 38-3. Body weights of offspring (F₁) before weaning

EMEE 250 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F03025	7.0	(5)	9.1	(4)	6.8	(6)	7.9	(4)
F03026	6.9	(11)	10.7	(11)	6.7	(7)	9.9	(6)
F03027	7.1	(9)	10.1	(9)	6.6	(6)	9.4	(6)
F03028	7.5	(1)	13.9	(1)	7.2	(4)	13.4	(4)
F03029	7.1	(5)	10.8	(5)	6.5	(10)	9.6	(10)
F03030	6.7	(7)	10.0	(7)	6.2	(7)	9.4	(7)
F03031	6.5	(4)	9.0	(4)	6.5	(9)	9.2	(9)
F03032	7.0	(5)	12.7	(5)	6.7	(6)	12.7	(6)
F03033	Not pregnant							
F03034	6.6	(10)	9.5	(10)	6.3	(7)	9.8	(7)
F03035	7.3	(7)	11.7	(7)	6.5	(5)	10.5	(5)
Number of dams	10		10		10		10	
Mean	7.0		10.8		6.6		10.2	
S.D.	0.3		1.6		0.3		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.

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 38-4. Body weights of offspring (F₁) before weaning

EMEE 1000 mg/kg

Dam No.	Days after birth			
	Male body weight		Female body weight	
	0	4	0	4
F04037	Total litter loss on day 0			
F04038	Total litter loss in utero			
F04039	5.7	(7)	5.2	(4) Total litter loss on day 1
F04040	Not pregnant			
F04041	Total litter loss in utero			
F04042	Total litter loss on day 0			
F04043	Not pregnant			
F04044	7.0	(2)	6.2	(2) Total litter loss on day 1
F04045	Total litter loss in utero			
F04046	Not pregnant			
F04047	Total litter loss on day 0			
F04048	Total litter loss on day 0			
Number of dams	2		2	
Mean	6.4		5.7	
S.D.				
Significance	---		---	
Statistical method	NA	NA	NA	NA

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

NS: Not significantly different from the control group.

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 39-1. General conditions in offspring (F₁) before weaning

Control (vehicle: water for injection)

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F01001	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01002	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01003	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01004	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01005	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01006	Number of offspring	17	17	17	16	16
	General appearance, No abnormality	17	17	16	16	16
	General appearance, Death	0	0	1	0	0
F01007	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01008	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01009	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01010	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01011	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01012	Number of offspring	16	16	16	15	15
	General appearance, No abnormality	16	16	15	15	15
	General appearance, Death	0	0	1	0	0
Number of offspring		176	176	176	174	174
General appearance, No abnormality		176	176	174	174	174
General appearance, Death				2		
Abnormal findings of offspring Lack of nursing						

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats

Appendix 39-2. General conditions in offspring (F₁) before weaning

EMEE 62.5 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F02013	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02014	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02015	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02016	Number of offspring	16	16	15	15	15
	General appearance, No abnormality	16	15	15	15	15
	General appearance, Death	0	1	0	0	0
F02017	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02018	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02019	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F02020	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02021	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02022	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02023	Number of offspring	18	18	18	17	17
	General appearance, No abnormality	18	18	17	17	17
	General appearance, Death	0	0	1	0	0
F02024	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
Number of offspring		186	186	185	184	184
General appearance, No abnormality		186	185	184	184	184
General appearance, Death			1	1		
Abnormal findings of offspring, Lack of nursing						

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 39-3. General conditions in offspring (F₁) before weaning

EMEE 250 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F03025	Number of offspring	11	11	9	8	8
	General appearance, No abnormality	11	9	8	8	8
	General appearance, Death	0	2	1	0	0
F03026	Number of offspring	18	18	18	18	18
	General appearance, No abnormality	18	18	18	18	17
	General appearance, Death	0	0	0	0	1
F03027	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03028	Number of offspring	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5
F03029	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
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	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F03033	Not pregnant					
F03034	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F03035	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
	Number of offspring	131	131	129	128	128
	General appearance, No abnormality	131	129	128	128	127
	General appearance, Death		2	1		1
	Abnormal findings of offspring, Lack of nursing					

Combined repeat dose and reproductive/developmental toxicity screening test of 1-Ethoxy-2-(2-methoxyethoxy)ethane by oral administration in rats
 Appendix 39-4. General conditions in offspring (F₁) before weaning

EMEE 1000 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F04037	Total litter loss on day 0					
F04038	Total litter loss in utero					
F04039	Number of offspring	11	11	0	0	0
	General appearance, Death	0	11	0	0	0
	Abnormal findings of offspring, Lack of nursing	11	0	0	0	0
F04040	Not pregnant					
F04041	Total litter loss in utero					
F04042	Total litter loss on day 0					
F04043	Not pregnant					
F04044	Number of offspring	4	4	0	0	0
	General appearance, No abnormality	4	0	0	0	0
	General appearance, Death	0	4	0	0	0
F04045	Total litter loss in utero					
F04046	Not pregnant					
F04047	Total litter loss on day 0					
F04048	Total litter loss on day 0					
	Number of offspring	15	15			
	General appearance, No abnormality	4				
	General appearance, Death		15			
	Abnormal findings of offspring, Lack of nursing	11				

信頼性保証書

表題 1-Ethoxy-2-(2-methoxyethoxy)ethane のラットを用いる反復投与毒性・生殖発生毒性併合試験

試験番号 R-13-002

この試験に関する信頼性保証部門による査察および監査状況等は下記のとおりであった。

査察・監査項目	査察・監査年月日	運営管理者および試験責任者への報告年月日
試験計画書	2013 年 9 月 26 日	2013 年 9 月 26 日
試験計画書変更書		
R-13-002-No.1	2013 年 10 月 15 日	2013 年 10 月 15 日
R-13-002-No.2	2013 年 12 月 19 日	2013 年 12 月 19 日
動物の受入れおよび検疫	2013 年 10 月 7 日	2013 年 10 月 7 日
群分け、検体調製および含量試験	2013 年 10 月 21 日	2013 年 10 月 22 日
体重測定、給餌量測定、投与および一般状態の観察	2013 年 10 月 22 日	2013 年 10 月 22 日
性周期観察	2013 年 10 月 23 日	2013 年 10 月 23 日
詳細な症状観察	2013 年 10 月 29 日	2013 年 10 月 29 日
交尾確認	2013 年 11 月 6 日	2013 年 11 月 6 日
尿検査	2013 年 11 月 27、28 日	2013 年 11 月 28 日
分娩状態および出生児の観察	2013 年 11 月 28 日	2013 年 11 月 28 日
機能検査	2013 年 11 月 29 日、 2013 年 12 月 2 日	2013 年 12 月 2 日
出生児剖検、雄動物剖検、血液学的検査、血液生化学的検査、器官重量測定および固定	2013 年 12 月 3 日	2013 年 12 月 3 日
病理組織学検査(標本作製:包埋)	2013 年 12 月 19 日	2013 年 12 月 19 日
報告書草案および生データ	2014 年 2 月 24～26 日	2014 年 2 月 26 日
最終報告書	2014 年 3 月 26 日	2014 年 3 月 26 日

試験は、「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成 23 年 3 月 31 日、薬食発 0331 第 8 号、平成 23・03・29 製局第 6 号、環企発第 110331010 号)を遵守して実施され、また、この報告書は試験に使用された方法および手順を正確に記載し、記載された結果は試験の生データを正確に反映していることを保証する。

2014 年 3 月 26 日

一般財団法人食品薬品安全センター 秦野研究所
信頼性保証部門責任者

