

最終報告書

2-イソブトキシエタノールのラットを用いる 反復投与毒性・生殖発生毒性併合試験

厚生労働省医薬食品局審査管理課 化学物質安全対策室 委託

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被験物質 2-イソブトキシエタノール

試験項目 反復投与毒性ならびに生殖発生毒性試験

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試験資料保管場所 秦野研究所資料保存室

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

2014 年 1 月 14 日

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(検疫を含む)

尿検査

血液学検査

(採血を含む)

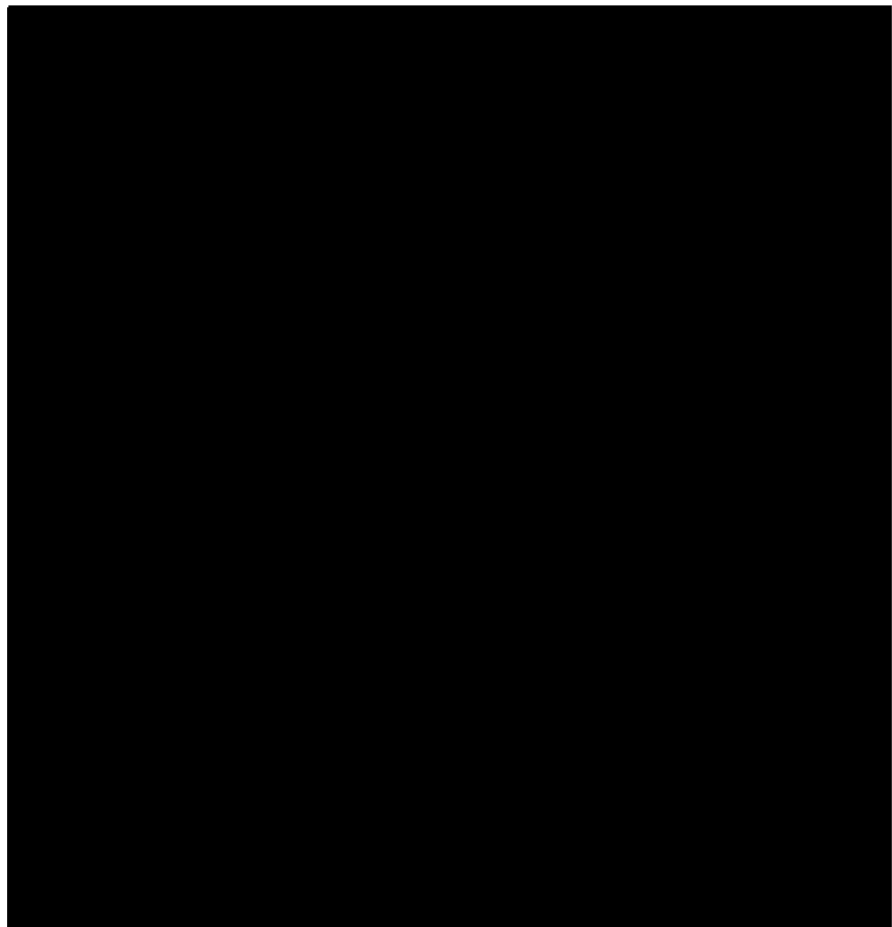
血液生化学検査

病理学検査

被験物質管理

検体調製

化学分析



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信頼性保証書

要約

2-イソブトキシエタノールの反復投与毒性ならびに生殖発生毒性試験を化審法ガイドラインに従って実施した。CrI:CD (SD)ラットに被験物質を日局注射用水で希釈して0、15、50ならびに150 mg/kgの用量で、雌雄各12匹/群に強制経口投与した。雄は42日間投与した後に剖検し、雌は交配前2週間および妊娠期間を通して哺育4日までの42～47日間投与し、出生児は哺育4日、分娩雌は哺育5日に剖検した。また、0および150 mg/kgの用量では非交配雌(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150 mg/kg群の雄5例は、14日間飼育して剖検した。

1. 反復投与毒性および回復性

赤色尿が150 mg/kg群の非交配雌を含む雌雄全例と50 mg/kg群の交配雌に観察された。その他、150 mg/kg群の交配雌2例と非交配雌1例に蒼白、排便量減少、消瘦、自発運動低下などが一過性に観察され、そのうちの分娩雌2例は尾の先端が黒色に変化した。150 mg/kg群の雄、交配雌および非交配雌では、投与1～2日の摂餌量が有意に低下し、投与4日のみ体重が低下傾向を示した。

血液学検査では、赤血球数、血色素濃度、ヘマトクリット値、MCHCの低下とMCV、MCHおよび網状赤血球比率の増加が150 mg/kg群の雄および非交配雌でみられ、赤血球数、血色素濃度の低下は50 mg/kg群の雄でも観察された。分娩雌では網状赤血球比率の増加が50 mg/kg以上、赤血球数の低下が150 mg/kgの群で観察された。骨髓塗抹検査では、赤芽球系細胞の増加が150 mg/kg群の雄および非交配雌と50 mg/kg以上の群の分娩雌でみられ、骨髓球比率の低下が15 mg/kg以上の群の雄および分娩雌で認められた。脾臓重量の増加は50 mg/kg以上の群の分娩雌と150 mg/kg群の雄および非交配雌で、肝臓および心臓の重量増加は150 mg/kg群の分娩雌および非交配雌でみられた。病理組織学検査では、肝臓の髄外造血、脾臓の褐色色素沈着の増加、肝臓のクッパー細胞に褐色色素沈着、さらには腎臓の近位尿細管に褐色色素沈着が50 mg/kg以上の群の雄および分娩雌と150 mg/kg群の非交配雌で観察され、赤脾髄領域の増加が50 mg/kg以上の群の分娩雌と150 mg/kg群の雄および非交配雌で認められ、大腿骨骨髓の赤芽球過形成は15 mg/kg以上の群の雄および分娩雌と150 mg/kg群の非交配雌で認められた。150 mg/kg群の分娩雌にみられた尾先端の黒色化については、壊死と潰瘍が確認された。

回復終了時の病理組織学検査では、肝臓および腎臓の褐色色素沈着が150 mg/kg群の雄および非交配雌で観察された。

2. 生殖発生毒性

性周期、交尾率および妊娠率、さらには妊娠期間、出産率、分娩状態および哺育状態に被験物質投与の影響は認められなかった。また、黄体数、着床数および着床率、出生児の生存率や形態、さらには哺育0日および哺育4日の出生児体重にも、被験物質投与の影響はみられなかった。

3. 無毒性量

大腿骨骨髓の赤芽球過形成と赤芽球系細胞の増加に伴う骨髓球比率の低下が 15 mg/kg 群の雄および分娩雌で認められたことから、雌雄動物の反復投与毒性に対する無毒性量 (NOAEL) は 15 mg/kg/day 未満と判断された。

150 mg/kg までの用量に親動物の生殖能力ならびに出生児の発育に及ぼす影響が認められなかったことから、生殖発生毒性に対する無毒性量は 150 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 2-イソブトキシエタノールを経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

試験ガイドラインとGLP

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

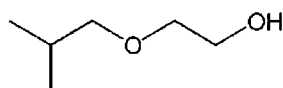
動物愛護

全ての実験操作は、「動物の愛護及び管理に関する法律」(昭和 48 年 10 月 1 日 法律第 105 号、平成 24 年 9 月 5 日 一部改正)、「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」(平成 18 年 4 月 28 日、環境省告示第 88 号)および「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」(平成 18 年 6 月 1 日、科発第 0601001 号)を遵守し、「財団法人食品薬品安全センター秦野研究所動物実験に関する指針」(平成 2 年 10 月 1 日、平成 22 年 10 月 1 日改正)に基づいて実施した。本試験における動物実験計画は、秦野研究所動物実験委員会の審査を受け、承認されている(動物実験承認番号:1120193A)。なお、承認された動物実験計画からの変更はなかった。

材料と方法

1. 被験物質

被験物質である 2-イソブトキシエタノール(別名:エチレングリコールモノイソブチルエーテル、CAS No. 4439-24-1、分子式: $C_6H_{14}O_2$ 、分子量:118.17、性状:無色澄明の液体、沸点:約 160℃(初留点)、密度:0.891 g/mL(20℃)、ロット番号:PER2952、含量:99.6%(毛管カラム GC)、Annex A、以下、2-IBE)は、XXXXXXXXXXより購入し(被験物質入手:2012 年 7 月 3 日)、使用時まで室温、遮光、密閉(実測値 20.1~24.6℃)で保管した。2-IBE の構造式を次に示す。



被験物質の安定性については、実験開始前および実験終了後に秦野研究所にて赤外吸収スペクトルを測定し、スペクトルに変化がなかったことが確認されている(試験番号:M-12-022)。

2. 動物および飼育方法

日本チャールス・リバー厚木飼育センターより 8.5 週齢の Sprague-Dawley (SD) 系 [CrI:CD(SD)、SPF] ラット雄 55 匹、雌 83 匹を購入し、飼育室(12 号室)に収容した。入荷日も含めて 13 日間、検疫と飼育環境への馴化のため飼育した。その間毎日、動物の一般状態を観察し、入荷日(検疫 1 日)および検疫終了日に体重を測定した。検疫・馴化期間中は動物の尾に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 2 日から毎日、性周期を観察した。入荷動物の入荷時および検疫終了時の体重は下記の通りであった。

動物入荷日	:2012 年 9 月 19 日
入荷時体重	:雄 259.0~308.4 g、雌 188.3~219.5 g
検疫終了日	:2012 年 10 月 1 日
検疫終了時体重	:雄 321.8~439.7 g、雌 209.0~288.5 g

検疫・馴化期間中、雄動物の 1 例(馴化番号 6)で検疫 10 日に半眼、検疫終了日の詳細な症状観察時に雄動物の 1 例(馴化番号 17)で背部に痂皮形成が認められた。また、雌動物の 1 例(馴化番号 35)は体重増加量が 10.6 g と他の例より低値であった。これらの動物と規則的な性周期の回帰が認められなかった 14 匹は群分けの対象から除外し、検疫終了時の体重に基づく体重別層化無作為抽出法により群分けを行った。なお、雌動物の 1 例(馴化番号 82)で検疫 8 日に紅涙がみられたが、その後異常は認められなかったことから、群分けの対象とした。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、他の予備試験(試験番号:S-12-034)に使用した。

動物は許容温度 21.0～25.0℃、許容湿度 40.0～75.0%、換気設定約 15 回/時間、明暗サイクル 12 時間(7 時～19 時)点灯、12 時間(19 時～7 時)消灯に設定された飼育室内で、金属製金網床ケージ(220w×270d×190h mm)に 1 匹ずつ(交配時は 2 匹)収容し、固型飼料(CE-2、日本クレア)と水道水(秦野市水道局給水)を自由に摂取させて飼育した(剖検前の絶食に関しては剖検の項を参照)。雌動物は分娩例全例について、妊娠 18 日から哺育 4 日までラット用プラスチック製繁殖ケージ(350w×400d×180h mm)に 1 匹ずつ収容し、床敷として紙パルプ製チップ(ペパークリーン、日本エスエルシー)を適宜供給した。飼育期間中の動物室の温度は 23.0～25.0℃、湿度は 41.5～74.0%であった。また、供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを確認した。

3. 投与検体

1) 調製

被験物質を秤量し、媒体(日局注射用水、製造元:光製薬、製造番号:C23VS1)を加え攪拌混和させ、3 w/v%液を調製した。さらに 3 w/v%液を媒体によって希釈し、1 ならびに 0.3 w/v%液を段階的に調製した。調製した検体は冷蔵・遮光下(実測値 1～12℃)で保管し、安定性の保証期間内に使用した。

2) 安定性試験

日局注射用水を媒体とした 0.02 および 20 w/v%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:M-12-022)。

3) 含量試験

初回調製検体(調製日:2012 年 10 月 1 日)について、0.3、1 および 3 w/v%濃度の被験物質含量を測定した。その結果、平均含量は調製指示濃度の 102.2～103.6%であり、各測定値のばらつきはそれぞれ平均値の 94.2～104.2%で規定範囲内にあった(Annex B)。

調製検体中の被験物質含量測定は Annex C、第 2 項に従った。

4. 投与量の設定および投与方法

本試験の投与量は、本被験物質を用いて行った「2-イソブトキシエタノールのラットを用いる反復投与毒性・生殖発生毒性併合試験(予備試験)」(試験番号:R-12-013)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、日局注射用水)、50、150 および 500 mg/kg の 2-IBE を 8 週齢の雌雄各 3 匹の SD 系ラットに 14 日間、反復強制経口投与した結果、雌の 500 mg/kg 群において 1 例が死亡し、生存例にも体表温低下、下腹部の汚れ等の重篤な症状と体重減少が観察された。150 mg/kg 群では、雌雄とも初回投与の後に赤色尿や体重減少が一過性にみられ、その後の一般状態および体重推移に

異常は認められなかったが、赤血球数および血色素量の低下、網状赤血球および脾臓重量の増加など貧血を示唆する明確な毒性影響が観察された。50 mg/kg 群の雄では明確な毒性徴候は認められなかったが、雌においては貧血を示唆する変化が観察された。

したがって、高用量には毒性影響を生じさせるが死亡や重度の苦痛を引き起こさない 150 mg/kg を、中用量には用量相関性を明確にする 50 mg/kg を設定し、低用量には無毒性量 (NOEL) が得られると期待される 15 mg/kg を設定した。

本試験では、雄動物は交配前 2 週間、交配期間を通して剖検前日まで (総投与回数 42 回)、雌動物は交配前 2 週間、交配期間、妊娠期間を通して分娩後の哺育 4 日まで (総投与回数 42～47 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)、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 52 分) に投与した。投与容量は 5 mL/kg とし、雄、サテライト群、ならびに交配前ならびに交配中の雌では週 1 回測定する体重を基に、交尾が確認された雌では最新の測定日の体重を基に投与液量を算出した。なお、対照群には媒体である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抛り、ラット用胃管による強制経口投与とした。

本試験の群構成および動物番号を以下に示した。

群	投与物質	投与量 (mg/kg)	濃度 (w/v%)	投与容量 (mL/kg)	動物番号	
					雄	雌
対照群	日局注射用水 (媒体)	0	0	5	M01001～M01012*	F01001～F01012
低用量群	2-IBE	15	0.3	5	M02013～M02024	F02013～F02024
中用量群	2-IBE	50	1	5	M03025～M03036	F03025～F03036
高用量群	2-IBE	150	3	5	M04037～M04048*	F04037～F04048
対照群 (サテライト群)	日局注射用水 (媒体)	0	0	5	—	F05049～F05058*
高用量群 (サテライト群)	2-IBE	150	3	5	—	F06059～F06068*

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

5. 検査法

1) 親動物 (F₀)

① 一般状態の観察

全例について、飼育期間中は毎日 1 回、投与期間中は投与前後の毎日 2 回以上観察した。症状が発現した場合、速やかな回復が期待されない所見を除き、症状が発現している間、断続的に、可能な限り観察を継続した。

② 回復および遅発毒性の観察

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

号の大きい各 5 例を最終投与翌日(回復 1 日)から 14 日間、毎日 1 回以上、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 02 分～16 時 45 分)に行った。

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

④機能検査

雄動物は動物番号の若い各群 5 例について、投与 39 日に自発運動測定と握力測定を実施し、投与 42 日に詳細な症状観察に引き続いて刺激に対する感覚運動反応を検査した。分娩例は投与期間が近接し、出来るだけ分娩から日数が経過した各群 5 例、サテライト群は動物番号の若い各群 5 例について、投与最終週に自発運動測定、握力測定および刺激に対する感覚運動反応を検査した。

(1) 刺激に対する感覚運動反応

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

(2) 握力測定

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

(3) 自発運動測定

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

⑤体重測定

雄および雌動物のサテライト群は、投与 1、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た。

⑥摂餌量測定

雄および雌動物のサテライト群は、投与 1～2、7～8、14～15、29～30、35～36、41～42 日、回復 6～7、12～13 日に測定し、サテライト群は投与 21～22 日にも測定した。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 日に測定した。

⑦尿検査

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

投与 37 日の検査では当日の投与後に、回復 13 日の検査では一般状態の観察終了後に動物を代

謝ケージに收容し、以下の項目について検査した。ただし、色調・濁度、試験紙による検査および尿沈渣は、採尿開始後約 4～8 時間の時点で採取した蓄尿で、その他の項目は約 24 時間の蓄尿で行った。

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

⑧性周期観察

雌については、検疫 2 日から性周期を観察し、群分け後、投与開始以降も引き続き交配雌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を正常と判断した。

⑨交配

投与 15 日の 15 時 30 分より同群内の雄と交配雌を 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。分娩例の投与終了時剖検では、投与期間が近接した各群の 5 例について採血を行った。サテライト群の投与終了時剖検では各群の動物番号が若い 5 例、回復 15 日にお

る剖検では回復観察に供した全例について採血を行った。いずれも解剖前 18～24 時間絶食させた後、腹部後大静脈から以下の(1)、(2)、(3)の順に注射筒を換えて採血した。

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

⑫血液学検査

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

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
骨髓塗抹検査	ライト・ギムザ染色	光学顕微鏡

網状赤血球比率(RET%)の測定では、直線性保証範囲外の高値を示す例がみられたが、RET%は赤血球中の網状赤血球を分画測定した粒子数から計算で求める値(比率)であり、赤血球数は直線性限界内にあったことから、試験評価に影響を及ぼさないと判断してデータを採用した。

⑬血液生化学検査

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

項目	測定法	使用機器
総蛋白濃度 (TP)	ビュレット法	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、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アミナーゼ活性 (γ -GTP)	IFCC 法	同上
アルカリフォスファターゼ活性 (ALP)	GSCC 法	同上
アスパラギン酸アミトランスフェラーゼ活性 (AST)	IFCC 法	同上
アラニンアミトランスフェラーゼ活性 (ALT)	IFCC 法	同上
乳酸脱水素酵素活性 (LDH)	JSCC 標準化対応法	同上
カルシウム濃度 (Ca)	OCPC 法	同上
総ビリルビン濃度 (tbil)	酵素法	同上
無機リン濃度 (IP)	モリブデン酸直接法	同上
胆汁酸濃度 (TBA)	酵素サイクリング法	同上
A/G 比	計算 (rALB/(TP-rALB))	同上
ナトリウムイオン濃度 (Na)	イオン電極法	全自動電解質分析装置 EA05 (エイアンドティー)
カリウムイオン濃度 (K)	同上	同上
塩素イオン濃度 (Cl)	同上	同上

⑭剖検および器官重量

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
交尾したが分娩しなかった例 (未分娩)	妊娠 26 日相当日	実施せず
サテライト群 (投与終了時剖検例)	投与 42 日の翌日	18～24 時間絶食
サテライト群 (回復観察例)	回復 15 日	18～24 時間絶食

全例について、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) および精囊 (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、精囊および凝固腺、卵巣、子宮、膣、膀胱、大腿骨および大

腿骨骨髓、骨格筋、坐骨神経、乳腺、および病変部を採取し、保存した。死亡動物以外の肺／気管支は 15 cm 水柱以下の圧力で、気管内に 10%中性緩衝ホルマリン溶液 5 mL 以下を注入し固定してから摘出して同固定液に保存した。精巣および精巣上体はブアン液に固定(長期保存は 10%中性緩衝ホルマリン溶液)し、その他の器官・組織は 10%中性緩衝ホルマリン溶液に固定した。

なお、未分娩例の器官重量値は評価対象から除外した。

⑮病理組織学検査

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

なお、投与期間終了時の剖検例で被験物質投与の影響が示唆された器官・組織については、低および中用量群の 5 例と回復期間終了時の剖検例についても病理組織学検査を実施した。

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

②剖検

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

6. データの解析法

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

その他のデータは、個体ごとに得られた値あるいは litter ごとの平均値を 1 標本とし、サテライト群内あるいはその他の群内で比較した。その際、解析の対象が 2 群の場合には、まず F 検定を行い、有意差が認められなければ Student's-t 検定を行った。F 検定において有意差が認められた場合は、Aspin-Welch 検定を行った。解析の対象が 3 群以上の場合は、先ず、Bartlett の方法により各群の分散の一致

性について検定(有意水準:5%)を行った。分散が一樣であった場合には、一元配置型の分散分析(有意水準:5%)を行い、群間に有意性が認められた場合は、Dunnett 法により多重比較を行った(有意水準:5%)。一方、いずれかの群で分散が 0 となった場合および分散が一樣でなかった場合には、Kruskal-Wallis の順位検定(有意水準:5%)を行い、群間に有意性が認められた場合には、Dunnett 型の検定法により多重比較を行った(有意水準:5%)。

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

2012 年 10 月 4 日の 11:00～14:26 に受変電設備の定期点検のために停電し、それに伴い動物飼育室内の照明が明期に消え、同日の 11:00～14:30 に空調が停止した。しかし、いずれの動物の一般状態にも上述事象に起因したと考えられる変化は認められず、また、温湿度(23.5～25.0℃、63.0～74.0%)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。

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

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

低用量群の雌 1 例(動物番号:F02014)は、妊娠 20 日相当日に分娩が確認されたことから、交尾確認日と実際の交尾日との間にズレがあったものと推察された。したがって、当該動物は妊娠期の体重および摂餌量の測定日が試験計画書から逸脱した可能性があると判断し、それらのデータは試験評価の対象から除外した。なお、同群のその他の動物から評価が十分できる例数のデータが得られていることから、試験成績の評価への影響はないと判断した。

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

試験成績

1. 親動物

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

初回投与の翌日に、150 mg/kg 群の非交配雌を含む雌雄全例と 50 mg/kg 群の交配雌 10 例に赤色尿が観察された。その後は、50 mg/kg 以上の群で赤色尿が散見されたが、投与期間終了後は消失した。

ただし、150 mg/kg 群の交配雌 2 例と非交配雌 1 例では、蒼白、排便量減少(無便を含む)、消瘦、自発運動低下または立毛が投与 3 日より 1～4 日間観察され、そのうちの交配雌 2 例(動物番号:F04038、F04044)では、妊娠期間中に尾の先端が黒色に変化した。その他、被験物質投与とは関連のない変化として、前肢、腰部あるいは頸部の脱毛が 15 mg/kg 群の雌 2 例、50 mg/kg 群の雌 1 例、150 mg/kg 群の雄 1 例および交配雌 1 例に認められた。回復観察中に被験物質投与の影響を示唆する異常は、雌雄とも観察されなかった。

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

雌雄の詳細な症状観察では、一般状態観察で異常がみられた 150 mg/kg 群の交配雌 1 例に蒼白および立毛が認められたが、被験物質投与による神経毒性を示唆する変化は認められなかった。

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

投与期間中の雄では、150 mg/kg 群の投与 4 日の体重が対照群より低値を示したが、有意差は認められなかった。回復期間中の雄では、150 mg/kg 群の体重が対照群より高値を示したが、これは 150 mg/kg 群において、対照群より体重が重い動物を回復観察に供したことが原因と考えられた。

投与期間中の交配雌では、150 mg/kg 群の投与 4 および 7 日の体重が対照群より低値を示したが、有意差は認められなかった。投与期間中の非交配雌でも、150 mg/kg 群の投与 4 日の体重が対照群より低値を示したが、有意差は認められなかった。回復期間中の非交配雌では、被験物質投与の影響を示唆する体重の変化は認められなかった。

妊娠期間中および哺育期間中の雌では、被験物質投与の影響を示唆する体重の変化は認められなかった。

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

投与期間中の雄では、150 mg/kg 群の投与 1 日(投与 1～2 日)の摂餌量が対照群と比較して有意に低下したが、投与 7 日以降の摂餌量には、被験物質投与の影響は認められなかった。回復期間中の雄では、被験物質投与の影響を示唆する摂餌量の変化は認められなかった。

投与期間中の交配雌では、150 mg/kg 群の投与 1 日(投与 1～2 日)の摂餌量が対照群と比較して有意に低下した。また、投与期間中の非交配雌でも、150 mg/kg 群の投与 1 日の摂餌量が対照群と比較して有意に低下した。回復期間中の非交配雌では、150 mg/kg 群の摂餌量が対照群より高値を示したが、有意差は認められなかった。

妊娠期間中および哺育期間中の雌では、被験物質投与の影響を示唆する摂餌量の変化は認められなかった。

5) 機能検査

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

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 16～Table 18, Appendix 16～Appendix 18)

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

③ 自発運動量測定 (Table 19～Table 21, Appendix 19～Appendix 21)

投与最終週に実施した非交配雌を含む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唆する変化は認められなかった。

6) 尿検査 (Table 22～Table 23, Appendix 22～Appendix 23)

投与期間中の雄では、150 mg/kg 群のナトリウムイオン濃度が対照群と比較して有意に増加したが、各電解質の排泄量には対照群と比較して有意差は認められなかった。その他の検査項目に被験物質投与の影響を示唆する変化は認められなかった。回復期間中の雄では、被験物質投与の影響を示唆する尿の変化は観察されなかった。

投与期間中の非交配雌では、150 mg/kg 群の 1 例(動物番号:F06060)に尿潜血が認められた以外に、被験物質投与の影響を示唆する変化は観察されなかった。回復期間中の非交配雌では、被験物質投与の影響を示唆する尿の変化は観察されなかった。

7) 血液学検査 (Table 24～Table 25, Appendix 24～Appendix 25)

① 雄動物

投与期間終了時の雄では、赤血球数および血色素が 50 mg/kg 以上の群で対照群と比較して有意に低下した。150 mg/kg 群ではさらにヘマトクリット値が有意に低下し、網状赤血球比率が有意に増加した。また、150 mg/kg 群では、MCV および MCH が有意な高値、MCHC が有意な低値を示した。その他、活性化部分トロンボプラスチン時間 (APTT) が 50 mg/kg 群(平均 24.8 sec)および 150 mg/kg 群(平均 23.3 sec)で有意に短縮したが、延長の変化ではないことから影響ではないと判断した。また、白血球分類では、150 mg/kg 群の好酸球比率(平均 0.7%)が対照群より有意に低下し、背景データの範囲(下表参照)を下回ったが、影響と考えられる増加とは逆の変化であった。

雄(投与終了時)	試験数*	サンプル数	平均	平均±2SD
APTT	4	20	27.5	24.1-30.9
好酸球比率	4	20	1.7	1.2-2.3

*: 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

回復期間終了時の雄では、150 mg/kg 群において、赤血球数の有意な低下、ヘマトクリット値、MCV および MCH の有意な増加、さらには網状赤血球比率の有意な低下が認められたが、貧血を示唆する変化は回復傾向にあった。

②雌動物

投与期間終了時の分娩雌でも貧血の傾向は観察され、赤血球数の有意な低下が 150 mg/kg 群、網状赤血球比率の有意な増加が 50 mg/kg 以上の群でみられた。

投与期間終了時の非交配雌では、150 mg/kg 群の赤血球数、血色素およびヘマトクリット値が対照群と比較して有意に低下し、網状赤血球比率は有意に増加した。また、同群の MCV および MCH が有意な高値を示し、MCHC は有意な低値を示した。活性化部分トロンボプラスチン時間、プロトロンビン時間および白血球分類に有意な変化はなかった。

回復期間終了時の非交配雌では、150 mg/kg 群の血色素、ヘマトクリット値、MCV および MCH が対照群と比較して有意に増加し、貧血を示唆する変化は消失した。

8) 骨髓塗抹検査 (Table 26～Table 27, Appendix 26～Appendix 27)

①雄動物

投与期間終了時の雄では、150 mg/kg 群で骨髓球系/赤芽球系の比が低値を示し、正染色赤芽球および総赤芽球系細胞の各比率が 150 mg/kg 群で対照群より有意に増加した。その他、赤芽球系細胞の増加に伴う相対変化と考えられる有意な比率の低下が、好中性後骨髓球は 15 mg/kg 以上の群で、好酸性後骨髓球およびリンパ球は 150 mg/kg 群で認められた。

回復期間終了時の雄では、被験物質投与の影響と考えられる有意な変化は認められなかった。

②雌動物

投与期間終了時の分娩雌では、50 mg/kg 以上の群で骨髓球系/赤芽球系の比が低値を示し、150 mg/kg 群で対照群より有意に低下した。また、多染色赤芽球および総赤芽球系細胞の各比率が 50 mg/kg 以上の群で対照群より有意に増加した。その他、赤芽球系細胞の増加に伴う相対変化と考えられる有意な比率の低下が、好中性骨髓球は 15 mg/kg 以上の群で、好中性後骨髓球は 150 mg/kg 群で、総顆粒球系細胞は 50 mg/kg 以上の群で認められた。

投与期間終了時の非交配雌でも、150 mg/kg 群の骨髓球系/赤芽球系の比が対照群と比較して有意に低下し、多染色赤芽球および総赤芽球系細胞の各比率が有意に増加した。その他、150 mg/kg 群の好中球とリンパ球の各比率が対照群より有意に低下した。

回復期間終了時の非交配雌では、150 mg/kg 群の前骨髓球の比率が対照群と比較して有意に増加し、好塩基性顆粒球および好塩基性赤芽球の比率が有意に低下したが、髓球系/赤芽球系の比に有意差はなかった。

9) 血液生化学検査 (Table 28～Table 29, Appendix 28～Appendix 29)

①雄動物

投与期間終了時の雄では、150 mg/kg 群の尿素窒素濃度が対照群より有意に低下したが、毒性を示唆する変化とは逆の変化であった。その他、同群の無機リン濃度が有意に増加したが、その他の項目に被験物質投与の影響を示唆する変化は認められなかった。

回復期間終了時の雄では、150 mg/kg 群の総ビリルビン濃度が対照群と比較して有意に低下したが、毒性を示唆する変化とは逆の変化であり、その他に被験物質投与の影響を示唆する変化は認められなかった。

②雌動物

投与期間終了時の分娩雌では、15および150 mg/kg群のLDHが対照群より高値を示したが、有意差は認められなかった。その他、15 mg/kg群の無機リン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。

投与期間終了時の非交配雌では、150 mg/kg群の総ビリルビン濃度が対照群より有意に低下したが、被験物質投与の影響を示唆する変化は認められなかった。

回復期間終了時の非交配雌では、150 mg/kg群のLDHが対照群より高値を示したが、有意差は認められなかった。

10) 器官重量 (Table 30～Table 31, Appendix 30～Appendix 31)

①雄動物

投与期間終了時の雄では、被験物質の用量に依存した脾臓重量の増加が認められ、150 mg/kg 群の脾臓重量が対照群より有意に増加した。生殖器を含むその他の器官には、被験物質投与の影響を示唆する重量の変化は認められなかった。

回復期間終了時の雄では、150 mg/kg 群の脾臓重量が高値を示し、絶対重量が対照群と比較して有意に増加した。その他、150 mg/kg 群の体重増加に伴う変化と考えられる相対重量の有意な低下が、精巣および精巣上体で認められたが、絶対重量に対照群との差はなかった。

②雌動物

投与期間終了時の分娩雌では、被験物質の用量に依存した脾臓重量の増加が認められ、50 mg/kg 以上の群で対照群と比較して有意に増加した。また、150 mg/kg 群の心臓、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。その他、15 および 50 mg/kg 群の副腎の絶対重量が対照群と比較して有意に増加したが、用量に依存した変化ではなかった。

投与期間終了時の非交配雌では、150 mg/kg 群の脾臓重量の他、心臓および肝臓の重量も対照群と比較して有意に増加した。その他の器官に被験物質投与の影響を示唆する重量の変化は認められなかった。

回復期間終了時の非交配雌では、150 mg/kg 群の腎臓重量が高値を示し、絶対重量が対照群と比較して有意に増加したが、同群の脾臓重量に対照群との差はなかった。

11) 剖検所見 (Table 32～Table 33, Appendix 32～Appendix 33)

①雄の投与終了時剖検例

投与 42 日の翌日に剖検した雄動物、対照群 7 例、15 mg/kg 群 12 例、50 mg/kg 群 12 例および 150 mg/kg 群 7 例の剖検所見は以下の通りである。

胃では、前胃粘膜の浮腫様変化が 150 mg/kg 群の 2 例に観察された。

脾臓では、大型化が 150 mg/kg 群の 7 例(全例)にみられた。

腎臓では、15 mg/kg 群の 1 例で両側性の淡色斑がみられた。

精巣上体では、片側尾部の黄白色結節が 150 mg/kg 群の 1 例にみられたが、対照群の 1 例にも認められた変化であった。

②雄の回復観察例

回復 15 日に剖検した雄動物、対照群 5 例および 150 mg/kg 群 5 例の剖検所見は以下の通りである。腎臓では、両側性の大型化が 150 mg/kg 群の 1 例にみられ、脾臓では、大型化が 150 mg/kg 群の 2 例にみられた。

その他、両前肢の脱毛が 150 mg/kg 群の 1 例に観察された。

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雌動物、対照群 12 例、15 mg/kg 群 11 例、50 mg/kg 群 12 例および 150 mg/kg 群 12 例の剖検所見は以下の通りである。

脾臓では、大型化が 50 mg/kg 群の 3 例と 150 mg/kg 群の 9 例に観察された。脾臓の大型化がみられた 150 mg/kg 群の 1 例(動物番号:F04048)では、肝臓の尾状葉に結節が認められた他、肺や腺胃粘膜に暗色点がみられ、他の 1 例(動物番号:F04040)では、顎下リンパ節の大型化を伴っていた。

胃では、上記の他、前胃粘膜の浮腫様変化が 150 mg/kg 群の 1 例で観察されたが、同様の変化は対照群の 1 例にも観察された。

尾では、先端が脱落し、黒色を呈した例が 150 mg/kg 群の 2 例で認められた。

皮膚では、被験物質投与とは関連のない変化と考えられる脱毛が 15 mg/kg 群の 2 例と 150 mg/kg 群の 1 例に認められた。

その他、50 mg/kg 群において肝臓の大型化が 1 例、胸腺の小型化が 2 例、副腎の大型化が 1 例、15 mg/kg 群において肺の暗色域が 1 例(動物番号:F02017)にみられたが、いずれも用量に依存した変化ではなく、胸腺の小型化は対照群の 1 例にも観察された。

④不妊例

妊娠 26 日相当日に剖検した不妊例、15 mg/kg 群 1 例に異常は認められなかった。

⑤サテライト群の投与終了時剖検例

投与 42 日の翌日に剖検した非交配雌、対照群 5 例および 150 mg/kg 群 5 例の剖検所見は以下の通りである。

脾臓では、大型化が 150 mg/kg 群の 4 例に観察された。

胃では、前胃粘膜の浮腫様変化が 150 mg/kg 群の 1 例に観察された。

⑥サテライト群の回復観察例

回復 15 日に剖検した非交配雌、対照群 5 例および 150 mg/kg 群 5 例の剖検所見は以下の通りである。

腎臓では、両側性の大型化と表面粗造が 150 mg/kg 群の 1 例に観察された。

脾臓では、大型化が 150 mg/kg 群の 1 例に観察された。なお、周囲組織と癒着した脾臓が対照群の 1 例(動物番号:F05054)で観察されたが、被験物質投与群には雌雄とも、同様の所見は観察されなかった。

12) 病理組織学検査 (Table 34～Table 35, Appendix 34～Appendix 35)

①雄の投与終了時剖検例

投与終了時剖検例のうち、対照群および 150 mg/kg 群の 5 例について病理組織学検査を実施し、さらに被験物質の影響が示唆された肝臓、脾臓、腎臓および骨髄については、15 および 50 mg/kg 群の 5 例についても病理組織学検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以下の通りである。

甲状腺では、150 mg/kg 群の 1 例に異所性の胸腺組織が観察されたが、被験物質投与の影響を示唆する所見ではなかった。

心臓では、150 mg/kg 群の 1 例にごく軽度の炎症性細胞浸潤が観察されたが、その他の動物に類似の所見はみられなかった。

肺では、150 mg/kg 群の 2 例に肺泡に泡沫細胞の集簇が観察されたが、ごく軽度な変化であった。

肝臓では、髄外造血とクッパー細胞の褐色色素沈着が 50 mg/kg 以上の群で観察され、150 mg/kg 群で両者の頻度および程度が対照群と比較して有意に増加した。その他に門脈周囲性の肝細胞の脂肪化、小肉芽腫および単細胞壊死が被験物質投与群で観察されたが、対照群と比較して程度および頻度の差はなかった。

脾臓では、脂肪浸潤と単細胞壊死が 150 mg/kg 群の各 1 例にみられたが、いずれもごく軽度な変化であり、単細胞壊死は対照群の 2 例にも認められた。

脾臓では、褐色色素沈着および髄外造血が対照群を含む各投与群で認められ、その程度が褐色色素沈着は 50 mg/kg 以上の群で、髄外造血は 150 mg/kg 群で対照群と比較して有意に増加した。また、赤脾髄領域の増加が 150 mg/kg 群で認められ、対照群と比較して程度および頻度が有意に増加した。

腎臓では、近位尿細管の褐色色素沈着が 50 mg/kg 以上の群で観察され、150 mg/kg 群で頻度および程度が対照群と比較して有意に増加した。その他、好塩基性尿細管、リンパ球浸潤および嚢胞が被験物質投与群で観察されたが、その頻度および程度は被験物質の影響を示唆するものではなかった。

精巣では、精細管委縮が 150 mg/kg 群の 2 例にみられたが、いずれもごく軽度な変化であった。

精巣上部では、剖検時に黄白色結節が認められた 150 mg/kg 群の 1 例および対照群の 1 例に精子肉芽腫が観察された以外に、異常はみられなかった。

前立腺では、被験物質の影響を示唆する変化は認められなかった。

大腿骨骨髓では、赤芽球の過形成が 15 mg/kg 以上の群で認められ、150 mg/kg 群の頻度および程度が対照群と比較して有意に増加した。

②雄の回復観察例

回復 15 日に剖検した対照群および 150 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、脾臓、腎臓および骨髓について病理組織学検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以下の通りである。

肝臓では、クッパー細胞の褐色色素沈着が 150 mg/kg 群の 1 例に認められたが、ごく軽度なものであった。また、投与期間終了時にみられた髄外造血はいずれの動物にも認められなかった。その他、門脈周囲性の肝細胞の脂肪化、小肉芽腫および単細胞壊死が 150 mg/kg 群で観察されたが、対照群と比較して程度および頻度の差はなかった。

脾臓では、褐色色素沈着および髄外造血が 150 mg/kg 群で認められたが、対照群と比較して程度および頻度の差はなかった。また、赤脾髄領域の増加が 150 mg/kg 群の 1 例に認められたが、ごく軽度なものであった。

腎臓では、近位尿細管の褐色色素沈着が 150 mg/kg 群で観察され、その頻度が対照群と比較して有意に増加した。その他、好塩基性尿細管が 150 mg/kg 群で観察されたが、被験物質の影響を示唆する頻度および程度はではなかった。

骨髓では、赤芽球の過形成が 150 mg/kg 群の 2 例で認められたが、ごく軽度な変化であった。

皮膚では、剖検時に脱毛がみられた 150 mg/kg 群の 1 例の脱毛部で毛胞の委縮が観察された。

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対照群および 150 mg/kg 群の 5 例について、病理組織検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以下の通りである。

下垂体では、ラトケ嚢遺残が 150 mg/kg 群の 1 例に観察されたが、対照群の 1 例にもみられた所見であった。

甲状腺では、150 mg/kg 群の 1 例に異所性の胸腺組織が観察されたが、被験物質投与の影響を示唆する所見ではなかった。

胸腺では、剖検時に小型化がみられた 50 mg/kg 群の 2 例と対照群の 1 例に委縮が観察されたのみであった。

肺では、150 mg/kg 群の 3 例に肺泡に泡沫細胞の集簇が観察されたが、ごく軽度な変化であった。その他、剖検時に暗色点がみられた 150 mg/kg 群の 1 例(動物番号:F04048)では胸膜の限局性肥厚が、また暗色域がみられた 15 mg/kg 群の 1 例(動物番号:F02017)では、褐色色素を含む肺泡内マクロファージの浸潤が認められた。

肝臓では、髄外造血が 15 mg/kg 以上の群、クッパー細胞の褐色色素沈着が 50 mg/kg 以上の群でそれぞれ観察され、50 mg/kg 以上の群で両者の頻度および程度が対照群と比較して有意に増加した。

その他、門脈周囲性の肝細胞の脂肪化、小肉芽腫および単細胞壊死が被験物質投与群で散見されたが、対照群と比較して程度および頻度の差はなかった。剖検時に肝臓の異常の認められた 150 mg/kg 群の 1 例(動物番号:F04048)では、尾状葉の結節部に限局性の壊死巣が観察された。

胃では、150 mg/kg 群の 1 例に胃底腺の拡張がみられたが、被験物質の影響を示唆する変化ではなかった。なお、剖検時に前胃粘膜の浮腫様変化がみられた 150 mg/kg 群の 1 例(動物番号:F04043)と腺胃粘膜に暗色点がみられた 150 mg/kg 群の 1 例(動物番号:F04048)に異常はなかった。

脾臓では、褐色色素沈着および髄外造血が対照群を含む各投与群で認められ、その程度が 50 mg/kg 以上の群で対照群と比較して有意に増加した。また、赤脾髄領域の増加が 50 mg/kg 以上の群で認められ、150 mg/kg 群の程度および頻度が対照群と比較して有意に増加した。その他、15 mg/kg 群の 1 例で軽度のうっ血がみられたが、用量に依存した所見ではなかった。

腎臓では、近位尿細管の褐色色素沈着が 50 mg/kg 以上の群で観察され、150 mg/kg 群で頻度および程度が対照群と比較して有意に増加した。その他、好塩基性尿細管およびリンパ球浸潤が被験物質投与群で観察されたが、被験物質の影響を示唆する変化ではなかった。

副腎では異常は認められず、剖検時に大型化がみられた 50 mg/kg 群の 1 例にも異常はなかった。

大腿骨骨髓では、赤芽球の過形成が被験物質投与群で認められ、50 mg/kg 以上の群で頻度が、150 mg/kg 群で程度が対照群と比較して有意に増加した。

皮膚では、剖検時に脱毛がみられた 15 mg/kg 群の 2 例と 150 mg/kg 群の 1 例の脱毛部で毛胞の萎縮が観察された。

尾では、剖検時に先端が黒色化した 150 mg/kg 群の 1 例について病理組織学検査を実施した結果、壊死と潰瘍が確認された。

④サテライト群の投与終了時剖検例

非交配雌の投与終了時剖検例、対照群 5 例および 150 mg/kg 群 5 例の病理組織所見は以下の通りである。

心臓では、150 mg/kg 群の 1 例にごく軽度の単核細胞浸潤が観察されたが、その他の動物に類似の所見はみられなかった。

肺では、150 mg/kg 群の 1 例に肺泡に泡沫細胞の集簇が観察されたが、ごく軽度な変化であった。

肝臓では、髄外造血とクッパー細胞の褐色色素沈着が 150 mg/kg 群で観察され、頻度および程度が対照群と比較して有意に増加した。その他に門脈周囲性の肝細胞の脂肪化、小肉芽腫および単細胞壊死が 150 mg/kg 群で観察されたが、対照群と比較して程度および頻度の差はなかった。

脾臓では、褐色色素沈着および髄外造血が対照群と 150 mg/kg 群で認められ、150 mg/kg 群の髄外造血は対照群と比較して程度が有意に増加した。また、赤脾髄領域の増加が 150 mg/kg 群の 3 例で認められたが、対照群と比較して程度および頻度の差はなかった。

腎臓では、近位尿細管の褐色色素沈着が 150 mg/kg 群で観察され、頻度および程度が対照群と比較して有意に増加した。その他、髄質の鉍質沈着が 150 mg/kg 群の 1 例で観察されたが、ごく軽度の変化であった。

大腿骨骨髓では、赤芽球の過形成が 150 mg/kg 群で認められ、その頻度が対照群と比較して有意に増加した。

⑤サテライト群の回復観察例

回復 15 日に剖検した非交配雌、対照群の 5 例および 150 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、脾臓、腎臓および骨髓について病理組織学検査を実施した。病理組織所見は、以下の通りである。

肝臓では、クッパー細胞の褐色色素沈着が 150 mg/kg 群で認められ、頻度および程度が対照群と比較して有意に増加した。その他、門脈周囲性の肝細胞の脂肪化および小肉芽腫が 150 mg/kg 群で観察されたが、対照群と比較して程度および頻度の差はなかった。

脾臓では、褐色色素沈着および髓外造血が 150 mg/kg 群で認められたが、対照群と比較して程度および頻度の差はなかった。

腎臓では、近位尿細管の褐色色素沈着が 150 mg/kg 群で観察され、その頻度および程度が対照群と比較して有意に増加した。その他、好塩基性尿細管、リンパ球の浸潤および髓質の鉍質沈着が 150 mg/kg 群で観察されたが、被験物質の影響を示唆する変化ではなかった。

大腿骨骨髓では、赤芽球の過形成が 150 mg/kg 群の 2 例で認められたが、ごく軽度な変化であった。

2. 生殖能力

1) 性周期および交配成績 (Table 36～Table 37, Appendix 36～Appendix 37)

投与開始後に 150 mg/kg 群の 2 例で性周期の異常が観察されたが、同群の交尾率および妊娠率はいずれも 100%であった。その他の群の交尾率、妊娠率、さらには投与期間中の平均発情回帰日数、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唆する変化は認められなかった。

2) 出産率および妊娠期間 (Table 38, Appendix 38)

妊娠期間および出産率に被験物質投与の影響は認められなかった。

3) 分娩および哺育状態

分娩状態は、いずれの動物も良好であった。また、いずれの動物の哺育状態についても、異常は認められなかった。

4) 黄体数、着床数および着床率 (Table 38, Appendix 38)

黄体数、着床数および着床率に被験物質投与の影響は認められなかった。

3. 出生児

1) 生存 (Table 38, Appendix 38)

産児数、出産児数、分娩率、生児出産率、出生率、哺育 0 日および哺育 4 日の性比、新生児生存率に被験物質投与の影響は認められなかった。また、哺育 0 日に産児の外表奇形は観察されなかった。

2) 体重 (Table 39, Appendix 39)

哺育 0 日および哺育 4 日に測定した出生児体重には、雌雄とも被験物質投与の影響を示唆する変化は認められなかった。

3) 出生児観察 (Table 40～Table 41, Appendix 40)

死亡児および哺育 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 2-イソブトキシエタノールを経口投与し、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

初回投与の翌日に 150 mg/kg 群の雄と 50 mg/kg 以上の群の雌に赤色尿が観察された。類似物質の 2-(1-メチルエトキシ)エタノール¹⁾ や 2-tert-ブトキシエタノール²⁾ の反復経口投与毒性試験においても、初回投与後のみに着色尿が観察されていることから、本試験でみられた赤色尿はこれら物質に共通した急性影響と考えられる。さらに 150 mg/kg 群の雄、交配雌および非交配雌では、投与 1～2 日の摂餌量が低下し、投与 4 日のみ体重が低下傾向を示したことから、これらも被験物質投与の影響と考えられる。しかしながら、その後の体重推移および摂餌量には影響が認められず、投与 37 日に実施した尿検査においても非交配雌 1 例で潜血がみられた以外に被験物質投与の影響は観察されていないことから、被験物質の影響は、初回投与後に最も強く発現するものと推察される。ただし、150 mg/kg 群の分娩雌 2 例では、被験物質の反復投与により蒼白などの症状を呈し、尾先端が壊死したこと、50 mg/kg 群では雌のみに初回投与後の赤色尿が観察されたことなどから、雌動物は雄動物よりも毒性症状が発現しやすいと考えられた。

投与終了時の血液学検査では、赤血球数の低下が 50 mg/kg 以上の群の雄および分娩雌と 150 mg/kg 群の非交配雌に、血色素濃度の低下が 50 mg/kg 以上の群の雄と 150 mg/kg 群の非交配雌に観察されたことから、これらの動物では貧血を起こしていたことが示された。また、網状赤血球比率の増加が 150 mg/kg 群の雄および 50 mg/kg 以上の群の分娩雌さらには 150 mg/kg 群の非交配雌でみら

れ、肝臓や脾臓の病理組織学検査では髄外造血、骨髄では赤芽球の過形成、骨髄塗抹検査では骨髄球系/赤芽球系の比の低下が認められ、脾臓の赤脾髄領域の増加が 50 mg/kg 以上の群の分娩雌と 150 mg/kg 群の雄および非交配雌で認められていることから、慢性的な貧血に対して造血機能が亢進していたものと推察される。大腿骨骨髄では赤芽球の過形成が 15 mg/kg 以上の群の雄および分娩雌と 150 mg/kg 群の非交配雌で認められ、赤芽球系細胞の増加に伴う相対変化と考えられる好中性後骨髄球比率の低下は 15 mg/kg 以上の群の雄で、好中性骨髄球比率の低下は 15 mg/kg 以上の群の分娩雌で認められている。なお、15 mg/kg 群の分娩雌 1 例でみられた肝臓の髄外造血については、同例に溶血性貧血を示唆する変化が認められていないことから、分娩に伴う変化と推察し、被験物質の影響ではないと判断した。

投与終了時の器官重量測定で 50 mg/kg 以上の群の分娩雌および 150 mg/kg 群の雄および非交配雌でみられた脾臓重量の増加は、髄外造血の亢進に伴う変化で被験物質の影響と考えられる。また、150 mg/kg 群の分娩雌でみられた肝臓の相対重量(平均 33.993 mg/g)の増加と同群の非交配雌でみられた肝臓の絶対重量(平均 7921.6 mg)および相対重量(平均 27.686 mg/g)の増加は、いずれも背景データの範囲(下表参照)を上回ったことから、髄外造血の亢進に伴う変化と推察された。150 mg/kg 群の分娩雌でみられた心臓の相対重量(3.489 mg/g)の増加と非交配雌でみられた心臓の絶対重量(平均 991.2 g)と相対重量(平均 3.461 mg/g)の増加についても、心筋の病理組織学的変化はみられていないが、貧血に対する代償性の肥大を来している可能性が考えられた。150 mg/kg 群の分娩雌でみられた腎臓の相対重量(平均 7.026 mg/g)の増加は、背景データの範囲(下表参照)内であることから、被験物質の影響ではないと判断した。

分娩雌(投与終了時)	試験数*	サンプル数	平均	平均±2SD
肝臓の相対重量	4	47	32.488	31.309-33.668
心臓の相対重量	4	47	3.313	3.076-3.549
腎臓の相対重量	4	47	6.599	6.034-7.164

*: 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

非交配雌(投与終了時)	試験数*	サンプル数	平均	平均±2SD
肝臓の絶対重量	4	20	6931.8	6430.5-7433.0
肝臓の相対重量	4	20	25.140	23.580-26.701
心臓の絶対重量	4	20	883.5	815.5-951.5
心臓の相対重量	4	20	3.210	2.989-3.430

*: 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

投与終了時剖検例の病理組織学検査から、50 mg/kg 以上の群の雄および分娩雌、さらには 150 mg/kg 群の非交配雌でみられた脾臓の褐色色素沈着の増加、肝臓のクッパー細胞の褐色色素沈

着、さらには腎臓の近位尿細管の褐色色素沈着は、溶血した赤血球由来のヘモジデリン色素と考えられ、被験物質投与により溶血性貧血が誘発されたと判断される。また、150 mg/kg 群の分娩雌にみられた尾先端の黒色化については、壊死と潰瘍が確認されたことから、溶血による貧血状態を反映した循環障害によるものと推察された。類似物質の 2-ブトキシエタノールでは、インビトロの実験³⁾ からその代謝物のブトキシ酢酸が赤血球内の ATP を減少させ、赤血球の溶血を起こすと推定されていることから、本被験物質も同様の機序により溶血を起こしたものと推察される。なお、2-ブトキシエタノールは、精巣の委縮を誘発することも報告⁴⁾ されているが、本試験における精巣重量および精巣の病理組織学検査では、精巣毒性を示唆する所見は認められなかった。

投与終了時の血液生化学検査では、150 mg/kg 群の雄で無機リン濃度(平均 6.9 mg/dL)が増加し、背景データ(下表参照)から逸脱したが、腎臓の機能障害を示唆する変化は認められていないことから、被験物質の影響ではないと判断した。

雄(投与終了時)	試験数*	サンプル数	平均	平均±2SD
血中無機リン濃度	4	20	6.0	5.6-6.4

*: 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

投与期間中の雄では、尿中ナトリウムイオン濃度が 150 mg/kg 群で増加したが、血中ナトリウムイオン濃度に被験物質の影響を示唆する変化がみられていないことから、偶発的な変化と判断した。

2. 毒性の回復性

回復観察中に赤色尿は観察されなかった。回復終了時の血液学検査では、150 mg/kg 群の雄で赤血球数の低下が認められたが対照群と差はわずかであり、その他貧血を示唆する変化はいずれも回復傾向にあった。

回復期間終了時の病理組織学検査では、投与終了時にみられた肝臓および腎臓の褐色色素沈着が 150 mg/kg 群の雄および非交配雌に観察されたが、肝臓での髓外造血は消失し、骨髓での赤芽球の過形成もごく軽度なものが観察されたのみであった。また、回復期間終了時の骨髓検査でも被験物質投与の影響を示唆する変化は認められなかったことから、被験物質により誘発される造血機能の亢進は、投与終了後すみやかに正常に戻るものと推察された。

3. 生殖発生毒性

投与開始後の性周期、交尾率および妊娠率に被験物質投与の影響を示唆する変化は認められなかった。妊娠期間、出産率、分娩状態および哺育状態に被験物質投与の影響は認められなかった。また、黄体数、着床数および着床率にも被験物質投与の影響は認められなかった。これらのことから、150 mg/kg までの用量は、親動物に生殖毒性を示さないと考えられる。類似物質の 2-tert-ブトキシエタノール²⁾ や 2-(1-メチルエトキシ)エタノール⁵⁾ の生殖発生毒性試験においても親動物の性周期、交尾お

よび受胎能力、妊娠期間、分娩ならびに哺育状態等の項目に影響は認められていない。また、出生児の生存率や形態、さらには哺育 0 日および哺育 4 日の出生児体重にも、被験物質投与の影響はみられなかったことから、150 mg/kg までの投与量は、次世代にも影響を及ぼさないと考えられる。

4. 無毒性量

大腿骨骨髓の赤芽球過形成と赤芽球系細胞の増加に伴う骨髓球比率の低下が 15 mg/kg 群の雄および分娩雌で認められたことから、雌雄動物の反復投与毒性に対する無毒性量 (NOAEL) は 15 mg/kg/day 未満と判断された。

150 mg/kg までの用量に親動物への生殖毒性ならびに出生児への発生毒性を示唆する変化は認められなかったことから、生殖発生毒性に対する無毒性量は 150 mg/kg/day と判断された。

参考文献

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Annex A

検査成績書 093-02635

<https://www.siyaku.com/cgi-bin/gx.cgi/AppLogic+ufg...>

検 査 成 績 書

財団法人食品薬品安全センター 秦野研究所/化学物質管理室 御
虫2012年7月3日
和光純薬工業株式会
社

Code No. 093-02635

2-イソブトキシエタノール (エチレングリコールモノイソブチルエーテル)

規格/等級	和光一級
Lot No.	PER2952
数量	500ml

検査項目	検査成績	規格値
外観	無色澄明の液体	無色～僅かにうすい黄色、 澄明の液体
密度(20℃)	0.891g/ml	0.887～0.895g/ml
屈折率 $n_{20/D}$	1.4155	1.411～1.417
水分	0.09%	0.2%以下
酸(CH ₃ COOHとして)	0.05%以下	0.05%以下
含量(毛管カラムGC)	99.6%	97.0%以上
検査年月日	2007/12/21	

判定	合格	検査責任者	
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成績書発行番号 9861464

Annex B

SOP/CHE/001
採用開始 2010年4月23日

試験番号	R - 12 - 014
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含 量 試 験 結 果

被験物質：2-イソブトキシエタノール
ロット番号：PER2952
媒 体：日局注射用水

調製年月日：2012年10月1日
測定年月日：2012年10月1日

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 $B/A \times 100$ (%)	平均含量 (%)	ばらつき $B/C \times 100$ (%)
1	3.00	3.017	3.106	100.6	103.6	97.1
2		3.217		107.2		103.6
3		3.086		102.9		99.4
4	10.0	10.40	10.21	104.0	102.2	101.9
5		10.64		106.4		104.2
6		9.617		96.2		94.2
7	30.0	30.03	31.03	100.1	103.5	96.8
8		30.95		103.2		99.7
9		32.12		107.1		103.5

含量の判断基準(溶液検体)

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

Annex C

1. 被験物質原体の安定性の測定方法

① 使用機器

フーリエ変換赤外分光光度計 (FTIR-8300) 島津製作所

② 測定条件

測定方法 液膜法
波数範囲 4000～400 cm^{-1}

③ 測定方法

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

2. 投与検体中の被験物質含量測定法

① 試薬

蒸留水 (HPLC用) 和光純薬工業
アセトニトリル (HPLC用) 和光純薬工業
1,3-ベンゾジオキソール (和光一級) 和光純薬工業

② 使用機器

電子天秤 (R200D) ザルトリウス
ガスクロマトグラフ (GC) システム 島津製作所
主要構成: GC-14B (ガスクロマトグラフ)、AOC-20i (オートインジェクタ)、C-R7A または C-R7A plus (データ処理装置)

③ 内部標準溶液 (以下、IS 溶液) の調製

1,3-ベンゾジオキソール 約10 mgを精密に量り、アセトニトリルに溶解して20 mLとする。この液2 mLを採り、アセトニトリルで100 mLとする (約10 $\mu\text{g/mL}$)。

④ 標準溶液の調製

被験物質 約50 mgを精密に量り、蒸留水に溶解して正確に25 mLとし、標準原液 (約2 mg/mL) とする。この標準原液1.5、1及び1.5 mLを正確にとり、蒸留水を加えてそれぞれ正確に20、10及び10 mLとし、標準溶液 (約150、200および300 $\mu\text{g/mL}$ 、各濃度 $n=1$) を調製する。これらの標準溶液とIS溶液を1:4 (v/v) の割合で混合し、測定用標準溶液とする。

⑤ 試料溶液の調製

投与検体の1 mLを正確にとり、蒸留水で適宜希釈し、検量線の範囲内となるように試料溶液を調製する。これらの試料溶液とIS溶液を1:4 (v/v) の割合で混合し、測定用試料溶液とする。測定用試料溶液は、投与検体の採取から $n=3$ で調製する。

⑥ 検量線の作成および投与検体中被験物質濃度の算出

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

⑦ ガスクロマトグラフ測定条件

検出器	水素炎イオン化検出器 (FID)
	水素60 kPa、空気50 kPa、メイクアップガス30 kPa (ヘリウム)
分析カラム	TC-624 (長さ30 m、内径0.53 mm、膜厚3.0 μm 、GLサイエンス)
キャリアガス	ヘリウム (100 kPa)
カラム温度	80°C (4分) → 30°C / 分 → 250°C (2分)
注入口設定温度	250°C
検出器設定温度	250°C
試料注入量	0.5 μL
試料注入方式	スプリットレス (サンプリング時間0.5分)
オートインジェクタ洗浄液	アセトニトリル
モニター時間	7分

Annex C (continued)

システムの適合性	分析開始前に、測定用標準溶液(約200 µg/mL)を3回測定し、2-IBEのピーク保持時間およびISに対するピーク面積比の相対標準偏差(%)がそれぞれ±3.0%以内および±5.0%以内であることを確認する。
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⑧ 数値の取り扱い

- 1) システム適合性におけるピーク保持時間、ピーク面積は機器の出力値をそのまま使用する。ピーク保持時間の平均値は、四捨五入して小数点以下第3位まで、ピーク面積比およびその平均値は切り捨てて小数点以下第3位まで表示する。また、相対標準偏差は四捨五入して小数点以下第1位まで求める。
- 2) その他は、SOP/CHE/001に従う。

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

Table 1-1. General conditions of male rats

[illegible]

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

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

Group	Number of males and general conditions	Days of administration																							
		26		27		28		29		30		31		32		33		34		35		36		37	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	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	7
	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
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 15 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
	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
	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
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 50 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
	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
	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
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 150 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	7
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	7
	Forelimb, Alopecia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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
	Forelimb, Alopecia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 150 mg/kg	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Forelimb, Alopecia	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

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

Table 2-1. General conditions of female rats

[illegible]

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Excretion, Decrease in amount of faeces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Skin, Pale skin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2-IBE 150 mg/kg	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	General appearance, No abnormality	10	10	0	8	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	Excretion, Reddish urine	0	0	10	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Excretion, Decrease in amount of faeces	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Skin, Pale skin	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Pre: Before administration, Post: after administration.																																																			
(Continued)																																																			

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

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

Group	Number of females and general conditions	Days of administration																																		
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre		
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	5		
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5	
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2-IBE 150 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	5	
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	8	10	9	10	10	10	8	10	10	10	9	10	10	10	9	10	7	10	10	10	9	10	10	10	5
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	2	0	1	0	0	0	2	0	0	0	1	0	0	0	1	0	3	0	0	0	1	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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
2-IBE 150 mg/kg	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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
	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
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Lumbus, 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
	Excretion, Reddish urine.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, 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
	Skin, Crust formation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 15 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	10	10	10	10	9	9
	Forelimb, Alopecia.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Lumbus, 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
	Excretion, Reddish urine.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, 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
	Skin, Crust formation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 50 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	11	11	11	11	11	11	11	11	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	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
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Lumbus, Alopecia.	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Reddish urine.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, 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
	Skin, Crust formation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 150 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	11	11	11	11	11	11	10	10	10	10	9	9	9	9	7	9
	Forelimb, Alopecia.	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Lumbus, 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
	Excretion, Reddish urine.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, 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
	Skin, Crust formation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

(Continued)

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

Table 3(continued). General conditions in dams during pregnancy

Group	Number of dams and general conditions	Days of pregnancy																									
		14		15		16		17		18		19		20		21		22		23		24		25		26	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
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
	Forelimb, Alopecia.	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
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, 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
	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
	General appearance, Emaciation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Reddish urine.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Crust formation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 15 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	10	10	10	10	5	5	0	0	0	0	0	0	0	0
	General appearance, No abnormality	9	9	9	9	9	9	9	9	9	9	9	9	8	8	8	8	4	4	0	0	0	0	0	0	0	0
	Forelimb, Alopecia.	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	0	0	0	0	0	0	0	0
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, 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
	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
	General appearance, Emaciation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Reddish urine.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Crust formation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 50 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	7	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	7	7	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	
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, 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
	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
	General appearance, Emaciation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Reddish urine.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Crust formation.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 150 mg/kg	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	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	4	4	0	0	0	0	0	0	0	0
	Forelimb, Alopecia.	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
	Tail, Distal, Black.	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0
	Neck, Alopecia.	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
	Fur, Hair, Coat, Piloerection.	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation.	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin.	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces.	1	0	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Reddish urine.	2	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Crust formation.	1	1	1	1	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.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	10	10	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	10	10	12	12	12	12	12	12	12	12	12	12
	Forelimb, Alopecia.	0	0	0	0	0	0	0	0	0	0	0	0
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation.	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, Alopecia.	0	0	0	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
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 15 mg/kg	Number of dams	8	8	11	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	7	7	9	9	9	9	9	9	9	9	9	9
	Forelimb, Alopecia.	1	1	2	2	2	2	2	2	2	2	2	2
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation.	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, Alopecia.	0	0	0	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
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 50 mg/kg	Number of dams	8	8	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	8	8	12	12	12	12	12	12	12	12	12	12
	Forelimb, Alopecia.	0	0	0	0	0	0	0	0	0	0	0	0
	Tail, Distal, Black.	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation.	0	0	0	0	0	0	0	0	0	0	0	0
	Neck, Alopecia.	0	0	0	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
	Skin, Pale skin.	0	0	0	0	0	0	0	0	0	0	0	0
2-IBE 150 mg/kg	Number of dams	9	9	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	7	7	9	9	9	9	9	9	9	9	9	9
	Forelimb, Alopecia.	0	0	1	1	1	1	1	1	1	1	1	1
	Tail, Distal, Black.	2	2	2	2	2	2	2	2	2	2	2	2
	General appearance, Emaciation.	1	1	1	1	1	1	1	1	1	1	1	1
	Neck, Alopecia.	0	0	1	1	1	1	1	1	1	1	1	1
	Fur, Hair, Coat, Piloerection.	1	1	1	1	1	1	0	0	0	0	0	0
	Skin, Pale skin.	1	1	1	1	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

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

Table 5. Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of administration						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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 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
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Stereotypy] observed (rearing)	Control (vehicle: water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0		
	2-IBE (150 mg/kg)	12	2	0	1	0	0	0	0	0	0

^a the recovery test was performed in 5 animals for each of the 0 and 150 mg/kg groups

^b Values represent number of animals with the findings.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	1 ^b	0	1	0	1	0	0	0	0
	2-IBE (15 mg/kg)	12	0	1	0	1	1	1	0		
	2-IBE (50 mg/kg)	12	1	4	0	1	1	2	2		
	2-IBE (150 mg/kg)	12	4	2	2	1	0	3	1	0	0
[Defecation] (frequency/30sec)	Control (vehicle; water for injection)	12	0 ^b	0	0	0	0	0	0	0	0
	2-IBE (15 mg/kg)	12	0	1	0	0	0	0	0		
	2-IBE (50 mg/kg)	12	0	0	0	0	0	1	0		
	2-IBE (150 mg/kg)	12	3	1	1	0	2	0	0	0	0

^a the recovery test was performed in 5 animals for each of the 0 and 150 mg/kg groups^b Values represent total score of each group.

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

Table 6-1. Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of administration						The lactation period
				8	15	24	30	36	42	
[Posture in home-cage] Crouching position	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	
[Locomotor in home-cage] Decrease in locomotor activity	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	
[Handling behavior] No resistance	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	
[Heart beats] bradycardia	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	
[Body temperature] hypothermia	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	
[Fur] Moist fur	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	
[Skin color/Mucous membrane] Abnormal (pale skin)	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	1	0	
[Lacrimation] observed	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	
[Piloerection] severe	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	1	0	
[Respiratory rate] Hypopnea	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	
[Stereotypy] observed	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	

^a 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 2-isobutoxyethanol 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 administration						The lactation period
				8	15	24	30	36	42	
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	12	0 ^a	0	0	0	1	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	1	0	0	
	2-IBE (50 mg/kg)	12	1	0	0	0	1	0	0	
	2-IBE (150 mg/kg)	12	1	0	0	0	0	0	1	
[Defecation] (frequency/30sec)	Control (vehicle: water for injection)	12	0 ^a	0	0	0	0	0	0	0 (1)
	2-IBE (15 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (50 mg/kg)	12	0	0	0	0	0	0	0	
	2-IBE (150 mg/kg)	12	0	0	0	0	0	0	0	

^a Values represent total score of each group.

Figures in parenthese indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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 administration						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
	2-IBE (150 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
	2-IBE (150 mg/kg)	10	0	0	0	0	0	0	0	0	0
[Handling behavior] No resistance	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	2-IBE (150 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
	2-IBE (150 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
	2-IBE (150 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
	2-IBE (150 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
	2-IBE (150 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
	2-IBE (150 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
	2-IBE (150 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
	2-IBE (150 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
	2-IBE (150 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 150 mg/kg groups^b Values represent number of animals with the findings.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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 administration						Days of recovery ^a	
				8	15	24	30	36	42	7	14
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	3	0	0
	2-IBE (150 mg/kg)	10	2	1	0	0	0	0	0	0	0
[Defecation] (frequency/30sec)	Control (vehicle: water for injection)	10	0 ^b	0	0	0	0	0	0	0	0
	2-IBE (150 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 150 mg/kg groups^b Values represent total score of each group.

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

Table 7-1. Body weights of male rats

Group	Control (vehicle: water for injection)			2-IBE 15 mg/kg			2-IBE 50 mg/kg			2-IBE 150 mg/kg		
Number of males	12			12			12			12		
Days of administration												
1	387.5	±	23.3	391.2	±	22.4	390.2	±	20.4	390.5	±	23.8
4	399.1	±	23.7	404.9	±	24.4	402.7	±	22.4	394.3	±	27.1
7	411.8	±	24.8	416.5	±	26.1	415.3	±	22.8	408.3	±	28.8
14	434.9	±	29.1	442.0	±	33.8	442.2	±	31.5	437.5	±	33.4
21	452.5	±	33.0	459.7	±	33.9	466.6	±	33.6	461.0	±	36.2
28	477.2	±	35.0	483.6	±	35.4	495.3	±	38.9	489.2	±	40.6
35	499.2	±	40.9	503.3	±	40.3	520.5	±	41.3	508.4	±	43.1
42	505.8	±	43.6	514.5	±	43.7	533.6	±	41.4	521.6	±	45.3

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

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

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

Group	Control (vehicle: water for injection)	2-IBE 150 mg/kg
Number of males	5	5
Days of recovery		
1	486.5 ± 52.3	516.1 ± 44.5
7	497.6 ± 52.7	538.6 ± 50.5
14	506.8 ± 48.8	546.9 ± 46.2

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

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

Table 8-1. Body weights of female rats

Group	Control (vehicle: water for injection)	2-IBE 15 mg/kg	2-IBE 50 mg/kg	2-IBE 150 mg/kg
Number of females	12	12	12	12
Days of administration				
1	251.7 ± 11.5	255.6 ± 13.0	253.3 ± 12.0	255.4 ± 14.6
4	260.6 ± 13.7	262.6 ± 13.6	260.6 ± 14.6	248.3 ± 23.3
7	268.8 ± 17.2	268.3 ± 15.8	269.0 ± 15.3	258.0 ± 17.7
14	279.9 ± 19.1	275.7 ± 16.2	283.0 ± 16.3	273.7 ± 13.8

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

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

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

Group	Control (vehicle: water for injection)			2-IBE 150 mg/kg		
Number of females	10			10		
Days of administration						
	1	253.5	± 16.3	254.8	± 9.5	
	4	260.5	± 15.8	250.6	± 10.4	
	7	267.1	± 17.0	262.7	± 9.3	
	14	276.0	± 18.6	278.4	± 10.5	
	21	284.4	± 21.9	291.4	± 10.2	
	28	290.3	± 20.3	303.1	± 15.7	
	35	297.3	± 21.2	306.8	± 15.5	
	42	304.5	± 25.2	309.1	± 12.3	

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

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

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

Group	Control (vehicle: water for injection)			2-IBE 150 mg/kg		
Number of females	5			5		
Days of recovery						
1	306.7	±	19.0	313.7	±	16.6
7	317.3	±	18.2	329.8	±	13.8
14	321.3	±	20.7	336.3	±	16.0

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

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

Table 9. Body weights of dams during pregnancy

Group	Control (vehicle: water for injection)	2-IBE 15 mg/kg	2-IBE 50 mg/kg	2-IBE 150 mg/kg
Number of dams	12	10	12	12
Days of pregnancy				
0	287.3 ± 20.7	290.9 ± 15.4	288.6 ± 12.8	283.2 ± 16.1
7	324.3 ± 22.5	325.3 ± 15.3	324.6 ± 14.8	316.3 ± 17.5
14	361.1 ± 26.1	358.6 ± 19.4	359.1 ± 17.6	346.2 ± 31.6
20	439.5 ± 31.7	438.8 ± 26.9	442.4 ± 20.7	417.2 ± 51.8

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 2-isobutoxyethanol by oral administration in rats

Table 10. Body weights of dams during lactation

Group	Control (vehicle: water for injection)	2-IBE 15 mg/kg	2-IBE 50 mg/kg	2-IBE 150 mg/kg
Number of dams	12	11	12	12
Days of lactation				
0	327.0 ± 23.7	327.6 ± 25.5	323.6 ± 16.1	317.4 ± 38.1
4	341.4 ± 30.1	349.6 ± 18.1	346.7 ± 12.4	335.5 ± 26.9

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 2-isobutoxyethanol by oral administration in rats

Table 11-1. Food consumption of male rats

Group	Control (vehicle: water for injection)			2-IBE 15 mg/kg			2-IBE 50 mg/kg			2-IBE 150 mg/kg		
Number of males	12			12			12			12		
Days of administration												
1	29.6	±	2.1	30.8	±	3.6	28.6	±	2.7	20.1	±	4.6 **
7	26.8	±	3.1	29.1	±	3.2	27.6	±	3.2	28.5	±	3.4
14	26.9	±	2.9	28.1	±	3.8	26.6	±	2.7	29.1	±	3.5
29	27.8	±	3.5	28.2	±	2.4	29.6	±	3.8	29.7	±	4.0
35	25.8	±	3.1	27.0	±	4.9	26.8	±	3.3	28.0	±	3.9
41	25.8	±	3.5	27.5	±	3.8	28.3	±	2.8	29.1	±	3.1

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

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

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

Group	Control (vehicle: water for injection)			2-IBE 150 mg/kg		
Number of males	5			5		
Days of recovery						
	6	27.1	± 5.2	32.1	± 3.1	
	12	27.1	± 5.1	32.4	± 2.5	

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

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

Table 12-1. Food consumption of female rats

Group	Control (vehicle: water for injection)	2-IBE 15 mg/kg	2-IBE 50 mg/kg	2-IBE 150 mg/kg
Number of females	12	12	12	12
Days of administration				
1	20.2 ± 2.8	20.7 ± 3.1	20.5 ± 2.8	10.6 ± 4.3 **
7	20.8 ± 3.7	21.4 ± 2.3	19.6 ± 3.4	21.7 ± 2.2
14	22.3 ± 3.3	20.5 ± 3.3	21.5 ± 2.8	20.7 ± 4.0

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

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

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

Group	Control (vehicle: water for injection)			2-IBE 150 mg/kg		
Number of females	10			10		
Days of administration						
1	21.7	±	2.9	9.5	±	3.6 **
7	20.9	±	3.4	22.8	±	2.5
14	20.7	±	2.4	22.2	±	2.5
21	20.9	±	1.8	20.9	±	2.7
29	21.0	±	3.0	22.7	±	2.5
35	18.3	±	4.2	19.8	±	2.6
41	20.8	±	3.7	19.8	±	2.3

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

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

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

Group	Control (vehicle: water for injection)	2-IBE 150 mg/kg
Number of females	5	5
Days of recovery		
6	21.5 ± 1.3	24.9 ± 3.9
12	23.1 ± 2.3	24.9 ± 3.1

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

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

Table 13. Food consumption in dams during pregnancy

Group	Control (vehicle: water for injection)		2-IBE 15 mg/kg		2-IBE 50 mg/kg		2-IBE 150 mg/kg	
Number of dams	12		10		12		12	
Days of pregnancy								
0	20.6	± 3.0	21.1	± 4.1	20.8	± 2.3	21.0	± 3.2
7	28.3	± 3.8	26.1	± 2.2	27.6	± 3.3	25.4	± 2.9
14	27.9	± 1.7	27.4	± 2.2	27.6	± 2.3	25.1	± 7.9
20	20.2	± 3.6	24.9	± 5.3	20.4	± 6.5	23.1	± 6.2

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 2-isobutoxyethanol by oral administration in rats

Table 14. Food consumption in dams during lactation

Group	Control (vehicle: water for injection)	2-IBE 15 mg/kg	2-IBE 50 mg/kg	2-IBE 150 mg/kg
Number of dams	12	11	12	12
Days of lactation				
3	38.5 ± 10.0	43.7 ± 4.5	44.4 ± 6.1	42.8 ± 8.4

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

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

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

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

Group	Control (vehicle: water for injection)	2-IBE (15 mg/kg)	2-IBE (50 mg/kg)	2-IBE (150 mg/kg)
<u>Male, Administration period</u>				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
<u>Female, dam</u>				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
<u>Female, Administration period</u>				
Number of animals	5			5
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Preyer's reaction	100			100
Withdrawal reflex	100			100
Eyelid reflex	100			100

Values represent % of animals showing normal responses.

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

Table 16. Assessment of grip strength of male rats at the last week of the dosing period

Group	Control (vehicle: water for injection)	2-IBE (15 mg/kg)	2-IBE (50 mg/kg)	2-IBE (150 mg/kg)
Number of males	5	5	5	5
<u>Administration period</u>				
Forelimb	0.720 ± 0.198	0.726 ± 0.300	0.913 ± 0.180	0.871 ± 0.234
Hindlimb	0.712 ± 0.051	0.689 ± 0.112	0.724 ± 0.090	0.680 ± 0.179

Each value shows mean (kg) ±S.D.

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

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

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

Group	Control (vehicle: water for injection)	2-IBE (15 mg/kg)	2-IBE (50 mg/kg)	2-IBE (150 mg/kg)
Number of females	5	5	5	5
<u>Administration period</u>				
Forelimb	0.775 ± 0.253	0.846 ± 0.211	0.693 ± 0.174	0.796 ± 0.137
Hindlimb	0.592 ± 0.130	0.648 ± 0.172	0.675 ± 0.169	0.685 ± 0.178

Each value shows mean (kg) ±S.D.

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

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

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

Group	Control (vehicle: water for injection)			2-IBE (150 mg/kg)		
Number of females	5			5		
<u>Administration period</u>						
Forelimb	0.717	±	0.175	0.806	±	0.159
Hindlimb	0.671	±	0.095	0.668	±	0.144

Each value shows mean (kg) ± S.D.

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

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

Table 19. Motor activity of male rats at the last week of the dosing period

Group	Control (vehicle: water for injection)		2-IBE (15 mg/kg)		2-IBE (50 mg/kg)		2-IBE (150 mg/kg)	
Number of males	5		5		5		5	
<u>Administration period</u>								
Ambulation (counts)								
5min	1147	± 134	1097	± 119	1279	± 234	1105	± 245
10min	930	± 94	1035	± 114	1063	± 275	828	± 272
15min	911	± 112	935	± 138	809	± 272	779	± 256
20min	688	± 274	684	± 282	750	± 392	480	± 362
Total	3676	± 266	3751	± 478	3901	± 1029	3191	± 1039
Rearing (counts)								
5min	39	± 9	33	± 5	36	± 4	38	± 8
10min	22	± 5	25	± 6	28	± 13	25	± 7
15min	16	± 4	23	± 5	21	± 9	17	± 8
20min	15	± 15	14	± 9	16	± 9	7	± 10
Total	92	± 27	95	± 12	101	± 28	88	± 30

Each value shows mean±S.D.

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

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

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

Group	Control (vehicle: water for injection)		2-IBE (15 mg/kg)		2-IBE (50 mg/kg)		2-IBE (150 mg/kg)	
Number of females	5		5		5		5	
<u>Administration period</u>								
Ambulation (counts)								
5min	1119	± 127	1029	± 97	1182	± 368	968	± 263
10min	845	± 149	622	± 158	876	± 395	668	± 220
15min	527	± 78	503	± 128	593	± 394	567	± 195
20min	459	± 274	398	± 153	344	± 163	312	± 285
Total	2949	± 454	2553	± 328	2995	± 1008	2515	± 830
Rearing (counts)								
5min	34	± 8	20	± 6	21	± 10	22	± 16
10min	15	± 8	6	± 5	9	± 3	17	± 18
15min	7	± 4	7	± 6	4	± 4	10	± 9
20min	4	± 3	5	± 4	2	± 1	2	± 2
Total	59	± 20	38	± 10	37	± 14	50	± 43

Each value shows mean±S.D.

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

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

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

Group	Control (vehicle: water for injection)			2-IBE (150 mg/kg)		
Number of females	5			5		
<u>Administration period</u>						
Ambulation (counts)						
5min	1133	±	78	1147	±	141
10min	1017	±	84	938	±	125
15min	867	±	125	882	±	104
20min	823	±	231	630	±	262
Total	3840	±	412	3597	±	452
Rearing (counts)						
5min	32	±	9	36	±	7
10min	28	±	10	24	±	5
15min	23	±	8	22	±	5
20min	20	±	6	18	±	19
Total	103	±	28	101	±	28

Each value shows mean±S.D.

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

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

Table 22-1. Urinalysis in male rats

Group	Number of males	Quality ^{a)}																			
		Color	Turbidity	pH				Protein			Glucose	Ketone		Bilirubin	Occult blood			Urobilinogen			
		Light yellow	-	6.5	7.0	7.5	8.0	±	+	2+	-	-	±	+	-	-	±	+	±	+	2+
Control (vehicle: water for injection)	5	5	5	1	2	0	2	1	3	1	5	2	1	2	5	5	0	0	4	0	1
2-IBE (15 mg/kg)	5	5	5	0	3	2	0	3	2	0	5	2	3	0	5	4	1	0	5	0	0
2-IBE (50 mg/kg)	5	5	5	1	2	1	1	0	5	0	5	0	5	0	5	5	0	0	5	0	0
2-IBE (150 mg/kg)	5	5	5	0	0	3	2	1	4	0	5	4	1	0	5	5	0	0	5	0	0

Group	Number of males	Urinary sediments ^{a)}						Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}					
		-	-	-	-	±	-			(mEq/L)	Na	K	Cl	(mEq/24 hr)	Na
Control (vehicle: water for injection)	5	5	5	5	1	4	5	19.3 ±6.5	1.054 ±0.014	89.7 ±15.8	179.3 ±33.3	112.9 ±27.6	1.68 ±0.53	3.30 ±0.76	2.07 ±0.56
2-IBE (15 mg/kg)	5	5	5	5	0	5	5	19.2 ±4.3	1.051 ±0.012	98.3 ±26.4	173.4 ±27.4	109.0 ±27.2	1.79 ±0.19	3.24 ±0.35	2.00 ±0.20
2-IBE (50 mg/kg)	5	5	5	5	1	4	5	16.4 ±3.0	1.060 ±0.012	97.5 ±19.9	178.1 ±32.1	112.6 ±35.3	1.60 ±0.42	2.90 ±0.69	1.82 ±0.61
2-IBE (150 mg/kg)	5	5	5	5	0	5	5	16.7 ±2.0	1.063 ±0.004	135.9 ±32.0	* 195.4 ±19.3	153.1 ±27.3	2.23 ±0.34	3.24 ±0.39	2.51 ±0.28

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

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

a), values represent as number of animals

b), values represent as mean ± S.D.

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

Table 22-2. Urinalysis in male rats of the recovery period

Group	Number of males	Quality ^{a)}																
		Color	Turbidity	pH				Protein			Glucose		Ketone		Bilirubin	Occult blood	Urobilinogen	
		Light yellow	-	7.0	7.5	8.0	8.5	±	+	2+	-	-	±	+	-	-	±	+
Control (vehicle: water for injection)	5	5	5	4	1	0	0	0	4	1	5	0	3	2	5	5	0	5
2-IBE (150 mg/kg)	5	5	5	0	3	2	0	1	4	0	5	3	1	1	5	5	3	2

Group	Number of males	Urinary sediments ^{a)}						Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells			(mEq/L)			(mEq/24 hr)		
		-	-	-	±	+	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	4	1	5	14.7 ±4.1	1.066 ±0.015	103.5 ±32.3	208.6 ±30.9	136.9 ±39.3	1.46 ±0.46	2.97 ±0.52	1.92 ±0.50
2-IBE (150 mg/kg)	5	5	5	5	4	1	5	25.0 ±14.5	1.050 ±0.023	95.6 ±41.8	172.3 ±52.3	111.8 ±48.5	1.95 ±0.20	3.73 ±0.78	2.27 ±0.16

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

Turbidity, -: negative; +: slight; 2+: moderate

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 <1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

a), values represent as number of animals

b), values represent as mean ± S.D.

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

Table 23-1. Urinalysis in female rats, satellite group

Group	Number of females	Quality ^{a)}																					
		Color		Turbidity		pH					Protein				Glucose		Ketone		Bilirubin	Occult blood			Urobilinogen
		Light yellow	brown	-	2+	6.5	7.0	7.5	8.0	-	±	+	2+	-	-	±	-	-	±	3+	±		
Control (vehicle: water for injection)	5	5	0	5	0	0	3	1	1	2	2	1	0	5	4	1	5	5	0	0	5		
2-IBE (150 mg/kg)	5	4	1	4	1	2	2	1	0	0	4	0	1	5	5	0	5	4	0	1	5		

Group	Number of females	Urinary sediments ^{a)}								Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells	White blood cells		Casts	Crystals		Epithelial cells	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}					
			-	±		-	±		-			±	(mEq/L)	Na	K	Cl	(mEq/24 hr)
Control (vehicle: water for injection)	5	5	5	0	5	1	4	5	0	12.6	1.050	83.8	146.7	98.5	0.98	1.79	1.14
										±2.7	±0.017	±39.5	±43.0	±50.9	±0.36	±0.46	±0.48
2-IBE (150 mg/kg)	5	5	4	1	5	0	5	3	2	13.4	1.054	86.9	150.1	92.8	1.08	1.92	1.18
										±2.7	±0.016	±53.6	±47.2	±42.9	±0.45	±0.41	±0.37

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

Turbidity, -: negative; ±: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

a), values represent as number of animals

b), values represent as mean ± S.D.

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

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

Group	Number of females	Quality ^{a)}																
		Color	Turbidity	pH					Protein			Glucose		Ketone		Bilirubin	Occult blood	Urobilinogen
		Light yellow	-	6.5	7.0	7.5	8.0	8.5	-	±	+	-	-	±	-	-	±	+
Control (vehicle: water for injection)	5	5	5	0	5	0	0	0	0	3	2	5	3	2	5	5	3	2
2-IBE (150 mg/kg)	5	5	5	0	2	1	1	1	1	3	1	5	5	0	5	5	4	1

Group	Number of females	Urinary sediments ^{a)}						Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	(mEq/L)			(mEq/24 hr)					
		-	-	-	-	±	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	1	4	5	11.8 ±4.3	1.065 ±0.019	141.6 ±57.4	209.9 ±42.8	162.6 ±68.6	1.52 ±0.31	2.36 ±0.63	1.72 ±0.33
2-IBE (150 mg/kg)	5	5	5	5	0	5	5	14.9 ±2.7	1.057 ±0.008	120.9 ±21.2	177.2 ±19.0	128.0 ±20.0	1.78 ±0.33	2.61 ±0.39	1.88 ±0.35

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

Turbidity, -: negative; +: slight; 2+: moderate

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<1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

a), values represent as number of animals

b), values represent as mean ± S.D.

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

Table 24-1. Hematological findings of male rats at the end of the dosing period

Group	Control (vehicle: water for injection)	2-IBE (15 mg/kg)	2-IBE (50 mg/kg)	2-IBE (150 mg/kg)
Number of males	5	5	5	5
RBC ($\times 10^4/\mu\text{L}$)	821 $\pm$ 23	846 $\pm$ 25	733 $\pm$ 40 **	617 $\pm$ 52 **
Hemoglobin (g/dL)	15.1 $\pm$ 0.6	15.4 $\pm$ 0.7	13.8 $\pm$ 0.7 *	12.5 $\pm$ 0.7 **
Hematocrit (%)	43.7 $\pm$ 1.6	44.5 $\pm$ 1.7	41.4 $\pm$ 1.9	38.8 $\pm$ 1.5 **
MCV (fL)	53.2 $\pm$ 2.8	52.6 $\pm$ 1.1	56.5 $\pm$ 0.9	63.0 $\pm$ 4.1 **
MCH (pg)	18.4 $\pm$ 0.9	18.2 $\pm$ 0.5	18.8 $\pm$ 0.3	20.3 $\pm$ 0.7 **
MCHC (g/dL)	34.6 $\pm$ 0.3	34.7 $\pm$ 0.4	33.3 $\pm$ 0.6	32.2 $\pm$ 1.2 *
Platelet ($\times 10^4/\mu\text{L}$)	100.7 $\pm$ 10.5	105.7 $\pm$ 7.3	111.0 $\pm$ 9.7	97.9 $\pm$ 10.0
PT (sec)	20.1 $\pm$ 2.3	21.7 $\pm$ 5.1	16.9 $\pm$ 2.5	17.0 $\pm$ 2.9
APTT (sec)	28.1 $\pm$ 1.8	26.7 $\pm$ 1.2	24.8 $\pm$ 2.6 *	23.3 $\pm$ 2.0 **
WBC ($\times 10^2/\mu\text{L}$)	112.8 $\pm$ 25.4	100.6 $\pm$ 21.1	107.4 $\pm$ 30.4	85.1 $\pm$ 16.3
Differential leukocyte count (%)				
Neutrophil	19.5 $\pm$ 2.7	14.4 $\pm$ 3.5	18.1 $\pm$ 7.7	15.1 $\pm$ 3.1
Eosinophil	1.6 $\pm$ 0.5	1.1 $\pm$ 0.3	1.2 $\pm$ 0.2	0.7 $\pm$ 0.3 **
Basophil	0.1 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.1	0.0 $\pm$ 0.0
Monocyte	3.7 $\pm$ 0.6	4.4 $\pm$ 0.6	4.5 $\pm$ 1.2	4.9 $\pm$ 1.4
Lymphocyte	75.2 $\pm$ 3.5	80.1 $\pm$ 4.2	76.2 $\pm$ 8.0	79.4 $\pm$ 3.2
Reticulocyte count (%)	3.47 $\pm$ 0.44	2.94 $\pm$ 0.47	6.44 $\pm$ 1.24	11.51 $\pm$ 2.05 **

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

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

Table 24-2. Hematological findings of male rats at the end of the recovery period

Group	Control (vehicle: water for injection)		2-IBE (150 mg/kg)	
Number of males	5		5	
RBC ($\times 10^4/\mu\text{L}$)	882	± 23	841	± 15 **
Hemoglobin (g/dL)	15.4	± 0.6	15.9	± 0.4
Hematocrit (%)	43.7	± 1.3	45.8	± 1.2 *
MCV (fL)	49.6	± 1.5	54.4	± 1.4 **
MCH (pg)	17.5	± 0.5	18.9	± 0.4 **
MCHC (g/dL)	35.2	± 0.6	34.8	± 0.2
Platelet ($\times 10^4/\mu\text{L}$)	118.2	± 15.8	113.0	± 9.7
PT (sec)	19.7	± 2.0	18.0	± 1.1
APTT (sec)	27.4	± 3.3	28.1	± 1.2
WBC ($\times 10^2/\mu\text{L}$)	88.7	± 11.6	94.8	± 15.8
Differential leukocyte count (%)				
Neutrophil	12.4	± 3.7	14.4	± 5.5
Eosinophil	1.5	± 0.6	1.1	± 0.6
Basophil	0.0	± 0.0	0.0	± 0.0
Monocyte	3.6	± 1.0	3.2	± 1.1
Lymphocyte	82.5	± 3.8	81.2	± 6.7
Reticulocyte count (%)	3.39	± 0.41	2.26	± 0.21 **

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

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

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

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

Group	Control (vehicle: water for injection)		2-IBE (15 mg/kg)		2-IBE (50 mg/kg)		2-IBE (150 mg/kg)	
Number of females	5		5		5		5	
RBC ($\times 10^4/\mu\text{L}$)	671	$\pm$ 46	649	$\pm$ 101	573	$\pm$ 46	525	$\pm$ 113 *
Hemoglobin (g/dL)	13.0	$\pm$ 1.1	13.2	$\pm$ 0.7	12.4	$\pm$ 0.4	12.3	$\pm$ 0.7
Hematocrit (%)	38.6	$\pm$ 2.9	39.8	$\pm$ 0.9	38.0	$\pm$ 1.1	40.1	$\pm$ 3.3
MCV (fL)	57.4	$\pm$ 2.5	62.9	$\pm$ 12.4	66.5	$\pm$ 3.5	79.3	$\pm$ 18.8
MCH (pg)	19.3	$\pm$ 0.5	20.6	$\pm$ 2.7	21.6	$\pm$ 1.0	24.1	$\pm$ 3.8
MCHC (g/dL)	33.7	$\pm$ 1.2	33.1	$\pm$ 1.8	32.5	$\pm$ 0.5	30.9	$\pm$ 2.8
Platelet ($\times 10^4/\mu\text{L}$)	111.4	$\pm$ 14.7	115.6	$\pm$ 9.8	113.0	$\pm$ 24.2	111.9	$\pm$ 8.4
PT (sec)	12.5	$\pm$ 0.5	13.0	$\pm$ 0.5	13.1	$\pm$ 0.5	13.1	$\pm$ 0.4
APTT (sec)	19.9	$\pm$ 1.9	19.5	$\pm$ 1.0	19.8	$\pm$ 0.4	19.6	$\pm$ 1.4
WBC ($\times 10^2/\mu\text{L}$)	83.0	$\pm$ 31.5	105.3	$\pm$ 25.5	66.6	$\pm$ 32.5	65.5	$\pm$ 20.7
Differential leukocyte count (%)								
Neutrophil	28.9	$\pm$ 9.8	32.7	$\pm$ 15.7	26.4	$\pm$ 11.0	27.1	$\pm$ 11.5
Eosinophil	0.6	$\pm$ 0.3	0.7	$\pm$ 0.2	0.4	$\pm$ 0.2	0.7	$\pm$ 0.5
Basophil	0.0	$\pm$ 0.0	0.0	$\pm$ 0.0	0.0	$\pm$ 0.0	0.0	$\pm$ 0.0
Monocyte	4.7	$\pm$ 2.6	4.0	$\pm$ 0.9	5.1	$\pm$ 1.6	4.4	$\pm$ 1.1
Lymphocyte	65.7	$\pm$ 8.0	62.6	$\pm$ 15.8	68.1	$\pm$ 10.0	67.7	$\pm$ 11.1
Reticulocyte count (%)	6.46	$\pm$ 1.89	14.08	$\pm$ 9.49	19.07	$\pm$ 7.25 *	21.71	$\pm$ 11.10 *

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

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

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

Table 25-2. Hematological findings of female rats at the end of the dosing period, satellite group

Group	Control (vehicle: water for injection)		2-IBE (150 mg/kg)	
Number of females	5		5	
RBC ($\times 10^4/\mu\text{L}$)	762	± 19	503	± 25 **
Hemoglobin (g/dL)	14.3	± 0.5	11.1	± 0.5 **
Hematocrit (%)	40.3	± 1.8	35.8	± 2.4 **
MCV (fL)	52.9	± 1.4	71.4	± 5.2 **
MCH (pg)	18.7	± 0.2	22.2	± 1.1 **
MCHC (g/dL)	35.4	± 0.6	31.1	± 0.9 **
Platelet ($\times 10^4/\mu\text{L}$)	96.8	± 7.4	96.3	± 21.6
PT (sec)	12.2	± 0.4	12.4	± 0.7
APTT (sec)	19.1	± 2.2	18.0	± 1.5
WBC ($\times 10^2/\mu\text{L}$)	51.5	± 24.5	44.3	± 14.0
Differential leukocyte count (%)				
Neutrophil	11.8	± 2.7	9.6	± 2.5
Eosinophil	1.2	± 0.4	0.9	± 0.6
Basophil	0.0	± 0.1	0.0	± 0.0
Monocyte	2.3	± 0.9	2.1	± 0.7
Lymphocyte	84.6	± 3.8	87.4	± 3.2
Reticulocyte count (%)	3.83	± 0.51	15.10	± 2.13 **

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

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

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

Table 25-3. Hematological findings of female rats at the end of the recovery period

Group	Control (vehicle: water for injection)		2-IBE (150 mg/kg)	
Number of females	5		5	
RBC ($\times 10^4/\mu\text{L}$)	815	± 65	791	± 40
Hemoglobin (g/dL)	14.7	± 0.9	16.5	± 0.4 **
Hematocrit (%)	42.3	± 1.9	47.7	± 1.1 **
MCV (fL)	52.0	± 2.6	60.4	± 3.4 **
MCH (pg)	18.0	± 0.6	20.8	± 1.0 **
MCHC (g/dL)	34.7	± 0.6	34.5	± 0.5
Platelet ($\times 10^4/\mu\text{L}$)	122.0	± 27.3	93.8	± 7.3
PT (sec)	12.0	± 0.7	12.7	± 0.4
APTT (sec)	20.8	± 0.6	24.5	± 8.2
WBC ($\times 10^2/\mu\text{L}$)	56.2	± 23.7	42.5	± 6.5
Differential leukocyte count (%)				
Neutrophil	14.1	± 3.7	11.9	± 4.4
Eosinophil	1.5	± 0.3	1.4	± 0.4
Basophil	0.0	± 0.0	0.0	± 0.0
Monocyte	3.1	± 0.5	3.3	± 1.0
Lymphocyte	81.3	± 4.0	83.3	± 5.0
Reticulocyte count (%)	4.22	± 3.07	1.94	± 0.40

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

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

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

Table 26-1. Myelogram in male rats at the end of the dosing period

Group	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
Control (vehicle: water for injection)	1.3 ±0.8 (5)	2.4 ±1.0 (5)	5.5 ±1.7 (5)	13.8 ±1.8 (5)	20.5 ±3.5 (5)	1.4 ±1.0 (5)	1.9 ±0.7 (5)	0.4 ±0.4 (5)	0.6 ±0.3 (5)	47.9 ±2.9 (5)	0.2 ±0.1 (5)
2-IBE (15 mg/kg)	2.1 ±0.4 (5)	3.3 ±1.2 (5)	5.1 ±2.5 (5)	10.0 ** ±1.7 (5)	24.5 ±5.3 (5)	0.7 ±0.3 (5)	1.3 ±0.4 (5)	0.7 ±0.7 (5)	0.5 ±0.6 (5)	48.1 ±7.8 (5)	0.2 ±0.3 (5)
2-IBE (50 mg/kg)	1.0 ±0.4 (5)	3.7 ±1.3 (5)	4.4 ±1.4 (5)	9.4 ** ±0.7 (5)	21.4 ±4.6 (5)	1.0 ±0.5 (5)	1.9 ±0.3 (5)	0.6 ±0.5 (5)	0.8 ±0.1 (5)	44.1 ±5.8 (5)	0.3 ±0.1 (5)
2-IBE (150 mg/kg)	2.8 ±1.9 (5)	2.8 ±0.7 (5)	4.4 ±2.0 (5)	8.1 ** ±0.9 (5)	19.9 ±5.2 (5)	1.1 ±0.4 (5)	1.0 * ±0.6 (5)	0.2 ±0.3 (5)	0.5 ±0.6 (5)	41.0 ±7.2 (5)	0.4 ±0.3 (5)

Group	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid / Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
Control (vehicle: water for injection)	5.9 ±2.1 (5)	17.8 ±1.4 (5)	9.4 ±1.9 (5)	33.2 ±4.6 (5)	1.47 ±0.26 (5)	1.5 ±0.7 (5)	16.3 ±3.2 (5)	0.4 ±0.3 (5)	0.4 ±0.3 (5)	0.2 ±0.3 (5)
2-IBE (15 mg/kg)	5.2 ±3.2 (5)	15.0 ±2.2 (5)	10.1 ±3.9 (5)	30.5 ±4.9 (5)	1.63 ±0.52 (5)	2.2 ±1.6 (5)	18.3 ±6.8 (5)	0.5 ±0.3 (5)	0.1 ±0.1 (5)	0.3 ±0.4 (5)
2-IBE (50 mg/kg)	5.4 ±1.0 (5)	18.9 ±4.9 (5)	13.3 ±4.1 (5)	37.9 ±7.9 (5)	1.22 ±0.37 (5)	3.4 ±1.0 (5)	13.9 ±4.3 (5)	0.2 ±0.3 (5)	0.2 ±0.2 (5)	0.2 ±0.5 (5)
2-IBE (150 mg/kg)	10.9 ±5.6 (5)	21.2 ±3.1 (5)	14.7 * ±1.4 (5)	47.1 ** ±5.7 (5)	0.90 ±0.29 (5)	2.3 ±0.4 (5)	9.1 * ±1.6 (5)	0.2 ±0.2 (5)	0.1 ±0.2 (5)	0.4 ±0.4 (5)

Values represent as mean ± S.D.

Parentheses indicate the number of animals.

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

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

Table 26-2. Myelogram in male rats at the end of the recovery period

Group	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
Control (vehicle: water for injection)	3.7 ±1.2 (5)	3.6 ±0.9 (5)	2.1 ±0.2 (5)	11.2 ±0.8 (5)	21.2 ±4.0 (5)	0.9 ±0.3 (5)	1.9 ±0.6 (5)	0.6 ±0.3 (5)	0.8 ±0.4 (5)	46.0 ±4.7 (5)	0.2 ±0.2 (5)
2-IBE (150 mg/kg)	2.5 ±0.6 (5)	5.5 ±2.1 (5)	3.1 ±1.5 (5)	10.8 ±1.5 (5)	24.6 ±2.3 (5)	0.9 ±0.6 (5)	1.5 ±0.8 (5)	0.5 ±0.4 (5)	0.7 ±0.3 (5)	50.0 ±3.5 (5)	0.3 ±0.3 (5)

Group	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid / Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
Control (vehicle: water for injection)	5.9 ±2.6 (5)	17.6 ±3.9 (5)	10.9 ±2.4 (5)	34.7 ±6.0 (5)	1.37 ±0.31 (5)	2.2 ±0.6 (5)	16.6 ±6.0 (5)	0.4 ±0.2 (5)	0.1 ±0.1 (5)	0.1 ±0.2 (5)
2-IBE (150 mg/kg)	4.2 ±1.2 (5)	15.4 ±3.3 (5)	8.6 ±1.3 (5)	28.4 ±4.3 (5)	1.80 ±0.40 (5)	3.2 ±1.3 (5)	17.7 ±2.8 (5)	0.4 ±0.3 (5)	0.2 ±0.2 (5)	0.2 ±0.2 (5)

Values represent as mean ± S.D.

Parentheses indicate the number of animals.

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

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

Table 27-1. Myelogram in female rats at the end of the dosing period

Group	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
Control (vehicle: water for injection)	2.5 ±0.7 (5)	3.1 ±0.7 (5)	5.9 ±1.8 (5)	12.3 ±3.5 (5)	19.4 ±4.9 (5)	1.0 ±0.5 (5)	1.8 ±1.0 (5)	0.6 ±0.7 (5)	0.9 ±0.4 (5)	47.4 ±7.5 (5)	0.5 ±0.5 (5)
2-IBE (15 mg/kg)	1.9 ±0.9 (5)	3.4 ±1.2 (5)	3.5 * ±1.1 (5)	13.2 ±1.5 (5)	18.5 ±1.7 (5)	1.1 ±0.5 (5)	2.6 ±1.1 (5)	0.6 ±0.4 (5)	0.8 ±0.4 (5)	45.7 ±3.8 (5)	0.2 ±0.3 (5)
2-IBE (50 mg/kg)	2.3 ±1.1 (5)	2.5 ±0.8 (5)	2.7 ** ±0.6 (5)	9.7 ±1.5 (5)	15.8 ±1.5 (5)	1.2 ±0.5 (5)	1.8 ±0.7 (5)	0.6 ±0.5 (5)	1.3 ±0.9 (5)	38.0 * ±2.5 (5)	0.6 ±0.7 (5)
2-IBE (150 mg/kg)	2.4 ±1.0 (5)	3.7 ±0.8 (5)	1.7 ** ±0.6 (5)	8.6 * ±1.6 (5)	14.4 ±2.4 (5)	1.3 ±0.6 (5)	1.7 ±0.8 (5)	0.8 ±0.4 (5)	1.1 ±0.5 (5)	35.6 ** ±4.4 (5)	0.5 ±0.5 (5)

Group	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid / Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
Control (vehicle: water for injection)	10.4 ±3.4 (5)	20.9 ±4.0 (5)	15.0 ±2.6 (5)	46.8 ±7.8 (5)	1.06 ±0.34 (5)	1.9 ±0.5 (5)	3.1 ±0.8 (5)	0.5 ±0.4 (5)	0.2 ±0.1 (5)	0.1 ±0.1 (5)
2-IBE (15 mg/kg)	5.8 ±2.2 (5)	22.5 ±2.3 (5)	16.8 ±2.5 (5)	45.3 ±3.9 (5)	1.02 ±0.15 (5)	1.4 ±0.9 (5)	6.7 ±3.4 (5)	0.4 ±0.2 (5)	0.3 ±0.2 (5)	0.2 ±0.2 (5)
2-IBE (50 mg/kg)	9.0 ±3.2 (5)	27.8 ** ±1.8 (5)	17.7 ±3.7 (5)	55.1 * ±3.5 (5)	0.69 ±0.09 (5)	2.3 ±0.5 (5)	3.8 ±1.4 (5)	0.4 ±0.3 (5)	0.0 ±0.1 (5)	0.3 ±0.4 (5)
2-IBE (150 mg/kg)	11.3 ±5.3 (5)	31.6 ** ±3.0 (5)	14.7 ±2.5 (5)	58.1 ** ±3.5 (5)	0.62 * ±0.11 (5)	2.5 ±0.9 (5)	3.3 ±1.5 (5)	0.3 ±0.2 (5)	0.1 ±0.1 (5)	0.1 ±0.2 (5)

Values represent as mean ± S.D.

Parentheses indicate the number of animals.

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

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

Table 27-2. Myelogram in female rats at the end of the dosing period, satellite group

Group	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
Control (vehicle: water for injection)	2.9 ±1.4 (5)	3.2 ±1.5 (5)	3.6 ±1.6 (5)	12.0 ±1.2 (5)	19.7 ±4.0 (5)	1.5 ±0.7 (5)	3.1 ±1.3 (5)	0.7 ±0.6 (5)	1.1 ±0.8 (5)	47.7 ±7.4 (5)	0.2 ±0.1 (5)
2-IBE (150 mg/kg)	2.4 ±0.6 (5)	2.6 ±0.6 (5)	3.1 ±2.2 (5)	9.8 ±3.4 (5)	14.5 * ±2.4 (5)	0.8 ±0.3 (5)	2.2 ±0.8 (5)	0.3 ±0.2 (5)	0.7 ±0.5 (5)	36.5 ±8.9 (5)	0.2 ±0.2 (5)

Group	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid / Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
Control (vehicle: water for injection)	4.5 ±2.6 (5)	16.0 ±2.5 (5)	11.2 ±2.9 (5)	31.9 ±6.9 (5)	1.60 ±0.64 (5)	2.8 ±1.1 (5)	16.7 ±4.5 (5)	0.7 ±0.4 (5)	0.1 ±0.1 (5)	0.0 ±0.1 (5)
2-IBE (150 mg/kg)	15.5 ±10.4 (5)	22.3 * ±3.6 (5)	12.6 ±2.9 (5)	50.6 * ±11.5 (5)	0.79 * ±0.36 (5)	3.3 ±1.7 (5)	9.3 * ±2.1 (5)	0.2 ±0.2 (5)	0.1 ±0.2 (5)	0.0 ±0.0 (5)

Values represent as mean ± S.D.

Parentheses indicate the number of animals.

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

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

Table 27-3. Myelogram in female rats at the end of the recovery period, satellite group

Group	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
Control (vehicle: water for injection)	2.9 ±1.9 (5)	2.0 ±0.6 (5)	3.5 ±0.7 (5)	10.8 ±2.3 (5)	22.9 ±5.2 (5)	1.2 ±0.5 (5)	2.1 ±0.9 (5)	0.9 ±0.5 (5)	1.5 ±0.6 (5)	47.8 ±6.4 (5)	0.2 ±0.1 (5)
2-IBE (150 mg/kg)	2.7 ±1.0 (5)	4.1 * ±1.5 (5)	4.0 ±1.1 (5)	12.8 ±2.3 (5)	21.0 ±3.4 (5)	1.4 ±0.5 (5)	2.0 ±0.5 (5)	0.7 ±0.4 (5)	0.6 * ±0.4 (5)	49.4 ±7.5 (5)	0.1 ±0.1 (5)

Group	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid / Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
Control (vehicle: water for injection)	5.5 ±1.0 (5)	15.1 ±4.0 (5)	8.5 ±1.4 (5)	29.2 ±4.6 (5)	1.67 ±0.34 (5)	3.0 ±0.7 (5)	19.1 ±8.4 (5)	0.6 ±0.4 (5)	0.1 ±0.3 (5)	0.2 ±0.3 (5)
2-IBE (150 mg/kg)	3.3 * ±1.1 (5)	10.0 ±3.9 (5)	8.2 ±2.8 (5)	21.6 ±6.0 (5)	2.49 ±1.03 (5)	3.8 ±1.1 (5)	24.1 ±4.0 (5)	0.8 ±0.5 (5)	0.1 ±0.1 (5)	0.2 ±0.3 (5)

Values represent as mean ± S.D.

Parentheses indicate the number of animals.

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

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

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

Group		Control (vehicle: water for injection)	2-IBE 15 mg/kg	2-IBE 50 mg/kg	2-IBE 150 mg/kg
Number of males		5	5	5	5
Total protein	g/dL	5.8 ± 0.2	5.6 ± 0.1	5.7 ± 0.3	5.5 ± 0.4
Albumin	g/dL	3.6 ± 0.1	3.5 ± 0.1	3.5 ± 0.2	3.5 ± 0.3
A/G		1.65 ± 0.12	1.64 ± 0.14	1.60 ± 0.19	1.78 ± 0.15
Glucose	mg/dL	140 ± 9	140 ± 5	137 ± 12	135 ± 19
Total cholesterol	mg/dL	51 ± 12	45 ± 11	56 ± 9	40 ± 13
Triglyceride	mg/dL	33 ± 11	43 ± 15	45 ± 12	54 ± 37
Phospholipid	mg/dL	84 ± 12	74 ± 9	88 ± 6	75 ± 19
AST	U/L	62 ± 13	65 ± 13	59 ± 5	80 ± 24
ALT	U/L	30 ± 4	34 ± 5	30 ± 4	41 ± 22
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0
LDH	U/L	104 ± 51	105 ± 69	168 ± 167	185 ± 111
Bile acid	μmol/L	13.0 ± 10.3	8.5 ± 1.4	13.4 ± 14.0	12.5 ± 6.8
BUN	mg/dL	15 ± 1	15 ± 2	14 ± 1	12 ± 1 *
Creatinine	mg/dL	0.6 ± 0.1	0.5 ± 0	0.5 ± 0	0.5 ± 0
Total bilirubin	mg/dL	0.06 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.06 ± 0.02
ALP	U/L	321 ± 36	379 ± 64	350 ± 28	359 ± 109
Inorganic phosphorus	mg/dL	6.2 ± 0.6	6.1 ± 0.4	6.6 ± 0.2	6.9 ± 0.3 *
Ca	mg/dL	9.8 ± 0.2	9.5 ± 0.3	9.8 ± 0.5	9.7 ± 0.2
Na	mEq/L	142.7 ± 1.1	142.4 ± 0.4	142.6 ± 0.8	142.7 ± 0.8
K	mEq/L	3.89 ± 0.11	3.88 ± 0.19	3.92 ± 0.10	4.04 ± 0.17
Cl	mEq/L	106.5 ± 1.3	106.4 ± 0.5	105.6 ± 0.9	106.2 ± 2.2

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

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

Table 28-2. Biochemical findings of male rats at the end of the recovery period

Group		Control (vehicle: water for injection)	2-IBE 150 mg/kg
Number of males		5	5
Total protein	g/dL	5.5 ± 0.2	5.5 ± 0.4
Albumin	g/dL	3.7 ± 0.2	3.7 ± 0.3
A/G		2.18 ± 0.11	2.04 ± 0.18
Glucose	mg/dL	155 ± 20	149 ± 14
Total cholesterol	mg/dL	44 ± 9	43 ± 8
Triglyceride	mg/dL	22 ± 8	26 ± 7
Phospholipid	mg/dL	76 ± 14	74 ± 6
AST	U/L	59 ± 6	57 ± 6
ALT	U/L	24 ± 3	26 ± 3
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	156 ± 75	131 ± 69
Bile acid	μmol/L	10.8 ± 4.6	9.7 ± 4.3
BUN	mg/dL	14 ± 1	15 ± 2
Creatinine	mg/dL	0.6 ± 0	0.6 ± 0
Total bilirubin	mg/dL	0.07 ± 0.02	0.04 ± 0 *
ALP	U/L	331 ± 55	249 ± 61
Inorganic phosphorus	mg/dL	7.1 ± 0.6	6.7 ± 0.5
Ca	mg/dL	9.3 ± 0.3	9.1 ± 0.4
Na	mEq/L	142.9 ± 0.8	143.4 ± 0.9
K	mEq/L	4.61 ± 1.14	3.98 ± 0.16
Cl	mEq/L	105.4 ± 2.0	105.6 ± 0.5

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

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

Table 29-1. Biochemical findings of female rats at the end of the dosing period

Group		Control (vehicle: water for injection)	2-IBE 15 mg/kg	2-IBE 50 mg/kg	2-IBE 150 mg/kg
Number of females		5	5	5	5
Total protein	g/dL	5.7 ± 0.5	5.8 ± 0.3	5.7 ± 0.3	5.6 ± 0.4
Albumin	g/dL	4.0 ± 0.4	4.0 ± 0.3	4.0 ± 0.2	3.8 ± 0.3
A/G		2.26 ± 0.12	2.18 ± 0.15	2.47 ± 0.21	2.21 ± 0.13
Glucose	mg/dL	122 ± 12	130 ± 15	128 ± 18	113 ± 11
Total cholesterol	mg/dL	48 ± 6	52 ± 16	52 ± 11	45 ± 8
Triglyceride	mg/dL	22 ± 10	29 ± 14	41 ± 13	38 ± 7
Phospholipid	mg/dL	91 ± 13	103 ± 20	105 ± 15	98 ± 12
AST	U/L	87 ± 24	86 ± 16	81 ± 17	83 ± 19
ALT	U/L	46 ± 22	41 ± 5	41 ± 5	42 ± 10
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0
LDH	U/L	111 ± 60	159 ± 92	74 ± 53	177 ± 133
Bile acid	μmol/L	13.0 ± 10.1	20.6 ± 11.2	12.9 ± 4.0	10.4 ± 2.7
BUN	mg/dL	14 ± 3	14 ± 4	17 ± 4	14 ± 2
Creatinine	mg/dL	0.7 ± 0.1	0.6 ± 0.1	0.6 ± 0	0.5 ± 0.1
Total bilirubin	mg/dL	0.07 ± 0.02	0.07 ± 0.01	0.05 ± 0	0.05 ± 0.01
ALP	U/L	162 ± 23	156 ± 36	147 ± 35	203 ± 88
Inorganic phosphorus	mg/dL	7.3 ± 0.8	6.0 ± 0.7 **	7.0 ± 0.3	6.5 ± 0.4
Ca	mg/dL	9.8 ± 0.5	9.4 ± 0.4	9.5 ± 0.4	9.4 ± 0.3
Na	mEq/L	143.1 ± 2.2	141.2 ± 1.3	140.9 ± 1.1	141.3 ± 0.8
K	mEq/L	3.76 ± 0.23	3.86 ± 0.37	4.08 ± 0.33	4.12 ± 0.28
Cl	mEq/L	108.2 ± 1.9	106.9 ± 1.8	106.7 ± 0.9	106.5 ± 0.6

Each value shows mean ± S.D.

Figures in parentheses indicate number of females.

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

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

Table 29-2. Biochemical findings of female rats at the end of the dosing period, satellite group

Group		Control (vehicle: water for injection)	2-IBE 150 mg/kg
Number of females		5	5
Total protein	g/dL	5.7 ± 0.2	5.5 ± 0.4
Albumin	g/dL	4.0 ± 0.2	4.0 ± 0.3
A/G		2.30 ± 0.25	2.63 ± 0.31
Glucose	mg/dL	117 ± 21	117 ± 17
Total cholesterol	mg/dL	61 ± 17	48 ± 13
Triglyceride	mg/dL	16 ± 13	15 ± 3
Phospholipid	mg/dL	110 ± 23	92 ± 16
AST	U/L	70 ± 20	63 ± 18
ALT	U/L	33 ± 22	24 ± 9
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	59 ± 18	44 ± 14
Bile acid	μmol/L	21.0 ± 25.0	16.3 ± 8.4
BUN	mg/dL	18 ± 3	17 ± 4
Creatinine	mg/dL	0.7 ± 0.1	0.6 ± 0.1
Total bilirubin	mg/dL	0.08 ± 0.02	0.06 ± 0.01 *
ALP	U/L	167 ± 34	179 ± 47
Inorganic phosphorus	mg/dL	4.9 ± 0.7	5.1 ± 0.8
Ca	mg/dL	9.0 ± 0.3	9.3 ± 0.3
Na	mEq/L	143.2 ± 1.4	142.1 ± 1.6
K	mEq/L	3.67 ± 0.28	3.96 ± 0.29
Cl	mEq/L	108.4 ± 1.2	107.3 ± 1.7

Each value shows mean ± S.D.

Figures in parentheses indicate number of females.

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

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

Table 29-3. Biochemical findings of female rats at the end of the recovery period

Group		Control (vehicle: water for injection)	2-IBE 150 mg/kg
Number of females		5	5
Total protein	g/dL	5.8 ± 0.2	5.8 ± 0.5
Albumin	g/dL	4.0 ± 0.2	4.2 ± 0.6
A/G		2.42 ± 0.49	2.50 ± 0.44
Glucose	mg/dL	125 ± 16	126 ± 9
Total cholesterol	mg/dL	65 ± 6	63 ± 14
Triglyceride	mg/dL	15 ± 2	22 ± 11
Phospholipid	mg/dL	117 ± 6	117 ± 22
AST	U/L	67 ± 17	65 ± 14
ALT	U/L	26 ± 8	27 ± 10
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	80 ± 21	154 ± 85
Bile acid	μmol/L	24.1 ± 24.5	13.0 ± 3.9
BUN	mg/dL	17 ± 2	17 ± 2
Creatinine	mg/dL	0.7 ± 0.1	0.7 ± 0.1
Total bilirubin	mg/dL	0.08 ± 0.01	0.07 ± 0.02
ALP	U/L	174 ± 19	213 ± 51
Inorganic phosphorus	mg/dL	5.1 ± 0.3	5.3 ± 0.6
Ca	mg/dL	9.4 ± 0.2	9.3 ± 0.7
Na	mEq/L	143.5 ± 0.8	143.6 ± 0.5
K	mEq/L	3.80 ± 0.21	4.13 ± 0.63
Cl	mEq/L	109.1 ± 0.6	108.8 ± 1.1

Each value shows mean ± S.D.

Figures in parentheses indicate number of females.

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

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

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

Group		Control (vehicle: water for injection)		2-IBE 15 mg/kg		2-IBE 50 mg/kg		2-IBE 150 mg/kg	
Number of males		7		12		12		7	
Body weight	(g)	494.6	± 34.5	485.0	± 44.5	505.3	± 39.9	488.3	± 48.5
Brain	(mg)	2088.4	± 59.1	2044.2	± 66.5	2074.7	± 65.4	2000.3	± 83.9
	(mg/g)	4.236	± 0.250	4.239	± 0.311	4.125	± 0.291	4.124	± 0.368
Thymus	(mg)	316.1	± 54.1	314.9	± 99.2	316.2	± 47.8	290.2	± 98.8
	(mg/g)	0.643	± 0.125	0.646	± 0.188	0.628	± 0.097	0.588	± 0.168
Heart	(mg)	1425.3	± 195.9	1493.6	± 162.5	1504.8	± 139.4	1511.7	± 207.1
	(mg/g)	2.881	± 0.333	3.082	± 0.226	2.978	± 0.138	3.093	± 0.261
Liver	(mg)	12774.5	± 990.6	12517.4	± 1583.4	13609.2	± 1632.0	13469.0	± 2490.6
	(mg/g)	25.842	± 1.294	25.750	± 1.411	26.874	± 1.681	27.383	± 2.591
Kidney (R)	(mg)	1577.1	± 168.3	1534.4	± 169.8	1696.6	± 244.6	1657.2	± 208.0
	(mg/g)	3.186	± 0.191	3.164	± 0.201	3.355	± 0.383	3.401	± 0.338
Kidney (L)	(mg)	1551.4	± 148.7	1546.0	± 213.3	1671.0	± 227.7	1635.1	± 198.2
	(mg/g)	3.134	± 0.145	3.180	± 0.224	3.307	± 0.368	3.358	± 0.346
Kidneys	(mg)	3128.5	± 310.6	3080.4	± 376.0	3367.7	± 464.8	3292.3	± 397.4
	(mg/g)	6.320	± 0.311	6.345	± 0.390	6.662	± 0.730	6.759	± 0.659
Spleen	(mg)	858.0	± 162.0	868.2	± 173.7	968.6	± 175.9	1368.8	± 281.8 **
	(mg/g)	1.732	± 0.287	1.790	± 0.315	1.914	± 0.292	2.803	± 0.501 **
Testis (R)	(mg)	1672.8	± 66.0	1695.9	± 96.3	1621.0	± 117.7	1614.9	± 215.6
	(mg/g)	3.397	± 0.275	3.515	± 0.265	3.220	± 0.269	3.322	± 0.448
Testis (L)	(mg)	1655.2	± 74.9	1682.2	± 120.6	1599.6	± 107.0	1603.4	± 229.7
	(mg/g)	3.360	± 0.261	3.484	± 0.266	3.177	± 0.240	3.295	± 0.447
Testes	(mg)	3328.0	± 139.4	3378.1	± 213.3	3220.5	± 221.5	3218.3	± 443.7
	(mg/g)	6.757	± 0.534	6.998	± 0.522	6.397	± 0.504	6.616	± 0.891
Epididymis (R)	(mg)	645.4	± 37.4	620.9	± 34.7	606.5	± 34.0	638.2	± 63.6
	(mg/g)	1.310	± 0.118	1.289	± 0.125	1.207	± 0.113	1.320	± 0.205
Epididymis (L)	(mg)	614.2	± 41.0	616.3	± 34.9	596.3	± 47.3	620.4	± 53.4
	(mg/g)	1.244	± 0.088	1.278	± 0.104	1.185	± 0.111	1.279	± 0.148
Epididymides	(mg)	1259.6	± 68.1	1237.1	± 64.3	1202.8	± 78.0	1258.6	± 109.1
	(mg/g)	2.555	± 0.192	2.566	± 0.223	2.392	± 0.218	2.599	± 0.346

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

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

Table 30-1(continued). Organ weights of male rats at the end of the dosing period

Group		Control (vehicle: water for injection)			2-IBE 15 mg/kg			2-IBE 50 mg/kg			2-IBE 150 mg/kg		
Number of males		7			12			12			7		
Body weight	(g)	494.6	±	34.5	485.0	±	44.5	505.3	±	39.9	488.3	±	48.5
Prostate, ventral	(mg)	591.5	±	121.2	603.7	±	130.6	629.9	±	91.2	630.3	±	116.4
	(mg/g)	1.209	±	0.288	1.254	±	0.297	1.253	±	0.199	1.306	±	0.292
Seminal vesicles	(mg)	1758.7	±	346.1	1627.1	±	212.6	1721.7	±	215.4	1767.6	±	316.5
	(mg/g)	3.550	±	0.597	3.390	±	0.606	3.430	±	0.533	3.662	±	0.797
Thyroid gland	(mg)	20.9	±	5.9	20.8	±	5.4	20.5	±	4.7	21.2	±	4.7
	(mg/g)	0.042	±	0.012	0.043	±	0.011	0.041	±	0.009	0.043	±	0.007
Adrenal gland (R)	(mg)	26.4	±	5.1	26.7	±	4.5	27.2	±	4.2	27.8	±	4.4
	(mg/g)	0.053	±	0.009	0.056	±	0.011	0.054	±	0.007	0.057	±	0.009
Adrenal gland (L)	(mg)	27.9	±	6.8	28.0	±	3.6	29.1	±	3.9	28.4	±	4.2
	(mg/g)	0.056	±	0.012	0.058	±	0.008	0.058	±	0.009	0.058	±	0.009
Adrenal glands	(mg)	54.4	±	11.7	54.7	±	7.6	56.3	±	7.7	56.2	±	8.5
	(mg/g)	0.110	±	0.020	0.114	±	0.018	0.112	±	0.015	0.116	±	0.017

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

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

Table 30-2. Organ weights of male rats at the end of the recovery period

Group		Control (vehicle: water for injection)		2-IBE 150 mg/kg	
Number of males		5		5	
Body weight	(g)	479.4 ±	48.8	518.9 ±	46.7
Brain	(mg)	1965.5 ±	62.6	2027.0 ±	86.3
	(mg/g)	4.124 ±	0.316	3.925 ±	0.297
Thymus	(mg)	241.2 ±	38.6	282.7 ±	44.5
	(mg/g)	0.511 ±	0.114	0.547 ±	0.095
Heart	(mg)	1393.3 ±	156.2	1475.5 ±	194.6
	(mg/g)	2.906 ±	0.108	2.840 ±	0.245
Liver	(mg)	11507.3 ±	1414.1	13396.2 ±	1593.2
	(mg/g)	24.004 ±	1.609	25.769 ±	0.867
Kidney (R)	(mg)	1485.1 ±	165.6	1635.6 ±	151.8
	(mg/g)	3.098 ±	0.136	3.158 ±	0.237
Kidney (L)	(mg)	1476.6 ±	171.9	1582.3 ±	121.6
	(mg/g)	3.080 ±	0.156	3.055 ±	0.158
Kidneys	(mg)	2961.7 ±	335.0	3217.8 ±	270.4
	(mg/g)	6.177 ±	0.277	6.212 ±	0.391
Spleen	(mg)	783.9 ±	65.3	1041.6 ±	268.5 *
	(mg/g)	1.648 ±	0.206	1.986 ±	0.315
Testis (R)	(mg)	1766.9 ±	131.0	1667.1 ±	166.6
	(mg/g)	3.701 ±	0.302	3.215 ±	0.209 *
Testis (L)	(mg)	1758.2 ±	139.8	1693.5 ±	191.9
	(mg/g)	3.684 ±	0.329	3.261 ±	0.153 *
Testes	(mg)	3525.1 ±	265.1	3360.5 ±	349.2
	(mg/g)	7.385 ±	0.620	6.476 ±	0.330 *
Epididymis (R)	(mg)	631.0 ±	41.0	634.3 ±	45.2
	(mg/g)	1.323 ±	0.100	1.227 ±	0.101
Epididymis (L)	(mg)	640.0 ±	35.4	609.8 ±	29.0
	(mg/g)	1.340 ±	0.071	1.180 ±	0.078 **
Epididymides	(mg)	1271.0 ±	73.1	1244.1 ±	59.8
	(mg/g)	2.662 ±	0.167	2.407 ±	0.156 *

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

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

Table 30-2(continued). Organ weights of male rats at the end of the recovery period

Group		Control (vehicle: water for injection)		2-IBE 150 mg/kg	
Number of males		5		5	
Body weight	(g)	479.4	± 48.8	518.9	± 46.7
Prostate, ventral	(mg)	591.1	± 140.0	594.9	± 143.7
	(mg/g)	1.235	± 0.284	1.149	± 0.277
Seminal vesicles	(mg)	1240.3	± 196.9	1549.3	± 449.3
	(mg/g)	2.594	± 0.397	3.024	± 0.936
Thyroid gland	(mg)	18.6	± 4.5	17.4	± 3.4
	(mg/g)	0.039	± 0.011	0.034	± 0.006
Adrenal gland (R)	(mg)	24.2	± 3.9	26.7	± 6.4
	(mg/g)	0.051	± 0.005	0.051	± 0.010
Adrenal gland (L)	(mg)	25.8	± 3.7	27.8	± 5.5
	(mg/g)	0.054	± 0.004	0.053	± 0.009
Adrenal glands	(mg)	50.0	± 7.4	54.4	± 11.9
	(mg/g)	0.104	± 0.009	0.105	± 0.019

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

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

Table 31-1. Organ weights of female rats at the end of the dosing period

Group		Control (vehicle: water for injection)		2-IBE 15 mg/kg		2-IBE 50 mg/kg		2-IBE 150 mg/kg	
Number of females		12		11		12		12	
Body weight	(g)	306.1	± 27.9	311.0	± 18.8	307.5	± 7.1	298.3	± 25.3
Brain	(mg)	1895.0	± 82.2	1913.4	± 57.3	1864.8	± 47.2	1926.7	± 62.1
	(mg/g)	6.228	± 0.521	6.171	± 0.368	6.066	± 0.155	6.495	± 0.493
Thymus	(mg)	164.8	± 61.7	223.9	± 48.7	193.9	± 63.9	194.0	± 46.8
	(mg/g)	0.529	± 0.161	0.719	± 0.147	0.630	± 0.201	0.652	± 0.154
Heart	(mg)	981.3	± 77.5	997.3	± 70.8	1021.4	± 57.5	1039.9	± 97.2
	(mg/g)	3.221	± 0.300	3.207	± 0.125	3.321	± 0.151	3.489	± 0.190 **
Liver	(mg)	9644.8	± 656.5	9965.9	± 712.8	9903.2	± 441.6	10148.1	± 1231.4
	(mg/g)	31.635	± 2.249	32.078	± 1.901	32.214	± 1.466	33.993	± 2.545 *
Kidney (R)	(mg)	984.8	± 116.4	1020.4	± 88.3	979.3	± 58.5	1052.0	± 85.7
	(mg/g)	3.220	± 0.263	3.281	± 0.189	3.185	± 0.180	3.535	± 0.229 **
Kidney (L)	(mg)	961.7	± 93.3	1013.3	± 87.3	971.2	± 69.0	1038.7	± 83.3
	(mg/g)	3.144	± 0.149	3.257	± 0.159	3.158	± 0.201	3.491	± 0.236 **
Kidneys	(mg)	1946.5	± 204.5	2033.8	± 172.5	1950.4	± 126.3	2090.7	± 164.7
	(mg/g)	6.364	± 0.395	6.538	± 0.333	6.342	± 0.376	7.026	± 0.448 **
Spleen	(mg)	699.9	± 98.2	732.2	± 96.7	954.2	± 232.6 **	1132.7	± 286.4 **
	(mg/g)	2.296	± 0.348	2.358	± 0.304	3.105	± 0.773 **	3.794	± 0.889 **
Ovary (R)	(mg)	51.6	± 10.2	49.5	± 8.5	55.8	± 5.1	50.6	± 5.2
	(mg/g)	0.169	± 0.035	0.159	± 0.027	0.181	± 0.016	0.170	± 0.013
Ovary (L)	(mg)	52.5	± 12.8	50.3	± 7.3	53.0	± 8.8	50.3	± 6.9
	(mg/g)	0.172	± 0.044	0.162	± 0.018	0.172	± 0.028	0.170	± 0.024
Ovaries	(mg)	104.1	± 18.1	99.8	± 13.5	108.8	± 9.4	100.9	± 8.6
	(mg/g)	0.342	± 0.064	0.321	± 0.039	0.354	± 0.027	0.339	± 0.026
Uterus	(mg)	666.0	± 103.8	600.3	± 71.1	659.6	± 80.3	653.6	± 113.4
	(mg/g)	2.190	± 0.379	1.933	± 0.227	2.147	± 0.269	2.202	± 0.394
Thyroid gland	(mg)	18.5	± 4.1	15.4	± 3.1	15.9	± 3.5	16.1	± 3.9
	(mg/g)	0.061	± 0.013	0.049	± 0.010	0.052	± 0.012	0.054	± 0.013
Adrenal gland (R)	(mg)	31.5	± 1.7	34.9	± 4.9	36.0	± 4.7	33.2	± 5.0
	(mg/g)	0.104	± 0.011	0.113	± 0.018	0.117	± 0.015	0.112	± 0.017
Adrenal gland (L)	(mg)	33.5	± 3.1	38.7	± 4.2 *	38.6	± 5.6 *	36.1	± 4.6
	(mg/g)	0.110	± 0.012	0.125	± 0.018	0.126	± 0.018	0.121	± 0.014
Adrenal glands	(mg)	65.0	± 4.0	73.7	± 8.3 *	74.6	± 10.2 *	69.3	± 9.2
	(mg/g)	0.214	± 0.020	0.238	± 0.034	0.243	± 0.032	0.233	± 0.029

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

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

Table 31-2. Organ weights of female rats at the end of the dosing period, satellite group

Group		Control (vehicle: water for injection)		2-IBE 150 mg/kg	
Number of females		5		5	
Body weight	(g)	282.8	± 31.4	286.3	± 7.1
Brain	(mg)	1864.8	± 72.7	1900.7	± 63.6
	(mg/g)	6.649	± 0.663	6.644	± 0.330
Thymus	(mg)	298.7	± 98.4	353.7	± 47.8
	(mg/g)	1.051	± 0.311	1.234	± 0.154
Heart	(mg)	859.3	± 56.0	991.2	± 82.1 *
	(mg/g)	3.056	± 0.249	3.461	± 0.262 *
Liver	(mg)	7016.3	± 625.3	7921.6	± 356.5 *
	(mg/g)	24.871	± 1.150	27.686	± 1.492 *
Kidney (R)	(mg)	902.3	± 97.7	961.9	± 41.5
	(mg/g)	3.197	± 0.208	3.359	± 0.090
Kidney (L)	(mg)	913.8	± 116.3	926.6	± 23.2
	(mg/g)	3.233	± 0.211	3.237	± 0.047
Kidneys	(mg)	1816.1	± 212.1	1888.6	± 59.6
	(mg/g)	6.430	± 0.403	6.596	± 0.097
Spleen	(mg)	566.1	± 43.4	931.1	± 173.9 **
	(mg/g)	2.018	± 0.247	3.243	± 0.540 **
Ovary (R)	(mg)	47.4	± 13.7	44.9	± 12.9
	(mg/g)	0.170	± 0.053	0.157	± 0.044
Ovary (L)	(mg)	41.4	± 6.1	44.8	± 14.1
	(mg/g)	0.148	± 0.032	0.156	± 0.048
Ovaries	(mg)	88.8	± 13.5	89.8	± 24.8
	(mg/g)	0.318	± 0.064	0.313	± 0.084
Uterus	(mg)	739.7	± 269.5	594.6	± 266.8
	(mg/g)	2.680	± 1.139	2.090	± 0.977
Thyroid gland	(mg)	13.3	± 3.1	15.7	± 5.2
	(mg/g)	0.047	± 0.011	0.055	± 0.018
Adrenal gland (R)	(mg)	32.1	± 3.2	29.6	± 4.7
	(mg/g)	0.114	± 0.014	0.103	± 0.015
Adrenal gland (L)	(mg)	34.4	± 3.5	33.5	± 4.8
	(mg/g)	0.122	± 0.014	0.117	± 0.015
Adrenal glands	(mg)	66.4	± 6.5	63.1	± 9.3
	(mg/g)	0.236	± 0.027	0.220	± 0.028

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

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

Table 31-3. Organ weights of female rats at the end of the recovery period

Group		Control (vehicle; water for injection)		2-IBE 150 mg/kg	
Number of females		5		5	
Body weight	(g)	299.7	± 22.6	313.4	± 14.6
Brain	(mg)	1875.0	± 114.8	1839.6	± 97.0
	(mg/g)	6.274	± 0.480	5.881	± 0.437
Thymus	(mg)	246.5	± 36.4	309.5	± 66.9
	(mg/g)	0.824	± 0.121	0.993	± 0.248
Heart	(mg)	908.7	± 55.6	1016.3	± 100.5
	(mg/g)	3.044	± 0.292	3.243	± 0.283
Liver	(mg)	7381.9	± 816.5	7930.0	± 648.0
	(mg/g)	24.760	± 3.661	25.303	± 1.770
Kidney (R)	(mg)	908.5	± 48.8	1054.4	± 105.1 *
	(mg/g)	3.041	± 0.240	3.379	± 0.476
Kidney (L)	(mg)	868.2	± 60.6	1001.6	± 109.6 *
	(mg/g)	2.906	± 0.262	3.209	± 0.470
Kidneys	(mg)	1776.6	± 108.4	2056.0	± 212.0 *
	(mg/g)	5.948	± 0.498	6.588	± 0.940
Spleen	(mg)	710.2	± 296.9	673.4	± 67.5
	(mg/g)	2.413	± 1.153	2.150	± 0.201
Ovary (R)	(mg)	48.4	± 14.6	47.3	± 6.3
	(mg/g)	0.163	± 0.054	0.151	± 0.023
Ovary (L)	(mg)	41.5	± 11.7	43.9	± 5.6
	(mg/g)	0.139	± 0.040	0.141	± 0.018
Ovaries	(mg)	89.8	± 21.2	91.3	± 10.5
	(mg/g)	0.301	± 0.077	0.292	± 0.037
Uterus	(mg)	575.5	± 250.9	728.7	± 403.4
	(mg/g)	1.957	± 0.942	2.295	± 1.166
Thyroid gland	(mg)	16.6	± 3.0	15.5	± 3.3
	(mg/g)	0.055	± 0.006	0.050	± 0.011
Adrenal gland (R)	(mg)	30.0	± 2.9	33.4	± 2.3
	(mg/g)	0.100	± 0.010	0.107	± 0.009
Adrenal gland (L)	(mg)	31.5	± 4.1	34.7	± 3.8
	(mg/g)	0.105	± 0.016	0.111	± 0.011
Adrenal glands	(mg)	61.5	± 6.2	68.1	± 5.8
	(mg/g)	0.206	± 0.024	0.217	± 0.018

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

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

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

	Group	<u>Control (Vehicle)</u>		<u>2-IBE 15 mg/kg</u>		<u>2-IBE 50 mg/kg</u>		<u>2-IBE 150 mg/kg</u>	
Findings	Grade	-	P	-	P	-	P	-	P
Epididymis									
Nodule, yellowish white, caudal, unilateral		6	1	12	0	12	0	6	1
Forestomach									
Edematous, mucosa		7	0	12	0	12	0	5	2
Kidney									
Pale colored area, bilateral		7	0	11	1	12	0	7	0
Spleen									
Enlargement		7	0	12	0	12	0	0	7

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

Numerals represent the number of animals.

Vehicle: water for injection

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

Table 32-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group Grade	Control (Vehicle)		2-IBE 150 mg/kg	
		-	P	-	P
Kidney					
Enlargement, bilateral		5	0	4	1
Skin					
Alopecia, both forelimbs		5	0	4	1
Spleen					
Enlargement		5	0	3	2

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

Numerals represent the number of animals.

Vehicle: water for injection

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

Table 33-1. Macroscopic findings of female rats at the end of the dosing period

Findings	Group Grade	Control (Vehicle)		2-IBE 15 mg/kg		2-IBE 50 mg/kg		2-IBE 150 mg/kg	
		-	P	-	P	-	P	-	P
Adrenal gland									
Enlargement, bilateral		12	0	11	0	11	1	12	0
Forestomach									
Edematous, mucosa		11	1	11	0	12	0	11	1
Glandular stomach									
Dark colored spot, mucosa		12	0	11	0	12	0	11	1
Liver									
Enlargement		12	0	11	0	11	1	12	0
Nodule, caudal lobe, hard, mosaic		12	0	11	0	12	0	11	1
Lung									
Dark colored area, all lobes		12	0	10	1	12	0	12	0
Dark colored spot, left lobe, dorsal		12	0	11	0	12	0	11	1
Lymph node, submandibular									
Enlargement		12	0	11	0	12	0	11	1
Skin									
Alopecia, both forelimbs/neck		12	0	9	2	12	0	11	1
Spleen									
Enlargement		12	0	11	0	9	3	3	9
Tail									
Loss, edge, dark color		12	0	11	0	12	0	10	2
Thymus									
Small		11	1	11	0	10	2	12	0

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

Numerals represent the number of animals.

Vehicle: water for injection

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

Table 33-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)		2-IBE 150 mg/kg	
	Grade	-	P	-	P
Forestomach					
Edematous, mucosa		5	0	4	1
Spleen					
Enlargement		5	0	1	4

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

Numerals represent the number of animals.

Vehicle: water for injection

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

Table 33-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group	Control (Vehicle)		2-IBE 150 mg/kg	
	Grade	-	P	-	P
Kidney					
Enlargement, bilateral		5	0	4	1
Rough surface, bilateral		5	0	4	1
Spleen					
Enlargement		5	0	4	1
Rough surface, adhesion with connective tissue		4	1	5	0

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

Numerals represent the number of animals.

Vehicle: water for injection

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

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

Findings	Group Grade	Control (Vehicle)							2-IBE 15 mg/kg							2-IBE 50 mg/kg							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5						2	0					12	0						12	5						2	
Spinal cord		5						2	0					12	0						12	5						2	
Pituitary gland																													
Remnant, Rathke's pouch		4						1 2	0					0 12	0						0 12	5						0 2	
Submandibular gland		5						2	0					12	0						12	5						2	
Sublingual gland		5						2	0					12	0						12	5						2	
Lymph node, submandibular		5						2	0					12	0						12	5						2	
Thyroid gland																													
Ectopic thymic tissue		5						0 2	0					0 12	0						0 12	4						1 2	
Parathyroid gland		5						2	0					12	0						12	5						2	
Thymus		5						2	0					12	0						12	5						2	
Heart																													
Cellular infiltration, inflammatory, ventricle, right, subepicardial, focal		5	0	0	0	0	0	2	0	0	0	0	0	12	0	0	0	0	0	0	12	4	1	0	0	0	0	2	
Cellular infiltration, mononuclear cell, septum, focal		4	1	0	0	0	0	2	0	0	0	0	0	12	0	0	0	0	0	0	12	5	0	0	0	0	0	2	
Trachea		5						2	0					12	0						12	5						2	
Lung																													
Accumulation, foam cell, alveolus		5	0	0	0	0	0	2	0	0	0	0	0	12	0	0	0	0	0	0	12	3	2	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.

Vehicle: water for injection

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

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

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

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

Findings	Group Grade	Control (Vehicle)							2-IBE 15 mg/kg							2-IBE 50 mg/kg							2-IBE 150 mg/kg							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Liver																														
Deposit, pigment, brown, Kupffer cell		5	0	0	0	0		2	5	0	0	0	0		7	2	3	0	0	0		7	0	3	2	0	0		2	**,##
Fatty change, hepatocyte, periportal		3	1	1	0	0		2	1	4	0	0	0		7	1	2	2	0	0		7	1	3	1	0	0		2	
Hematopoiesis, extramedullary		5	0	0	0	0		2	5	0	0	0	0		7	4	1	0	0	0		7	0	5	0	0	0		2	**,##
Microgranuloma		1	4	0	0	0		2	2	3	0	0	0		7	1	3	1	0	0		7	0	5	0	0	0		2	
Single cell necrosis		3	2	0	0	0		2	4	1	0	0	0		7	2	3	0	0	0		7	2	3	0	0	0		2	
Pancreas																														
Infiltration, fatty		5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2	
Single cell necrosis		3	2	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2	
Stomach																														
		5						2	0						12	0						12	6						1	
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	0	4	1	0		2	0	0	2	3	0		7	0	0	0	4	1		7 *	0	0	0	7	0		*	
Hematopoiesis, extramedullary		0	1	3	1	0		2	0	3	2	0	0		7	0	0	1	2	2		7	0	0	0	3	4		**	
Increase, red pulp		5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	1	4	2	0	0		*,##	

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Vehicle: water for injection

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

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

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

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

Findings	Group Grade	Control (Vehicle)						2-IBE 15 mg/kg						2-IBE 50 mg/kg						2-IBE 150 mg/kg														
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE					
Kidney																																		
	Basophilic tubule, cortex	4		1	0	0	0		2	4		1	0	0	0		7	2		3	0	0	0		7	1		4	0	0	0		2	
	Cellular infiltration, lymphocyte, interstitial	5		0	0	0	0		2	4		1	0	0	0		7	5		0	0	0	0		7	5		0	0	0	0		2	
	Cyst, medulla	5						0	2	5						0	7	5						0	7	4					1	2		
	Deposit, pigment, brown, proximal tubule	5		0	0	0	0		2	5		0	0	0	0		7	2		3	0	0	0		7	0		2	3	0	0		2	
**,,##																																		
Urinary bladder		5							2	0							12	0							12	5							2	
Adrenal gland		5							2	0							12	0							12	5							2	
Testis																																		
	Atrophy, seminiferous tubule, bilateral	5		0	0	0	0	0		2	0		0	0	0	0		12	0		0	0	0	0		12	3		2	0	0	0		2
Epididymis																																		
	Granuloma, spermatic, unilateral	4						1	2	0					0	12	0						0	12	5					1		1		
Prostate																																		
	Cellular infiltration, lymphocyte, interstitial	4		0	1	0	0		2	0		0	0	0	0		12	0		0	0	0	0		12	5		0	0	0	0		2	
Seminal vesicle		5							2	0							12	0							12	5							2	
Coagulating gland		5							2	0							12	0							12	5							2	
Eyeball		5							2	0							12	0							12	5							2	
Harderian gland		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																																		
	Hyperplasia, erythroblast	5		0	0	0	0	0		2	4		1	0	0	0		7	3		2	0	0	0		7	0		2	3	0	0		2
**,,##																																		

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Vehicle: water for injection

Not significantly different from control.

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

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

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

Table 34-2. Histopathological findings of male rats at the end of the recovery period

Findings	Group Grade	Control (Vehicle)							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		0						5	0						5
Spinal cord		0						5	0						5
Pituitary gland		0						5	0						5
Submandibular gland		0						5	0						5
Sublingual gland		0						5	0						5
Lymph node, submandibular		0						5	0						5
Thyroid gland		0						5	0						5
Parathyroid gland		0						5	0						5
Thymus		0						5	0						5
Heart		0						5	0						5
Trachea		0						5	0						5
Lung		0						5	0						5
Bronchus		0						5	0						5

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Vehicle: water for injection

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

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

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

Table 34-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group Grade	Control (Vehicle)							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Deposit, pigment, brown, Kupffer cell		5	0	0	0	0			4	1	0	0	0		
Fatty change, hepatocyte, periportal		2	3	0	0	0			1	3	1	0	0		
Hyperplasia, bile duct		4	1	0	0	0			5	0	0	0	0		
Microgranuloma		0	5	0	0	0			2	3	0	0	0		
Single cell necrosis		4	1	0	0	0			4	1	0	0	0		
Pancreas															
		0						5	0						5
Stomach															
		0						5	0						5
Duodenum															
		0						5	0						5
Jejunum															
		0						5	0						5
Ileum															
		0						5	0						5
Cecum															
		0						5	0						5
Colon															
		0						5	0						5
Rectum															
		0						5	0						5
Lymph node, mesenteric															
		0						5	0						5
Spleen															
Deposit, pigment, brown		0	0	1	4	0			0	0	1	4	0		
Hematopoiesis, extramedullary		0	1	2	2	0			0	4	1	0	0		
Increase, red pulp		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.

Vehicle: water for injection

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

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

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

Table 34-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group Grade	Control (Vehicle)						2-IBE 150 mg/kg								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Kidney																
Basophilic tubule, cortex		1	4	0	0	0			3	2	0	0	0			
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0			5	0	0	0	0			
Deposit, pigment, brown, proximal tubule		5	0	0	0	0			1	4	0	0	0		#	
Urinary bladder																
		0						5	0						5	
Adrenal gland																
		0						5	0						5	
Testis																
		0						5	0						5	
Epididymis																
		0						5	0						5	
Prostate																
		0						5	0						5	
Seminal vesicle																
		0						5	0						5	
Coagulating gland																
		0						5	0						5	
Eyeball																
		0						5	0						5	
Harderian gland																
		0						5	0						5	
Sciatic nerve																
		0						5	0						5	
Skeletal muscle																
		0						5	0						5	
Femur																
		0						5	0						5	
Marrow, femur																
Hyperplasia, erythroblast		5	0	0	0	0			3	2	0	0	0			
Skin																
Atrophy, hair follicle									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.

Vehicle: water for injection

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

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

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

Table 35-1. Histopathological findings of female rats at the end of the dosing period

Findings	Group Grade	Control (Vehicle)							2-IBE 15 mg/kg							2-IBE 50 mg/kg							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5						7	0						11	0							12	5					7
Spinal cord		5						7	0						11	0							12	5					7
Pituitary gland																													
Remnant, Rathke's pouch		4						1	7	0				0	11	0					0	12	4					1	7
Submandibular gland		5						7	0						11	0							12	5					7
Sublingual gland		5						7	0						11	0							12	5					7
Lymph node, submandibular		5						7	0						11	0							12	5					7
Thyroid gland																													
Ectopic thymic tissue		5						0	7	0				0	11	0					0	12	4					1	7
Parathyroid gland		5						7	0						11	0							12	5					7
Thymus																													
Atrophy		4	0	1	0	0		7	0	0	0	0	0	0	11	0	2	0	0	0	0	10	5	0	0	0	0	0	7
Heart		5						7	0						11	0							12	5					7
Trachea		5						7	0						11	0							12	5					7
Lung																													
Accumulation, foam cell, alveolus		5	0	0	0	0		7	1	0	0	0	0	0	10	0	0	0	0	0	0	12	3	3	0	0	0	0	6
Cellular infiltration, macrophage, alveolus, including brown pigment		5	0	0	0	0		7	0	0	1	0	0	0	10	0	0	0	0	0	0	12	6	0	0	0	0	0	6
Thickening, pleura, focal		5	0	0	0	0		7	1	0	0	0	0	0	10	0	0	0	0	0	0	12	5	1	0	0	0	0	6
Bronchus		5						7	0						11	0							12	6					6

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Vehicle: water for injection

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

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

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

Table 35-1(continued). Histopathological findings of female rats at the end of the dosing period

Findings	Group Grade	Control (Vehicle)							2-IBE 15 mg/kg							2-IBE 50 mg/kg							2-IBE 150 mg/kg								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE		
Liver																															
Deposit, pigment, brown, Kupffer cell		5	0	0	0	0		7	5	0	0	0	0		6	0	5	0	0	0		7	** , ##	0	3	3	0	0		6	** , ##
Fatty change, hepatocyte, periportal		4	0	1	0	0		7	4	1	0	0	0		6	5	0	0	0	0		7		2	3	1	0	0		6	
Hematopoiesis, extramedullary		5	0	0	0	0		7	4	1	0	0	0		6	0	5	0	0	0		7	** , ##	0	6	0	0	0		6	** , ##
Microgranuloma		3	2	0	0	0		7	2	3	0	0	0		6	3	2	0	0	0		7		2	4	0	0	0		6	
Necrosis, focal		5					0	7	5					0	6	5					0	7		5				1	6		
Single cell necrosis		5	0	0	0	0		7	5	0	0	0	0		6	4	1	0	0	0		7		4	2	0	0	0		6	
Pancreas		5						7	0						11	0						12		5					7		
Stomach																															
Dilatation, gland, fundic		5	0	0	0	0		7	0	0	0	0	0		11	0	0	0	0	0		12		6	1	0	0	0		5	
Edema, submucosa layer, forestomach		4	1	0	0	0		7	0	0	0	0	0		11	0	0	0	0	0		12		7	0	0	0	0		5	
Duodenum		5						7	0						11	0						12		5					7		
Jejunum		5						7	0						11	0						12		5					7		
Ileum		5						7	0						11	0						12		5					7		
Cecum		5						7	0						11	0						12		5					7		
Colon		5						7	0						11	0						12		5					7		
Rectum		5						7	0						11	0						12		5					7		
Lymph node, mesenteric		5						7	0						11	0						12		5					7		
Spleen																															
Congestion		5	0	0	0	0		7	4	0	1	0	0		6	7	0	0	0	0		5		10	0	0	0	0		2	
Deposit, pigment, brown		0	0	2	3	0		7	0	1	2	2	0		6	0	3	4	0	0		5	*	0	5	4	1	0		2	*
Hematopoiesis, extramedullary		0	0	2	3	0		7	0	0	1	4	0		6	0	0	0	2	5		5	*	0	0	0	3	7		2	*
Increase, red pulp		5	0	0	0	0		7	5	0	0	0	0		6	4	3	0	0	0		5		3	6	1	0	0		2	*, #

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Vehicle: water for injection

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

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

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Findings	Group Grade	Control (Vehicle)							2-IBE 15 mg/kg							2-IBE 50 mg/kg							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney																													
Basophilic tubule, cortex		4	0	0	1	0		7	4	1	0	0	0		6	5	0	0	0	0		7	3	2	0	0	0		7
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0		7	5	0	0	0	0		6	4	1	0	0	0		7	5	0	0	0	0		7
Degeneration/necrosis, proximal tubule		4	1	0	0	0		7	5	0	0	0	0		6	5	0	0	0	0		7	5	0	0	0	0		7
Deposit, pigment, brown, proximal tubule		5	0	0	0	0		7	5	0	0	0	0		6	2	3	0	0	0		7	0	1	4	0	0		7 ** , ##
Urinary bladder		5						7	0						11	0						12	5						7
Adrenal gland																													
Cellular infiltration, lymphocyte, zona reticularis, sinusoid		4	1	0	0	0		7	0	0	0	0	0		11	1	0	0	0	0		11	5	0	0	0	0		7
Ovary		5						7	0						11	0						12	5						7
Uterus		5						7	0						11	0						12	5						7
Vagina		5						7	0						11	0						12	5						7
Eyeball		5						7	0						11	0						12	5						7
Harderian gland																													
Hyperpigmentation		4	1	0	0	0		7	0	0	0	0	0		11	0	0	0	0	0		12	5	0	0	0	0		7
Sciatic nerve		5						7	0						11	0						12	5						7
Skeletal muscle		5						7	0						11	0						12	5						7
Femur		5						7	0						11	0						12	5						7
Marrow, femur																													
Hyperplasia, erythroblast		5	0	0	0	0		7	4	1	0	0	0		6	1	4	0	0	0		7 #	0	5	0	0	0		7 ** , ##
Skin																													
Atrophy, hair follicle									0	2	0	0	0										0	1	0	0	0		
Tail																													
Necrosis																							0					1	
Ulcer																							0					1	

P : Non-graded change NE: Not examined

erals represent the number of animals.

Vehicle: water for injection

Not significantly different from

*P<0.05, **P<0.01 : Significantly different

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

REMARKS: 0805; 0906; 0907; 0908; 0909; 0910; 0911; 0912; 0913; 0914; 0915; 0916; 0917; 0918; 0919; 0920; 0921; 0922; 0923; 0924; 0925; 0926; 0927; 0928; 0929; 0930; 0931; 0932; 0933; 0934; 0935; 0936; 0937; 0938; 0939; 0940; 0941; 0942; 0943; 0944; 0945; 0946; 0947; 0948; 0949; 0950; 0951; 0952; 0953; 0954; 0955; 0956; 0957; 0958; 0959; 0960; 0961; 0962; 0963; 0964; 0965; 0966; 0967; 0968; 0969; 0970; 0971; 0972; 0973; 0974; 0975; 0976; 0977; 0978; 0979; 0980; 0981; 0982; 0983; 0984; 0985; 0986; 0987; 0988; 0989; 0990; 0991; 0992; 0993; 0994; 0995; 0996; 0997; 0998; 0999; 1000; 1001; 1002; 1003; 1004; 1005; 1006; 1007; 1008; 1009; 1010; 1011; 1012; 1013; 1014; 1015; 1016; 1017; 1018; 1019; 1020; 1021; 1022; 1023; 1024; 1025; 1026; 1027; 1028; 1029; 1030; 1031; 1032; 1033; 1034; 1035; 1036; 1037; 1038; 1039; 1040; 1041; 1042; 1043; 1044; 1045; 1046; 1047; 1048; 1049; 1050; 1051; 1052; 1053; 1054; 1055; 1056; 1057; 1058; 1059; 1060; 1061; 1062; 1063; 1064; 1065; 1066; 1067; 1068; 1069; 1070; 1071; 1072; 1073; 1074; 1075; 1076; 1077; 1078; 1079; 1080; 1081; 1082; 1083; 1084; 1085; 1086; 1087; 1088; 1089; 1090; 1091; 1092; 1093; 1094; 1095; 1096; 1097; 1098; 1099; 1100; 1101; 1102; 1103; 1104; 1105; 1106; 1107; 1108; 1109; 1110; 1111; 1112; 1113; 1114; 1115; 1116; 1117; 1118; 1119; 1120; 1121; 1122; 1123; 1124; 1125; 1126; 1127; 1128; 1129; 1130; 1131; 1132; 1133; 1134; 1135; 1136; 1137; 1138; 1139; 1140; 1141; 1142; 1143; 1144; 1145; 1146; 1147; 1148; 1149; 1150; 1151; 1152; 1153; 1154; 1155; 1156; 1157; 1158; 1159; 1160; 1161; 1162; 1163; 1164; 1165; 1166; 1167; 1168; 1169; 1170; 1171; 1172; 1173; 1174; 1175; 1176; 1177; 1178; 1179; 1180; 1181; 1182; 1183; 1184; 1185; 1186; 1187; 1188; 1189; 1190; 1191; 1192; 1193; 1194; 1195; 1196; 1197; 1198; 1199; 1200; 1201; 1202; 1203; 1204; 1205; 1206; 1207; 1208; 1209; 1210; 1211; 1212; 1213; 1214; 1215; 1216; 1217; 1218; 1219; 1220; 1221; 1222; 1223; 1224; 1225; 1226; 1227; 1228; 1229; 1230; 1231; 1232; 1233; 1234; 1235; 1236; 1237; 1238; 1239; 1240; 1241; 1242; 1243; 1244; 1245; 1246; 1247; 1248; 1249; 1250; 1251; 1252; 1253; 1254; 1255; 1256; 1257; 1258; 1259; 1260; 1261; 1262; 1263; 1264; 1265; 1266; 1267; 1268; 1269; 1270; 1271; 1272; 1273; 1274; 1275; 1276; 1277; 1278; 1279; 1280; 1281; 1282; 1283; 1284; 1285; 1286; 1287; 1288; 1289; 1290; 1291; 1292; 1293; 1294; 1295; 1296; 1297; 1298; 1299; 1300; 1301; 1302; 1303; 1304; 1305; 1306; 1307; 1308; 1309; 1310; 1311; 1312; 1313; 1314; 1315; 1316; 1317; 1318; 1319; 1320; 1321; 1322; 1323; 1324; 1325; 1326; 1327; 1328; 1329; 1330; 1331; 1332; 1333; 1334; 1335; 1336; 1337; 1338; 1339; 1340; 1341; 1342; 1343; 1344; 1345; 1346; 1347; 1348; 1349; 1350; 1351; 1352; 1353; 1354; 1355; 1356; 1357; 1358; 1359; 1360; 1361; 1362; 1363; 1364; 1365; 1366; 1367; 1368; 1369; 1370; 1371; 1372; 1373; 1374; 1375; 1376; 1377; 1378; 1379; 1380; 1381; 1382; 1383; 1384; 1385; 1386; 1387; 1388; 1389; 1390; 1391; 1392; 1393; 1394; 1395; 1396; 1397; 1398; 1399; 1400; 1401; 1402; 1403; 1404; 1405; 1406; 1407; 1408; 1409; 1410; 1411; 1412; 1413; 1414; 1415; 1416; 1417; 1418; 1419; 1420; 1421; 1422; 1423; 1424; 1425; 1426; 1427; 1428; 1429; 1430; 1431; 1432; 1433; 1434; 1435; 1436; 1437; 1438; 1439; 1440; 1441; 1442; 1443; 1444; 1445; 1446; 1447; 1448; 1449; 1450; 1451; 1452; 1453; 1454; 1455; 1456; 1457; 1458; 1459; 1460; 1461; 1462; 1463; 1464; 1465; 1466; 1467; 1468; 1469; 1470; 1471; 1472; 1473; 1474; 1475; 1476; 1477; 1478; 1479; 1480; 1481; 1482; 1483; 1484; 1485; 1486; 1487; 1488; 1489; 1490; 1491; 1492; 1493; 1494; 1495; 1496; 1497; 1498; 1499; 1500; 1501; 1502; 1503; 1504; 1505; 1506; 1507; 1508; 1509; 1510; 1511; 1512; 1513; 1514; 1515; 1516; 1517; 1518; 1519; 1520; 1521; 1522; 1523; 1524; 1525; 1526; 1527; 1528; 1529; 1530; 1531; 1532; 1533; 1534; 1535; 1536; 1537; 1538; 1539; 1540; 1541; 1542; 1543; 1544; 1545; 1546; 1547; 1548; 1549; 1550; 1551; 1552; 1553; 1554; 1555; 1556; 1557; 1558; 1559; 1560; 1561; 1562; 1563; 1564; 1565; 1566; 1567; 1568; 1569; 1570; 1571; 1572; 1573; 1574; 1575; 1576; 1577; 1578; 1579; 1580; 1581; 1582; 1583; 1584; 1585;

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

Table 35-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Grade	Control (Vehicle)							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5							5						
Spinal cord		5							5						
Pituitary gland															
Remnant, Rathke's pouch		4					1		5					0	
Submandibular gland		5							5						
Sublingual gland		5							5						
Lymph node, submandibular		5							5						
Thyroid gland															
Ectopic thymic tissue		3					2		5					0	
Parathyroid gland		5							5						
Thymus		5							5						
Heart															
Cellular infiltration, mononuclear cell, septum, focal		5	0	0	0	0	0		4	1	0	0	0	0	
Trachea		5							5						
Lung															
Accumulation, foam cell, alveolus		5	0	0	0	0	0		4	1	0	0	0	0	
Granuloma, foreign body		4	1	0	0	0	0		5	0	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.

Vehicle: water for injection

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

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

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

Table 35-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Grade	Control (Vehicle)							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Deposit, pigment, brown, Kupffer cell		5	0	0	0	0			0	0	5	0	0		** , ##
Fatty change, hepatocyte, periportal		1	4	0	0	0			3	2	0	0	0		
Hematopoiesis, extramedullary		5	0	0	0	0			0	5	0	0	0		** , ##
Microgranuloma		1	4	0	0	0			2	3	0	0	0		
Single cell necrosis		5	0	0	0	0			4	1	0	0	0		
Pancreas															
		5							5						
Stomach															
		5							5						
Duodenum															
		5							5						
Jejunum															
		5							5						
Ileum															
		5							5						
Cecum															
		5							5						
Colon															
		5							5						
Rectum															
		5							5						
Lymph node, mesenteric															
		5							5						
Spleen															
Deposit, pigment, brown		0	0	0	5	0			0	0	0	5	0		
Hematopoiesis, extramedullary		0	5	0	0	0			0	0	0	2	3		**
Increase, red pulp		5	0	0	0	0			2	2	1	0	0		

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Vehicle: water for injection

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

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

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

Table 35-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Grade	Control (Vehicle)							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney															
Basophilic tubule, cortex		4	1	0	0	0			5	0	0	0	0		
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0			5	0	0	0	0		
Deposit, pigment, brown, proximal tubule		5	0	0	0	0			0	1	4	0	0		** , ##
Mineralization, medulla		5	0	0	0	0			4	1	0	0	0		
Urinary bladder															
		5							5						
Adrenal gland															
		5							5						
Ovary															
		5							5						
Uterus															
		5							5						
Vagina															
		5							5						
Eyeball															
		5							5						
Harderian gland															
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															
Hyperplasia, erythroblast		5	0	0	0	0			1	2	2	0	0		#

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Vehicle: water for injection

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

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

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

Table 35-3. Histopathological findings of female rats at the end of the recovery period

Findings	Group Grade	Control (Vehicle)							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		0						5	0						5
Spinal cord		0						5	0						5
Pituitary gland		0						5	0						5
Submandibular gland		0						5	0						5
Sublingual gland		0						5	0						5
Lymph node, submandibular		0						5	0						5
Thyroid gland		0						5	0						5
Parathyroid gland		0						5	0						5
Thymus		0						5	0						5
Heart		0						5	0						5
Trachea		0						5	0						5
Lung		0						5	0						5
Bronchus		0						5	0						5

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Vehicle: water for injection

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

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

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

Table 35-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group Grade	Control (Vehicle)							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Deposit, pigment, brown, Kupffer cell		5	0	0	0	0			0	5	0	0	0		** , ##
Fatty change, hepatocyte, periportal		4	1	0	0	0			4	1	0	0	0		
Hematopoiesis, extramedullary		4	1	0	0	0			5	0	0	0	0		
Microgranuloma		0	5	0	0	0			1	4	0	0	0		
Pancreas															
		0						5	0						5
Stomach															
		0						5	0						5
Duodenum															
		0						5	0						5
Jejunum															
		0						5	0						5
Ileum															
		0						5	0						5
Cecum															
		0						5	0						5
Colon															
		0						5	0						5
Rectum															
		0						5	0						5
Lymph node, mesenteric															
		0						5	0						5
Spleen															
Deposit, pigment, brown		0	0	0	5	0			0	0	1	4	0		
Edema, capsule, with infiltration of inflammatory cell		4	0	1	0	0			5	0	0	0	0		
Hematopoiesis, extramedullary		0	3	1	1	0			0	5	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.

Vehicle: water for injection

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

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

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

Table 35-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group Grade	Control (Vehicle)							2-IBE 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney															
Basophilic tubule, cortex		4	1	0	0	0			4	1	0	0	0		
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0			4	1	0	0	0		
Deposit, pigment, brown, proximal tubule		5	0	0	0	0			0	5	0	0	0		** , ##
Mineralization, medulla		5	0	0	0	0			4	1	0	0	0		
Urinary bladder		0						5	0						5
Adrenal gland		0						5	0						5
Ovary		0						5	0						5
Uterus		0						5	0						5
Vagina		0						5	0						5
Eyeball		0						5	0						5
Harderian gland		0						5	0						5
Sciatic nerve		0						5	0						5
Skeletal muscle		0						5	0						5
Femur		0						5	0						5
Marrow, femur															
Hyperplasia, erythroblast		5	0	0	0	0	0		3	2	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.

Vehicle: water for injection

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

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

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

Table 36. Results of observations about estrous cycle

Dose	Control (vehicle: water for injection)	2-IBE (15 mg/kg)	2-IBE (50 mg/kg)	2-IBE (150 mg/kg)
Number of animals examined	12	12	12	12
<u>Pre-treatment period</u>				
Number of animals showing type of cycle				
4-day cycle	9	10	10	11
4/5-day cycle	2	2	0	1
5-day cycle	1	0	2	0
Mean length of estrous cycle in days; Mean±S.D. (N)	4.2 ± 0.3 (12)	4.1 ± 0.2 (12)	4.2 ± 0.4 (12)	4.0 ± 0.1 (12)
<u>Treatment period</u>				
Number of animals showing each type of cycle				
4-day cycle	9	12	10	10
4/5-day cycle	1	0	1	0
5-day cycle	2	0	1	0
uncycle	0	0	0	1
irregular	0	0	0	1
Mean length of estrous cycle in days; Mean±S.D. (N)	4.2 ± 0.4 (12)	4.0 ± 0.0 (12)	4.1 ± 0.3 (12)	4.1 ± 0.3 (11)
Frequency of animals that show abnormal estrous cycles after the treatment	0 / 12	0 / 12	0 / 12	2 / 12
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.1 ± 0.3 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)

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

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

Table 37. Results of observations about reproductive performance

Dose	Control (vehicle: water for injection)	2-IBE (15 mg/kg)	2-IBE (50 mg/kg)	2-IBE (150 mg/kg)
Number of mated pares [A]	12	12	12	12
Number of copulated pares [B]	12	12	12	12
Copulation index [(B/A)×100, %]	100.0	100.0	100.0	100.0
Number of fertile males [C]	12	11	12	12
Fertility index [(C/B)×100, %]	100.0	91.7	100.0	100.0
Paring days until copulation ; Mean±S.D. (N)	2.4 ± 1.4 (12)	3.3 ± 1.5 (12)	2.3 ± 1.2 (12)	2.8 ± 1.0 (12)

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

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

Table 38. Observation of offspring (F₁)

Group	Control (vehicle: water for injection)	2-IBE 15 mg/kg	2-IBE 50 mg/kg	2-IBE 150 mg/kg
Number of dams	12	10	12	12
Gestation length (days)				
Mean ± S.D. per dam	22.3 ± 0.5	22.2 ± 0.4	22.3 ± 0.5	22.2 ± 0.4
Number of corpora lutea				
Total	196	164	197	190
Mean ± S.D. per dam	16.3 ± 1.4	14.9 ± 3.6 (11)	16.4 ± 2.7	15.8 ± 1.3
Number of implantation scars				
Total	189	161	192	184
Mean ± S.D. per dam	15.8 ± 1.5	14.6 ± 3.4 (11)	16.0 ± 2.3	15.3 ± 1.3
Implantation index (%) ^{a)}	96.4 ± 3.2	98.5 ± 3.4 (11)	97.9 ± 4.5	96.9 ± 3.3
Delivery index (dams,%) ^{b)}	100.0	100.0	100.0	100.0
Number of offspring at birth				
Total	181	151	182	169
Mean ± S.D. per dam	15.1 ± 1.2	13.7 ± 2.9 (11)	15.2 ± 2.5	14.1 ± 1.7
Number of live offspring at birth				
Male	89	77	87	77
Female	92	69	91	91
Total	181	146	178	168
Mean ± S.D. per dam	15.1 ± 1.2	13.3 ± 2.8 (11)	14.8 ± 2.5	14.0 ± 1.7
Sex ratio ^{c)}				
Mean ± S.D. per dam	0.49 ± 0.12	0.54 ± 0.10 (11)	0.49 ± 0.07	0.46 ± 0.15
Number of dead offspring				
Total	0	5	4	1
Mean ± S.D. per dam	0.0 ± 0.0	0.5 ± 1.0 (11)	0.3 ± 0.5	0.1 ± 0.3
Delivery index (offspring) ^{d)}				
Mean% ± S.D. per dam	96.1 ± 6.8	94.7 ± 8.1 (11)	94.8 ± 6.8	91.9 ± 7.9
Birth index ^{e)}				
Mean% ± S.D. per dam	96.1 ± 6.8	91.8 ± 9.6 (11)	92.6 ± 6.8	91.3 ± 8.0
Live birth index ^{f)}				
Mean% ± S.D. per dam	100.0 ± 0.0	97.0 ± 6.9 (11)	97.8 ± 3.3	99.4 ± 2.0
Number of offspring on day 4				
Male	88	75	86	68
Female	90	66	89	82
Sex ratio ^{c)}				
Mean ± S.D. per dam	0.49 ± 0.12	0.54 ± 0.10 (11)	0.49 ± 0.08	0.49 ± 0.22
Viability index ^{g)}				
Mean% ± S.D. per dam	98.3 ± 4.3	96.9 ± 8.6 (11)	98.6 ± 3.4	90.2 ± 26.9
Number of external abnormalities ^{h)}	0	0	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.0 ± 0.0 (11)	0.0 ± 0.0	0.0 ± 0.0

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

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

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

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

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

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

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

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

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

Figures in parentheses indicate number of dams.

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

Table 39. Body weights of offspring (F₁) before weaning

Group	Control (vehicle: water for injection)				2-IBE 15 mg/kg			2-IBE 50 mg/kg			2-IBE 150 mg/kg					
Number of dams	12				11			12			12					
Male																
Days after birth																
0	6.5	±	0.4	(12)	7.0	±	0.7	(11)	6.4	±	0.5	(12)	6.4	±	0.8	(12)
4	10.0	±	1.3	(12)	11.2	±	1.8	(11)	10.3	±	1.0	(12)	10.2	±	1.2	(12)
Number of dams	12				11			12			12					
Female																
Days after birth																
0	6.2	±	0.4	(12)	6.7	±	0.7	(11)	6.1	±	0.5	(12)	6.1	±	0.7	(12)
4	9.7	±	1.2	(12)	11.1	±	1.8	(11)	10.0	±	0.9	(12)	10.0	±	1.3	(11)

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

Figures in parentheses indicate number of dams.

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

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

Table 40. 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	181	181	181	181	179
	General appearance, No abnormality	181	181	181	179	178
	General appearance, Death				2	1
2-IBE 15 mg/kg	Number of offspring	146	146	146	143	141
	General appearance, No abnormality	146	146	143	141	141
	General appearance, Death			3	2	
2-IBE 50 mg/kg	Number of offspring	178	178	177	176	175
	General appearance, No abnormality	178	177	176	175	175
	General appearance, Death		1	1	1	
2-IBE 150 mg/kg	Number of offspring	168	168	158	150	150
	General appearance, No abnormality	168	158	150	150	150
	General appearance, Death		10	8		

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

Table 41. Morphological observations of offspring (F₁)

Dose	Control (vehicle: water for injection)	2-IBE (15 mg/kg)	2-IBE (50 mg/kg)	2-IBE (150 mg/kg)
Dead offspring				
Number of dead offspring ^{a)}	3	10	7	19
Number of missing offspring	3	1	2	6
Number of dead offspring examined	0 (0) ^{b)}	9 (2) ^{b)}	5 (1) ^{b)}	13 (3) ^{b)}
Number of dead offspring with external changes	0	0	0	0
Number of dead offspring with visceral changes	0	0	0	0
Live offspring				
Number of live offspring examined (postnatal day 0)	181	146	178	168
Number of live offspring with external changes	0	0	0	0
Number of live offspring examined (postnatal day 4)	178	141	175	150
Number of live offspring with external changes	0	0	0	0
Number of live offspring with visceral changes	0	0	0	0

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

a) including missing offspring

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

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

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

[illegible]

(Continued)

Pre: Before administration, Post: after administration.

:- General appearance, No abnormality.

a: Excretion, Reddish urine.

b: Forelimb, Alopecia.

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

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

Control (vehicle: water for injection)

Male No.	Days of administration																																		
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre		
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

a: Excretion, Reddish urine.

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

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

[illegible]

Pre: Before administration, Post: after administration.

+: General appearance, No abnormality.

a: Excretion, Reddish urine.

b: Forelimb, Alopecia.

(Continued)

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

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

2-IBE 15 mg/kg

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

a: Excretion, Reddish urine.

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

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

[illegible]

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

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

2-IBE 50 mg/kg

Male No.	Days of administration																																		
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre		
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	10	12	12	12	12	12	12	12	12	12	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

a: Excretion, Reddish urine.

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

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

2-IBE 150 mg/kg		Days of administration																																																
Male No.	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		
M04037	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04038	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04039	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04040	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04041	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04042	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04043	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04044	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b	b	b	b	
M04045	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04046	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04047	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04048	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
-	12	12	0	12	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11		
a	0	0	12	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Reddish urine.

b: Forelimb, Alopecia.

(Continued)

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

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

2-IBE 150 mg/kg

Male No.	Days of administration																																		
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre		
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04044	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	10	11	11	11	10	11	11	11	11	11	11	11	11	7	
b	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	0	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

a: Excretion, Reddish urine.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

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

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

2-IBE 150 mg/kg

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

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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		19		20		21				
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	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	9	9	4	4	2	2	1	1	1	1	1	0	0	0	0
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	4	4	2	2	1	1	1	1	1	0	0	0	0
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Reddish urine.

b: Lumbar, Alopecia.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

e: General appearance, Emaciation.

f: Behavior, Decrease in locomotor activity.

g: Excretion, No-feces.

h: Fur, Hair, Coat, Piloerection.

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

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

2-IBE 15 mg/kg																																												
Female No.		Days of administration																																										
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	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	11	11	8	8	5	5	1	1	1	1	1	1	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	11	11	8	8	5	5	1	1	1	1	1	1	1	1	
a		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
g		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Reddish urine.

b: Lumbar, Alopecia.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

e: General appearance, Emaciation.

f: Behavior, Decrease in locomotor activity.

g: Excretion, No-feces.

h: Fur, Hair, Coat, Piloerection.

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

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

2-IBE 50 mg/kg																																														
Female No.		Days of administration																																												
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21				
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	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		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03027		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03028		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03029		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03030		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03031		-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03032		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03033		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b
F03034		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03036		-	-	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	8	8	4	4	3	3	0	0	0	0	0	0	0	0	
-		12	12	2	12	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	7	7	4	4	3	3	0	0	0	0	0	0	0	0	
a		0	0	10	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	
c		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
e		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
f		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
g		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
h		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Reddish urine.

b: Lumbus, Alopecia.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

e: General appearance, Emaciation.

f: Behavior, Decrease in locomotor activity.

g: Excretion, No-feces.

h: Fur, Hair, Coat, Piloerection.

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

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

2-IBE 150 mg/kg																																														
Female No.		Days of administration																																												
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21				
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F04038		-	-	a	-	d	c,d,f	c,d	c	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04039		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04040		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04041		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04042		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04043		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04044		-	-	a	-	d	c,d,f,h	a,c,e,f,g	c,e,f	c,d,e	c,e	c,d,e	c,e	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04045		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04046		-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047		-	-	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	12	12	12	12	12	12	12	12	12	12	12	12	12
-		12	12	0	12	9	10	10	10	11	11	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
a		0	0	12	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c		0	0	0	0	0	2	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d		0	0	0	0	2	2	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e		0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f		0	0	0	0	0	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
g		0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h		0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Reddish urine.

b: Lumbus, Alopecia.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

e: General appearance, Emaciation.

f: Behavior, Decrease in locomotor activity.

g: Excretion, No-feces.

h: Fur, Hair, Coat, Piloerection.

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

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

[illegible]

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

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

Control (vehicle: water for injection)

Female No.	Days of administration																																		
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F05049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Reddish urine.

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

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

[illegible]

(Continued)

Pre: Before administration, Post: after administration.

+: General appearance. No abnormality.

a: Excretion. Reddish urine.

d: Excretion, Decrease in amount of feces.

c: Skin, Pale skin.

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

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

2-IBE 150 mg/kg

Female No.	Days of administration																																		
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre		
F06059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	a	-	-	-	-	-	-	-	-	
F06060	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	
F06061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	
F06062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06064	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06066	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06068	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5	
-	10	10	10	10	10	10	10	10	10	10	8	10	9	10	10	10	8	10	10	10	9	10	10	10	9	10	7	10	10	10	9	10	10	5	
a	0	0	0	0	0	0	0	0	0	0	2	0	1	0	0	0	2	0	0	0	1	0	0	0	1	0	3	0	0	0	1	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Reddish urine.

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

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

2-IBE 150 mg/kg

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

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
k	0	0	0	0	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	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
l	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	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.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

k: Lumbus, Alopecia.

a: Excretion, Reddish urine.

j: Neck, Alopecia.

l: Skin, Crust formation.

h: Fur, Hair, Coat, Piloerection.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	
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	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	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		
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
d	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		
l	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.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

j: Neck, Alopecia.

h: Fur, Hair, Coat, Piloerection.

e: General appearance, Emaciation.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

a: Excretion, Reddish urine.

l: Skin, Crust formation.

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

Appendix 3-2. General conditions in dams during pregnancy

2-IBE 15 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b	b	b	b	b	b	
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b	b	
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02023	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>	-	>
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	10	10	10	10	9	9	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
k	0	0	0	0	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	0	0	0	
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
l	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d	0	0	0	0	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)

(Continued)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

k: Lumbus, Alopecia.

a: Excretion, Reddish urine.

j: Neck, Alopecia.

l: Skin, Crust formation.

h: Fur, Hair, Coat, Piloerection.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

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

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

2-IBE 15 mg/kg		Days of pregnancy																							
Dam No.	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	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02020	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02023	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>	>
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	10	10	10	10	5	5	0	0	0	0	0	0	0
-	9	9	9	9	9	9	9	9	9	9	9	9	8	8	8	8	4	4	0	0	0	0	0	0	0
b	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	0	0	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	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
l	0	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.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

j: Neck, Alopecia.

h: Fur, Hair, Coat, Piloerection.

e: General appearance, Emaciation.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

a: Excretion, Reddish urine.

l: Skin, Crust formation.

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

Appendix 3-3. General conditions in dams during pregnancy

2-IBE 50 mg/kg

Dam No.	Days of pregnancy																											
	0		1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03033	k	k	k	k	k	k	k	k	k	k	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	11	11	11	11	11	11	11	11	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
k	1	1	1	1	1	1	1	1	1	1	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	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
l	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	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.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

k: Lumbus, Alopecia.

a: Excretion, Reddish urine.

j: Neck, Alopecia.

l: Skin, Crust formation.

h: Fur, Hair, Coat, Piloerection.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

(Continued)

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

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

2-IBE 50 mg/kg		Days of pregnancy																							
Dam No.	14		15		16		17		18		19		20		21		22		23		24		25		26
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	7	0	0	0	0	0	0	0
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	7	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
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	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
l	0	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.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

j: Neck, Alopecia.

h: Fur, Hair, Coat, Piloerection.

e: General appearance, Emaciation.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

a: Excretion, Reddish urine.

l: Skin, Crust formation.

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

Appendix 3-4. General conditions in dams during pregnancy

2-IBE 150 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	i	i	i	i	i	i
F04039	-	-	-	-	-	-	-	-	-	-	-	-	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b,j,l	b,j,l
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	i	i	i	i	i	i	i,a	i	i,a,h,c,d	i,h,c
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-
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	11	11	11	11	11	11	10	10	10	10	9	9	9	9	7	9
b	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2	2	2	2	2
k	0	0	0	0	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	1	0	3	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
l	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
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	1	1	1
d	0	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	0

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

k: Lumbus, Alopecia.

a: Excretion, Reddish urine.

j: Neck, Alopecia.

l: Skin, Crust formation.

h: Fur, Hair, Coat, Piloerection.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

(Continued)

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

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

Dam No.	Days of pregnancy																							
	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
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04038	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	-	-	-	-	-	-	-	-
F04039	bj,l	bj,l	bj,l	bj,l	bj	bj	bj	bj	bj	bj	bj	bj	bj	bj	bj	bj	bj	bj	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04044	i,h,e,c,d,a	i,h,e,c	i,h,e,c,d,a	i,h,e,c,d	i,h,e,c,d,a	i,h,e,c	i,h,e,c,d	i,h,e,c	i,h,e,c,d	i,h,e,c	i,h,e,c	i,h,e,c	i,h,e	i,h,e	i,h,e	i,h,e	-	-	-	-	-	-	-	-
F04045	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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
-	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	4	4	0	0	0	0	0	0
b	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
i	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0
j	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
h	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0
e	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0
c	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0
d	1	0	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
a	2	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
l	1	1	1	1	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.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

j: Neck, Alopecia.

h: Fur, Hair, Coat, Piloerection.

e: General appearance, Emaciation.

c: Skin, Pale skin.

d: Excretion, Decrease in amount of feces.

a: Excretion, Reddish urine.

l: Skin, Crust formation.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	10	10	12	12	12	12	12	12	12	12	12
-	10	10	12	12	12	12	12	12	12	12	12
b	0	0	0	0	0	0	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

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

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

e: General appearance, Emaciation.

j: Neck, Alopecia.

h: Fur, Hair, Coat, Piloerection.

c: Skin, Pale skin.

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

Appendix 4-2. General conditions in dams during lactation

2-IBE 15 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	#	#	b	b	b	b	b	b	b	b	b
F02016	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-
F02018	#	#	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-
F02020	b	b	b	b	b	b	b	b	b	b	b
F02021	#	#	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-
Number of dams	8	8	11	11	11	11	11	11	11	11	11
-	7	7	9	9	9	9	9	9	9	9	9
b	1	1	2	2	2	2	2	2	2	2	2
i	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

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

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

e: General appearance, Emaciation.

j: Neck, Alopecia.

h: Fur, Hair, Coat, Piloerection.

c: Skin, Pale skin.

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

Appendix 4-3. General conditions in dams during lactation

2-IBE 50 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F03025	-	-	-	-	-	-	-	-	-	-	-
F03026	#	#	-	-	-	-	-	-	-	-	-
F03027	#	#	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-
F03030	#	#	-	-	-	-	-	-	-	-	-
F03031	#	#	-	-	-	-	-	-	-	-	-
F03032	-	-	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-
F03034	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-
Number of dams	8	8	12	12	12	12	12	12	12	12	12
-	8	8	12	12	12	12	12	12	12	12	12
b	0	0	0	0	0	0	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

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

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

e: General appearance, Emaciation.

j: Neck, Alopecia.

h: Fur, Hair, Coat, Piloerection.

c: Skin, Pale skin.

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

Appendix 4-4. General conditions in dams during lactation

2-IBE 150 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	-	-	-	-	-	-	-	-	-	-	-
F04038	i	i	i	i	i	i	i	i	i	i	i
F04039	#	#	b,j	b,j	b,j	b,j	b,j	b,j	b,j	b,j	b,j
F04040	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-
F04042	#	#	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	-	-	-	-	-	-
F04044	i,e,h,c	i,e,h,c	i,e,h,c	i,e,h,c	i,e,h	i,e,h	i,e	i,e	i,e	i,e	i,e
F04045	-	-	-	-	-	-	-	-	-	-	-
F04046	#	#	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-
Number of dams	9	9	12	12	12	12	12	12	12	12	12
-	7	7	9	9	9	9	9	9	9	9	9
b	0	0	1	1	1	1	1	1	1	1	1
i	2	2	2	2	2	2	2	2	2	2	2
e	1	1	1	1	1	1	1	1	1	1	1
j	0	0	1	1	1	1	1	1	1	1	1
h	1	1	1	1	1	1	0	0	0	0	0
c	1	1	1	1	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

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

-: General appearance, No abnormality.

b: Forelimb, Alopecia.

i: Tail, Distal, Black.

e: General appearance, Emaciation.

j: Neck, Alopecia.

h: Fur, Hair, Coat, Piloerection.

c: Skin, Pale skin.

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

Appendix 5-1. 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)}																																							
	Posture in home-cage										Locomotor in home-cage										Handling behavior										Heart beats										Body temperature									
	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					
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							
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							
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							
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							
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							
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							
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							
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				
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				
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				
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				
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				
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	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)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	

^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)]

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 2-isobutoxyethanol by oral administration in rats

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

Control (vehicle: water for injection)

[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, hypopnea]

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

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 2-isobutoxyethanol by oral administration in rats

Appendix 5-1(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	1	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	1	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M01012	0	0	0	0	1	0	0	0	0		0	0	0	0	0	0	0	0	0	
Total	1	0	1	0	1	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 2-isobutoxyethanol by oral administration in rats

Appendix 5-2. Detailed clinical observations of male rats

2-IBE (15 mg/kg)

Male 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						
	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	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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	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)	

^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)]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE(15 mg/kg)

Male No.	Removing from cage / Observations made while handling ^{b)}												Open-field observations ^{c)}																													
	Fur							Skin color / Mucuous membranes							Lacrimation							Piloerection							Respiratory rate							Stereotypy						
	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 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							
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									
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									
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									
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									
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									
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									
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									
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									
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									
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									
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									
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									
Total	1:0	1:0	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	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)									

^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 / Mucuous 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)]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (15 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	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0
M02016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02017	0	1	0	0	1	1	0	0	0	0	0	0	0	0
M02018	0	0	0	1	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	0	0	0	0	0	0	0	0	1	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	0	1	0	1	1	1	0	0	1	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

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

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 2-isobutoxyethanol by oral administration in rats

Appendix 5-3. Detailed clinical observations of male rats

2-IBE (50 mg/kg)

Male 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						
	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	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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	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)	

^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/ Mucuous 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)]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (50 mg/kg)

Male No.	Removing from cage / Observations made while handling ^{a)}							Open-field observations ^{a)}													
	Fur							Skin color / Mucous membranes							Lacrimation						
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M03025	2	2	2	2	2	2	2	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
M03027	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
M03029	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
M03031	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
M03033	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
M03035	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
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	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)

^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)]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (50 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	1	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	1	0	0	0	0	0	0	0	0	0	0	0	0	0
M03029	0	1	0	1	0	1	1	0	0	0	0	0	1	0
M03030	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03032	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03033	0	1	0	0	0	0	0	0	0	0	0	0	0	0
M03034	0	2	0	0	0	1	1	0	0	0	0	0	0	0
M03035	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	1	4	0	1	1	2	2	0	0	0	0	0	1	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 2-isobutoxyethanol by oral administration in rats

Appendix 5-4. Detailed clinical observations of male rats

2-IBE (150 mg/kg)

Male No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}																				Body temperature																	
	Posture in home-cage										Locomotor in home-cage										Handling behavior																				Heart beats							
	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			
M04037	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
M04038	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
M04039	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
M04040	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
M04041	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
M04042	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
M04043	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2					
M04044	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M04045	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M04046	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
M04048	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	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	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	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)	(12)	(5)	(5)	(12)	(12)	(12)

^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)]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (150 mg/kg)

Male No.	Removing from cage / Observations made while handling ^{b)}																Open-field observations ^{c)}																																					
	Fur		Skin color / Mucuous membranes														Lacrimation								Piloerection								Respiratory rate								Stereotypy													
			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							
M04037	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	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					
M04038	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2					
M04039	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2					
M04040	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2					
M04041	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2					
M04042	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2					
M04043	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		3	2	3	2	2	2	2	2				
M04044	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
M04045	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
M04046	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
M04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
M04048	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	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	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	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)	(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)

^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, hypopnea]

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

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (150 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	1	0	1	0	0	0	1				0	1	0	0	0	0	0			
M04038	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M04039	0	1	1	0	0	1	0				1	0	1	0	2	0	0			
M04040	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M04041	1	0	0	0	0	0	0				0	0	0	0	0	0	0			
M04042	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M04043	1	0	0	1	0	1	0				0	0	0	0	0	0	0			
M04044	0	0	0	0	0	0	0	0	0		2	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	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M04047	0	0	0	0	0	1	0	0	0		0	0	0	0	0	0	0	0	0	
M04048	1	1	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
Total score	4	2	2	1	0	3	1	0	0		3	1	1	0	2	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 2-isobutoxyethanol by oral administration in rats

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

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	L ^c	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	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				
F01002	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2				
F01003	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2				
F01004	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2				
F01005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	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	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	

^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; 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 (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]

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 2-isobutoxyethanol 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 ^{b)}																Open-field observations ^{c)}																															
	Skin color / Mucuous membranes								Lacrimation								Piloerection								respiratory rate								Stereotypy															
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	L ^c	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	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									
F01002	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
F01003	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
F01004	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
F01005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2								
F01006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
F01007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
F01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
F01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
F01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
F01011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
F01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2									
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	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	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0								
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)								

^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; 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 (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]

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 2-isobutoxyethanol 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	L ^c	Pre	T8	T15	T24	T30	T36	T42	L
F01001	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01002	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01003	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01004	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01005	0	0	0	0	1	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	0	0	0	0	0	0	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	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)

^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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (15 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	L ^c	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L										
F02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	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	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	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	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	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	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	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	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	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	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	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	2	2	2	2	2	2
Total score (N)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (0)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (12)	1:0 (0)		

^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; 1, no resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Für [2, normal; 1, Moist für]

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]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (15 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}																Open-field observations ^{c)}																								
	Skin color / Mucuous membranes								Lacrimation								Piloerection								respiratory rate								Stereotypy								
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	L ^c	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	
F02013	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	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	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)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)

^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; 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 (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]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (15 mg/kg)

Female No.	Open-field observations ^{c)}															
	Urination								Defecation							
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	L ^c	Pre	T8	T15	T24	T30	T36	T42	L
F02013	0	0	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	1	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	0	0		0	0	0	0	0	0	0	
Total score	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)

^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 2-isobutoxyethanol by oral administration in rats

Appendix 6-1-3. 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; 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 (pale skin)]

Lacrimation [2, not observed; 1, observed]

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

respiratory rate[2, normal; 1, hypopnea]

stereotypyl 2, not observed: 3, observed 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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (50 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}																Open-field observations ^{c)}																							
	Skin color / Mucuous membranes								Lacrimation								Piloerection								respiratory rate								Stereotypy							
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	L ^c	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L
F03025	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	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	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)

^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; 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 (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]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (50 mg/kg)

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

^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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (150 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	L ^c	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	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	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	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	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	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	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	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	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	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	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	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	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	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						
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	

^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; 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 (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]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (150 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}																Open-field observations ^{c)}																									
	Skin color / Mucuous membranes								Lacrimation								Piloerection								respiratory rate								Stereotypy									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	L ^c	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	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		
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		
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		
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		
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		
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		
F04044	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2		2	2	2	2	2	4	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		
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		
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		
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		
Total score	1:0	1:0	1:0	1:0	1:0	1:1	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	4:1	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	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)

^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; 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 (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]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (150 mg/kg)

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

^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 2-isobutoxyethanol 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 ^{a1}									Removing from cage / Observations made while handling ^{a1}																																												
	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									
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						
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					
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					
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					
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					
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					
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					
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					
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					
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	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					
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	

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

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; 4, severe]

respiratory rate[2, normal; 1, hypopneal]

stereotypy[2, not observed: 3, observed]

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, bizzare behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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 / Mucuous membranes										Lacrimation								Pilorection								respiratory rate								Stereotypy												
	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		
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	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	
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	
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	
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	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	1:0	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)	(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; 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]

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

respiratory rate[2, normal; 1, hypopnea]

stereotypy[2, not observed; 3, observed]

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 2-isobutoxyethanol 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	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05052	0	0	0	0	0	0	3			0	0	0	0	0	0	0		
F05053	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05054	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05055	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05056	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05057	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05058	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	0	0	0	0	0	0	3	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 2-isobutoxyethanol by oral administration in rats

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

[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: 4, severe]

respiratory rate[2, normal: 1, hypopneal]

stereotypy[2, not observed; 3, observed]

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, nictitalk opening, tremor, convulsion, ear, bizarre behavior, straub tail, vocalization, touch response, with draw reflex, pinna reflex).

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

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

2-IBE (150 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}																Open-field observations ^{c)}																																						
	Skin color / Mucuous membranes										Lacrimation						Piloerection								respiratory rate								Stereotypy																						
	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	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	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	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	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	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	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	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	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	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	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	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)	(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)	(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; 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; 4, severe]

respiratory rate [2, normal; 1, hypopnea]

stereotypy [2, not observed; 3, observed]

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 2-isobutoxyethanol by oral administration in rats

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

2-IBE (150 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	0	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F06066	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F06067	2	1	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	2	1	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 2-isobutoxyethanol 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	416.9	429.3	435.7	465.2	482.9	505.4	534.1	543.9
M01002	395.0	418.1	435.2	469.4	502.5	536.0	563.3	566.6
M01003	398.8	406.7	422.9	442.1	461.9	487.1	516.9	521.5
M01004	404.3	409.0	430.1	452.2	474.3	497.7	524.9	536.2
M01005	375.7	383.7	393.3	418.8	431.1	462.0	479.4	478.3
M01006	346.6	361.2	375.0	396.6	416.2	437.8	459.8	464.7
M01007	413.9	428.7	440.8	462.7	478.8	501.1	528.2	530.4
M01008	387.8	390.2	402.6	421.7	438.2	459.7	472.8	478.3
M01009	412.8	427.5	441.3	474.0	492.2	519.9	548.2	570.6
M01010	370.5	378.2	388.1	409.7	419.0	446.2	460.4	453.1
M01011	369.1	378.0	390.6	403.1	412.5	436.7	444.9	454.5
M01012	358.3	378.6	386.1	403.1	420.4	436.7	457.6	471.5
Number of males	12	12	12	12	12	12	12	12
Mean	387.5	399.1	411.8	434.9	452.5	477.2	499.2	505.8
S.D.	23.3	23.7	24.8	29.1	33.0	35.0	40.9	43.6

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

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

2-IBE 15 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M02013	357.8	373.8	384.4	404.4	426.3	450.2	465.5	468.1
M02014	388.4	405.8	407.9	422.7	431.7	461.2	476.8	484.7
M02015	363.2	371.7	383.6	405.0	419.4	442.2	454.5	463.0
M02016	427.5	445.3	461.7	499.3	511.5	536.7	560.4	566.1
M02017	401.2	415.5	436.4	453.2	467.4	496.5	517.1	510.2
M02018	359.0	367.8	382.5	396.0	414.1	433.8	443.3	456.6
M02019	392.0	405.0	408.0	421.5	443.1	454.7	476.6	488.8
M02020	416.5	431.0	438.1	479.0	496.8	529.2	548.2	578.0
M02021	401.1	417.0	433.9	472.2	490.9	508.7	536.3	550.8
M02022	380.5	390.5	400.5	430.2	443.5	472.3	489.1	501.9
M02023	405.4	419.9	440.8	474.0	491.5	514.8	545.7	561.7
M02024	402.0	415.7	420.5	446.5	479.9	502.6	526.1	543.6
Number of males	12	12	12	12	12	12	12	12
Mean	391.2	404.9	416.5	442.0	459.7	483.6	503.3	514.5
S.D.	22.4	24.4	26.1	33.8	33.9	35.4	40.3	43.7
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

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

2-IBE 50 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M03025	422.0	439.4	450.0	487.2	516.6	564.5	586.2	594.4
M03026	388.1	397.1	411.8	430.4	456.3	478.0	495.3	498.3
M03027	405.0	415.3	431.7	473.2	505.3	529.9	559.3	563.3
M03028	406.6	424.4	439.9	464.3	487.1	521.3	555.1	567.8
M03029	380.1	385.7	399.9	424.0	447.6	475.1	501.3	507.9
M03030	357.5	364.1	373.3	387.7	406.9	422.8	439.3	448.4
M03031	384.9	398.8	413.8	450.1	469.3	492.6	516.4	536.3
M03032	410.3	423.2	429.6	446.6	482.9	518.0	544.8	553.0
M03033	385.6	397.0	407.8	443.3	462.9	496.3	522.6	554.1
M03034	360.6	375.0	386.1	391.2	413.3	443.0	472.0	488.9
M03035	374.0	391.0	404.1	431.5	456.4	481.7	503.5	524.7
M03036	408.0	421.8	435.1	476.6	494.4	520.0	550.3	565.7
Number of males	12	12	12	12	12	12	12	12
Mean	390.2	402.7	415.3	442.2	466.6	495.3	520.5	533.6
S.D.	20.4	22.4	22.8	31.5	33.6	38.9	41.3	41.4
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

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

2-IBE 150 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M04037	383.4	376.8	392.5	412.5	422.9	455.7	477.3	487.2
M04038	373.5	373.1	384.0	410.6	436.8	463.4	483.6	486.7
M04039	393.1	396.7	410.7	442.1	470.8	510.7	528.3	535.1
M04040	410.1	425.0	445.7	485.0	513.5	548.0	575.0	594.4
M04041	355.6	355.8	363.6	384.3	410.2	431.2	447.2	451.8
M04042	431.4	436.4	448.1	473.9	494.5	524.9	544.9	558.5
M04043	415.7	423.3	434.8	456.5	485.6	512.6	531.5	549.1
M04044	378.7	387.7	401.9	424.0	446.9	470.6	497.1	512.8
M04045	359.9	362.9	383.1	416.2	436.1	465.5	469.0	491.7
M04046	387.6	389.2	403.6	441.5	462.1	484.4	502.2	513.3
M04047	418.0	425.9	445.5	490.8	520.7	556.8	578.2	594.5
M04048	378.4	378.9	386.2	413.0	431.5	447.1	465.9	484.4
Number of males	12	12	12	12	12	12	12	12
Mean	390.5	394.3	408.3	437.5	461.0	489.2	508.4	521.6
S.D.	23.8	27.1	28.8	33.4	36.2	40.6	43.1	45.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	479.3	483.1	488.4
M01009	577.5	589.7	593.3
M01010	449.8	455.7	474.3
M01011	454.5	476.2	485.5
M01012	471.6	483.1	492.5
Number of males	5	5	5
Mean	486.5	497.6	506.8
S.D.	52.3	52.7	48.8

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

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

2-IBE 150 mg/kg

Male No.	Days of recovery		
	1	7	14
M04044	504.6	534.8	546.1
M04045	484.6	506.3	516.6
M04046	519.2	534.3	535.3
M04047	590.8	623.3	625.6
M04048	481.2	494.3	510.8
Number of males	5	5	5
Mean	516.1	538.6	546.9
S.D.	44.5	50.5	46.2
Significance	NS	NS	NS
Statistical method	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	21
F01001	236.7	247.7	250.2	255.7	
F01002	264.0	280.3	296.0	305.7	
F01003	251.7	258.0	258.9	283.5	
F01004	239.7	240.3	240.2	253.6	
F01005	237.5	251.9	257.1	274.2	
F01006	256.0	269.9	274.3	286.6	
F01007	261.2	256.8	274.2	290.0	
F01008	258.4	274.5	287.4	298.4	
F01009	242.9	251.5	260.2	256.0	
F01010	255.4	258.8	269.1	271.1	
F01011	244.2	253.1	264.3	274.8	
F01012	272.5	284.9	293.6	309.5	
Number of females	12	12	12	12	
Mean	251.7	260.6	268.8	279.9	
S.D.	11.5	13.7	17.2	19.1	

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

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

2-IBE 15 mg/kg

Female No.	Days of administration				
	1	4	7	14	21
F02013	249.6	246.6	258.4	273.2	
F02014	258.0	258.3	250.4	265.6	296.9
F02015	254.2	263.0	268.1	264.2	
F02016	259.3	266.8	270.8	280.6	
F02017	260.3	268.8	275.9	275.4	
F02018	285.8	289.6	298.7	312.1	
F02019	238.6	244.4	246.4	263.8	
F02020	251.1	263.5	268.5	274.6	
F02021	251.1	266.6	279.0	279.8	
F02022	256.5	273.0	285.4	288.6	
F02023	235.7	240.7	247.4	245.7	
F02024	267.4	269.4	270.1	285.1	
Number of females	12	12	12	12	
Mean	255.6	262.6	268.3	275.7	
S.D.	13.0	13.6	15.8	16.2	
Significance	NS	NS	NS	NS	
Statistical method	AN	AN	AN	AN	

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

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

2-IBE 50 mg/kg

Female No.	Days of administration				
	1	4	7	14	21
F03025	241.4	257.8	262.8	273.2	
F03026	237.9	238.8	247.9	262.0	
F03027	252.6	262.2	263.1	289.8	
F03028	238.9	245.5	247.9	264.7	
F03029	256.5	253.5	267.7	273.8	
F03030	259.4	267.7	268.1	284.7	
F03031	265.3	270.9	278.4	283.4	
F03032	263.1	265.3	278.7	298.0	
F03033	242.9	251.4	264.6	272.3	
F03034	277.0	293.5	304.3	319.4	
F03035	248.0	249.6	263.5	277.6	
F03036	256.9	271.4	280.7	297.5	
Number of females	12	12	12	12	
Mean	253.3	260.6	269.0	283.0	
S.D.	12.0	14.6	15.3	16.3	
Significance	NS	NS	NS	NS	
Statistical method	AN	AN	AN	AN	

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

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

2-IBE 150 mg/kg

Female No.	Days of administration				
	1	4	7	14	21
F04037	253.1	253.5	250.8	264.9	
F04038	255.1	222.0	245.7	263.1	
F04039	270.6	265.0	275.3	294.0	
F04040	282.5	276.3	283.9	287.3	
F04041	237.5	245.1	251.1	253.7	
F04042	262.0	251.9	256.5	273.9	
F04043	264.0	261.6	269.0	288.8	
F04044	238.7	189.1	219.7	264.9	
F04045	249.5	258.6	273.3	285.6	
F04046	241.6	248.5	250.0	255.5	
F04047	240.6	241.9	247.9	268.3	
F04048	269.9	266.2	272.9	283.8	
Number of females	12	12	12	12	
Mean	255.4	248.3	258.0	273.7	
S.D.	14.6	23.3	17.7	13.8	
Significance	NS	NS	NS	NS	
Statistical method	AN	AN	AN	AN	

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	254.2	269.6	274.5	269.4	265.8	279.0	281.8	292.9
F05050	289.0	295.6	299.4	311.1	328.5	334.6	340.9	354.7
F05051	256.1	256.3	263.4	271.8	280.3	276.5	287.7	285.8
F05052	236.5	248.7	257.0	260.9	267.4	264.9	269.8	272.0
F05053	239.1	243.8	245.3	265.3	281.9	282.2	298.4	303.8
F05054	243.8	253.0	259.3	261.7	265.3	284.6	286.0	290.6
F05055	253.0	260.8	266.7	272.1	285.3	295.1	298.2	301.5
F05056	272.9	274.5	289.9	310.0	318.6	315.1	325.3	341.0
F05057	245.1	256.4	266.4	272.2	273.5	287.4	299.4	307.5
F05058	244.9	245.9	249.3	265.8	277.4	283.4	285.8	294.9
Number of females	10	10	10	10	10	10	10	10
Mean	253.5	260.5	267.1	276.0	284.4	290.3	297.3	304.5
S.D.	16.3	15.8	17.0	18.6	21.9	20.3	21.2	25.2

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

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

2-IBE 150 mg/kg

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F06059	244.9	242.8	251.1	270.7	285.1	291.9	297.9	301.3
F06060	247.7	243.1	262.6	274.8	295.3	309.4	307.1	301.7
F06061	248.9	244.5	258.6	273.0	281.7	285.3	296.8	302.4
F06062	267.1	265.7	271.9	273.9	280.0	295.5	293.3	298.3
F06063	258.4	243.8	263.2	295.3	307.4	333.7	330.3	323.3
F06064	263.2	257.8	268.3	283.3	292.6	299.6	302.0	301.5
F06065	268.6	270.1	279.2	296.3	305.2	316.3	323.7	326.8
F06066	257.2	248.5	266.1	277.8	296.6	316.6	325.7	326.9
F06067	250.9	249.1	258.1	276.1	291.4	298.9	308.1	313.2
F06068	241.2	240.3	248.2	262.8	278.2	284.1	282.9	295.5
Number of females	10	10	10	10	10	10	10	10
Mean	254.8	250.6	262.7	278.4	291.4	303.1	306.8	309.1
S.D.	9.5	10.4	9.3	10.5	10.2	15.7	15.5	12.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	AW	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.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	289.1	312.6	311.7
F05055	305.7	310.1	307.5
F05056	337.8	349.5	357.9
F05057	306.7	308.6	315.5
F05058	294.1	305.8	313.7
Number of females	5	5	5
Mean	306.7	317.3	321.3
S.D.	19.0	18.2	20.7

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

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

2-IBE 150 mg/kg

Female No.	Days of recovery		
	1	7	14
F06064	302.5	323.4	325.3
F06065	327.2	330.4	346.6
F06066	331.0	348.9	357.1
F06067	316.1	334.7	335.4
F06068	291.6	311.7	317.2
Number of females	5	5	5
Mean	313.7	329.8	336.3
S.D.	16.6	13.8	16.0
Significance	NS	NS	NS
Statistical method	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	26
F01001	248.7	277.8	307.7	378.1	
F01002	317.6	349.3	377.0	458.5	
F01003	288.9	325.9	365.4	444.9	
F01004	265.3	300.7	330.5	408.3	
F01005	287.2	323.2	360.4	423.3	
F01006	288.6	324.0	360.1	450.5	
F01007	293.7	337.5	378.5	452.7	
F01008	308.6	354.2	394.0	462.9	
F01009	276.3	309.9	343.7	418.7	
F01010	280.0	310.7	348.9	421.8	
F01011	273.6	326.8	366.9	452.1	
F01012	318.6	351.4	400.4	502.0	
Number of dams	12	12	12	12	
Mean	287.3	324.3	361.1	439.5	
S.D.	20.7	22.5	26.1	31.7	

>: Excluded from analysis (not pregnant)

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

Appendix 9-2. Body weights of dams during pregnancy

2-IBE 15 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F02013	275.8	323.9	361.5	434.9	
F02015	279.3	314.0	347.5	427.3	
F02016	297.7	319.2	344.8	428.8	
F02017	295.5	330.2	371.2	469.4	
F02018	326.5	365.1	405.1	484.1	
F02019	276.0	315.9	352.0	431.7	
F02020	285.8	315.8	349.6	432.6	
F02021	293.9	332.5	369.2	455.5	
F02022	298.5	321.1	341.1	384.7	
F02023	> 254.6	> 259.7	> 273.8	> 276.0	> 280.3
F02024	280.4	315.5	344.4	438.6	
Number of dams	10	10	10	10	
Mean	290.9	325.3	358.6	438.8	
S.D.	15.4	15.3	19.4	26.9	
Significance	NS	NS	NS	NS	
Statistical method	AN	AN	AN	KW	

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

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

Appendix 9-3. Body weights of dams during pregnancy

2-IBE 50 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F03025	286.5	321.2	357.0	443.8	
F03026	266.1	297.4	331.0	401.3	
F03027	288.9	328.5	360.0	439.0	
F03028	284.8	318.8	360.2	450.7	
F03029	280.4	323.4	351.6	448.4	
F03030	287.9	329.8	371.0	440.5	
F03031	292.6	323.6	354.0	441.7	
F03032	286.4	323.2	350.8	459.3	
F03033	281.6	322.4	361.3	452.1	
F03034	318.4	361.5	403.5	477.7	
F03035	285.2	312.4	342.1	406.8	
F03036	303.9	332.5	366.7	447.9	
Number of dams	12	12	12	12	
Mean	288.6	324.6	359.1	442.4	
S.D.	12.8	14.8	17.6	20.7	
Significance	NS	NS	NS	NS	
Statistical method	AN	AN	AN	KW	

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

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

Appendix 9-4. Body weights of dams during pregnancy

2-IBE 150 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F04037	280.2	322.9	362.9	457.7	
F04038	265.3	308.0	341.9	444.4	
F04039	301.6	335.2	369.3	436.4	
F04040	302.8	334.6	373.8	444.8	
F04041	260.7	280.7	327.0	399.1	
F04042	283.4	317.6	347.5	438.4	
F04043	306.2	339.7	382.7	456.1	
F04044	269.0	300.7	261.4	276.5	
F04045	296.6	326.5	356.4	438.3	
F04046	272.2	302.9	332.2	401.8	
F04047	268.9	303.0	339.5	367.7	
F04048	291.0	324.1	359.5	445.6	
Number of dams	12	12	12	12	
Mean	283.2	316.3	346.2	417.2	
S.D.	16.1	17.5	31.6	51.8	
Significance	NS	NS	NS	NS	
Statistical method	AN	AN	AN	KW	

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	277.1	309.1
F01002	341.5	347.4
F01003	313.2	363.6
F01004	303.6	323.5
F01005	331.2	353.8
F01006	321.3	319.6
F01007	352.9	365.9
F01008	339.0	289.1
F01009	308.5	330.5
F01010	335.2	342.6
F01011	336.4	347.0
F01012	364.4	404.3
Number of dams	12	12
Mean	327.0	341.4
S.D.	23.7	30.1

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

Appendix 10-2. Body weights of dams during lactation

2-IBE 15 mg/kg

Dam No.	Days of lactation	
	0	4
F02013	311.9	344.7
F02014	296.4	346.2
F02015	336.9	339.8
F02016	312.7	328.0
F02017	335.7	356.5
F02018	388.5	397.8
F02019	318.3	349.3
F02020	321.0	333.0
F02021	347.3	350.0
F02022	333.6	353.9
F02024	301.7	346.1
Number of dams	11	11
Mean	327.6	349.6
S.D.	25.5	18.1
Significance	NS	NS
Statistical method	AN	KW

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

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

Appendix 10-3. Body weights of dams during lactation

2-IBE 50 mg/kg

Dam No.	Days of lactation	
	0	4
F03025	322.4	342.4
F03026	319.5	331.1
F03027	335.3	349.5
F03028	318.7	348.4
F03029	292.7	347.9
F03030	362.0	365.7
F03031	331.3	328.1
F03032	323.0	365.7
F03033	327.0	359.8
F03034	318.0	342.8
F03035	321.9	334.4
F03036	311.7	344.1
Number of dams	12	12
Mean	323.6	346.7
S.D.	16.1	12.4
Significance	NS	NS
Statistical method	AN	KW

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

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

Appendix 10-4. Body weights of dams during lactation

2-IBE 150 mg/kg

Dam No.	Days of lactation	
	0	4
F04037	323.8	312.2
F04038	321.6	340.1
F04039	366.4	347.6
F04040	342.2	360.9
F04041	297.5	327.3
F04042	324.7	345.5
F04043	352.1	370.3
F04044	224.5	267.3
F04045	329.1	350.0
F04046	320.6	326.3
F04047	271.1	327.6
F04048	335.3	351.1
Number of dams	12	12
Mean	317.4	335.5
S.D.	38.1	26.9
Significance	NS	NS
Statistical method	AN	KW

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	28.1	28.6	28.5	26.3	28.0
M01002	31.0	30.7	29.5	33.4	29.2	28.5
M01003	29.8	23.3	29.1	25.7	26.9	29.8
M01004	31.3	27.8	30.4	31.6	29.6	27.6
M01005	25.0	26.9	23.8	23.6	23.4	22.7
M01006	27.8	23.3	24.4	27.3	22.0	25.4
M01007	32.9	26.9	26.1	29.2	25.3	24.2
M01008	30.3	25.4	24.9	26.3	25.4	24.1
M01009	30.7	33.2	31.6	33.6	31.7	32.5
M01010	28.6	25.0	25.1	23.4	24.4	21.0
M01011	30.1	28.3	27.2	25.7	22.2	21.6
M01012	27.5	22.6	22.2	25.0	22.7	24.2
Number of males	12	12	12	12	12	12
Mean	29.6	26.8	26.9	27.8	25.8	25.8
S.D.	2.1	3.1	2.9	3.5	3.1	3.5

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

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

2-IBE 15 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02013	25.8	28.9	26.0	27.9	24.0	25.0
M02014	26.2	25.6	25.8	25.8	23.8	27.9
M02015	27.1	28.1	27.5	25.5	25.1	23.4
M02016	35.0	32.7	34.0	31.0	28.4	29.6
M02017	34.0	27.2	26.3	27.9	24.6	25.3
M02018	27.6	25.5	24.8	27.2	22.6	23.1
M02019	30.1	27.6	27.3	25.6	23.3	28.2
M02020	35.7	36.1	35.6	32.0	39.1	35.7
M02021	34.5	31.8	29.2	29.2	30.7	26.7
M02022	28.8	25.8	22.2	25.3	22.3	23.8
M02023	32.6	30.7	29.9	30.5	29.0	30.8
M02024	31.6	29.2	28.4	31.0	30.6	30.8
Number of males	12	12	12	12	12	12
Mean	30.8	29.1	28.1	28.2	27.0	27.5
S.D.	3.6	3.2	3.8	2.4	4.9	3.8
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

NA: Not analyzed.

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

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

2-IBE 50 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03025	32.2	31.4	31.9	37.1	32.6	30.6
M03026	28.7	26.3	26.6	27.1	26.0	27.8
M03027	27.9	31.0	31.3	30.1	27.3	28.4
M03028	32.7	27.2	27.3	33.3	32.8	31.1
M03029	27.0	24.3	25.0	28.5	25.1	30.7
M03030	23.7	21.7	23.8	23.6	22.7	22.5
M03031	27.0	27.2	23.5	24.0	22.3	28.6
M03032	31.9	27.5	27.3	32.7	26.7	27.6
M03033	29.5	27.8	27.1	30.5	29.0	32.5
M03034	26.6	24.5	24.7	29.7	24.5	27.0
M03035	26.8	29.4	25.9	30.1	26.1	25.0
M03036	29.0	32.5	25.2	28.2	27.0	28.3
Number of males	12	12	12	12	12	12
Mean	28.6	27.6	26.6	29.6	26.8	28.3
S.D.	2.7	3.2	2.7	3.8	3.3	2.8
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

NA: Not analyzed.

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

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

2-IBE 150 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04037	22.9	30.3	28.4	31.6	27.9	30.8
M04038	13.8	24.6	26.6	27.3	25.8	26.5
M04039	13.6	28.1	29.0	34.5	31.2	25.0
M04040	24.7	34.1	32.4	32.2	34.4	34.9
M04041	17.8	23.2	24.0	26.4	25.7	26.0
M04042	24.0	30.3	30.8	30.1	21.2	27.3
M04043	27.1	29.7	29.1	33.8	31.4	34.0
M04044	19.5	26.4	31.0	24.0	23.9	26.8
M04045	13.6	26.0	25.2	24.6	26.7	29.6
M04046	20.1	30.4	28.3	28.7	31.8	29.2
M04047	21.3	33.2	37.3	36.2	30.6	30.3
M04048	22.9	26.0	27.5	26.9	25.2	28.9
Number of males	12	12	12	12	12	12
Mean	20.1	28.5	29.1	29.7	28.0	29.1
S.D.	4.6	3.4	3.5	4.0	3.9	3.1
Significance	**	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	23.7	22.2
M01009	36.3	34.2
M01010	25.0	25.1
M01011	25.3	30.4
M01012	25.2	23.4
Number of males	5	5
Mean	27.1	27.1
S.D.	5.2	5.1

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

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

2-IBE 150 mg/kg

Male No.	Days of recovery	
	6	12
M04044	31.8	31.0
M04045	28.5	29.0
M04046	33.0	33.3
M04047	36.7	33.0
M04048	30.5	35.5
Number of males	5	5
Mean	32.1	32.4
S.D.	3.1	2.5
Significance	NS	NS
Statistical method	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	20.8	19.2	18.1
F01002	23.6	23.2	25.4
F01003	14.4	19.6	25.1
F01004	19.2	17.9	17.0
F01005	20.1	26.6	27.1
F01006	20.4	25.8	22.6
F01007	22.2	16.6	24.2
F01008	23.6	24.8	25.1
F01009	18.9	20.2	20.1
F01010	16.1	22.0	18.5
F01011	22.8	16.4	22.2
F01012	19.9	16.8	22.7
Number of females	12	12	12
Mean	20.2	20.8	22.3
S.D.	2.8	3.7	3.3

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

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

2-IBE 15 mg/kg

Female No.	Days of administration		
	1	7	14
F02013	22.9	17.6	22.2
F02014	20.8	20.2	14.9
F02015	14.3	21.2	21.3
F02016	24.9	20.6	18.6
F02017	19.5	22.1	21.6
F02018	21.5	26.8	25.1
F02019	22.0	20.9	18.6
F02020	24.9	20.0	22.5
F02021	20.9	23.2	24.2
F02022	20.9	23.4	22.1
F02023	15.9	19.9	20.3
F02024	19.7	21.2	14.6
Number of females	12	12	12
Mean	20.7	21.4	20.5
S.D.	3.1	2.3	3.3
Significance	NS	NS	NS
Statistical method	DU	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

NA: Not analyzed.

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

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

2-IBE 50 mg/kg

Female No.	Days of administration		
	1	7	14
F03025	22.2	20.5	19.9
F03026	15.9	16.7	21.5
F03027	17.2	19.6	21.3
F03028	18.3	19.5	15.8
F03029	24.8	11.4	20.6
F03030	23.9	20.8	18.2
F03031	17.5	20.5	21.7
F03032	20.2	20.4	25.3
F03033	21.3	20.3	23.1
F03034	21.0	25.8	26.2
F03035	21.1	17.3	21.0
F03036	22.4	22.3	23.1
Number of females	12	12	12
Mean	20.5	19.6	21.5
S.D.	2.8	3.4	2.8
Significance	NS	NS	NS
Statistical method	DU	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

NA: Not analyzed.

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

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

2-IBE 150 mg/kg

Female No.	Days of administration		
	1	7	14
F04037	10.8	20.3	13.9
F04038	3.5	20.6	25.0
F04039	13.7	20.5	25.0
F04040	10.1	23.7	22.2
F04041	9.9	19.3	20.2
F04042	10.6	20.7	17.6
F04043	9.3	23.9	15.9
F04044	2.7	19.3	18.2
F04045	15.3	25.1	25.5
F04046	14.1	21.1	19.3
F04047	10.6	20.3	20.2
F04048	17.0	25.1	25.7
Number of females	12	12	12
Mean	10.6	21.7	20.7
S.D.	4.3	2.2	4.0
Significance	**	NS	NS
Statistical method	DU	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	24.6	20.0	17.1	20.1	18.0	13.9	20.4
F05050	26.1	26.3	19.7	21.2	27.0	22.3	23.7
F05051	23.8	15.1	20.7	19.5	19.2	12.3	15.3
F05052	20.2	21.7	17.1	19.8	20.6	14.2	15.9
F05053	18.7	17.8	22.6	21.6	22.6	17.3	23.7
F05054	16.3	19.2	21.1	19.1	17.3	24.4	16.7
F05055	21.3	25.7	23.7	19.5	18.0	21.7	21.3
F05056	22.8	21.3	23.2	25.3	23.7	15.7	25.6
F05057	23.1	20.0	22.4	21.9	21.7	21.3	23.7
F05058	20.5	22.2	19.2	20.6	21.8	20.3	21.8
Number of females	10	10	10	10	10	10	10
Mean	21.7	20.9	20.7	20.9	21.0	18.3	20.8
S.D.	2.9	3.4	2.4	1.8	3.0	4.2	3.7

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

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

2-IBE 150 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06059	5.5	21.6	21.3	21.5	25.2	14.7	21.0
F06060	3.3	21.1	22.3	15.7	19.4	22.8	15.5
F06061	14.1	16.8	25.2	22.1	23.0	17.5	20.8
F06062	12.5	24.7	19.3	18.4	19.9	20.1	16.9
F06063	8.4	25.7	26.0	24.5	25.3	20.3	20.7
F06064	10.6	23.6	20.3	18.0	21.5	17.6	19.8
F06065	13.8	24.2	24.2	23.5	21.9	20.7	18.7
F06066	8.4	22.4	23.8	20.7	25.6	23.5	20.7
F06067	11.0	24.5	20.0	22.3	19.7	20.7	20.2
F06068	7.0	23.3	19.2	22.2	25.2	20.2	23.5
Number of females	10	10	10	10	10	10	10
Mean	9.5	22.8	22.2	20.9	22.7	19.8	19.8
S.D.	3.6	2.5	2.5	2.7	2.5	2.6	2.3
Significance	**	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	23.2	22.5
F05055	21.5	20.3
F05056	22.4	26.7
F05057	20.0	22.6
F05058	20.5	23.4
Number of females	5	5
Mean	21.5	23.1
S.D.	1.3	2.3

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

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

2-IBE 150 mg/kg

Female No.	Days of recovery	
	6	12
F06064	25.0	20.9
F06065	18.9	28.7
F06066	29.3	27.2
F06067	26.9	24.5
F06068	24.4	23.0
Number of females	5	5
Mean	24.9	24.9
S.D.	3.9	3.1
Significance	NS	NS
Statistical method	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	15.2	21.5	24.6	20.9
F01002	22.3	24.8	28.0	22.3
F01003	20.5	27.6	27.1	19.9
F01004	18.7	28.9	27.7	18.5
F01005	21.4	29.7	28.8	17.0
F01006	18.8	27.9	28.8	20.6
F01007	26.2	30.6	29.8	22.5
F01008	23.2	35.2	29.3	10.7
F01009	19.7	24.3	26.0	19.7
F01010	17.3	25.8	25.8	23.6
F01011	23.6	31.7	29.4	23.7
F01012	20.6	32.0	29.0	22.9
Number of dams	12	12	12	12
Mean	20.6	28.3	27.9	20.2
S.D.	3.0	3.8	1.7	3.6

>: Excluded from analysis (not pregnant)

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

Appendix 13-2. Food consumption in dams during pregnancy

2-IBE 15 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	25.0	25.9	27.6	28.3
F02015	20.7	23.9	23.7	22.3
F02016	21.7	23.3	25.6	18.7
F02017	17.8	26.9	31.2	25.0
F02018	26.1	25.0	28.5	23.7
F02019	25.4	30.8	26.7	18.9
F02020	20.4	25.9	27.6	30.7
F02021	21.6	27.9	28.1	25.9
F02022	20.4	24.1	25.2	35.2
F02023	> 20.9	> 19.7	> 15.6	> 17.9
F02024	12.2	27.2	29.5	20.7
Number of dams	10	10	10	10
Mean	21.1	26.1	27.4	24.9
S.D.	4.1	2.2	2.2	5.3
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

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

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

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

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

Appendix 13-3. Food consumption in dams during pregnancy

2-IBE 50 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03025	23.8	27.1	27.5	21.4
F03026	18.0	23.7	23.5	22.8
F03027	21.1	25.3	25.5	20.0
F03028	18.7	30.3	31.1	25.0
F03029	20.7	33.1	28.2	13.5
F03030	20.8	32.0	29.5	24.1
F03031	16.3	22.8	26.6	20.1
F03032	22.2	25.8	28.2	25.1
F03033	19.7	29.5	30.0	27.3
F03034	21.1	29.6	27.7	2.9
F03035	23.5	25.1	24.6	22.0
F03036	23.1	26.4	29.2	21.1
Number of dams	12	12	12	12
Mean	20.8	27.6	27.6	20.4
S.D.	2.3	3.3	2.3	6.5
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

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

Appendix 13-4. Food consumption in dams during pregnancy

2-IBE 150 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	24.8	24.6	26.8	21.3
F04038	23.6	28.7	34.7	25.1
F04039	23.1	25.5	23.5	23.1
F04040	20.2	27.4	28.1	24.3
F04041	16.9	22.7	25.1	27.8
F04042	19.6	22.8	29.3	25.3
F04043	22.0	28.0	25.0	31.5
F04044	19.7	19.4	1.7	14.3
F04045	25.7	29.0	26.1	25.3
F04046	22.4	26.5	28.2	21.7
F04047	19.6	23.5	25.2	8.7
F04048	14.7	26.1	27.6	28.5
Number of dams	12	12	12	12
Mean	21.0	25.4	25.1	23.1
S.D.	3.2	2.9	7.9	6.2
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol 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	41.2
F01002	37.9
F01003	44.5
F01004	33.9
F01005	39.0
F01006	36.9
F01007	39.7
F01008	10.0
F01009	45.3
F01010	42.8
F01011	39.1
F01012	51.2
Number of dams	12
Mean	38.5
S.D.	10.0

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

Appendix 14-2. Food consumption in dams during lactation

2-IBE 15 mg/kg

Dam No.	Days of lactation
	3
F02013	44.9
F02014	48.8
F02015	37.3
F02016	42.2
F02017	46.7
F02018	42.1
F02019	48.6
F02020	41.3
F02021	41.1
F02022	37.5
F02024	50.1
Number of dams	11
Mean	43.7
S.D.	4.5
Significance	NS
Statistical method	AN

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

Appendix 14-3. Food consumption in dams during lactation

2-IBE 50 mg/kg

Dam No.	Days of lactation
	3
F03025	45.2
F03026	37.9
F03027	45.3
F03028	48.7
F03029	51.2
F03030	42.8
F03031	35.7
F03032	49.0
F03033	52.8
F03034	47.0
F03035	33.2
F03036	44.3
Number of dams	12
Mean	44.4
S.D.	6.1
Significance	NS
Statistical method	AN

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

Appendix 14-4. Food consumption in dams during lactation

2-IBE 150 mg/kg

Dam No.	Days of lactation
	3
F04037	22.2
F04038	43.8
F04039	36.4
F04040	41.8
F04041	42.0
F04042	48.2
F04043	46.8
F04044	45.0
F04045	45.7
F04046	36.4
F04047	55.2
F04048	49.9
Number of dams	12
Mean	42.8
S.D.	8.4
Significance	NS
Statistical method	AN

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

Appendix 15-1. Functional findings of male and female rats at the end 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

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F01002	2	2	2	2	+	+	+
F01006	2	2	2	2	+	+	+
F01007	2	2	2	2	+	+	+
F01008	2	2	2	2	+	+	+
F01011	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

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

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

2-IBE (15 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

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F02013	2	2	2	2	+	+	+
F02015	2	2	2	2	+	+	+
F02017	2	2	2	2	+	+	+
F02020	2	2	2	2	+	+	+
F02021	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

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

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

2-IBE (50 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

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F03026	2	2	2	2	+	+	+
F03027	2	2	2	2	+	+	+
F03029	2	2	2	2	+	+	+
F03032	2	2	2	2	+	+	+
F03035	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

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

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

2-IBE (150 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

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F04038	2	2	2	2	+	+	+
F04039	2	2	2	2	+	+	+
F04040	2	2	2	2	+	+	+
F04041	2	2	2	2	+	+	+
F04047	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

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

Appendix 15-5. Functional findings of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female, Administration period

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

2 or +, normal

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

Appendix 15-6. Functional findings of female rats at the end of the dosing period, satellite group

2-IBE (150 mg/kg)

Female, Administration period

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F06059	2	2	2	2	+	+	+
F06060	2	2	2	2	+	+	+
F06061	2	2	2	2	+	+	+
F06062	2	2	2	2	+	+	+
F06063	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

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

Appendix 16-1. Assessment of grip strength of male rats

Control (vehicle: water for injection)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M01001	0.924	0.689
M01002	0.465	0.794
M01003	0.564	0.698
M01004	0.776	0.721
M01005	0.870	0.657
Number of males	5	5
Mean	0.720	0.712
S.D.	0.198	0.051

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

Appendix 16-2. Assessment of grip strength of male rats

2-IBE (15 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M02013	0.566	0.771
M02014	0.328	0.516
M02015	0.742	0.732
M02016	0.878	0.640
M02017	1.116	0.785
Number of males	5	5
Mean	0.726	0.689
S.D.	0.300	0.112

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

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

Appendix 16-3. Assessment of grip strength of male rats

2-IBE (50 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M03025	0.989	0.599
M03026	0.975	0.770
M03027	0.828	0.758
M03028	1.123	0.824
M03029	0.652	0.667
Number of males	5	5
Mean	0.913	0.724
S.D.	0.180	0.090

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

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

Appendix 16-4. Assessment of grip strength of male rats

2-IBE (150 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M04037	0.917	0.669
M04038	1.154	0.586
M04039	1.019	0.989
M04040	0.617	0.621
M04041	0.646	0.536
Number of males	5	5
Mean	0.871	0.680
S.D.	0.234	0.179

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

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

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

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F01002	1.041	0.535
F01006	0.866	0.693
F01007	0.426	0.553
F01008	0.937	0.751
F01011	0.604	0.427
Number of females	5	5
Mean	0.775	0.592
S.D.	0.253	0.130

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

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

2-IBE (15 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F02013	0.839	0.518
F02015	1.043	0.724
F02017	0.628	0.607
F02020	1.074	0.906
F02021	0.646	0.483
Number of females	5	5
Mean	0.846	0.648
S.D.	0.211	0.172

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

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

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

2-IBE (50 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F03026	0.766	0.551
F03027	0.955	0.566
F03029	0.512	0.808
F03032	0.580	0.904
F03035	0.651	0.547
Number of females	5	5
Mean	0.693	0.675
S.D.	0.174	0.169

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

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

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

2-IBE (150 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F04038	0.910	0.694
F04039	0.903	0.712
F04040	0.681	0.598
F04041	0.617	0.470
F04047	0.868	0.953
Number of females	5	5
Mean	0.796	0.685
S.D.	0.137	0.178

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

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

Appendix 18-1. Assessment of grip strength of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F05049	0.644	0.722
F05050	0.670	0.796
F05051	0.876	0.643
F05052	0.910	0.653
F05053	0.487	0.542
Number of females	5	5
Mean	0.717	0.671
S.D.	0.175	0.095

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

Appendix 18-2. Assessment of grip strength of female rats, satellite group

2-IBE (150 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F06059	0.714	0.809
F06060	0.995	0.806
F06061	0.611	0.546
F06062	0.770	0.497
F06063	0.940	0.680
Number of females	5	5
Mean	0.806	0.668
S.D.	0.159	0.144

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

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

Appendix 19-1. Motor activity of male rats

Control (vehicle: water for injection)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1223	876	966	993	4058	51	23	21	41	136
M01002	991	835	753	836	3415	29	17	13	9	68
M01003	1230	877	1053	640	3800	43	19	20	11	93
M01004	1013	1022	917	711	3663	32	30	16	13	91
M01005	1277	1041	866	260	3444	40	19	11	3	73
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1147	930	911	688	3676	39	22	16	15	92
S.D.	134	94	112	274	266	9	5	4	15	27

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

Appendix 19-2. Motor activity of male rats

2-IBE (15 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02013	890	894	905	429	3118	32	28	29	6	95
M02014	1105	950	818	864	3737	28	16	16	22	82
M02015	1176	1168	898	737	3979	40	29	22	23	114
M02016	1146	1048	1174	1025	4393	31	21	22	15	89
M02017	1166	1117	879	366	3528	35	30	25	4	94
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1097	1035	935	684	3751	33	25	23	14	95
S.D.	119	114	138	282	478	5	6	5	9	12

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

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

Appendix 19-3. Motor activity of male rats

2-IBE (50 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03025	1051	820	936	766	3573	33	19	16	7	75
M03026	1209	929	910	588	3636	41	20	20	10	91
M03027	1191	863	325	229	2608	36	20	24	11	91
M03028	1273	1256	900	865	4294	39	49	34	27	149
M03029	1673	1449	973	1301	5396	32	34	10	24	100
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1279	1063	809	750	3901	36	28	21	16	101
S.D.	234	275	272	392	1029	4	13	9	9	28

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

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

Appendix 19-4. Motor activity of male rats

2-IBE (150 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04037	999	587	773	104	2463	39	18	18	0	75
M04038	1289	1032	1103	925	4349	44	28	27	17	116
M04039	1136	1031	680	294	3141	26	19	8	0	53
M04040	743	478	421	271	1913	34	25	12	0	71
M04041	1356	1010	916	808	4090	47	34	22	20	123
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1105	828	779	480	3191	38	25	17	7	88
S.D.	245	272	256	362	1039	8	7	8	10	30

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

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

Appendix 20-1. Motor activity of female rats

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01002	1227	731	536	564	3058	33	11	7	5	56
F01006	1125	743	656	734	3258	39	11	11	7	68
F01007	977	776	496	52	2301	27	13	6	0	46
F01008	1260	1089	455	627	3431	44	30	9	6	89
F01011	1005	884	490	318	2697	26	11	0	0	37
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1119	845	527	459	2949	34	15	7	4	59
S.D.	127	149	78	274	454	8	8	4	3	20

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

Appendix 20-2. Motor activity of female rats

2-IBE (15 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02013	1021	757	634	542	2954	19	2	9	5	35
F02015	878	365	457	425	2125	11	0	2	12	25
F02017	1039	711	520	515	2785	23	8	3	4	38
F02020	1143	578	310	345	2376	26	9	3	2	40
F02021	1065	701	595	162	2523	23	11	17	1	52
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1029	622	503	398	2553	20	6	7	5	38
S.D.	97	158	128	153	328	6	5	6	4	10

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

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

Appendix 20-3. Motor activity of female rats

2-IBE (50 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03026	1024	793	926	430	3173	17	6	8	3	34
F03027	892	562	85	254	1793	9	9	0	1	19
F03029	964	734	346	404	2448	19	7	6	3	35
F03032	1227	725	578	523	3053	36	12	7	3	58
F03035	1801	1565	1031	110	4507	26	13	1	0	40
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1182	876	593	344	2995	21	9	4	2	37
S.D.	368	395	394	163	1008	10	3	4	1	14

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

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

Appendix 20-4. Motor activity of female rats

2-IBE (150 mg/kg)

Female No.	Administration period									
	Ambulation					Rearing				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04038	1119	476	596	383	2574	47	49	23	0	119
F04039	789	642	568	47	2046	9	9	2	0	20
F04040	937	622	349	11	1919	10	3	0	0	13
F04041	667	558	454	425	2104	15	10	10	4	39
F04047	1328	1044	868	693	3933	31	12	13	4	60
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	968	668	567	312	2515	22	17	10	2	50
S.D.	263	220	195	285	830	16	18	9	2	43

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

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

Appendix 21-1. Motor activity of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05049	1250	1126	934	683	3993	47	44	31	16	138
F05050	1046	935	767	893	3641	25	20	15	17	77
F05051	1140	1045	949	867	4001	33	32	33	28	126
F05052	1081	929	702	531	3243	26	21	16	13	76
F05053	1148	1048	985	1143	4324	31	21	21	24	97
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1133	1017	867	823	3840	32	28	23	20	103
S.D.	78	84	125	231	412	9	10	8	6	28

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

Appendix 21-2. Motor activity of female rats, satellite group

2-IBE (150 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06059	1069	944	939	841	3793	39	28	28	33	128
F06060	1070	845	912	324	3151	35	19	26	2	82
F06061	1274	911	803	958	3946	43	29	17	43	132
F06062	1322	1148	1005	549	4024	39	25	20	9	93
F06063	1002	841	749	479	3071	25	20	19	4	68
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1147	938	882	630	3597	36	24	22	18	101
S.D.	141	125	104	262	452	7	5	5	19	28

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

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

Appendix 22-1-1. Urinalysis in male rats

Control (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M01002	Light yellow	-	6.5	+	-	+	-	-	±	-	-	-	-	-
M01003	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	±	-
M01004	Light yellow	-	8.0	+	-	-	-	-	±	-	-	-	±	-
M01005	Light yellow	-	7.0	2+	-	+	-	-	2+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)			
			Na	K	Cl	Na	K	Cl	
M01001	15.5	1.066	107.4	203.7	§	139.5	1.66	3.16	2.16
M01002	23.1	1.039	64.1	140.3	§	71.8	1.48	3.24	1.66
M01003	21.7	1.048	91.6	163.7		110.2	1.99	3.55	2.39
M01004	26.1	1.044	89.8	165.8		105.8	2.34	4.33	2.76
M01005	9.9	1.071	95.4	222.9	§	137.3	0.94	2.21	1.36
Number of males	5	5	5	5		5	5	5	5
Mean	19.3	1.054	89.7	179.3		112.9	1.68	3.30	2.07
±S.D.	6.5	0.014	15.8	33.3		27.6	0.53	0.76	0.56

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

Appendix 22-1-2. Urinalysis in male rats

2-IBE (15 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02013	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M02014	Light yellow	-	7.0	±	-	±	-	-	±	-	-	-	±	-
M02015	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M02016	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
M02017	Light yellow	-	7.0	±	-	-	-	±	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M02013	22.0	1.042	83.2	158.0	90.5	1.83	3.48	1.99
M02014	25.1	1.035	59.4	135.1	71.2	1.49	3.39	1.79
M02015	16.2	1.055	112.0	203.1	118.0	1.81	3.29	1.91
M02016	14.8	1.063	123.2	177.9	133.9	1.82	2.63	1.98
M02017	17.7	1.058	113.6	193.1	131.3	2.01	3.42	2.32
Number of males	5	5	5	5	5	5	5	5
Mean	19.2	1.051	98.3	173.4	109.0	1.79	3.24	2.00
±S.D.	4.3	0.012	26.4	27.4	27.2	0.19	0.35	0.20

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

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

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

Appendix 22-1-3. Urinalysis in male rats

2-IBE (50 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03025	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	-	-
M03026	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M03027	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M03028	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	±	-
M03029	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)			
			Na	K	Cl	Na	K	Cl	
M03025	17.1	1.061	103.9	184.6	§	101.8	1.78	3.16	1.74
M03026	11.5	1.064	86.7	176.5	§	120.6	1.00	2.03	1.39
M03027	16.2	1.066	118.6	185.9	§	131.8	1.92	3.01	2.14
M03028	17.8	1.070	109.6	216.1	§	150.7	1.95	3.85	2.68
M03029	19.4	1.040	68.5	127.5	§	58.0	1.33	2.47	1.13
Number of males	5	5	5	5	5	5	5	5	5
Mean	16.4	1.060	97.5	178.1		112.6	1.60	2.90	1.82
±S.D.	3.0	0.012	19.9	32.1		35.3	0.42	0.69	0.61

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

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

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

Appendix 22-1-4. Urinalysis in male rats

2-IBE (150 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04037	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	-
M04038	Light yellow	-	7.5	+	-	-	-	-	±	-	-	-	±	-
M04039	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
M04040	Light yellow	-	8.0	+	-	-	-	-	±	-	-	-	±	-
M04041	Light yellow	-	7.5	+	-	-	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)			
			Na	K	Cl	Na	K	Cl	
M04037	13.6	1.064	180.1	202.1	§	187.8	2.45	2.75	2.55
M04038	16.3	1.067	153.2	224.1	§	161.6	2.50	3.65	2.63
M04039	17.3	1.066	131.1	192.3	§	165.4	2.27	3.33	2.86
M04040	19.1	1.061	118.2	185.6		127.1	2.26	3.54	2.43
M04041	17.0	1.057	97.1	172.7	§	123.5	1.65	2.94	2.10
Number of males	5	5	5	5		5	5	5	5
Mean	16.7	1.063	135.9	* 195.4		153.1	2.23	3.24	2.51
±S.D.	2.0	0.004	32.0	19.3		27.3	0.34	0.39	0.28

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

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

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

Appendix 22-2-1. Urinalysis in male rats of the recovery period

Control (vehicle: water for injection)

Quality										Urinary sediments				
Male No.	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01008	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-
M01009	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-
M01010	Light yellow	-	7.0	2+	-	±	-	-	+	-	-	-	±	-
M01011	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	+	-
M01012	Light yellow	-	7.5	+	-	+	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)			
			Na	K	Cl	Na	K	Cl	
M01008	11.1	1.075	127.6	235.3	§	167.0	1.42	2.61	1.85
M01009	19.3	1.058	92.9	187.0	§	113.5	1.79	3.61	2.19
M01010	10.0	1.084	107.9	232.6	§	149.8	1.08	2.33	1.50
M01011	15.1	1.067	135.3	222.8		173.9	2.04	3.36	2.63
M01012	17.8	1.046	54.0	165.5		80.4	0.96	2.95	1.43
Number of males	5	5	5	5		5	5	5	5
Mean	14.7	1.066	103.5	208.6		136.9	1.46	2.97	1.92
±S.D.	4.1	0.015	32.3	30.9		39.3	0.46	0.52	0.50

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

Appendix 22-2-2. Urinalysis in male rats of the recovery period

2-IBE (150 mg/kg)

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

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M04044	15.7	1.066	119.8	198.9	150.1	1.88	3.12	2.36
M04045	31.3	1.029	58.6	128.6	67.7	1.83	4.03	2.12
M04046	15.6	1.063	109.4	216.1	133.7	1.71	3.37	2.09
M04047	14.8	1.070	144.2	214.0 §	155.8	2.13	3.17	2.31
M04048	47.8	1.022	45.9	104.0 §	51.8	2.19	4.97	2.48
Number of males	5	5	5	5	5	5	5	5
Mean	25.0	1.050	95.6	172.3	111.8	1.95	3.73	2.27
±S.D.	14.5	0.023	41.8	52.3	48.5	0.20	0.78	0.16

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

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

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

Appendix 23-1-1. Urinalysis in female rats, satellite group

Control (vehicle: water for injection)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05049	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
F05050	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F05051	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	-	-
F05052	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F05053	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05049	10.0	1.063	116.3	170.6	139.9	1.16	1.71	1.40
F05050	9.8	1.067	119.1	180.1	§ 147.0	1.17	1.76	1.44
F05051	16.0	1.025	21.3	76.6	§ 20.7	§ 0.34	1.23	0.33
F05052	12.8	1.043	83.4	134.1	§ 83.5	1.07	1.72	1.07
F05053	14.6	1.051	78.7	172.2	101.4	1.15	2.51	1.48
Number of females	5	5	5	5	5	5	5	5
Mean	12.6	1.050	83.8	146.7	98.5	0.98	1.79	1.14
±S.D.	2.7	0.017	39.5	43.0	50.9	0.36	0.46	0.48

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

Appendix 23-1-2. Urinalysis in female rats, satellite group

2-IBE (150 mg/kg)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06059	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	±
F06060	brown	2+	6.5	2+	-	-	-	3+	±	-	±	-	±	±
F06061	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F06062	Light yellow	-	6.5	±	-	-	-	-	±	-	-	-	±	-
F06063	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06059	12.3	1.055	84.8	160.1	95.6	1.04	1.97	1.18
F06060	12.2	1.065	58.5	170.7	66.3	0.71	2.08	0.81
F06061	15.2	1.048	64.6	152.6	94.7	0.98	2.32	1.44
F06062	10.3	1.072	179.7	196.3	§ 160.4	1.85	2.02	1.65
F06063	17.2	1.030	47.0	71.0	§ 47.2	0.81	1.22	0.81
Number of females	5	5	5	5	5	5	5	5
Mean	13.4	1.054	86.9	150.1	92.8	1.08	1.92	1.18
±S.D.	2.7	0.016	53.6	47.2	42.9	0.45	0.41	0.37

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

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

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

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

Control (vehicle: water for injection)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells ^{a)}	White blood cells ^{a)}	Casts ^{a)}	Crystals ^{b)}	Epithelial cells ^{b)}
F05054	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	-	-
F05055	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-
F05056	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F05057	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F05058	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05054	12.9	1.066	131.9	241.9	159.1	1.70	3.12	2.05
F05055	6.2	1.094	242.3	261.0	280.0	1.50	1.62	1.74
F05056	15.9	1.047	114.2	165.8	§ 105.1	1.82	2.64	1.67
F05057	8.4	1.068	119.0	212.6	143.1	1.00	1.79	1.20
F05058	15.6	1.050	100.5	168.0	125.8	1.57	2.62	1.96
Number of females	5	5	5	5	5	5	5	5
Mean	11.8	1.065	141.6	209.9	162.6	1.52	2.36	1.72
±S.D.	4.3	0.019	57.4	42.8	68.6	0.31	0.63	0.33

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Turbidity, -: negative; +: slight; 2+: moderate

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 < 1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

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

2-IBE (150 mg/kg)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells ^{a)}	White blood cells ^{a)}	Casts ^{a)}	Crystals ^{b)}	Epithelial cells ^{b)}
F06064	Light yellow	-	8.5	±	-	-	-	-	±	-	-	-	±	-
F06065	Light yellow	-	7.0	±	-	-	-	-	+	-	-	-	±	-
F06066	Light yellow	-	7.5	+	-	-	-	-	±	-	-	-	±	-
F06067	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F06068	Light yellow	-	8.0	-	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06064	12.0	1.067	132.1	188.6	135.2	1.59	2.26	1.62
F06065	17.8	1.057	127.7	183.2 §	136.6	2.27	3.26	2.43
F06066	16.7	1.053	113.8	159.8	119.9	1.90	2.67	2.00
F06067	12.1	1.063	143.0	199.1	150.3	1.73	2.41	1.82
F06068	15.8	1.047	87.8	155.1	97.9	1.39	2.45	1.55
Number of females	5	5	5	5	5	5	5	5
Mean	14.9	1.057	120.9	177.2	128.0	1.78	2.61	1.88
±S.D.	2.7	0.008	21.2	19.0	20.0	0.33	0.39	0.35

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

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

Turbidity, -: negative; +: slight; 2+: moderate

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<1000 mg/dL; 4+: 1000 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 <

Red blood cells, -: not observed

White blood cells, -: not observed; ±: a few

Casts, -: not observed

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

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

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

Appendix 24-1-1. Hematological findings of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M01001	820	15.0	43.2	52.7	18.3	34.7	98.5	22.7	25.8
M01002	838	14.9	42.9	51.2	17.8	34.7	105.4	21.9	30.5
M01003	846	15.7	45.0	53.2	18.6	34.9	116.1	19.4	28.4
M01004	813	14.3	41.6	51.2	17.6	34.4	94.7	20.0	28.8
M01005	787	15.6	45.6	57.9	19.8	34.2	88.7	16.7	27.0
Number of males	5	5	5	5	5	5	5	5	5
Mean	821	15.1	43.7	53.2	18.4	34.6	100.7	20.1	28.1
S.D.	23	0.6	1.6	2.8	0.9	0.3	10.5	2.3	1.8

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M01001	94.3	23.6	2.1	0.1	4.2	70.0	4.19
M01002	129.0	19.8	1.9	0.0	3.6	74.7	3.42
M01003	149.4	18.1	0.9	0.1	2.9	78.0	3.44
M01004	90.6	19.5	1.5	0.1	4.5	74.4	3.33
M01005	100.7	16.3	1.4	0.1	3.4	78.8	2.99
Number of males	5	5	5	5	5	5	5
Mean	112.8	19.5	1.6	0.1	3.7	75.2	3.47
S.D.	25.4	2.7	0.5	0.0	0.6	3.5	0.44

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

Appendix 24-1-2. Hematological findings of male rats at the end of the dosing period

2-IBE (15 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M02013	825	15.5	44.5	53.9	18.8	34.8	98.4	25.7	25.8
M02014	887	16.4	46.9	52.9	18.5	35.0	99.9	21.9	28.3
M02015	827	14.5	42.7	51.6	17.5	34.0	107.0	16.3	27.5
M02016	839	15.0	43.1	51.4	17.9	34.8	116.9	16.9	25.3
M02017	852	15.8	45.2	53.1	18.5	35.0	106.2	27.6	26.5
Number of males	5	5	5	5	5	5	5	5	5
Mean	846	15.4	44.5	52.6	18.2	34.7	105.7	21.7	26.7
S.D.	25	0.7	1.7	1.1	0.5	0.4	7.3	5.1	1.2

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M02013	101.3	12.6	1.4	0.1	4.7	81.2	2.95
M02014	83.2	11.9	0.7	0.0	4.0	83.4	2.57
M02015	76.6	20.2	1.4	0.0	5.4	73.0	2.48
M02016	114.4	12.1	1.1	0.0	4.0	82.8	3.66
M02017	127.4	15.4	0.8	0.0	3.9	79.9	3.05
Number of males	5	5	5	5	5	5	5
Mean	100.6	14.4	1.1	0.0	4.4	80.1	2.94
S.D.	21.1	3.5	0.3	0.0	0.6	4.2	0.47

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

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

Appendix 24-1-3. Hematological findings of male rats at the end of the dosing period

2-IBE (50 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M03025	706	13.5	40.3	57.1	19.1	33.5	105.5	14.6	22.2
M03026	732	14.0	41.5	56.7	19.1	33.7	122.8	15.1	23.6
M03027	724	13.5	40.1	55.4	18.6	33.7	116.8	20.9	28.5
M03028	702	13.0	40.4	57.5	18.5	32.2	97.8	16.0	23.2
M03029	802	14.9	44.7	55.7	18.6	33.3	112.1	17.7	26.3
Number of males	5	5	5	5	5	5	5	5	5
Mean	733 **	13.8 *	41.4	56.5	18.8	33.3	111.0	16.9	24.8 *
S.D.	40	0.7	1.9	0.9	0.3	0.6	9.7	2.5	2.6

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M03025	146.0	15.8	1.4	0.1	5.2	77.5	8.31
M03026	114.5	16.9	1.0	0.0	2.8	79.3	5.66
M03027	79.0	16.1	1.1	0.0	5.8	77.0	5.83
M03028	74.2	31.0	1.2	0.0	4.9	62.9	7.09
M03029	123.2	10.5	1.4	0.1	3.7	84.3	5.30
Number of males	5	5	5	5	5	5	5
Mean	107.4	18.1	1.2	0.0	4.5	76.2	6.44
S.D.	30.4	7.7	0.2	0.1	1.2	8.0	1.24

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

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

Appendix 24-1-4. Hematological findings of male rats at the end of the dosing period

2-IBE (150 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M04037	691	13.3	40.5	58.6	19.2	32.8	113.9	20.1	25.1
M04038	625	12.6	39.1	62.6	20.2	32.2	92.1	20.0	23.1
M04039	556	11.7	38.8	69.8	21.0	30.2	87.9	15.9	24.5
M04040	633	13.0	39.1	61.8	20.5	33.2	95.8	15.0	23.9
M04041	582	11.9	36.3	62.4	20.4	32.8	99.6	13.9	20.1
Number of males	5	5	5	5	5	5	5	5	5
Mean	617 **	12.5 **	38.8 **	63.0 **	20.3 **	32.2 *	97.9	17.0	23.3 **
S.D.	52	0.7	1.5	4.1	0.7	1.2	10.0	2.9	2.0

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M04037	97.9	16.9	0.4	0.0	5.0	77.7	10.84
M04038	73.9	9.9	0.5	0.0	5.3	84.3	10.29
M04039	62.1	14.5	1.1	0.0	6.3	78.1	14.67
M04040	93.6	17.7	1.0	0.1	5.1	76.1	9.44
M04041	98.0	16.3	0.5	0.0	2.6	80.6	12.31
Number of males	5	5	5	5	5	5	5
Mean	85.1	15.1	0.7 **	0.0	4.9	79.4	11.51 **
S.D.	16.3	3.1	0.3	0.0	1.4	3.2	2.05

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

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

Appendix 24-2-1. Hematological findings of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M01008	870	15.4	43.6	50.1	17.7	35.3	96.2	16.4	23.0
M01009	878	14.9	41.9	47.7	17.0	35.6	133.2	20.7	30.6
M01010	873	14.8	43.1	49.4	17.0	34.3	126.1	20.7	30.7
M01011	922	16.2	45.2	49.0	17.6	35.8	128.2	19.4	26.4
M01012	866	15.7	44.8	51.7	18.1	35.0	107.2	21.5	26.1 §
Number of males	5	5	5	5	5	5	5	5	5
Mean	882	15.4	43.7	49.6	17.5	35.2	118.2	19.7	27.4
S.D.	23	0.6	1.3	1.5	0.5	0.6	15.8	2.0	3.3

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M01008	92.9	10.6	1.0	0.0	4.4	84.0	3.46
M01009	92.0	12.1	1.3	0.0	4.9	81.7	3.64
M01010	97.7	11.0	1.8	0.0	3.1	84.1	2.81
M01011	68.4	18.9	2.3	0.0	2.5	76.3	3.86
M01012	92.7	9.6	0.9	0.0	3.2	86.3	3.17
Number of males	5	5	5	5	5	5	5
Mean	88.7	12.4	1.5	0.0	3.6	82.5	3.39
S.D.	11.6	3.7	0.6	0.0	1.0	3.8	0.41

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.

The re-measured values were employed as the data.

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

Appendix 24-2-2. Hematological findings of male rats at the end of the recovery period

2-IBE (150 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M04044	823	15.2	43.9	53.3	18.5	34.6	114.6	19.9	28.2 §
M04045	828	16.1	46.5	56.2	19.4	34.6	98.6	17.4	26.1
M04046	853	15.9	45.4	53.2	18.6	35.0	124.8	17.0	28.1
M04047	845	16.3	47.0	55.6	19.3	34.7	110.0	17.6	29.2
M04048	855	16.1	46.0	53.8	18.8	35.0	117.1	18.3	29.1 §
Number of males	5	5	5	5	5	5	5	5	5
Mean	841 **	15.9	45.8 *	54.4 **	18.9 **	34.8	113.0	18.0	28.1
S.D.	15	0.4	1.2	1.4	0.4	0.2	9.7	1.1	1.2

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M04044	99.9	20.7	1.0	0.0	5.1	73.2	2.29
M04045	88.4	11.3	0.9	0.0	2.5	85.3	2.21
M04046	105.4	19.3	2.1	0.1	2.9	75.6	2.40
M04047	109.8	7.8	0.6	0.0	2.3	89.3	1.92
M04048	70.3	13.0	1.0	0.0	3.4	82.6	2.47
Number of males	5	5	5	5	5	5	5
Mean	94.8	14.4	1.1	0.0	3.2	81.2	2.26 **
S.D.	15.8	5.5	0.6	0.0	1.1	6.7	0.21

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

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.

The re-measured values were employed as the data.

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

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

Control (vehicle: water for injection)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F01002	685	13.8	39.7	58.0	20.1	34.8	103.0	12.3	19.0
F01006	607	11.4	34.8	57.3	18.8	32.8	97.5	12.2	19.1
F01007	685	13.5	42.0	61.3	19.7	32.1	112.1	13.3	23.3
F01008	649	12.4	36.3	55.9	19.1	34.2	108.5	12.2	19.2
F01011	731	13.9	40.0	54.7	19.0	34.8	135.7	12.7	19.1
Number of females	5	5	5	5	5	5	5	5	5
Mean	671	13.0	38.6	57.4	19.3	33.7	111.4	12.5	19.9
S.D.	46	1.1	2.9	2.5	0.5	1.2	14.7	0.5	1.9

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F01002	128.0	36.3	0.7	0.1	4.4	58.5	6.78
F01006	82.7	34.5	0.4	0.0	1.3	63.8	5.74
F01007	39.8	12.3	1.0	0.0	7.3	79.4	9.59
F01008	88.7	27.6	0.2	0.0	7.4	64.8	5.20
F01011	75.7	33.7	0.9	0.0	3.2	62.2	4.97
Number of females	5	5	5	5	5	5	5
Mean	83.0	28.9	0.6	0.0	4.7	65.7	6.46
S.D.	31.5	9.8	0.3	0.0	2.6	8.0	1.89

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

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

2-IBE (15 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F02013	720	13.8	40.7	56.5	19.2	33.9	106.3	13.2	20.6
F02015	695	13.5	39.8	57.3	19.4	33.9	130.8	12.9	19.0
F02017	471	12.0	40.0	84.9	25.5	30.0	113.2	13.9	18.1
F02020	679	13.3	40.2	59.2	19.6	33.1	119.0	12.6	19.7
F02021	681	13.3	38.4	56.4	19.5	34.6	108.7	12.6	20.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	649	13.2	39.8	62.9	20.6	33.1	115.6	13.0	19.5
S.D.	101	0.7	0.9	12.4	2.7	1.8	9.8	0.5	1.0

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F02013	135.7	58.2	0.9	0.0	4.2	36.7	9.90
F02015	125.9	25.2	0.5	0.0	3.5	70.8	10.88
F02017	99.3	26.6	0.5	0.0	2.7	70.2	30.97
F02020	72.4	17.6	0.8	0.0	5.1	76.5	8.43
F02021	93.4	36.1	0.6	0.0	4.6	58.7	10.21
Number of females	5	5	5	5	5	5	5
Mean	105.3	32.7	0.7	0.0	4.0	62.6	14.08
S.D.	25.5	15.7	0.2	0.0	0.9	15.8	9.49

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

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

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

2-IBE (50 mg/kg)									
Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F03026	552	12.3	37.4	67.8	22.3	32.9	112.3	13.1	19.6
F03027	553	12.0	38.0	68.7	21.7	31.6	117.2	13.3	20.3
F03029	526	11.9	36.5	69.4	22.6	32.6	90.3	12.4	19.9
F03032	590	12.7	38.9	65.9	21.5	32.6	94.1	13.7	19.2
F03035	645	12.9	39.2	60.8	20.0	32.9	151.1	12.9	19.8
Number of females	5	5	5	5	5	5	5	5	5
Mean	573	12.4	38.0	66.5	21.6	32.5	113.0	13.1	19.8
S.D.	46	0.4	1.1	3.5	1.0	0.5	24.2	0.5	0.4

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F03026	45.4	20.1	0.2	0.0	7.5	72.2	29.72
F03027	116.7	31.1	0.4	0.0	3.3	65.2	23.18
F03029	82.4	42.4	0.5	0.0	3.8	53.3	16.34
F03032	45.6	13.8	0.4	0.0	5.3	80.5	13.13
F03035	42.7	24.6	0.7	0.0	5.4	69.3	12.96
Number of females	5	5	5	5	5	5	5
Mean	66.6	26.4	0.4	0.0	5.1	68.1	19.07 *
S.D.	32.5	11.0	0.2	0.0	1.6	10.0	7.25

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

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

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

2-IBE (150 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F04038	444	11.3	36.6	82.4	25.5	30.9	114.0	13.4	20.6
F04039	444	12.4	44.0	99.1	27.9	28.2	110.6	13.5	20.1
F04040	694	13.2	38.2	55.0	19.0	34.6	104.8	13.0	21.1
F04041	589	12.6	38.6	65.5	21.4	32.6	125.3	12.5	18.2
F04047	455	12.2	43.1	94.7	26.8	28.3	105.0	13.2	17.9
Number of females	5	5	5	5	5	5	5	5	5
Mean	525 **	12.3	40.1	79.3	24.1	30.9	111.9	13.1	19.6
S.D.	113	0.7	3.3	18.8	3.8	2.8	8.4	0.4	1.4

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F04038	77.5	37.1	0.4	0.0	4.4	58.1	32.47
F04039	61.2	22.0	0.5	0.0	5.6	71.9	32.17
F04040	51.4	30.7	1.6	0.0	4.9	62.8	7.92
F04041	94.5	36.2	0.5	0.0	2.6	60.7	13.01
F04047	42.7	9.6	0.5	0.0	4.7	85.2	22.96
Number of females	5	5	5	5	5	5	5
Mean	65.5	27.1	0.7	0.0	4.4	67.7	21.71 *
S.D.	20.7	11.5	0.5	0.0	1.1	11.1	11.10

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

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

Appendix 25-2-1. Hematological findings of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F05049	746	13.8	38.6	51.7	18.5	35.8	99.7	11.5	16.0
F05050	774	14.5	40.5	52.3	18.7	35.8	96.6	12.2	19.1
F05051	771	14.2	40.1	52.0	18.4	35.4	84.7	12.2	19.4
F05052	738	13.9	39.2	53.1	18.8	35.5	98.4	12.6	22.2
F05053	783	14.9	43.3	55.3	19.0	34.4	104.6	12.4	18.6
Number of females	5	5	5	5	5	5	5	5	5
Mean	762	14.3	40.3	52.9	18.7	35.4	96.8	12.2	19.1
S.D.	19	0.5	1.8	1.4	0.2	0.6	7.4	0.4	2.2

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F05049	60.7	15.9	1.5	0.2	3.8	78.6	3.90
F05050	89.3	8.3	0.7	0.0	1.9	89.1	3.09
F05051	29.3	12.3	1.0	0.0	1.7	85.0	3.78
F05052	46.2	10.9	1.3	0.0	1.7	86.1	4.53
F05053	32.1	11.8	1.6	0.0	2.2	84.4	3.87
Number of females	5	5	5	5	5	5	5
Mean	51.5	11.8	1.2	0.0	2.3	84.6	3.83
S.D.	24.5	2.7	0.4	0.1	0.9	3.8	0.51

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

Appendix 25-2-2. Hematological findings of female rats at the end of the dosing period, satellite group

2-IBE (150 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F06059	524	11.6	37.4	71.4	22.1	31.0	70.0	12.0	15.7
F06060	472	11.1	36.1	76.5	23.5	30.7	79.7	11.8	18.0
F06061	479	10.6	34.0	71.0	22.1	31.2	114.2	12.4	18.5
F06062	521	10.7	32.8	63.0	20.5	32.6	120.2	12.3	19.8
F06063	517	11.7	38.7	74.9	22.6	30.2	97.4	13.6	17.8
Number of females	5	5	5	5	5	5	5	5	5
Mean	503 **	11.1 **	35.8 **	71.4 **	22.2 **	31.1 **	96.3	12.4	18.0
S.D.	25	0.5	2.4	5.2	1.1	0.9	21.6	0.7	1.5

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F06059	39.6	7.9	0.5	0.0	2.0	89.6	16.18
F06060	45.1	12.0	0.9	0.0	3.1	84.0	15.24
F06061	32.3	9.5	1.9	0.0	1.9	86.7	17.96
F06062	68.0	12.1	0.6	0.0	2.2	85.1	12.52
F06063	36.7	6.5	0.8	0.0	1.1	91.6	13.62
Number of females	5	5	5	5	5	5	5
Mean	44.3	9.6	0.9	0.0	2.1	87.4	15.10 **
S.D.	14.0	2.5	0.6	0.0	0.7	3.2	2.13

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

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

Appendix 25-3-1. Hematological findings of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F05054	722	13.3	39.1	54.2	18.4	34.0	164.9	11.9	21.0
F05055	898	15.6	43.8	48.8	17.4	35.6	122.4	12.1	21.3
F05056	796	14.9	43.4	54.5	18.7	34.3	121.4	12.1	19.8
F05057	843	14.6	42.0	49.8	17.3	34.8	90.0	11.1	21.3 §
F05058	816	15.0	43.2	52.9	18.4	34.7	111.4	13.0	20.7 §
Number of females	5	5	5	5	5	5	5	5	5
Mean	815	14.7	42.3	52.0	18.0	34.7	122.0	12.0	20.8
S.D.	65	0.9	1.9	2.6	0.6	0.6	27.3	0.7	0.6

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F05054	96.1	13.3	1.1	0.1	2.7	82.8	9.64
F05055	49.1	15.6	1.6	0.0	2.6	80.2	1.99
F05056	40.1	14.8	1.2	0.0	3.7	80.3	3.18
F05057	37.6	8.4	1.9	0.0	2.7	87.0	3.15
F05058	58.0	18.6	1.6	0.0	3.6	76.2	3.15
Number of females	5	5	5	5	5	5	5
Mean	56.2	14.1	1.5	0.0	3.1	81.3	4.22
S.D.	23.7	3.7	0.3	0.0	0.5	4.0	3.07

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.

The re-measured values were employed as the data.

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

Appendix 25-3-2. Hematological findings of female rats at the end of the recovery period

2-IBE (150 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F06064	776	16.3	48.0	61.9	21.0	34.0	85.2	13.3	23.2
F06065	805	16.3	47.6	59.1	20.2	34.2	102.2	12.9	23.1
F06066	752	16.1	46.3	61.6	21.4	34.8	96.1	12.3 §	17.4 §
F06067	769	17.0	49.4	64.2	22.1	34.4	87.3	12.4	38.6
F06068	855	16.7	47.3	55.3	19.5	35.3	98.1	12.4	20.1
Number of females	5	5	5	5	5	5	5	5	5
Mean	791	16.5 **	47.7 **	60.4 **	20.8 **	34.5	93.8	12.7	24.5
S.D.	40	0.4	1.1	3.4	1.0	0.5	7.3	0.4	8.2

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F06064	53.3	9.2	0.9	0.0	2.1	87.8	2.31
F06065	38.0	7.2	1.8	0.0	4.2	86.8	1.98
F06066	41.3	17.9	1.7	0.0	4.6	75.8	2.26
F06067	37.2	10.2	1.6	0.0	3.0	85.2	1.81
F06068	42.7	15.2	1.2	0.0	2.8	80.8	1.32
Number of females	5	5	5	5	5	5	5
Mean	42.5	11.9	1.4	0.0	3.3	83.3	1.94
S.D.	6.5	4.4	0.4	0.0	1.0	5.0	0.40

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

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.

The re-measured values were employed as the data.

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

Appendix 26-1-1. Myelogram in male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
M01001	2.7	3.1	4.0	14.8	15.2	2.3	1.5	0.2	0.4	44.3	0.2
M01002	0.4	3.8	5.8	11.0	21.5	1.3	2.9	0.2	0.4	47.3	0.0
M01003	1.2	1.2	8.2	15.5	21.3	0.6	2.4	0.0	0.8	51.1	0.2
M01004	1.2	2.2	4.3	13.2	24.7	2.6	1.2	0.4	1.0	50.7	0.2
M01005	1.2	1.8	5.1	14.7	20.0	0.4	1.6	1.0	0.4	46.1	0.2
Mean	1.3	2.4	5.5	13.8	20.5	1.4	1.9	0.4	0.6	47.9	0.2
±S.D.	0.8	1.0	1.7	1.8	3.5	1.0	0.7	0.4	0.3	2.9	0.1
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Male No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
M01001	7.3	19.3	12.7	39.5	1.12	2.3	12.9	0.4	0.4	0.2
M01002	8.3	18.7	9.4	36.3	1.30	1.9	14.0	0.2	0.2	0.0
M01003	4.2	18.3	8.9	31.6	1.62	1.6	15.5	0.2	0.0	0.0
M01004	3.4	17.0	7.9	28.4	1.78	0.6	18.7	0.6	0.8	0.2
M01005	6.1	15.8	8.1	30.3	1.52	1.0	20.6	0.8	0.4	0.8
Mean	5.9	17.8	9.4	33.2	1.47	1.5	16.3	0.4	0.4	0.2
±S.D.	2.1	1.4	1.9	4.6	0.26	0.7	3.2	0.3	0.3	0.3
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

Appendix 26-1-2. Myelogram in male rats at the end of the dosing period

2-IBE (15 mg/kg)

Male No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
M02013	2.0	2.9	6.9	11.2	31.2	1.0	1.8	0.0	1.6	58.5	0.4
M02014	1.6	2.7	8.3	9.1	21.5	0.6	0.8	0.6	0.2	45.3	0.0
M02015	2.1	5.3	2.7	9.3	29.3	0.2	1.7	0.6	0.0	51.1	0.0
M02016	2.6	3.4	4.7	12.3	20.7	0.7	1.1	1.9	0.7	48.2	0.2
M02017	2.0	2.4	2.8	8.1	19.9	0.8	1.0	0.2	0.2	37.3	0.6
Mean	2.1	3.3	5.1	10.0	24.5	0.7	1.3	0.7	0.5	48.1	0.2
±S.D.	0.4	1.2	2.5	1.7	5.3	0.3	0.4	0.7	0.6	7.8	0.3
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Male No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
M02013	0.8	13.4	8.6	23.2	2.53	0.6	17.5	0.2	0.0	0.0
M02014	6.2	13.6	16.3	36.0	1.26	1.4	16.5	0.4	0.2	0.2
M02015	3.2	18.4	11.4	33.1	1.55	4.2	10.8	0.6	0.2	0.0
M02016	8.4	15.9	7.5	32.0	1.51	1.3	17.2	1.1	0.0	0.2
M02017	7.5	13.6	6.7	28.4	1.31	3.6	29.4	0.4	0.0	1.0
Mean	5.2	15.0	10.1	30.5	1.63	2.2	18.3	0.5	0.1	0.3
±S.D.	3.2	2.2	3.9	4.9	0.52	1.6	6.8	0.3	0.1	0.4
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

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

Appendix 26-1-3. Myelogram in male rats at the end of the dosing period

2-IBE (50 mg/kg)

Male No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
M03025	0.6	3.1	3.5	10.6	17.0	0.6	2.5	0.2	1.0	39.1	0.2
M03026	0.6	5.8	2.3	9.1	23.0	1.6	1.9	0.8	0.8	45.9	0.2
M03027	1.4	2.3	4.9	8.8	17.3	0.4	1.6	0.4	0.6	37.6	0.4
M03028	1.3	3.1	5.5	9.4	28.3	1.3	1.8	0.2	0.7	51.8	0.4
M03029	1.0	4.0	5.6	9.3	21.2	1.0	1.8	1.4	0.8	46.0	0.2
Mean	1.0	3.7	4.4	9.4	21.4	1.0	1.9	0.6	0.8	44.1	0.3
±S.D.	0.4	1.3	1.4	0.7	4.6	0.5	0.3	0.5	0.1	5.8	0.1
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Male No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
M03025	6.2	20.3	17.0	43.7	0.89	2.7	13.7	0.4	0.4	0.0
M03026	6.6	13.8	8.0	28.6	1.61	4.7	20.4	0.0	0.4	0.0
M03027	5.5	26.1	16.2	48.1	0.78	2.3	11.3	0.2	0.4	0.0
M03028	4.1	14.8	15.3	34.6	1.50	3.9	9.2	0.6	0.0	0.0
M03029	4.8	19.6	9.9	34.5	1.33	3.2	15.1	0.0	0.0	1.2
Mean	5.4	18.9	13.3	37.9	1.22	3.4	13.9	0.2	0.2	0.2
±S.D.	1.0	4.9	4.1	7.9	0.37	1.0	4.3	0.3	0.2	0.5
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

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

Appendix 26-1-4. Myelogram in male rats at the end of the dosing period

2-IBE (150 mg/kg)

Male No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
M04037	2.0	2.4	2.4	8.1	19.1	0.6	1.0	0.0	0.6	36.0	0.6
M04038	1.7	3.4	5.5	6.5	14.5	0.8	0.2	0.8	1.5	35.0	0.2
M04039	2.7	2.5	4.6	8.9	15.7	1.5	1.7	0.2	0.2	38.0	0.8
M04040	6.1	2.0	7.1	8.5	26.5	1.2	0.8	0.0	0.2	52.4	0.2
M04041	1.6	3.6	2.6	8.6	23.8	1.4	1.4	0.2	0.2	43.4	0.0
Mean	2.8	2.8	4.4	8.1	19.9	1.1	1.0	0.2	0.5	41.0	0.4
±S.D.	1.9	0.7	2.0	0.9	5.2	0.4	0.6	0.3	0.6	7.2	0.3
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Male No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
M04037	7.7	25.6	15.0	48.8	0.74	2.8	11.6	0.2	0.0	0.6
M04038	13.8	23.1	14.7	51.8	0.68	2.3	9.6	0.2	0.4	0.8
M04039	18.4	19.5	12.3	51.0	0.74	2.3	8.0	0.4	0.0	0.4
M04040	3.8	18.2	15.6	37.7	1.39	1.8	7.9	0.0	0.2	0.0
M04041	10.6	19.6	15.8	46.0	0.94	2.4	8.2	0.0	0.0	0.0
Mean	10.9	21.2	14.7	47.1	0.90	2.3	9.1	0.2	0.1	0.4
±S.D.	5.6	3.1	1.4	5.7	0.29	0.4	1.6	0.2	0.2	0.4
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

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

Appendix 26-2-1. Myelogram in male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
M01008	4.3	2.4	2.2	11.0	20.7	0.8	1.4	0.4	0.4	43.5	0.0
M01009	2.0	4.8	2.2	11.4	28.0	1.0	2.8	0.6	1.4	54.2	0.2
M01010	4.2	4.2	1.8	12.3	18.8	1.0	1.4	0.2	0.6	44.3	0.2
M01011	5.0	3.6	2.3	11.5	18.0	1.3	2.1	0.8	0.4	44.9	0.2
M01012	2.8	3.0	2.2	10.0	20.6	0.6	2.0	0.8	1.0	43.0	0.6
Mean	3.7	3.6	2.1	11.2	21.2	0.9	1.9	0.6	0.8	46.0	0.2
±S.D.	1.2	0.9	0.2	0.8	4.0	0.3	0.6	0.3	0.4	4.7	0.2
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Male No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
M01008	3.5	14.8	8.1	26.4	1.65	2.6	26.6	0.4	0.2	0.4
M01009	5.8	13.4	11.6	31.0	1.75	1.4	13.2	0.0	0.2	0.0
M01010	3.0	19.6	12.8	35.6	1.24	2.2	17.6	0.4	0.0	0.0
M01011	8.8	17.2	13.4	39.6	1.14	1.7	13.0	0.6	0.0	0.2
M01012	8.2	23.2	8.8	40.8	1.05	3.0	12.4	0.6	0.2	0.0
Mean	5.9	17.6	10.9	34.7	1.37	2.2	16.6	0.4	0.1	0.1
±S.D.	2.6	3.9	2.4	6.0	0.31	0.6	6.0	0.2	0.1	0.2
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

Appendix 26-2-2. Myelogram in male rats at the end of the recovery period

2-IBE (150 mg/kg)

Male No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
M04044	2.6	3.2	4.6	11.5	25.6	1.6	0.8	0.0	0.8	50.7	0.4
M04045	1.6	5.2	1.8	9.0	23.8	0.2	1.6	0.6	1.0	44.8	0.2
M04046	2.5	8.8	1.2	9.7	22.2	1.4	2.7	0.4	1.0	49.8	0.8
M04047	2.3	5.9	4.0	11.2	28.0	0.8	0.8	1.0	0.6	54.5	0.0
M04048	3.4	4.6	3.8	12.8	23.2	0.4	1.4	0.4	0.2	50.2	0.0
Mean	2.5	5.5	3.1	10.8	24.6	0.9	1.5	0.5	0.7	50.0	0.3
±S.D.	0.6	2.1	1.5	1.5	2.3	0.6	0.8	0.4	0.3	3.5	0.3
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Male No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
M04044	5.2	17.1	9.7	32.4	1.56	2.6	13.7	0.4	0.2	0.0
M04045	4.8	18.6	8.8	32.4	1.38	3.8	17.2	0.8	0.6	0.4
M04046	2.9	15.0	7.2	25.9	1.92	4.9	18.7	0.4	0.0	0.4
M04047	5.1	9.9	7.4	22.5	2.42	1.5	21.5	0.0	0.0	0.0
M04048	2.8	16.2	10.0	29.0	1.73	3.0	17.4	0.2	0.2	0.0
Mean	4.2	15.4	8.6	28.4	1.80	3.2	17.7	0.4	0.2	0.2
±S.D.	1.2	3.3	1.3	4.3	0.40	1.3	2.8	0.3	0.2	0.2
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

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

Appendix 27-1-1. Myelogram in female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
F01002	2.1	3.2	8.4	15.2	18.0	0.7	0.9	0.4	0.4	49.3	0.6
F01006	1.9	4.1	3.2	9.9	15.7	1.5	1.5	0.2	1.1	39.0	1.1
F01007	2.8	2.6	6.0	9.0	15.8	1.2	2.2	0.6	1.0	41.2	1.0
F01008	3.5	2.3	6.0	16.9	27.5	0.2	1.0	0.0	0.4	57.8	0.0
F01011	2.2	3.3	5.7	10.6	20.2	1.4	3.3	1.8	1.4	49.7	0.0
Mean	2.5	3.1	5.9	12.3	19.4	1.0	1.8	0.6	0.9	47.4	0.5
±S.D.	0.7	0.7	1.8	3.5	4.9	0.5	1.0	0.7	0.4	7.5	0.5
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Female No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
F01002	12.7	17.4	13.9	44.6	1.11	1.3	3.7	0.9	0.2	0.0
F01006	12.9	26.1	16.0	56.2	0.69	2.2	2.4	0.0	0.2	0.0
F01007	12.6	24.2	15.2	53.0	0.78	2.6	2.2	0.8	0.2	0.0
F01008	8.3	17.2	11.4	37.0	1.56	1.6	3.3	0.2	0.0	0.2
F01011	5.3	19.6	18.4	43.2	1.15	1.8	4.1	0.6	0.4	0.2
Mean	10.4	20.9	15.0	46.8	1.06	1.9	3.1	0.5	0.2	0.1
±S.D.	3.4	4.0	2.6	7.8	0.34	0.5	0.8	0.4	0.1	0.1
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

Appendix 27-1-2. Myelogram in female rats at the end of the dosing period

2-IBE (15 mg/kg)

Female No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
F02013	1.0	5.1	2.7	12.5	17.8	0.8	2.3	1.0	0.6	43.8	0.6
F02015	1.5	3.2	2.3	13.7	19.3	0.8	1.0	0.0	0.2	42.0	0.0
F02017	3.1	3.9	3.7	15.5	15.9	0.8	2.4	0.4	0.8	46.6	0.2
F02020	1.4	2.0	3.6	11.7	19.6	1.4	3.2	0.6	1.0	44.4	0.4
F02021	2.7	2.9	5.2	12.7	20.0	1.9	4.0	1.0	1.3	51.8	0.0
Mean	1.9	3.4	3.5	13.2	18.5	1.1	2.6	0.6	0.8	45.7	0.2
±S.D.	0.9	1.2	1.1	1.5	1.7	0.5	1.1	0.4	0.4	3.8	0.3
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Female No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
F02013	4.3	18.8	16.6	40.2	1.09	2.5	12.3	0.2	0.6	0.4
F02015	4.8	25.2	18.1	48.1	0.87	1.7	7.1	0.6	0.2	0.4
F02017	4.7	22.6	20.2	47.7	0.98	1.8	3.3	0.4	0.2	0.0
F02020	9.7	23.4	15.0	48.5	0.91	0.6	5.3	0.6	0.4	0.2
F02021	5.6	22.5	13.9	42.0	1.23	0.2	5.4	0.4	0.2	0.0
Mean	5.8	22.5	16.8	45.3	1.02	1.4	6.7	0.4	0.3	0.2
±S.D.	2.2	2.3	2.5	3.9	0.15	0.9	3.4	0.2	0.2	0.2
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

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

Appendix 27-1-3. Myelogram in female rats at the end of the dosing period

2-IBE (50 mg/kg)

Female No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
F03026	2.5	1.4	2.9	8.9	16.0	0.8	1.4	0.4	2.5	36.8	0.0
F03027	0.8	2.6	2.4	10.3	16.6	1.0	1.0	0.4	1.2	36.2	1.4
F03029	3.8	2.1	3.6	7.6	13.2	2.1	2.5	0.2	0.8	35.9	0.4
F03032	1.7	3.3	2.3	10.3	16.3	0.8	2.5	0.6	1.6	39.3	1.2
F03035	2.9	3.2	2.3	11.6	17.1	1.3	1.7	1.5	0.2	41.9	0.0
Mean	2.3	2.5	2.7	** 9.7	15.8	1.2	1.8	0.6	1.3	38.0	* 0.6
±S.D.	1.1	0.8	0.6	1.5	1.5	0.5	0.7	0.5	0.9	2.5	0.7
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Female No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
F03026	7.4	26.7	22.8	56.8	0.65	2.9	3.5	0.0	0.0	0.0
F03027	8.1	28.9	17.8	56.2	0.64	2.6	4.4	0.4	0.2	0.0
F03029	13.0	27.1	19.1	59.5	0.60	2.3	1.9	0.4	0.0	0.0
F03032	11.6	25.8	12.8	51.4	0.77	2.1	5.6	0.8	0.0	0.8
F03035	5.1	30.3	16.2	51.6	0.81	1.5	3.8	0.6	0.0	0.6
Mean	9.0	27.8	** 17.7	55.1	* 0.69	2.3	3.8	0.4	0.0	0.3
±S.D.	3.2	1.8	3.7	3.5	0.09	0.5	1.4	0.3	0.1	0.4
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

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

Appendix 27-1-4. Myelogram in female rats at the end of the dosing period

2-IBE (150 mg/kg)

Female No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
F04038	1.6	4.5	2.0	9.9	14.2	1.4	2.6	1.0	0.4	37.5	0.4
F04039	2.6	3.8	2.2	8.4	16.8	1.2	0.4	0.6	1.0	37.0	0.0
F04040	1.4	2.6	0.6	6.0	10.5	2.2	1.8	1.4	1.8	28.2	1.4
F04041	2.2	3.4	2.0	8.6	15.7	0.4	1.8	0.4	1.0	35.5	0.4
F04047	4.0	4.4	1.7	10.0	14.6	1.2	1.7	0.8	1.3	39.7	0.2
Mean	2.4	3.7	1.7	8.6	14.4	1.3	1.7	0.8	1.1	35.6	0.5
±S.D.	1.0	0.8	0.6	1.6	2.4	0.6	0.8	0.4	0.5	4.4	0.5
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Female No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
F04038	9.9	31.8	13.6	55.6	0.67	3.2	3.2	0.6	0.0	0.0
F04039	19.4	28.0	12.2	59.6	0.62	1.2	1.6	0.2	0.2	0.2
F04040	12.7	36.0	13.5	63.6	0.44	2.8	4.6	0.4	0.0	0.4
F04041	5.0	32.3	18.5	56.2	0.63	3.4	5.0	0.0	0.0	0.0
F04047	9.6	29.9	15.7	55.5	0.72	1.9	2.3	0.4	0.2	0.0
Mean	11.3	31.6	14.7	58.1	0.62	2.5	3.3	0.3	0.1	0.1
±S.D.	5.3	3.0	2.5	3.5	0.11	0.9	1.5	0.2	0.1	0.2
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

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

Appendix 27-2-1. Myelogram in female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
F05049	2.3	2.5	4.2	10.9	17.5	0.6	1.7	1.3	0.8	41.7	0.2
F05050	5.2	3.2	2.2	13.5	26.7	2.6	4.2	1.0	2.0	60.6	0.2
F05051	3.2	5.3	1.8	12.7	16.8	1.2	3.0	0.0	2.0	45.9	0.0
F05052	1.6	1.4	5.6	10.6	18.4	1.6	4.6	0.0	0.4	44.2	0.2
F05053	2.2	3.8	4.4	12.3	18.9	1.4	1.8	1.0	0.4	46.1	0.4
Mean	2.9	3.2	3.6	12.0	19.7	1.5	3.1	0.7	1.1	47.7	0.2
±S.D.	1.4	1.5	1.6	1.2	4.0	0.7	1.3	0.6	0.8	7.4	0.1
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Female No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
F05049	6.2	19.4	11.3	37.2	1.12	3.6	16.6	0.8	0.2	0.0
F05050	2.8	12.9	6.8	22.7	2.67	3.6	12.4	0.6	0.0	0.2
F05051	2.6	15.0	13.5	31.1	1.48	3.0	19.4	0.6	0.0	0.0
F05052	8.2	17.6	14.0	40.0	1.11	3.0	12.4	0.2	0.2	0.0
F05053	2.6	15.3	10.3	28.6	1.61	1.0	22.9	1.4	0.0	0.0
Mean	4.5	16.0	11.2	31.9	1.60	2.8	16.7	0.7	0.1	0.0
±S.D.	2.6	2.5	2.9	6.9	0.64	1.1	4.5	0.4	0.1	0.1
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

Appendix 27-2-2. Myelogram in female rats at the end of the dosing period, satellite group

2-IBE (150 mg/kg)

Female No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
F06059	3.4	3.2	2.2	12.8	16.0	1.4	3.2	0.4	1.4	44.0	0.4
F06060	2.4	3.0	2.2	9.8	14.0	0.6	2.2	0.0	0.2	34.4	0.2
F06061	1.8	1.6	2.2	4.8	11.4	0.8	2.0	0.4	0.6	25.6	0.2
F06062	2.4	2.4	7.0	13.2	17.6	0.6	2.4	0.4	1.0	47.0	0.0
F06063	2.2	2.8	2.0	8.4	13.7	0.6	1.0	0.4	0.2	31.3	0.0
Mean	2.4	2.6	3.1	9.8	14.5	0.8	2.2	0.3	0.7	36.5	0.2
±S.D.	0.6	0.6	2.2	3.4	2.4	0.3	0.8	0.2	0.5	8.9	0.2
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Female No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
F06059	5.0	23.0	13.6	42.0	1.05	5.6	8.2	0.2	0.0	0.0
F06060	17.4	16.8	16.2	50.6	0.68	4.0	11.0	0.0	0.0	0.0
F06061	31.4	23.4	11.0	66.0	0.39	1.6	6.2	0.2	0.4	0.0
F06062	7.2	21.6	8.6	37.4	1.26	3.6	11.2	0.6	0.2	0.0
F06063	16.5	26.7	13.7	57.0	0.55	1.6	10.0	0.2	0.0	0.0
Mean	15.5	22.3	12.6	50.6	0.79	3.3	9.3	0.2	0.1	0.0
±S.D.	10.4	3.6	2.9	11.5	0.36	1.7	2.1	0.2	0.2	0.0
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

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

Appendix 27-3-1. Myelogram in female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
F05054	1.9	1.2	3.3	7.0	30.8	0.8	2.9	0.4	2.1	50.4	0.2
F05055	1.1	2.1	2.6	11.7	19.8	1.5	2.6	0.6	1.3	43.4	0.4
F05056	4.5	2.2	4.5	12.8	22.2	1.6	2.6	0.8	0.8	52.0	0.2
F05057	5.3	2.7	3.5	12.3	24.5	0.6	1.6	1.8	2.2	54.4	0.2
F05058	1.7	1.7	3.6	10.3	17.3	1.5	0.8	0.8	1.3	39.0	0.0
Mean	2.9	2.0	3.5	10.8	22.9	1.2	2.1	0.9	1.5	47.8	0.2
±S.D.	1.9	0.6	0.7	2.3	5.2	0.5	0.9	0.5	0.6	6.4	0.1
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Female No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
F05054	7.0	20.0	8.7	35.9	1.41	3.3	9.9	0.6	0.0	0.0
F05055	5.3	11.1	8.3	25.1	1.73	2.6	28.7	0.2	0.0	0.0
F05056	5.3	15.0	10.6	31.1	1.67	3.9	12.4	0.6	0.0	0.0
F05057	5.5	11.2	7.8	24.7	2.21	2.0	17.6	1.2	0.0	0.2
F05058	4.2	18.1	6.9	29.1	1.34	3.2	26.9	0.4	0.6	0.8
Mean	5.5	15.1	8.5	29.2	1.67	3.0	19.1	0.6	0.1	0.2
±S.D.	1.0	4.0	1.4	4.6	0.34	0.7	8.4	0.4	0.3	0.3
(N)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

Appendix 27-3-2. Myelogram in female rats at the end of the recovery period

2-IBE (150 mg/kg)

Female No.	Myeloblast (%)	Promyelocyte (%)	Neutrophilic myelocyte (%)	Neutrophilic metamyelocyte (%)	Neutrophil (%)	Eosinophilic myelocyte (%)	Eosinophilic metamyelocyte (%)	Eosinophil (%)	Basophil, all types (%)	Total granulocyte (%)	Proerythroblast (%)
F06064	2.7	3.1	3.7	11.5	25.8	1.6	1.9	1.2	0.2	51.7	0.0
F06065	3.1	4.3	2.9	12.1	18.6	0.6	1.8	1.0	0.8	45.2	0.0
F06066	1.8	4.0	5.8	11.2	20.4	1.8	1.8	0.6	1.0	48.4	0.0
F06067	4.2	6.6	4.3	16.8	22.9	1.9	3.0	0.2	0.8	60.7	0.2
F06068	1.8	2.6	3.3	12.5	17.2	1.1	1.7	0.4	0.2	40.8	0.2
Mean	2.7	4.1	*	4.0	12.8	1.4	2.0	0.7	0.6	49.4	0.1
±S.D.	1.0	1.5		1.1	2.3	0.5	0.5	0.4	0.4	7.5	0.1
(N)	(5)	(5)		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Female No.	Basophilic erythroblast (%)	Polychromatic erythroblast (%)	Normoblast (%)	Total erythrocyte (%)	Myeloid/ Erythroid	Histiocyte (%)	Lymphocyte (%)	Plasma cell (%)	Megakaryocyte (%)	Mast cell (%)
F06064	4.1	10.7	5.4	20.2	2.56	3.3	23.9	0.8	0.0	0.2
F06065	1.8	7.6	9.2	18.6	2.43	4.5	30.7	0.2	0.2	0.6
F06066	3.8	8.8	11.8	24.4	1.98	2.8	23.6	0.8	0.0	0.0
F06067	2.6	6.6	5.3	14.7	4.12	3.0	19.8	1.5	0.2	0.0
F06068	4.2	16.4	9.4	30.3	1.35	5.5	22.7	0.7	0.0	0.0
Mean	3.3	*	10.0	8.2	21.6	3.8	24.1	0.8	0.1	0.2
±S.D.	1.1		3.9	2.8	6.0	1.1	4.0	0.5	0.1	0.3
(N)	(5)		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

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

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

Appendix 28-1-1. 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01001	5.9	3.8	1.81	150	51	49	89	75	34	0	127	18.4	16	0.6	0.06	367	5.4	9.7	142	3.79	106.2
M01002	6.0	3.6	1.50	144	36	29	66	74	33	0	91	28.6	14	0.5	0.07	293	5.9	9.8	142.3	3.95	105.0
M01003	5.7	3.5	1.59	127	58	19	88	61	30	0	74	7.8	16	0.7	0.04	322	7.0	9.6	143.6	3.98	105.6
M01004	5.8	3.6	1.64	142	45	31	79	57	27	0	180	4.2	14	0.5	0.06	344	6.3	10.0	144.1	3.76	107.4
M01005	5.4	3.4	1.70	139	66	36	99	45	26	0	48	5.9	13	0.5	0.05	278	6.2	9.7	141.7 §	3.99 §	108.3
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.8	3.6	1.65	140	51	33	84	62	30	0	104	13.0	15	0.6	0.06	321.00	6.2	9.8	142.7	3.89	106.5
S.D.	0.2	0.1	0.12	9	12	11	12	13	4	0	51	10.3	1	0.1	0.01	36	0.6	0.2	1.1	0.11	1.3

§: The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

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

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

2-IBE 15 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M02013	5.5	3.4	1.62	146	51	30	78	84	35	0	197	6.2	15	0.5	0.06	295	6.6	9.8	142.5	3.85	106.9
M02014	5.6	3.6	1.80	145	36	66	76	66	36	0	60	9.4	16	0.5	0.06	415	5.5	9.1	142.0	3.86	105.8
M02015	5.4	3.4	1.70	141	31	47	59	68	39	0	46	9.8	17	0.5	0.05	465	6.1	9.6	142.1	3.59	106.3
M02016	5.8	3.4	1.42	133	57	36	81	51	26	0	162	8.9	13	0.5	0.05	356	6.3	9.6	142.9	4.12	106.3
M02017	5.6	3.5	1.67	137	51	34	78	57	32	0	62	8.0	13	0.5	0.05	366	6.2	9.6	142.5	3.96	106.9
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.5	1.64	140	45	43	74	65	34	0	105	8.5	15	0.5	0.05	379	6.1	9.5	142.4	3.88	106.4
S.D.	0.1	0.1	0.14	5	11	15	9	13	5	0	69	1.4	2	0	0.01	64	0.4	0.3	0.4	0.19	0.5
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	DU	AN	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

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

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

Appendix 28-1-3. Biochemical findings of male rats at the end of the dosing period

2-IBE 50 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	Bile acid μ mol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M03025	5.6	3.6	1.80	150	53	63	88	54	29	0	450	8.2	13	0.5	0.07	369	6.9	10.2	143.2	3.97	106.9
M03026	5.3	3.4	1.79	143	58	36	89	54	28	1	56	7.9	16	0.5	0.05	323	6.5	9.3	141.4	3.96	104.5
M03027	5.9	3.6	1.57	144	45	51	80	65	29	0	81	6.6	13	0.5	0.06	366	6.6	9.7	142.6	3.77	105.9
M03028	5.7	3.3	1.38	124	70	43	97	64	27	0	61	5.7	13	0.5	0.04	375	6.5	9.6	142.7	4.02	105.9
M03029	6.2	3.7	1.48	125	52	32	85	59	38	0	191	38.4	13	0.5	0.07	315	6.6	10.4	143.3	3.88	104.9
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.5	1.60	137	56	45	88	59	30	0	168	13.4	14	0.5	0.06	350	6.6	9.8	142.6	3.92	105.6
S.D.	0.3	0.2	0.19	12	9	12	6	5	4	0	167	14.0	1	0	0.01	28	0.2	0.5	0.8	0.10	0.9
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	DU	AN	AN	AN	DU	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

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

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

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

2-IBE 150 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04037	5.9	3.9	1.95	145	34	41	74	109	59	0	279	21.1	13	0.5	0.09	545	7.1	9.8	142.5	3.79	104.1
M04038	5.0	3.3	1.94	140	26	49	57	60	26	0	41	12.3	13	0.5	0.06	310	7.4	9.4	142.5	4.14	107.1
M04039	5.6	3.5	1.67	133	59	42	92	71	26	0	280	4.8	11	0.5	0.05	261	6.8	10.0	142.7	4.09	106.0
M04040	5.9	3.7	1.68	152	48	118	97	103	70	0	94	7.1	11	0.5	0.05	334	6.6	9.6	141.8	3.96	104.4
M04041	5.1	3.2	1.68	104	33	22	57	58	25	0	230	17.4	13	0.4	0.05	344	6.7	9.6	144	4.21	109.4
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.5	1.78	135	40	54	75	80	41	0	185	12.5	12	0.5	0.06	359	6.9	9.7	142.7	4.04	106.2
S.D.	0.4	0.3	0.15	19	13	37	19	24	22	0	111	6.8	1	0	0.02	109	0.3	0.2	0.8	0.17	2.2
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	*	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	DU	AN	AN	AN	AN	DU	AN	AN	AN

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

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

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

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

Appendix 28-2-1. 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01008	5.4	3.6	2.00	161	34	34	69	57	25	0	115	18.7	14	0.6	0.08	378	6.7	9.3	142.2	3.97	105.5
M01009	5.6	3.9	2.29	147	50	25	85	65	29	0	279	9.5	15	0.6	0.08	299	7.4	9.6	142.5	4.16	103.3
M01010	5.7	3.9	2.17	184	56	20	95	51	24	0	117	10.4	13	0.7	0.05	371	7.1	9.6	143.4	6.64	105.1
M01011	5.5	3.8	2.24	157	44	18	73	57	21	0	177	8.1	15	0.6	0.05	356	7.8	9.1	142.5	4.21	104.5
M01012	5.1	3.5	2.19	128	35	14	60	63	23	0	93	7.2	13	0.6	0.07	250	6.4	8.8	144.1	4.05	108.7
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.7	2.18	155	44	22	76	59	24	0	156	10.8	14	0.6	0.07	331	7.1	9.3	142.9	4.61	105.4
S.D.	0.2	0.2	0.11	20	9	8	14	6	3	0	75	4.6	1	0	0.02	55	0.6	0.3	0.8	1.14	2.0

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

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

2-IBE 150 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04044	5.7	3.7	1.85	132	56	17	82	56	25	0	108	11.7	13	0.6	0.04	192	7.4	9.5	143.7	4.19	104.8
M04045	4.9	3.2	1.88	136	38	27	69	48	24	0	60	5.8	14	0.6	0.04	185	6.7	8.4	144.7	3.78	105.7
M04046	5.6	3.9	2.29	162	36	31	67	60	30	0	159	7.0	15	0.6	0.04	249	6.3	9.4	142.5	4.05	106.2
M04047	5.6	3.8	2.11	155	44	33	78	60	23	0	236	7.7	14	0.6	0.04	290	6.7	9.0	142.5	3.99	105.6
M04048	5.8	3.9	2.05	161	42	20	72	63	27	0	91	16.3	18	0.7	0.05	327	6.2	9.2	143.6	3.89	105.9
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.5	3.7	2.04	149	43	26	74	57	26	0	131	9.7	15	0.6	0.04	249	6.7	9.1	143.4	3.98	105.6
S.D.	0.4	0.3	0.18	14	8	7	6	6	3	0	69	4.3	2	0	0	61	0.5	0.4	0.9	0.16	0.5
Significance	NS	NS	NS	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	AW	TT	TT	TT	TT	AW	AW

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

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

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

Appendix 29-1-1. Biochemical findings of female rats at the end of the dosing period

Control (vehicle: water for injection)																					
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F01002	6.2	4.3	2.26	104	53	18	108	78	41	0	87	30.7	16	0.7	0.10	172	8.0	9.8	140.8	4.09	106.8
F01006	5.5	3.9	2.44	118	46	24	88	123	84	0	76	11.2	12	0.6	0.06	124	7.9	10.6	145.3	3.48	108.4
F01007	6.2	4.2	2.10	124	54	24	92	61	31	0	50	9.1	18	0.6	0.07	183	6.5	9.6	140.7	3.80	106.1
F01008	4.9	3.4	2.27	137	39	9	72	99	44	0	201	7.0	11	0.8	0.09	171	7.8	9.4	144.4	3.77	108.9
F01011	5.8	4.0	2.22	128	49	36	96	75	29	0	141	6.8	13	0.6	0.04	158	6.3	9.7	144.2	3.64	110.9
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.7	4.0	2.26	122	48	22	91	87	46	0	111	13.0	14	0.7	0.07	162	7.3	9.8	143.1	3.76	108.2
S.D.	0.5	0.4	0.12	12	6	10	13	24	22	0	60	10.1	3	0.1	0.02	23	0.8	0.5	2.2	0.23	1.9

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

Appendix 29-1-2. Biochemical findings of female rats at the end of the dosing period

2-IBE 15 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F02013	5.8	4.0	2.22	147	49	10	98	84	42	1	80	9.9	13	0.7	0.06	166	6.2	9.3	139.3	4.41	104.3
F02015	6.2	4.3	2.26	145	65	21	119	89	41	0	148	36.0	15	0.6	0.09	168	5.7	9.7	141.2	3.75	106.5
F02017	5.3	3.6	2.12	115	26	34	72	90	46	0	221	28.6	11	0.5	0.07	205	5.2	8.7	141.7	3.40	109.2
F02020	5.6	3.7	1.95	122	57	39	102	104	42	0	282	13.4	21	0.6	0.06	133	7.0	9.6	143.0	3.98	107.6
F02021	6.0	4.2	2.33	122	63	43	123	61	33	0	65	15.1	11	0.6	0.07	110	6.0	9.6	140.9	3.78	106.9
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.8	4.0	2.18	130	52	29	103	86	41	0	159	20.6	14	0.6	0.07	156	6.0	9.4	141.2	3.86	106.9
S.D.	0.3	0.3	0.15	15	16	14	20	16	5	0	92	11.2	4	0.1	0.01	36	0.7	0.4	1.3	0.37	1.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	NS	NS	NS
Statistical method	AN	AN	DU	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	AN	AN	KW	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 2-isobutoxyethanol by oral administration in rats

Appendix 29-1-3. Biochemical findings of female rats at the end of the dosing period

2-IBE 50 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F03026	5.3	3.8	2.53	126	43	58	93	62	39	0	36	6.2	17	0.5	0.05	124	7.4	9.6	140.1	4.13	107.0
F03027	5.5	4.0	2.67	152	58	28	106	65	34	0	54	15.6	12	0.6	0.06	128	6.9	8.8	139.9	4.49	105.3
F03029	6.0	4.2	2.33	104	67	31	128	89	44	0	57	16.0	22	0.6	0.05	152	6.8	9.8	140.8	4.28	106.6
F03032	5.7	3.9	2.17	122	39	39	91	96	45	0	55	12.5	17	0.6	0.05	125	6.6	9.7	141.4	3.76	107.2
F03035	5.8	4.2	2.63	134	52	49	109	95	45	0	167	14.0	19	0.6	0.05	205	7.2	9.8	142.5	3.72	107.5
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.7	4.0	2.47	128	52	41	105	81	41	0	74	12.9	17	0.6	0.05	147	7.0	9.5	140.9	4.08	106.7
S.D.	0.3	0.2	0.21	18	11	13	15	17	5	0	53	4.0	4	0	0	35	0.3	0.4	1.1	0.33	0.9
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
Statistical method	AN	AN	DU	AN	AN	AN	AN	AN	KW	AN	AN	KW	AN	AN	KW	AN	DU	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

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

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

Appendix 29-1-4. Biochemical findings of female rats at the end of the dosing period

2-IBE 150 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F04038	5.5	3.8	2.24	105	37	31	93	111	57	0	166	12.9	16	0.6	0.06	278	6.8	9.1	140.2	4.56	106.9
F04039	5.6	3.9	2.29	124	38	45	89	83	46	0	72	8.5	15	0.5	0.06	141	6.6	9.5	141.8	4.15	105.8
F04040	5.7	3.8	2.00	99	55	43	112	88	36	0	241	13.6	14	0.5	0.06	317	6.0	9.4	141.0	3.79	106.9
F04041	6.1	4.2	2.21	123	52	39	110	72	34	0	367	8.9	15	0.6	0.04	130	6.3	9.3	141.0	4.09	106.9
F04047	5.0	3.5	2.33	116	44	31	88	61	37	0	39	8.0	12	0.4	0.05	147	6.9	9.9	142.3	4.00	106.0
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.8	2.21	113	45	38	98	83	42	0	177	10.4	14	0.5	0.05	203	6.5	9.4	141.3	4.12	106.5
S.D.	0.4	0.3	0.13	11	8	7	12	19	10	0	133	2.7	2	0.1	0.01	88	0.4	0.3	0.8	0.28	0.6
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	AN	AN	AN	AN	AN	KW	AN	AN	KW	AN	AN	KW	AN	DU	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

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

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

Appendix 29-2-1. 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05049	5.3	3.8	2.53	86	35	7	74	85	30	0	58	12.6	16	0.7	0.11	159	5.1	8.7	142.5	3.67	108.7
F05050	5.7	3.8	2.00	143	62	38	113	55	26	1	50	6.4	17	0.6	0.07	223	6.0	9.3	141.1	4.11	107.4
F05051	5.7	4.1	2.56	113	76	13	130	54	15	0	48	10.0	14	0.7	0.08	135	4.6	9.0	143.8	3.48	107.9
F05052	5.9	4.1	2.28	129	76	14	129	60	21	0	91	65.5	21	0.8	0.09	169	4.7	9.4	143.9	3.38	107.7
F05053	5.9	4.0	2.11	113	55	7	106	97	71	0	49	10.3	21	0.7	0.07	147	4.1	8.7	144.6	3.70	110.3
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.7	4.0	2.30	117	61	16	110	70	33	0	59	21.0	18	0.7	0.08	167	4.9	9.0	143.2	3.67	108.4
S.D.	0.2	0.2	0.25	21	17	13	23	20	22	0	18	25.0	3	0.1	0.02	34	0.7	0.3	1.4	0.28	1.2

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

Appendix 29-2-2. Biochemical findings of female rats at the end of the dosing period, satellite group

2-IBE 150 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06059	5.1	3.8	2.92	126	60	20	105	68	26	0	48	16.1	11	0.7	0.07	261	6.2	9.2	140.3	4.44	105.6
F06060	5.4	3.7	2.18	102	56	15	94	52	20	0	30	5.3	19	0.6	0.05	146	4.7	9.2	142.8	3.96	109.0
F06061	5.9	4.3	2.69	136	36	14	85	48	17	0	47	26.1	15	0.6	0.06	164	4.2	9.5	141.2	3.92	106.3
F06062	5.8	4.3	2.87	97	58	17	109	92	38	0	65	22.7	22	0.7	0.06	150	5.2	9.5	141.9	3.79	106.4
F06063	5.2	3.7	2.47	123	32	11	68	57	19	0	32	11.4	18	0.6	0.06	173	5.4	8.9	144.4	3.69	109.3
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.5	4.0	2.63	117	48	15	92	63	24	0	44	16.3	17	0.6	0.06	179	5.1	9.3	142.1	3.96	107.3
S.D.	0.4	0.3	0.31	17	13	3	16	18	9	0	14	8.4	4	0.1	0.01	47	0.8	0.3	1.6	0.29	1.7
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	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 2-isobutoxyethanol by oral administration in rats

Appendix 29-3-1. Biochemical findings of female rats at the end of the recovery period

Control (vehicle: water for injection)																					
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05054	6.0	3.7	1.61	115	56	16	108	92	34	0	106	66.4	18	0.6	0.08	176	5.2	9.7	143.0	3.79	108.8
F05055	5.6	4.1	2.73	134	68	17	122	56	24	0	89	15.2	15	0.6	0.08	149	5.0	9.2	144.6	4.07	110.1
F05056	5.8	4.3	2.87	118	70	14	121	57	20	0	67	13.2	18	0.7	0.10	202	5.1	9.5	144.0	3.68	109.0
F05057	5.7	4.0	2.35	148	65	12	115	51	18	0	51	3.8	15	0.7	0.06	168	5.6	9.4	142.8	3.92	109.1
F05058	5.7	4.1	2.56	110	68	17	118	78	36	0	89	21.8	20	0.7	0.08	176	4.8	9.2	142.9	3.52	108.4
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.8	4.0	2.42	125	65	15	117	67	26	0	80	24.1	17	0.7	0.08	174	5.1	9.4	143.5	3.80	109.1
S.D.	0.2	0.2	0.49	16	6	2	6	17	8	0	21	24.5	2	0.1	0.01	19	0.3	0.2	0.8	0.21	0.6

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

Appendix 29-3-2. Biochemical findings of female rats at the end of the recovery period

2-IBE 150 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	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06064	6.4	4.6	2.56	124	71	13	129	49	23	0	77	17.4	18	0.7	0.10	245	4.8	9.6	143.9	4.12	108.8
F06065	6.2	4.6	2.88	127	77	26	140	55	18	0	207	16.0	15	0.7	0.07	264	5.1	9.5	143.7	3.63	107.6
F06066	5.7	4.2	2.80	139	65	39	121	79	41	0	77	10.3	16	0.6	0.06	224	5.2	9.6	142.7	3.80	108.6
F06067	5.0	3.2	1.78	113	40	15	82	60	20	1	273	8.1	16	0.7	0.06	132	6.3	8.1	143.8	5.22	110.6
F06068	5.9	4.2	2.47	126	64	19	114	81	32	0	134	13.4	19	0.6	0.06	199	5.0	9.5	143.7	3.89	108.3
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	5.8	4.2	2.50	126	63	22	117	65	27	0	154	13.0	17	0.7	0.07	213	5.3	9.3	143.6	4.13	108.8
S.D.	0.5	0.6	0.44	9	14	11	22	14	10	0	85	3.9	2	0.1	0.02	51	0.6	0.7	0.5	0.63	1.1
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
Statistical method	AW	TT	TT	TT	TT	AW	AW	TT	TT	TT	AW	AW	TT	TT	TT	TT	TT	TT	TT	TT	

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

NS: Not significantly different from the control group.

AW: Analysis by Aspin-Welch t-test.

TT: Analysis by Student's t-test.

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

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

Appendix 30-1-1. 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	518.9	2033.7	3.919	343.7	0.662	1690.2	3.257	14074.3	27.123	1593.1	3.070	1610.7	3.104	3203.8	6.174	768.6	1.481
M01002	541.1	2179.3	4.028	247.7	0.458	1379.7	2.550	13079.2	24.172	1922.1	3.552	1836.1	3.393	3758.2	6.945	970.7	1.794
M01003	495.7	2147.9	4.333	290.9	0.587	1622.4	3.273	13474.5	27.183	1530.1	3.087	1582.6	3.193	3112.7	6.279	1157.7	2.335
M01004	504.6	2061.3	4.085	360.6	0.715	1263.9	2.505	13092.7	25.947	1501.3	2.975	1489.6	2.952	2990.9	5.927	835.9	1.657
M01005	460.2	2048.8	4.452	397.0	0.863	1386.1	3.012	12409.1	26.965	1430.1	3.108	1467.2	3.188	2897.3	6.296	699.7	1.520
M01006	439.3	2032.7	4.627	262.1	0.597	1132.7	2.578	11000.4	25.041	1439.6	3.277	1366.3	3.110	2805.9	6.387	711.6	1.620
M01007	502.5	2115.3	4.210	310.5	0.618	1502.1	2.989	12291.6	24.461	1623.6	3.231	1507.0	2.999	3130.6	6.230	862.0	1.715
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	494.6	2088.4	4.236	316.1	0.643	1425.3	2.881	12774.5	25.842	1577.1	3.186	1551.4	3.134	3128.5	6.320	858.0	1.732
S.D.	34.5	59.1	0.250	54.1	0.125	195.9	0.333	990.6	1.294	168.3	0.191	148.7	0.145	310.6	0.311	162.0	0.287

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

Appendix 30-1-1(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	1748.5	3.370	1750.2	3.373	3498.7	6.743	587.2	1.132	601.4	1.159	1188.6	2.291
M01002	1561.5	2.886	1530.5	2.828	3092.0	5.714	701.9	1.297	641.8	1.186	1343.7	2.483
M01003	1683.4	3.396	1664.9	3.359	3348.3	6.755	632.0	1.275	614.6	1.240	1246.6	2.515
M01004	1658.0	3.286	1678.1	3.326	3336.1	6.611	631.0	1.250	631.5	1.251	1262.5	2.502
M01005	1703.4	3.701	1655.7	3.598	3359.1	7.299	627.8	1.364	533.6	1.159	1161.4	2.524
M01006	1619.6	3.687	1588.3	3.616	3207.9	7.302	667.5	1.519	613.7	1.397	1281.2	2.916
M01007	1735.3	3.453	1718.6	3.420	3453.9	6.873	670.6	1.335	662.8	1.319	1333.4	2.654
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1672.8	3.397	1655.2	3.360	3328.0	6.757	645.4	1.310	614.2	1.244	1259.6	2.555
S.D.	66.0	0.275	74.9	0.261	139.4	0.534	37.4	0.118	41.0	0.088	68.1	0.192

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

Appendix 30-1-1(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	420.5	0.810	1622.5	3.127	15.6	0.030	22.4	0.043	23.8	0.046	46.2	0.089
M01002	422.2	0.780	2453.3	4.534	20.0	0.037	33.8	0.062	37.3	0.069	71.1	0.131
M01003	647.6	1.306	1522.9	3.072	30.2	0.061	28.6	0.058	26.2	0.053	54.8	0.111
M01004	728.3	1.443	1748.1	3.464	26.8	0.053	31.9	0.063	37.8	0.075	69.7	0.138
M01005	620.7	1.349	1364.9	2.966	22.3	0.048	22.5	0.049	20.6	0.045	43.1	0.094
M01006	633.7	1.443	1842.1	4.193	13.9	0.032	25.0	0.057	26.3	0.060	51.3	0.117
M01007	667.7	1.329	1757.3	3.497	17.8	0.035	20.7	0.041	23.6	0.047	44.3	0.088
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	591.5	1.209	1758.7	3.550	20.9	0.042	26.4	0.053	27.9	0.056	54.4	0.110
S.D.	121.2	0.288	346.1	0.597	5.9	0.012	5.1	0.009	6.8	0.012	11.7	0.020

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

Appendix 30-1-2. Organ weights of male rats at the end of the dosing period

2-IBE 15 mg/kg																	
Male No.	Body weight (g)	Brain (mg)		Thymus (mg)		Heart (mg)		Liver (mg)		Kidney (R) (mg)		Kidney (L) (mg)		Kidneys (mg)		Spleen (mg)	
M02013	441.4	2054.4	4.654	157.9	0.358	1313.7	2.976	10815.2	24.502	1425.6	3.230	1333.2	3.020	2758.8	6.250	723.9	1.640
M02014	452.0	1979.2	4.379	355.0	0.785	1451.1	3.210	12108.5	26.789	1411.3	3.122	1409.5	3.118	2820.8	6.241	746.4	1.651
M02015	431.1	1997.3	4.633	256.6	0.595	1321.7	3.066	10298.5	23.889	1298.8	3.013	1282.2	2.974	2581.0	5.987	656.2	1.522
M02016	540.6	2036.5	3.767	399.0	0.738	1559.1	2.884	14120.2	26.119	1571.4	2.907	1676.7	3.102	3248.1	6.008	770.2	1.425
M02017	480.6	2047.3	4.260	502.1	1.045	1522.1	3.167	12654.2	26.330	1384.6	2.881	1441.4	2.999	2826.0	5.880	832.9	1.733
M02018	426.1	1940.4	4.554	256.8	0.603	1254.4	2.944	10066.5	23.625	1371.5	3.219	1423.4	3.341	2794.9	6.559	798.4	1.874
M02019	458.8	2019.0	4.401	211.9	0.462	1513.8	3.299	12605.8	27.476	1650.2	3.597	1545.3	3.368	3195.5	6.965	821.6	1.791
M02020	547.7	2120.7	3.872	250.0	0.456	1529.6	2.793	15126.7	27.619	1858.7	3.394	2059.6	3.760	3918.3	7.154	1004.0	1.833
M02021	527.2	2196.0	4.165	447.5	0.849	1541.7	2.924	14295.2	27.115	1668.7	3.165	1683.0	3.192	3351.7	6.358	1165.7	2.211
M02022	473.3	2064.7	4.362	291.4	0.616	1414.7	2.989	11957.7	25.265	1465.0	3.095	1414.0	2.988	2879.0	6.083	1165.2	2.462
M02023	531.0	2062.5	3.884	329.0	0.620	1646.2	3.100	12887.9	24.271	1738.9	3.275	1695.5	3.193	3434.4	6.468	728.5	1.372
M02024	510.5	2011.8	3.941	321.4	0.630	1855.2	3.634	13272.3	25.999	1568.6	3.073	1587.8	3.110	3156.4	6.183	1004.8	1.968
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	485.0	2044.2	4.239	314.9	0.646	1493.6	3.082	12517.4	25.750	1534.4	3.164	1546.0	3.180	3080.4	6.345	868.2	1.790
S.D.	44.5	66.5	0.311	99.2	0.188	162.5	0.226	1583.4	1.411	169.8	0.201	213.3	0.224	376.0	0.390	173.7	0.315
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	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.

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

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

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

Appendix 30-1-2(continued). Organ weights of male rats at the end of the dosing period

2-IBE 15 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	1620.3	3.671	1593.8	3.611	3214.1	7.282	595.0	1.348	577.7	1.309	1172.7	2.657
M02014	1643.7	3.637	1649.6	3.650	3293.3	7.286	549.2	1.215	557.7	1.234	1106.9	2.449
M02015	1608.7	3.732	1609.6	3.734	3218.3	7.465	625.5	1.451	584.5	1.356	1210.0	2.807
M02016	1939.4	3.587	2027.7	3.751	3967.1	7.338	621.9	1.150	680.1	1.258	1302.0	2.408
M02017	1769.3	3.681	1670.2	3.475	3439.5	7.157	680.9	1.417	650.1	1.353	1331.0	2.769
M02018	1656.7	3.888	1587.0	3.724	3243.7	7.613	627.1	1.472	624.9	1.467	1252.0	2.938
M02019	1734.2	3.780	1744.2	3.802	3478.4	7.582	615.9	1.342	633.8	1.381	1249.7	2.724
M02020	1772.6	3.236	1728.5	3.156	3501.1	6.392	647.6	1.182	624.5	1.140	1272.1	2.323
M02021	1643.7	3.118	1646.7	3.123	3290.4	6.241	642.4	1.219	642.6	1.219	1285.0	2.437
M02022	1608.3	3.398	1595.6	3.371	3203.9	6.769	634.2	1.340	613.4	1.296	1247.6	2.636
M02023	1651.3	3.110	1635.1	3.079	3286.4	6.189	574.5	1.082	584.0	1.100	1158.5	2.182
M02024	1703.1	3.336	1698.4	3.327	3401.5	6.663	636.3	1.246	621.8	1.218	1258.1	2.464
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1695.9	3.515	1682.2	3.484	3378.1	6.998	620.9	1.289	616.3	1.278	1237.1	2.566
S.D.	96.3	0.265	120.6	0.266	213.3	0.522	34.7	0.125	34.9	0.104	64.3	0.223
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	KW	AN	KW	AN	KW	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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.

NA: Not analyzed.

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

Appendix 30-1-2(continued). Organ weights of male rats at the end of the dosing period

2-IBE 15 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	587.4	1.331	1891.1	4.284	16.6	0.038	30.4	0.069	28.6	0.065	59.0	0.134
M02014	635.3	1.406	1539.2	3.405	25.8	0.057	25.0	0.055	22.3	0.049	47.3	0.105
M02015	745.7	1.730	1235.5	2.866	27.8	0.064	30.1	0.070	29.3	0.068	59.4	0.138
M02016	612.3	1.133	1450.8	2.684	32.9	0.061	22.7	0.042	29.4	0.054	52.1	0.096
M02017	561.6	1.169	1802.7	3.751	16.5	0.034	25.1	0.052	24.6	0.051	49.7	0.103
M02018	389.6	0.914	1742.7	4.090	17.0	0.040	25.3	0.059	26.9	0.063	52.2	0.123
M02019	824.2	1.796	1947.8	4.245	19.1	0.042	22.6	0.049	27.9	0.061	50.5	0.110
M02020	790.9	1.444	1420.6	2.594	21.0	0.038	24.5	0.045	25.7	0.047	50.2	0.092
M02021	478.2	0.907	1678.5	3.184	18.8	0.036	31.1	0.059	32.9	0.062	64.0	0.121
M02022	507.7	1.073	1629.5	3.443	21.2	0.045	23.7	0.050	25.3	0.053	49.0	0.104
M02023	503.8	0.949	1451.2	2.733	16.6	0.031	22.8	0.043	26.9	0.051	49.7	0.094
M02024	607.7	1.190	1735.9	3.400	16.1	0.032	37.2	0.073	35.6	0.070	72.8	0.143
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	603.7	1.254	1627.1	3.390	20.8	0.043	26.7	0.056	28.0	0.058	54.7	0.114
S.D.	130.6	0.297	212.6	0.606	5.4	0.011	4.5	0.011	3.6	0.008	7.6	0.018
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

Appendix 30-1-3. Organ weights of male rats at the end of the dosing period

2-IBE 50 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)
M03025	570.7	2205.9	3.865	255.4	0.448	1659.9	2.909	15595.2	27.326	1974.4	3.460	1843.1	3.230	3817.5	6.689	1119.7	1.962
M03026	478.2	1967.9	4.115	221.2	0.463	1452.8	3.038	12547.4	26.239	1399.9	2.927	1454.4	3.041	2854.3	5.969	1095.8	2.292
M03027	530.5	2065.1	3.893	387.4	0.730	1474.4	2.779	14400.7	27.146	1603.6	3.023	1574.1	2.967	3177.7	5.990	994.6	1.875
M03028	544.7	2155.6	3.957	350.1	0.643	1652.9	3.035	14205.0	26.079	1644.5	3.019	1665.6	3.058	3310.1	6.077	790.8	1.452
M03029	472.0	2051.1	4.346	357.2	0.757	1463.0	3.100	13163.6	27.889	1849.6	3.919	1684.8	3.569	3534.4	7.488	965.7	2.046
M03030	428.5	2050.3	4.785	270.2	0.631	1260.2	2.941	10359.6	24.176	1347.7	3.145	1443.4	3.368	2791.1	6.514	693.9	1.619
M03031	504.7	2095.5	4.152	310.9	0.616	1436.7	2.847	13159.1	26.073	1393.4	2.761	1356.1	2.687	2749.5	5.448	883.7	1.751
M03032	531.5	1993.3	3.750	304.5	0.573	1733.3	3.261	15470.9	29.108	1964.0	3.695	1868.8	3.516	3832.8	7.211	1339.0	2.519
M03033	508.8	2042.3	4.014	343.9	0.676	1459.8	2.869	15085.5	29.649	1938.7	3.810	2039.3	4.008	3978.0	7.818	887.6	1.744
M03034	462.9	2071.1	4.474	320.5	0.692	1386.9	2.996	11987.6	25.897	1519.8	3.283	1423.3	3.075	2943.1	6.358	794.6	1.717
M03035	497.9	2073.7	4.165	354.2	0.711	1421.4	2.855	12252.9	24.609	1742.3	3.499	1721.1	3.457	3463.4	6.956	979.1	1.966
M03036	533.0	2124.7	3.986	318.4	0.597	1655.9	3.107	15082.3	28.297	1981.7	3.718	1978.4	3.712	3960.1	7.430	1079.0	2.024
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	505.3	2074.7	4.125	316.2	0.628	1504.8	2.978	13609.2	26.874	1696.6	3.355	1671.0	3.307	3367.7	6.662	968.6	1.914
S.D.	39.9	65.4	0.291	47.8	0.097	139.4	0.138	1632.0	1.681	244.6	0.383	227.7	0.368	464.8	0.730	175.9	0.292
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	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.

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

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

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

Appendix 30-1-3(continued). Organ weights of male rats at the end of the dosing period

2-IBE 50 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	1758.1	3.081	1746.0	3.059	3504.1	6.140	654.7	1.147	711.4	1.247	1366.1	2.394
M03026	1626.9	3.402	1653.4	3.458	3280.3	6.860	587.6	1.229	560.3	1.172	1147.9	2.400
M03027	1763.4	3.324	1741.9	3.284	3505.3	6.608	628.2	1.184	589.8	1.112	1218.0	2.296
M03028	1614.1	2.963	1631.7	2.996	3245.8	5.959	547.2	1.005	526.5	0.967	1073.7	1.971
M03029	1559.8	3.305	1556.6	3.298	3116.4	6.603	602.6	1.277	625.2	1.325	1227.8	2.601
M03030	1528.5	3.567	1509.2	3.522	3037.7	7.089	591.7	1.381	572.9	1.337	1164.6	2.718
M03031	1399.0	2.772	1395.7	2.765	2794.7	5.537	572.8	1.135	568.4	1.126	1141.2	2.261
M03032	1742.9	3.279	1648.5	3.102	3391.4	6.381	567.0	1.067	557.6	1.049	1124.6	2.116
M03033	1698.0	3.337	1640.4	3.224	3338.4	6.561	623.0	1.224	604.6	1.188	1227.6	2.413
M03034	1696.7	3.665	1609.5	3.477	3306.2	7.142	644.0	1.391	603.3	1.303	1247.3	2.695
M03035	1463.8	2.940	1443.6	2.899	2907.4	5.839	615.7	1.237	602.7	1.210	1218.4	2.447
M03036	1600.4	3.003	1618.4	3.036	3218.8	6.039	643.6	1.208	633.1	1.188	1276.7	2.395
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1621.0	3.220	1599.6	3.177	3220.5	6.397	606.5	1.207	596.3	1.185	1202.8	2.392
S.D.	117.7	0.269	107.0	0.240	221.5	0.504	34.0	0.113	47.3	0.111	78.0	0.218
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	KW	AN	KW	AN	KW	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

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

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

Appendix 30-1-3(continued). Organ weights of male rats at the end of the dosing period

2-IBE 50 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	734.6	1.287	1650.2	2.892	17.9	0.031	29.0	0.051	28.4	0.050	57.4	0.101
M03026	648.9	1.357	1457.1	3.047	18.5	0.039	21.2	0.044	23.5	0.049	44.7	0.093
M03027	634.0	1.195	1658.0	3.125	21.1	0.040	27.3	0.051	26.7	0.050	54.0	0.102
M03028	643.3	1.181	2153.7	3.954	29.9	0.055	28.7	0.053	30.6	0.056	59.3	0.109
M03029	740.2	1.568	1703.2	3.608	23.0	0.049	24.3	0.051	26.7	0.057	51.0	0.108
M03030	551.7	1.288	1860.4	4.342	13.0	0.030	24.0	0.056	32.0	0.075	56.0	0.131
M03031	518.3	1.027	1398.5	2.771	22.1	0.044	32.1	0.064	30.8	0.061	62.9	0.125
M03032	616.9	1.161	1692.7	3.185	22.8	0.043	24.2	0.046	26.4	0.050	50.6	0.095
M03033	559.9	1.100	1919.4	3.772	15.1	0.030	34.1	0.067	35.6	0.070	69.7	0.137
M03034	635.0	1.372	1953.7	4.221	25.8	0.056	26.2	0.057	28.7	0.062	54.9	0.119
M03035	786.1	1.579	1622.0	3.258	16.4	0.033	22.9	0.046	24.4	0.049	47.3	0.095
M03036	489.5	0.918	1591.7	2.986	20.5	0.038	32.7	0.061	35.2	0.066	67.9	0.127
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	629.9	1.253	1721.7	3.430	20.5	0.041	27.2	0.054	29.1	0.058	56.3	0.112
S.D.	91.2	0.199	215.4	0.533	4.7	0.009	4.2	0.007	3.9	0.009	7.7	0.015
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

Appendix 30-1-4. Organ weights of male rats at the end of the dosing period

2-IBE 150 mg/kg																	
Male No.	Body weight (g)	Brain (mg)		Thymus (mg)		Heart (mg)		Liver (mg)		Kidney (R) (mg)		Kidney (L) (mg)		Kidneys (mg)		Spleen (mg)	
M04037	450.2	2085.7	4.633	203.6	0.452	1348.5	2.995	11234.5	24.954	1615.7	3.589	1463.1	3.250	3078.8	6.839	1150.6	2.556
M04038	453.5	1870.4	4.124	242.5	0.535	1465.4	3.231	11768.6	25.951	1555.4	3.430	1676.8	3.697	3232.2	7.127	1168.1	2.576
M04039	498.4	1978.6	3.970	223.5	0.448	1446.1	2.901	14530.9	29.155	1781.0	3.573	1779.5	3.570	3560.5	7.144	1892.0	3.796
M04040	556.0	1995.0	3.588	304.9	0.548	1538.3	2.767	16027.3	28.826	1584.7	2.850	1538.2	2.767	3122.9	5.617	1237.3	2.225
M04041	420.5	1925.1	4.578	215.5	0.512	1231.6	2.929	9916.3	23.582	1406.5	3.345	1404.8	3.341	2811.3	6.686	1129.9	2.687
M04042	529.1	2098.4	3.966	373.8	0.706	1828.2	3.455	16286.7	30.782	2057.9	3.889	1981.4	3.745	4039.3	7.634	1451.7	2.744
M04043	510.7	2048.6	4.011	467.7	0.916	1723.5	3.375	14518.7	28.429	1598.9	3.131	1601.9	3.137	3200.8	6.267	1552.0	3.039
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	488.3	2000.3	4.124	290.2	0.588	1511.7	3.093	13469.0	27.383	1657.2	3.401	1635.1	3.358	3292.3	6.759	1368.8	2.803
S.D.	48.5	83.9	0.368	98.8	0.168	207.1	0.261	2490.6	2.591	208.0	0.338	198.2	0.346	397.4	0.659	281.8	0.501
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	**
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	DU

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

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

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

Appendix 30-1-4(continued). Organ weights of male rats at the end of the dosing period

2-IBE 150 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	1774.4	3.941	1719.1	3.819	3493.5	7.760	731.4	1.625	688.7	1.530	1420.1	3.154
M04038	1522.5	3.357	1520.6	3.353	3043.1	6.710	628.0	1.385	589.8	1.301	1217.8	2.685
M04039	1315.8	2.640	1291.0	2.590	2606.8	5.230	539.4	1.082	543.3	1.090	1082.7	2.172
M04040	1651.4	2.970	1693.5	3.046	3344.9	6.016	651.2	1.171	624.0	1.122	1275.2	2.294
M04041	1404.7	3.341	1377.9	3.277	2782.6	6.617	631.7	1.502	573.7	1.364	1205.4	2.867
M04042	1700.0	3.213	1646.7	3.112	3346.7	6.325	590.4	1.116	661.6	1.250	1252.0	2.366
M04043	1935.3	3.790	1974.9	3.867	3910.2	7.657	695.2	1.361	661.5	1.295	1356.7	2.657
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1614.9	3.322	1603.4	3.295	3218.3	6.616	638.2	1.320	620.4	1.279	1258.6	2.599
S.D.	215.6	0.448	229.7	0.447	443.7	0.891	63.6	0.205	53.4	0.148	109.1	0.346
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	KW	AN	KW	AN	KW	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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.

NA: Not analyzed.

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

Appendix 30-1-4(continued). Organ weights of male rats at the end of the dosing period

2-IBE 150 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	644.7	1.432	1946.5	4.324	15.3	0.034	20.7	0.046	23.2	0.052	43.9	0.098
M04038	762.9	1.682	1640.0	3.616	22.1	0.049	28.3	0.062	30.6	0.067	58.9	0.130
M04039	653.9	1.312	1827.1	3.666	19.5	0.039	34.9	0.070	33.6	0.067	68.5	0.137
M04040	755.2	1.358	2196.4	3.950	27.6	0.050	31.0	0.056	32.3	0.058	63.3	0.114
M04041	642.2	1.527	2002.6	4.762	16.2	0.039	26.7	0.063	27.1	0.064	53.8	0.128
M04042	483.7	0.914	1310.1	2.476	20.8	0.039	25.4	0.048	22.8	0.043	48.2	0.091
M04043	469.8	0.920	1450.2	2.840	26.6	0.052	27.8	0.054	28.9	0.057	56.7	0.111
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	630.3	1.306	1767.6	3.662	21.2	0.043	27.8	0.057	28.4	0.058	56.2	0.116
S.D.	116.4	0.292	316.5	0.797	4.7	0.007	4.4	0.009	4.2	0.009	8.5	0.017
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

Appendix 30-2-1. 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	1901.1	4.081	242.9	0.521	1318.7	2.831	11072.7	23.771	1436.6	3.084	1414.1	3.036	2850.7	6.120	879.6	1.888
M01009	565.1	2057.2	3.640	186.4	0.330	1662.2	2.941	13829.7	24.473	1757.4	3.110	1766.5	3.126	3523.9	6.236	767.7	1.359
M01010	442.7	1999.8	4.517	242.0	0.547	1299.3	2.935	11442.6	25.847	1351.2	3.052	1406.7	3.178	2757.9	6.230	736.0	1.663
M01011	458.1	1930.8	4.215	295.6	0.645	1397.2	3.050	11208.4	24.467	1515.2	3.308	1478.4	3.227	2993.6	6.535	817.2	1.784
M01012	465.2	1938.5	4.167	239.3	0.514	1289.2	2.771	9983.1	21.460	1365.0	2.934	1317.5	2.832	2682.5	5.766	718.9	1.545
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	479.4	1965.5	4.124	241.2	0.511	1393.3	2.906	11507.3	24.004	1485.1	3.098	1476.6	3.080	2961.7	6.177	783.9	1.648
S.D.	48.8	62.6	0.316	38.6	0.114	156.2	0.108	1414.1	1.609	165.6	0.136	171.9	0.156	335.0	0.277	65.3	0.206

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

Appendix 30-2-1(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	1878.3	4.032	1811.6	3.889	3689.9	7.922	675.4	1.450	647.6	1.390	1323.0	2.840
M01009	1909.7	3.379	1907.9	3.376	3817.6	6.756	673.9	1.193	695.6	1.231	1369.5	2.423
M01010	1777.8	4.016	1831.4	4.137	3609.2	8.153	616.6	1.393	623.1	1.407	1239.7	2.800
M01011	1617.1	3.530	1551.8	3.387	3168.9	6.917	588.9	1.286	601.1	1.312	1190.0	2.598
M01012	1651.5	3.550	1688.2	3.629	3339.7	7.179	600.4	1.291	632.5	1.360	1232.9	2.650
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1766.9	3.701	1758.2	3.684	3525.1	7.385	631.0	1.323	640.0	1.340	1271.0	2.662
S.D.	131.0	0.302	139.8	0.329	265.1	0.620	41.0	0.100	35.4	0.071	73.1	0.167

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

Appendix 30-2-1(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	432.0	0.927	915.8	1.966	25.9	0.056	26.5	0.057	25.8	0.055	52.3	0.112
M01009	732.3	1.296	1432.7	2.535	17.5	0.031	29.7	0.053	31.9	0.056	61.6	0.109
M01010	745.0	1.683	1324.0	2.991	18.1	0.041	23.0	0.052	25.7	0.058	48.7	0.110
M01011	534.2	1.166	1312.6	2.865	18.1	0.040	20.4	0.045	23.1	0.050	43.5	0.095
M01012	512.1	1.101	1216.4	2.615	13.6	0.029	21.2	0.046	22.7	0.049	43.9	0.094
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	591.1	1.235	1240.3	2.594	18.6	0.039	24.2	0.051	25.8	0.054	50.0	0.104
S.D.	140.0	0.284	196.9	0.397	4.5	0.011	3.9	0.005	3.7	0.004	7.4	0.009

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

Appendix 30-2-2. Organ weights of male rats at the end of the recovery period

2-IBE 150 mg/kg

Male No.	Body weight (g)	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	517.9	675.3	1.304	1983.3	3.830	15.1	0.029	34.8	0.067	34.0	0.066	68.8	0.133
M04045	488.0	540.9	1.108	1278.0	2.619	21.2	0.043	24.6	0.050	26.0	0.053	50.6	0.104
M04046	513.6	790.4	1.539	2033.2	3.959	18.8	0.037	20.3	0.040	21.0	0.041	41.3	0.080
M04047	596.9	556.2	0.932	999.8	1.675	19.1	0.032	32.1	0.054	32.8	0.055	64.9	0.109
M04048	478.2	411.9	0.861	1452.1	3.037	12.8	0.027	21.6	0.045	25.0	0.052	46.6	0.097
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	518.9	594.9	1.149	1549.3	3.024	17.4	0.034	26.7	0.051	27.8	0.053	54.4	0.105
S.D.	46.7	143.7	0.277	449.3	0.936	3.4	0.006	6.4	0.010	5.5	0.009	11.9	0.019
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

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

NA: Not analyzed.

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

Appendix 30-2-2(continued). Organ weights of male rats at the end of the recovery period

2-IBE 150 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	1672.2	3.229	1604.6	3.098	3276.8	6.327	695.8	1.344	613.8	1.185	1309.6	2.529
M04045	1735.8	3.557	1677.6	3.438	3413.4	6.995	616.5	1.263	626.2	1.283	1242.7	2.547
M04046	1547.9	3.014	1606.5	3.128	3154.4	6.142	647.0	1.260	578.0	1.125	1225.0	2.385
M04047	1903.1	3.188	2027.2	3.396	3930.3	6.585	640.3	1.073	647.0	1.084	1287.3	2.157
M04048	1476.3	3.087	1551.4	3.244	3027.7	6.331	572.0	1.196	583.8	1.221	1155.8	2.417
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1667.1	3.215	1693.5	3.261	3360.5	6.476	634.3	1.227	609.8	1.180	1244.1	2.407
S.D.	166.6	0.209	191.9	0.153	349.2	0.330	45.2	0.101	29.0	0.078	59.8	0.156
Significance	NS	*	NS	*	NS	*	NS	NS	NS	**	NS	*
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

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

NA: Not analyzed.

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

Appendix 30-2-2(continued). Organ weights of male rats at the end of the recovery period

2-IBE 150 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	675.3	1.304	1983.3	3.830	15.1	0.029	34.8	0.067	34.0	0.066	68.8	0.133
M04045	540.9	1.108	1278.0	2.619	21.2	0.043	24.6	0.050	26.0	0.053	50.6	0.104
M04046	790.4	1.539	2033.2	3.959	18.8	0.037	20.3	0.040	21.0	0.041	41.3	0.080
M04047	556.2	0.932	999.8	1.675	19.1	0.032	32.1	0.054	32.8	0.055	64.9	0.109
M04048	411.9	0.861	1452.1	3.037	12.8	0.027	21.6	0.045	25.0	0.052	46.6	0.097
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	594.9	1.149	1549.3	3.024	17.4	0.034	26.7	0.051	27.8	0.053	54.4	0.105
S.D.	143.7	0.277	449.3	0.936	3.4	0.006	6.4	0.010	5.5	0.009	11.9	0.019
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

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

NA: Not analyzed.

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

Appendix 31-1-1. 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	272.3	1921.9	7.058	145.9	0.536	1084.3	3.982	9715.2	35.678	914.3	3.358	900.0	3.305	1814.3	6.663	870.9	3.198
F01002	313.3	1964.6	6.271	139.4	0.445	879.8	2.808	9613.7	30.685	997.7	3.184	975.2	3.113	1972.9	6.297	674.9	2.154
F01003	316.0	1883.7	5.961	225.4	0.713	981.0	3.104	9537.5	30.182	907.9	2.873	899.3	2.846	1807.2	5.719	674.7	2.135
F01004	274.1	1830.6	6.679	100.7	0.367	923.2	3.368	8797.4	32.096	878.1	3.204	851.9	3.108	1730.0	6.312	738.9	2.696
F01005	311.7	1870.2	6.000	212.7	0.682	918.1	2.945	9299.4	29.834	1033.6	3.316	997.9	3.201	2031.5	6.517	611.6	1.962
F01006	292.6	1816.4	6.208	127.9	0.437	945.8	3.232	9343.7	31.933	875.9	2.994	905.5	3.095	1781.4	6.088	681.0	2.327
F01007	329.0	1838.1	5.587	145.9	0.443	1056.4	3.211	9610.6	29.212	953.6	2.898	1027.4	3.123	1981.0	6.021	712.5	2.166
F01008	277.0	2001.7	7.226	64.0	0.231	874.0	3.155	9310.6	33.612	1054.5	3.807	955.4	3.449	2009.9	7.256	525.5	1.897
F01009	296.8	1834.9	6.182	188.6	0.635	1025.3	3.455	10112.8	34.073	928.3	3.128	914.0	3.080	1842.3	6.207	654.4	2.205
F01010	297.9	1825.7	6.129	146.7	0.492	976.5	3.278	10007.7	33.594	974.8	3.272	898.2	3.015	1873.0	6.287	673.0	2.259
F01011	320.5	1872.2	5.841	182.5	0.569	999.8	3.120	9026.8	28.165	992.5	3.097	1013.2	3.161	2005.7	6.258	701.1	2.188
F01012	371.8	2079.7	5.594	297.9	0.801	1111.8	2.990	11362.5	30.561	1306.2	3.513	1202.4	3.234	2508.6	6.747	880.3	2.368
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	306.1	1895.0	6.228	164.8	0.529	981.3	3.221	9644.8	31.635	984.8	3.220	961.7	3.144	1946.5	6.364	699.9	2.296
S.D.	27.9	82.2	0.521	61.7	0.161	77.5	0.300	656.5	2.249	116.4	0.263	93.3	0.149	204.5	0.395	98.2	0.348

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

Appendix 31-1-1(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	42.2	0.155	36.6	0.134	78.8	0.289	616.5	2.264	21.4	0.079	32.6	0.120	31.3	0.115	63.9	0.235
F01002	42.9	0.137	52.5	0.168	95.4	0.305	468.3	1.495	12.9	0.041	34.5	0.110	35.4	0.113	69.9	0.223
F01003	57.6	0.182	54.0	0.171	111.6	0.353	653.6	2.068	21.4	0.068	31.8	0.101	31.5	0.100	63.3	0.200
F01004	57.6	0.210	55.9	0.204	113.5	0.414	669.4	2.442	13.6	0.050	30.1	0.110	29.0	0.106	59.1	0.216
F01005	41.0	0.132	34.6	0.111	75.6	0.243	518.1	1.662	19.2	0.062	31.4	0.101	37.1	0.119	68.5	0.220
F01006	64.5	0.220	78.9	0.270	143.4	0.490	736.0	2.515	17.3	0.059	32.4	0.111	39.8	0.136	72.2	0.247
F01007	64.7	0.197	46.4	0.141	111.1	0.338	631.0	1.918	26.0	0.079	33.0	0.100	35.7	0.109	68.7	0.209
F01008	48.3	0.174	56.0	0.202	104.3	0.377	638.8	2.306	13.7	0.049	29.5	0.106	32.3	0.117	61.8	0.223
F01009	39.1	0.132	61.3	0.207	100.4	0.338	824.3	2.777	14.8	0.050	31.2	0.105	31.0	0.104	62.2	0.210
F01010	48.9	0.164	41.4	0.139	90.3	0.303	778.9	2.615	22.3	0.075	32.8	0.110	31.6	0.106	64.4	0.216
F01011	67.0	0.209	45.4	0.142	112.4	0.351	695.0	2.168	19.3	0.060	30.5	0.095	34.5	0.108	65.0	0.203
F01012	45.0	0.121	66.9	0.180	111.9	0.301	762.6	2.051	19.9	0.054	28.5	0.077	32.6	0.088	61.1	0.164
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	51.6	0.169	52.5	0.172	104.1	0.342	666.0	2.190	18.5	0.061	31.5	0.104	33.5	0.110	65.0	0.214
S.D.	10.2	0.035	12.8	0.044	18.1	0.064	103.8	0.379	4.1	0.013	1.7	0.011	3.1	0.012	4.0	0.020

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

Appendix 31-1-2. Organ weights of female rats at the end of the dosing period

2-IBE 15 mg/kg																	
Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	298.9	1893.5	6.335	153.8	0.515	955.7	3.197	9961.0	33.326	892.0	2.984	935.6	3.130	1827.6	6.114	721.2	2.413
F02014	301.9	1941.7	6.432	176.5	0.585	951.1	3.150	10654.2	35.290	968.8	3.209	963.3	3.191	1932.1	6.400	748.5	2.479
F02015	305.3	1792.9	5.873	251.7	0.824	947.0	3.102	9510.9	31.153	964.3	3.159	930.9	3.049	1895.2	6.208	626.2	2.051
F02016	286.0	1863.6	6.516	169.6	0.593	877.9	3.070	9034.4	31.589	1022.2	3.574	983.8	3.440	2006.0	7.014	681.6	2.383
F02017	336.7	1976.3	5.870	252.8	0.751	1095.2	3.253	11405.2	33.873	1086.8	3.228	1092.9	3.246	2179.7	6.474	677.0	2.011
F02018	350.7	1925.6	5.491	248.3	0.708	1079.7	3.079	10492.2	29.918	1229.9	3.507	1220.2	3.479	2450.1	6.986	902.4	2.573
F02019	312.0	1947.6	6.242	182.4	0.585	968.4	3.104	9926.4	31.815	1034.0	3.314	981.0	3.144	2015.0	6.458	672.7	2.156
F02020	299.1	1965.5	6.571	237.0	0.792	1021.9	3.417	9292.0	31.067	1027.4	3.435	1036.6	3.466	2064.0	6.901	683.2	2.284
F02021	320.7	1875.9	5.849	227.1	0.708	1097.6	3.423	9848.7	30.710	969.7	3.024	1017.3	3.172	1987.0	6.196	743.4	2.318
F02022	310.8	1885.0	6.065	318.8	1.026	1013.8	3.262	9192.6	29.577	1062.1	3.417	1057.5	3.403	2119.6	6.820	671.7	2.161
F02024	298.4	1979.9	6.635	245.4	0.822	961.6	3.223	10307.1	34.541	967.5	3.242	927.7	3.109	1895.2	6.351	926.2	3.104
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	311.0	1913.4	6.171	223.9	0.719	997.3	3.207	9965.9	32.078	1020.4	3.281	1013.3	3.257	2033.8	6.538	732.2	2.358
S.D.	18.8	57.3	0.368	48.7	0.147	70.8	0.125	712.8	1.901	88.3	0.189	87.3	0.159	172.5	0.333	96.7	0.304
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	KW	AN	KW	AN	AN	AN	DT	KW	DU	AN	DU	AN	DU	AN	DU	DT	DT

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

NS: Not significantly different from the control group.

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

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

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

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

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

Appendix 31-1-2(continued). Organ weights of female rats at the end of the dosing period

2-IBE 15 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	42.0	0.141	50.8	0.170	92.8	0.310	518.4	1.734	11.2	0.037	41.6	0.139	43.8	0.147	85.4	0.286
F02014	59.1	0.196	50.5	0.167	109.6	0.363	446.4	1.479	13.6	0.045	41.0	0.136	44.3	0.147	85.3	0.283
F02015	46.6	0.153	37.2	0.122	83.8	0.274	660.8	2.164	12.8	0.042	39.8	0.130	40.1	0.131	79.9	0.262
F02016	45.5	0.159	47.0	0.164	92.5	0.323	602.6	2.107	15.3	0.053	33.4	0.117	39.2	0.137	72.6	0.254
F02017	64.5	0.192	64.4	0.191	128.9	0.383	668.3	1.985	19.4	0.058	31.3	0.093	34.0	0.101	65.3	0.194
F02018	44.2	0.126	60.7	0.173	104.9	0.299	654.8	1.867	16.3	0.046	33.8	0.096	38.2	0.109	72.0	0.205
F02019	42.2	0.135	47.1	0.151	89.3	0.286	633.9	2.032	10.3	0.033	38.8	0.124	37.7	0.121	76.5	0.245
F02020	42.9	0.143	50.6	0.169	93.5	0.313	645.6	2.158	15.7	0.052	33.4	0.112	45.1	0.151	78.5	0.262
F02021	51.0	0.159	49.7	0.155	100.7	0.314	541.4	1.688	18.5	0.058	35.4	0.110	35.6	0.111	71.0	0.221
F02022	43.8	0.141	44.2	0.142	88.0	0.283	585.1	1.883	18.1	0.058	27.5	0.088	35.1	0.113	62.6	0.201
F02024	62.3	0.209	51.6	0.173	113.9	0.382	645.9	2.165	18.4	0.062	28.4	0.095	33.1	0.111	61.5	0.206
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	49.5	0.159	50.3	0.162	99.8	0.321	600.3	1.933	15.4	0.049	34.9	0.113	38.7	0.125	73.7	0.238
S.D.	8.5	0.027	7.3	0.018	13.5	0.039	71.1	0.227	3.1	0.010	4.9	0.018	4.2	0.018	8.3	0.034
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	*	NS
Statistical method	AN	KW	AN	KW	AN	KW	AN	AN	AN	AN	KW	AN	DU	AN	DT	AN

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

NS: Not significantly different from the control group.

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

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

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

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

NA: Not analyzed.

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

Appendix 31-1-3. Organ weights of female rats at the end of the dosing period

2-IBE 50 mg/kg																	
Female No.	Body weight (g)	Brain (mg)		Thymus (mg)		Heart (mg)		Liver (mg)		Kidney (R) (mg)		Kidney (L) (mg)		Kidneys (mg)		Spleen (mg)	
F03025	306.6	1820.6	5.938	152.3	0.497	1013.6	3.306	9533.8	31.095	1001.6	3.267	984.9	3.212	1986.5	6.479	825.0	2.691
F03026	293.8	1881.2	6.403	204.3	0.695	932.4	3.174	9078.9	30.902	964.8	3.284	926.9	3.155	1891.7	6.439	1348.8	4.591
F03027	307.4	1816.8	5.910	174.7	0.568	1008.3	3.280	9663.4	31.436	854.4	2.779	856.9	2.788	1711.3	5.567	1134.5	3.691
F03028	306.2	1889.4	6.170	92.1	0.301	971.5	3.173	10181.2	33.250	1007.0	3.289	1009.4	3.297	2016.4	6.585	838.3	2.738
F03029	303.4	1777.5	5.859	216.7	0.714	1011.2	3.333	10853.6	35.773	1029.3	3.393	1016.2	3.349	2045.5	6.742	711.0	2.343
F03030	321.9	1971.4	6.124	326.2	1.013	1110.7	3.450	10075.2	31.299	1042.0	3.237	1058.1	3.287	2100.1	6.524	1165.1	3.619
F03031	312.1	1873.7	6.004	153.9	0.493	989.9	3.172	9717.0	31.134	948.5	3.039	918.0	2.941	1866.5	5.980	999.5	3.202
F03032	315.3	1871.5	5.936	202.6	0.643	1125.8	3.571	9666.6	30.658	1001.8	3.177	1009.9	3.203	2011.7	6.380	944.1	2.994
F03033	308.6	1864.9	6.043	175.2	0.568	1035.4	3.355	10060.4	32.600	1002.1	3.247	974.7	3.158	1976.8	6.406	743.9	2.411
F03034	306.1	1880.5	6.143	123.3	0.403	1021.6	3.337	10248.9	33.482	929.5	3.037	912.1	2.980	1841.6	6.016	1297.7	4.239
F03035	299.7	1864.4	6.221	237.8	0.793	1070.8	3.573	9765.6	32.585	915.6	3.055	900.4	3.004	1816.0	6.059	722.7	2.411
F03036	308.9	1866.1	6.041	267.4	0.866	965.3	3.125	9993.4	32.352	1054.7	3.414	1086.5	3.517	2141.2	6.932	719.6	2.330
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	307.5	1864.8	6.066	193.9	0.630	1021.4	3.321	9903.2	32.214	979.3	3.185	971.2	3.158	1950.4	6.342	954.2	3.105
S.D.	7.1	47.2	0.155	63.9	0.201	57.5	0.151	441.6	1.466	58.5	0.180	69.0	0.201	126.3	0.376	232.6	0.773
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	**
Statistical method	KW	AN	KW	AN	AN	AN	DT	KW	DU	AN	DU	AN	DU	AN	DU	DT	DT

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

NS: Not significantly different from the control group.

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

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

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

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

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

Appendix 31-1-3(continued). Organ weights of female rats at the end of the dosing period

2-IBE 50 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	51.6	0.168	57.1	0.186	108.7	0.355	671.4	2.190	17.4	0.057	36.7	0.120	41.2	0.134	77.9	0.254
F03026	51.6	0.176	46.5	0.158	98.1	0.334	722.6	2.459	14.1	0.048	27.9	0.095	28.2	0.096	56.1	0.191
F03027	62.3	0.203	59.2	0.193	121.5	0.395	657.3	2.138	17.8	0.058	32.0	0.104	32.3	0.105	64.3	0.209
F03028	56.9	0.186	39.5	0.129	96.4	0.315	560.6	1.831	11.5	0.038	35.6	0.116	40.0	0.131	75.6	0.247
F03029	54.6	0.180	51.9	0.171	106.5	0.351	537.1	1.770	18.3	0.060	45.2	0.149	47.1	0.155	92.3	0.304
F03030	63.3	0.197	50.2	0.156	113.5	0.353	714.4	2.219	14.2	0.044	35.3	0.110	38.8	0.121	74.1	0.230
F03031	48.6	0.156	57.0	0.183	105.6	0.338	673.7	2.159	13.4	0.043	33.8	0.108	35.0	0.112	68.8	0.220
F03032	53.9	0.171	66.7	0.212	120.6	0.382	602.4	1.911	16.2	0.051	37.6	0.119	40.0	0.127	77.6	0.246
F03033	64.7	0.210	46.5	0.151	111.2	0.360	793.0	2.570	15.7	0.051	37.1	0.120	41.6	0.135	78.7	0.255
F03034	54.9	0.179	68.1	0.222	123.0	0.402	733.6	2.397	10.2	0.033	41.7	0.136	46.7	0.153	88.4	0.289
F03035	54.3	0.181	43.7	0.146	98.0	0.327	694.7	2.318	20.3	0.068	30.7	0.102	33.8	0.113	64.5	0.215
F03036	52.4	0.170	50.1	0.162	102.5	0.332	554.8	1.796	21.9	0.071	38.5	0.125	38.9	0.126	77.4	0.251
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	55.8	0.181	53.0	0.172	108.8	0.354	659.6	2.147	15.9	0.052	36.0	0.117	38.6	0.126	74.6	0.243
S.D.	5.1	0.016	8.8	0.028	9.4	0.027	80.3	0.269	3.5	0.012	4.7	0.015	5.6	0.018	10.2	0.032
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	*	NS
Statistical method	AN	KW	AN	KW	AN	KW	AN	AN	AN	AN	KW	AN	DU	AN	DT	AN

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

NS: Not significantly different from the control group.

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

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

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

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

NA: Not analyzed.

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

Appendix 31-1-4. Organ weights of female rats at the end of the dosing period

2-IBE 150 mg/kg																	
Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04037	286.3	1947.1	6.801	189.7	0.663	958.3	3.347	8029.0	28.044	989.8	3.457	944.1	3.298	1933.9	6.755	874.5	3.054
F04038	305.0	1856.3	6.086	186.8	0.612	1165.7	3.822	10538.1	34.551	1106.4	3.628	1052.1	3.450	2158.5	7.077	1186.0	3.889
F04039	307.0	1968.4	6.412	178.4	0.581	1170.4	3.812	9938.4	32.373	1112.5	3.624	1117.1	3.639	2229.6	7.263	1470.4	4.790
F04040	323.9	1953.4	6.031	287.9	0.889	1089.7	3.364	10028.5	30.962	1061.1	3.276	990.0	3.056	2051.1	6.333	1482.0	4.575
F04041	286.6	1981.8	6.915	248.0	0.865	1015.1	3.542	9633.6	33.613	881.7	3.076	928.3	3.239	1810.0	6.315	939.1	3.277
F04042	294.7	1954.7	6.633	154.4	0.524	1045.7	3.548	10431.0	35.395	1050.1	3.563	1048.3	3.557	2098.4	7.120	1269.2	4.307
F04043	329.2	1973.7	5.995	163.3	0.496	1096.0	3.329	11460.1	34.812	1077.9	3.274	1108.3	3.367	2186.2	6.641	924.7	2.809
F04044	235.5	1817.5	7.718	139.0	0.590	857.4	3.641	8033.1	34.111	909.9	3.864	889.0	3.775	1798.9	7.639	877.0	3.724
F04045	309.4	1905.8	6.160	149.8	0.484	1074.4	3.473	10963.3	35.434	1098.6	3.551	1047.2	3.385	2145.8	6.935	966.0	3.122
F04046	287.6	1908.9	6.637	254.2	0.884	942.4	3.277	10079.3	35.046	1093.5	3.802	1094.0	3.804	2187.5	7.606	716.8	2.492
F04047	288.6	1837.2	6.366	209.7	0.727	948.2	3.286	10317.4	35.750	1062.2	3.681	1094.2	3.791	2156.4	7.472	1581.5	5.480
F04048	325.9	2015.4	6.184	167.3	0.513	1116.0	3.424	12325.8	37.821	1180.1	3.621	1152.2	3.535	2332.3	7.156	1305.6	4.006
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	298.3	1926.7	6.495	194.0	0.652	1039.9	3.489	10148.1	33.993	1052.0	3.535	1038.7	3.491	2090.7	7.026	1132.7	3.794
S.D.	25.3	62.1	0.493	46.8	0.154	97.2	0.190	1231.4	2.545	85.7	0.229	83.3	0.236	164.7	0.448	286.4	0.889
Significance	NS	NS	NS	NS	NS	NS	**	NS	*	NS	**	NS	**	NS	**	**	**
Statistical method	KW	AN	KW	AN	AN	AN	DT	KW	DU	AN	DU	AN	DU	AN	DU	DT	DT

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

NS: Not significantly different from the control group.

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

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

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

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

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

Appendix 31-1-4(continued). Organ weights of female rats at the end of the dosing period

2-IBE 150 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04037	53.4	0.187	51.9	0.181	105.3	0.368	818.3	2.858	16.3	0.057	23.8	0.083	26.5	0.093	50.3	0.176
F04038	51.7	0.170	53.4	0.175	105.1	0.345	774.2	2.538	14.0	0.046	39.0	0.128	42.2	0.138	81.2	0.266
F04039	53.7	0.175	42.2	0.137	95.9	0.312	759.5	2.474	17.7	0.058	31.0	0.101	36.6	0.119	67.6	0.220
F04040	47.6	0.147	55.1	0.170	102.7	0.317	565.6	1.746	17.5	0.054	38.5	0.119	42.8	0.132	81.3	0.251
F04041	44.5	0.155	59.2	0.207	103.7	0.362	527.5	1.841	11.7	0.041	31.3	0.109	36.3	0.127	67.6	0.236
F04042	53.2	0.181	55.6	0.189	108.8	0.369	767.1	2.603	16.1	0.055	27.9	0.095	31.2	0.106	59.1	0.201
F04043	49.7	0.151	51.0	0.155	100.7	0.306	490.0	1.488	15.6	0.047	35.1	0.107	39.2	0.119	74.3	0.226
F04044	38.1	0.162	43.3	0.184	81.4	0.346	543.1	2.306	15.1	0.064	31.1	0.132	31.5	0.134	62.6	0.266
F04045	54.7	0.177	60.5	0.196	115.2	0.372	653.3	2.112	24.1	0.078	40.4	0.131	35.8	0.116	76.2	0.246
F04046	51.3	0.178	39.9	0.139	91.2	0.317	564.9	1.964	12.9	0.045	37.0	0.129	38.5	0.134	75.5	0.263
F04047	51.2	0.177	49.3	0.171	100.5	0.348	652.6	2.261	21.7	0.075	33.3	0.115	37.0	0.128	70.3	0.244
F04048	57.7	0.177	42.7	0.131	100.4	0.308	726.5	2.229	10.7	0.033	29.9	0.092	35.2	0.108	65.1	0.200
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	50.6	0.170	50.3	0.170	100.9	0.339	653.6	2.202	16.1	0.054	33.2	0.112	36.1	0.121	69.3	0.233
S.D.	5.2	0.013	6.9	0.024	8.6	0.026	113.4	0.394	3.9	0.013	5.0	0.017	4.6	0.014	9.2	0.029
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	AN	KW	AN	KW	AN	AN	AN	AN	KW	AN	DU	AN	DT	AN

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

NS: Not significantly different from the control group.

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

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

DT: Analysis by Dunnett type mean rank test.

DU: Analysis by Dunnett's test.

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

NA: Not analyzed.

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

Appendix 31-2-1. 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	275.1	1796.7	6.531	187.2	0.680	786.1	2.858	6452.0	23.453	873.2	3.174	837.7	3.045	1710.9	6.219	556.1	2.021
F05050	335.5	1866.0	5.562	370.4	1.104	919.0	2.739	8047.7	23.987	1066.8	3.180	1117.3	3.330	2184.1	6.510	596.4	1.778
F05051	266.8	1831.5	6.865	225.8	0.846	834.7	3.129	6780.6	25.415	904.0	3.388	894.4	3.352	1798.4	6.741	611.4	2.292
F05052	253.7	1842.8	7.264	286.0	1.127	844.3	3.328	6677.7	26.321	855.1	3.371	878.2	3.462	1733.3	6.832	567.4	2.236
F05053	282.9	1986.8	7.023	423.9	1.498	912.2	3.224	7123.4	25.180	812.5	2.872	841.4	2.974	1653.9	5.846	499.3	1.765
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	282.8	1864.8	6.649	298.7	1.051	859.3	3.056	7016.3	24.871	902.3	3.197	913.8	3.233	1816.1	6.430	566.1	2.018
S.D.	31.4	72.7	0.663	98.4	0.311	56.0	0.249	625.3	1.150	97.7	0.208	116.3	0.211	212.1	0.403	43.4	0.247

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

Appendix 31-2-1(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	68.9	0.250	43.3	0.157	112.2	0.408	371.4	1.350	10.1	0.037	33.1	0.120	36.7	0.133	69.8	0.254
F05050	37.5	0.112	41.4	0.123	78.9	0.235	562.5	1.677	13.9	0.041	31.2	0.093	34.1	0.102	65.3	0.195
F05051	38.9	0.146	41.2	0.154	80.1	0.300	1015.3	3.805	11.5	0.043	32.6	0.122	32.6	0.122	65.2	0.244
F05052	38.2	0.151	49.0	0.193	87.2	0.344	948.9	3.740	12.7	0.050	27.4	0.108	29.7	0.117	57.1	0.225
F05053	53.5	0.189	32.1	0.113	85.6	0.303	800.2	2.829	18.3	0.065	36.1	0.128	38.7	0.137	74.8	0.264
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	47.4	0.170	41.4	0.148	88.8	0.318	739.7	2.680	13.3	0.047	32.1	0.114	34.4	0.122	66.4	0.236
S.D.	13.7	0.053	6.1	0.032	13.5	0.064	269.5	1.139	3.1	0.011	3.2	0.014	3.5	0.014	6.5	0.027

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

Appendix 31-2-2. Organ weights of female rats at the end of the dosing period, satellite group

2-IBE 150 mg/kg																	
Female No.	Body weight (g)	Brain (mg)		Thymus (mg)		Heart (mg)		Liver (mg)		Kidney (R) (mg)		Kidney (L) (mg)		Kidneys (mg)		Spleen (mg)	
F06059	287.8	1969.0	6.842	397.9	1.383	949.4	3.299	7791.5	27.073	951.0	3.304	921.0	3.200	1872.0	6.505	922.3	3.205
F06060	288.6	1908.0	6.611	401.0	1.389	939.2	3.254	8471.7	29.354	946.2	3.279	949.8	3.291	1896.0	6.570	1123.3	3.892
F06061	279.0	1876.0	6.724	333.4	1.195	1050.8	3.766	7701.7	27.605	952.4	3.414	916.7	3.286	1869.1	6.699	738.4	2.647
F06062	279.9	1944.5	6.947	286.6	1.024	912.5	3.260	8066.9	28.821	926.2	3.309	895.8	3.200	1822.0	6.509	782.9	2.797
F06063	296.2	1806.1	6.098	349.5	1.180	1104.3	3.728	7576.0	25.577	1033.8	3.490	949.9	3.207	1983.7	6.697	1088.8	3.676
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	286.3	1900.7	6.644	353.7	1.234	991.2	3.461	7921.6	27.686	961.9	3.359	926.6	3.237	1888.6	6.596	931.1	3.243
S.D.	7.1	63.6	0.330	47.8	0.154	82.1	0.262	356.5	1.492	41.5	0.090	23.2	0.047	59.6	0.097	173.9	0.540
Significance	NS	NS	NS	NS	NS	*	*	*	*	NS	NS	NS	NS	NS	NS	**	**
Statistical method	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	AW	AW	AW	AW	TT

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

NS: Not significantly different from the control group.

AW: Analysis by Aspin-Welch t-test.

TT: Analysis by Student's t-test.

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

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

Appendix 31-2-2(continued). Organ weights of female rats at the end of the dosing period, satellite group

2-IBE 150 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	31.6	0.110	49.6	0.172	81.2	0.282	652.9	2.269	16.0	0.056	32.6	0.113	36.7	0.128	69.3	0.241
F06060	41.3	0.143	33.3	0.115	74.6	0.258	438.5	1.519	24.4	0.085	34.0	0.118	36.3	0.126	70.3	0.244
F06061	57.4	0.206	55.1	0.197	112.5	0.403	1033.4	3.704	14.6	0.052	23.9	0.086	30.7	0.110	54.6	0.196
F06062	34.8	0.124	26.9	0.096	61.7	0.220	479.9	1.715	10.9	0.039	25.0	0.089	26.3	0.094	51.3	0.183
F06063	59.6	0.201	59.3	0.200	118.9	0.401	368.1	1.243	12.8	0.043	32.4	0.109	37.5	0.127	69.9	0.236
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	44.9	0.157	44.8	0.156	89.8	0.313	594.6	2.090	15.7	0.055	29.6	0.103	33.5	0.117	63.1	0.220
S.D.	12.9	0.044	14.1	0.048	24.8	0.084	266.8	0.977	5.2	0.018	4.7	0.015	4.8	0.015	9.3	0.028
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

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.

NA: Not analyzed.

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

Appendix 31-3-1. 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	278.1	1865.6	6.708	272.7	0.981	970.7	3.490	8662.5	31.149	921.2	3.312	906.7	3.260	1827.9	6.573	1237.6	4.450
F05055	293.3	1981.5	6.756	261.4	0.891	822.3	2.804	6584.8	22.451	958.2	3.267	908.4	3.097	1866.6	6.364	573.4	1.955
F05056	338.1	1968.3	5.822	282.6	0.836	934.5	2.764	7631.4	22.571	943.8	2.791	917.3	2.713	1861.1	5.505	558.9	1.653
F05057	293.7	1864.7	6.349	200.2	0.682	893.9	3.044	7189.5	24.479	880.5	2.998	826.4	2.814	1706.9	5.812	544.9	1.855
F05058	295.5	1694.9	5.736	215.7	0.730	922.1	3.120	6841.4	23.152	838.7	2.838	782.0	2.646	1620.7	5.485	636.2	2.153
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	299.7	1875.0	6.274	246.5	0.824	908.7	3.044	7381.9	24.760	908.5	3.041	868.2	2.906	1776.6	5.948	710.2	2.413
S.D.	22.6	114.8	0.480	36.4	0.121	55.6	0.292	816.5	3.661	48.8	0.240	60.6	0.262	108.4	0.498	296.9	1.153

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

Appendix 31-3-1(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	67.8	0.244	36.6	0.132	104.4	0.375	873.1	3.140	13.0	0.047	28.6	0.103	35.7	0.128	64.3	0.231
F05055	44.2	0.151	37.1	0.126	81.3	0.277	817.0	2.786	18.0	0.061	33.9	0.116	33.7	0.115	67.6	0.230
F05056	52.5	0.155	43.2	0.128	95.7	0.283	395.9	1.171	21.0	0.062	31.8	0.094	33.1	0.098	64.9	0.192
F05057	49.9	0.170	60.6	0.206	110.5	0.376	459.4	1.564	15.0	0.051	29.2	0.099	29.5	0.100	58.7	0.200
F05058	27.4	0.093	29.9	0.101	57.3	0.194	332.2	1.124	16.1	0.054	26.6	0.090	25.4	0.086	52.0	0.176
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	48.4	0.163	41.5	0.139	89.8	0.301	575.5	1.957	16.6	0.055	30.0	0.100	31.5	0.105	61.5	0.206
S.D.	14.6	0.054	11.7	0.040	21.2	0.077	250.9	0.942	3.0	0.006	2.9	0.010	4.1	0.016	6.2	0.024

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

Appendix 31-3-2. Organ weights of female rats at the end of the recovery period

2-IBE 150 mg/kg																	
Female No.	Body weight (g)	Brain (mg)		Thymus (mg)		Heart (mg)		Liver (mg)		Kidney (R) (mg)		Kidney (L) (mg)		Kidneys (mg)		Spleen (mg)	
F06064	304.8	1800.7	5.908	252.5	0.828	921.5	3.023	6820.4	22.377	1008.0	3.307	970.5	3.184	1978.5	6.491	673.7	2.210
F06065	318.6	1848.1	5.801	317.1	0.995	959.9	3.013	8173.3	25.654	990.6	3.109	898.8	2.821	1889.4	5.930	731.4	2.296
F06066	334.0	1907.1	5.710	298.0	0.892	1170.4	3.504	8520.8	25.511	1000.8	2.996	997.0	2.985	1997.8	5.981	729.3	2.184
F06067	314.3	1697.1	5.400	260.5	0.829	967.4	3.078	8102.7	25.780	1032.0	3.283	955.0	3.038	1987.0	6.322	565.1	1.798
F06068	295.4	1945.2	6.585	419.3	1.419	1062.1	3.595	8032.9	27.193	1240.4	4.199	1186.8	4.018	2427.2	8.217	667.6	2.260
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	313.4	1839.6	5.881	309.5	0.993	1016.3	3.243	7930.0	25.303	1054.4	3.379	1001.6	3.209	2056.0	6.588	673.4	2.150
S.D.	14.6	97.0	0.437	66.9	0.248	100.5	0.283	648.0	1.770	105.1	0.476	109.6	0.470	212.0	0.940	67.5	0.201
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	*	NS	*	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	AW

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

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

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

Appendix 31-3-2(continued). Organ weights of female rats at the end of the recovery period

2-IBE 150 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	39.1	0.128	42.9	0.141	82.0	0.269	782.8	2.568	15.7	0.052	32.7	0.107	30.4	0.100	63.1	0.207
F06065	48.7	0.153	40.7	0.128	89.4	0.281	596.9	1.874	15.0	0.047	32.1	0.101	33.8	0.106	65.9	0.207
F06066	43.2	0.129	41.3	0.124	84.5	0.253	1401.0	4.195	11.4	0.034	35.8	0.107	40.3	0.121	76.1	0.228
F06067	55.0	0.175	53.8	0.171	108.8	0.346	401.3	1.277	20.7	0.066	30.6	0.097	32.5	0.103	63.1	0.201
F06068	50.7	0.172	41.0	0.139	91.7	0.310	461.4	1.562	14.9	0.050	35.6	0.121	36.6	0.124	72.2	0.244
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	47.3	0.151	43.9	0.141	91.3	0.292	728.7	2.295	15.5	0.050	33.4	0.107	34.7	0.111	68.1	0.217
S.D.	6.3	0.023	5.6	0.018	10.5	0.037	403.4	1.166	3.3	0.011	2.3	0.009	3.8	0.011	5.8	0.018
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

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

NA: Not analyzed.

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

Appendix 32-1. Macroscopic findings of male rats at the end of the dosing period

Findings	Group	Control (Vehicle)							2-IBE 15 mg/kg														2-IBE 50 mg/kg														2-IBE 150 mg/kg							
	Animal No.	M01001	M01002	M01003	M01004	M01005	M01006	M01007	M02013	M02014	M02015	M02016	M02017	M02018	M02019	M02020	M02021	M02022	M02023	M02024	M03025	M03026	M03027	M03028	M03029	M03030	M03031	M03032	M03033	M03034	M03035	M03036	M04037	M04038	M04039	M04040	M04041	M04042	M04043					
Epididymis																																												
Nodule, yellowish white, caudal, unilateral		-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P			
Forestomach																																												
Edematous, mucosa		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	P	-			
Kidney																																												
Pale colored area, bilateral		-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Spleen																																												
Enlargement		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	P	P	P	P			
Notes) - : No abnormal changes P : Non-graded change																																												
Vehicle: water for injection																																												

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

Appendix 32-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group	Control (Vehicle)					2-IBE 150 mg/kg				
	Animal No.	M01	M01	M01	M01	M01	M04	M04	M04	M04	M04
		008	009	010	011	012	044	045	046	047	048
Kidney											
Enlargement, bilateral		-	-	-	-	-	P	-	-	-	-
Skin											
Alopecia, both forelimbs		-	-	-	-	-	P	-	-	-	-
Spleen											
Enlargement		-	-	-	-	-	-	-	P	P	-
Notes) - : No abnormal changes P : Non-graded change											
Vehicle: water for injection											

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

Appendix 33-1. Macroscopic findings of female rats at the end of the dosing period

[illegible]

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

Appendix 33-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)					2-IBE 150 mg/kg				
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		049	050	051	052	053	059	060	061	062	063
Forestomach											
Edematous, mucosa		-	-	-	-	-	-	-	P	-	-
Spleen											
Enlargement		-	-	-	-	-	P	P	P	-	P
Notes) -: No abnormal changes P : Non-graded change											
Vehicle: water for injection											

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

Appendix 33-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		F05 054	F05 055	F05 056	F05 057	F05 058	F06 064	F06 065	F06 066	F06 067	F06 068
Kidney											
Enlargement, bilateral		-	-	-	-	-	-	-	-	-	P
Rough surface, bilateral		-	-	-	-	-	-	-	-	-	P
Spleen											
Enlargement		-	-	-	-	-	-	P	-	-	-
Rough surface, adhesion with connective tissue	P	-	-	-	-	-	-	-	-	-	-
Notes) - : No abnormal changes P : Non-graded change											
Vehicle: water for injection											

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

Appendix 34-1. Histopathological findings of male rats at the end of the dosing period

[illegible]

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

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

Findings	Group Animal No.	Control (Vehicle)						2-IBE 15 mg/kg												2-IBE 50 mg/kg												2-IBE 150 mg/kg																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
		M01	M01	M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Vehicle: water for injection

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

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

[illegible]

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

Appendix 34-2. Histopathological findings of male rats at the end of the recovery period

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
Brain		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Vehicle: water for injection

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

Appendix 34-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
Liver											
Deposit, pigment, brown, Kupffer cell		-	-	-	-	-	-	±	-	-	-
Fatty change, hepatocyte, periportal		±	±	-	-	±	±	±	-	+	±
Hyperplasia, bile duct		-	-	-	-	±	-	-	-	-	-
Microgranuloma		±	±	±	±	±	±	±	±	-	-
Single cell necrosis		-	±	-	-	-	-	-	±	-	-
Pancreas		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Duodenum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen											
Deposit, pigment, brown		+	2+	2+	2+	2+	+	2+	2+	2+	2+
Hematopoiesis, extramedullary		+	2+	±	+	2+	+	±	±	±	±
Increase, red pulp		-	-	-	-	-	-	-	-	±	-

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Vehicle: water for injection

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

Appendix 34-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
Kidney											
Basophilic tubule, cortex		±	±	±	-	±	-	-	-	±	±
Cellular infiltration, lymphocyte, interstitial		-	-	±	-	-	-	-	-	-	-
Deposit, pigment, brown, proximal tubule		-	-	-	-	-	-	±	±	±	±
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Testis		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Epididymis		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Prostate		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Seminal vesicle		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Coagulating gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur											
Hyperplasia, erythroblast		-	-	-	-	-	-	-	±	±	-
Skin											
Atrophy, hair follicle									±		

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Vehicle: water for injection

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

Appendix 35-1. Histopathological findings of female rats at the end of the dosing period

[illegible]

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

Appendix 35-1(continued). Histopathological findings of female rats at the end of the dosing period

[illegible]

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate : blanks, Subjected to autopsy on day 5 of lactation; NP, Not pregnant.

Vehicle: water for injection

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

Appendix 35-1(continued). Histopathological findings of female rats at the end of the dosing period

[illegible]

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

Appendix 35-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063
Brain		-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-
Pituitary gland Remnant, Rathke's pouch		-	-	P	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-
Thyroid gland Ectopic thymic tissue		-	-	P	-	P	-	-	-	-	-
Parathyroid gland		-	-	-	-	-	-	-	-	-	-
Thymus		-	-	-	-	-	-	-	-	-	-
Heart Cellular infiltration, mononuclear cell, septum, focal		-	-	-	-	-	-	-	-	±	-
Trachea		-	-	-	-	-	-	-	-	-	-
Lung Accumulation, foam cell, alveolus		-	-	-	-	-	±	-	-	-	-
Granuloma, foreign body		±	-	-	-	-	-	-	-	-	-
Bronchus		-	-	-	-	-	-	-	-	-	-

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Vehicle: water for injection

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

Appendix 35-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		049	050	051	052	053	059	060	061	062	063
Liver											
Deposit, pigment, brown, Kupffer cell		-	-	-	-	-	+	+	+	+	+
Fatty change, hepatocyte, periportal		±	-	±	±	±	-	-	±	-	±
Hematopoiesis, extramedullary		-	-	-	-	-	±	±	±	±	±
Microgranuloma		±	±	±	±	-	-	-	±	±	±
Single cell necrosis		-	-	-	-	-	-	-	-	±	-
Pancreas											
		-	-	-	-	-	-	-	-	-	-
Stomach											
		-	-	-	-	-	-	-	-	-	-
Duodenum											
		-	-	-	-	-	-	-	-	-	-
Jejunum											
		-	-	-	-	-	-	-	-	-	-
Ileum											
		-	-	-	-	-	-	-	-	-	-
Cecum											
		-	-	-	-	-	-	-	-	-	-
Colon											
		-	-	-	-	-	-	-	-	-	-
Rectum											
		-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric											
		-	-	-	-	-	-	-	-	-	-
Spleen											
Deposit, pigment, brown		2+	2+	2+	2+	2+	2+	2+	2+	2+	2+
Hematopoiesis, extramedullary		±	±	±	±	±	3+	2+	3+	2+	3+
Increase, red pulp		-	-	-	-	-	±	+	-	-	±

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Vehicle: water for injection

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

Appendix 35-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		049	050	051	052	053	059	060	061	062	063
Kidney											
Basophilic tubule, cortex		-	-	-	±	-	-	-	-	-	-
Cellular infiltration, lymphocyte, interstitial		-	-	-	±	-	-	-	-	-	-
Deposit, pigment, brown, proximal tubule		-	-	-	-	-	+	+	+	±	+
Mineralization, medulla		-	-	-	-	-	±	-	-	-	-
Urinary bladder											
		-	-	-	-	-	-	-	-	-	-
Adrenal gland											
		-	-	-	-	-	-	-	-	-	-
Ovary											
		-	-	-	-	-	-	-	-	-	-
Uterus											
		-	-	-	-	-	-	-	-	-	-
Vagina											
		-	-	-	-	-	-	-	-	-	-
Eyeball											
		-	-	-	-	-	-	-	-	-	-
Harderian gland											
Cellular infiltration, lymphocyte, interstitial		±	-	-	-	-	-	-	-	-	-
Sciatic nerve											
		-	-	-	-	-	-	-	-	-	-
Skeletal muscle											
		-	-	-	-	-	-	-	-	-	-
Femur											
		-	-	-	-	-	-	-	-	-	-
Marrow, femur											
Hyperplasia, erythroblast		-	-	-	-	-	-	±	+	±	+

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Vehicle: water for injection

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

Appendix 35-3. Histopathological findings of female rats at the end of the recovery period

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		054	055	056	057	058	064	065	066	067	068
Brain		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Vehicle: water for injection

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

Appendix 35-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		054	055	056	057	058	064	065	066	067	068
Liver											
Deposit, pigment, brown, Kupffer cell		-	-	-	-	-	±	±	±	±	±
Fatty change, hepatocyte, periportal		-	-	±	-	-	-	±	-	-	-
Hematopoiesis, extramedullary		±	-	-	-	-	-	-	-	-	-
Microgranuloma		±	±	±	±	±	±	±	±	±	-
Pancreas											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Duodenum											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric											
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen											
Deposit, pigment, brown		2+	2+	2+	2+	2+	2+	2+	2+	2+	+
Edema, capsule, with infiltration of inflammatory cell		+	-	-	-	-	-	-	-	-	-
Hematopoiesis, extramedullary		2+	±	±	±	+	±	±	±	±	±

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Vehicle: water for injection

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

Appendix 35-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group Animal No.	Control (Vehicle)					2-IBE 150 mg/kg				
		F05	F05	F05	F05	F05	F06	F06	F06	F06	F06
		054	055	056	057	058	064	065	066	067	068
Kidney											
Basophilic tubule, cortex		-	-	-	-	±	-	-	-	-	±
Cellular infiltration, lymphocyte, interstitial		±	-	-	-	-	±	-	-	-	-
Deposit, pigment, brown, proximal tubule		-	-	-	-	-	±	±	±	±	±
Mineralization, medulla		-	-	-	-	-	-	±	-	-	-
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ovary		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Uterus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Vagina		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur											
Hyperplasia, erythroblast		-	-	-	-	-	-	-	±	-	±
Notes) - : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked											
P : Non-graded change NE: Not examined M: Missing A: Autolysis											
Vehicle: water for injection											

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

Appendix 36-1. Results of observations about estrous cycle

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	E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1	
F01002	E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1	
F01003	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 PL	1	
F01004	D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1	
F01005	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 E D D P PL	2	
F01006	E D D P E D D P E D D P E	4-day	4.0	D D D P E D D P E D D D P E	4/5-day	4.5	PL	1	
F01007	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1	
F01008	E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1	
F01009	E D D P E E D D P E D D P	4/5-day	4.5	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1	
F01010	P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1	
F01011	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1	
F01012	E D D P E D D D P E D D D	4/5-day	4.5	P E D D D P E D D D P E D D	5-day	5.0	P PL	1	
Mean			4.2			4.2		1.1	
S.D.			0.3			0.4		0.3	
(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 2-isobutoxyethanol by oral administration in rats

Appendix 36-2. Results of observations about estrous cycle

2-IBE (15 mg/kg)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period			Stage	Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)		
F02013	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F02014	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 D E	4-day	4.0	D D P D D D PL	1
F02015	P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F02016	D 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 D E	4-day	4.0	D D P PL	1
F02017	P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F02018	E D D D P E D D P E D D P	4/5-day	4.5	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F02019	D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F02020	E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F02021	E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F02022	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
F02023	E D D D P E D D P E D D P	4/5-day	4.5	E D D P E D D P E D D P E D	4-day	4.0	D P E PL	1
F02024	D D E D D D E D D D E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
Mean			4.1			4.0		1.0
S.D.			0.2			0.0		0.0
(N)			(12)			(12)		(12)

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

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

Appendix 36-3. Results of observations about estrous cycle

2-IBE (50 mg/kg)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period			Stage	Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)		
F03025	D D E D D D P E D D D P E	5-day	5.0	D D D P E D D D P E D D D E	4/5-day	4.5	D D P PL	1
F03026	D D D E D D D E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F03027	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 P E E D D D	5-day	5.0	P PL	1
F03028	D P E D D P E D D D E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F03029	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F03030	D D E D D D E D D P E D D	4-day	4.0	D E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F03031	P E D D D E D D P E D D D	4-day	4.0	E D D P E D D P E D D D E D	4-day	4.0	D P PL	1
F03032	D D P E D D D E D D D E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F03033	E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03034	E D D P E D D P E D D P E	4-day	4.0	D D P E D D D E D D P E D D	4-day	4.0	P PL	1
F03035	D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F03036	E D D P E D D P E D D P E	4-day	4.0	D D D E D D P E D D P E D D	4-day	4.0	P PL	1
Mean			4.2			4.1		1.0
S.D.			0.4			0.3		0.0
(N)			(12)			(12)		(12)

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

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

Appendix 36-4. Results of observations about estrous cycle

2-IBE (150 mg/kg)

Z-DE (150 mg/kg)									
Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F04037	D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1	
F04038	D D P E D D P E D D P E D	4-day	4.0	D D D E D D P E D D P E D D	4-day	4.0	P PL	1	
F04039	D D P E D D P E D D P E D	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1	
F04040	P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1	
F04041	E D D P E D D P E D D P E	4-day	4.0	D D D E D D P E D D P E D D	4-day	4.0	P PL	1	
F04042	D D E D D P E D D P E D D	4-day	4.0	D E D D P E D D P E D D P E	4-day	4.0	D D P PL	1	
F04043	P E D D D P E D D P E D D	4/5-day	4.5	P E D D P E D D P E D D D E	4-day	4.0	D D P PL	1	
F04044	D D D P E D D P E D D P E	4-day	4.0	E D D D D D D D D D D D D D	uncycle		D D P PL	1	
F04045	E D D D E D D D E D D D E	4-day	4.0	D D D E D D P E D D P E D D	4-day	4.0	P PL	1	
F04046	D D D E D D D E D D D E D	4-day	4.0	D D E D D D P E D D P E D	irregular	5.0	D P PL	1	
F04047	D D P E D D P E D D P E D	4-day	4.0	D D E D D P E D D P E D D P	4-day	4.0	PL	1	
F04048	P E D D D E D D P E D D D	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	
Mean			4.0			4.1		1.0	
S.D.			0.1			0.3		0.0	
(N)			(12)			(11)		(12)	

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

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

Appendix 37-1. Results of observations about reproductive performance

Control (vehicle: water for injection)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M01001	F01001	+	+	2
M01002	F01002	+	+	2
M01003	F01003	+	+	2
M01004	F01004	+	+	4
M01005	F01005	+	+	6
M01006	F01006	+	+	1
M01007	F01007	+	+	1
M01008	F01008	+	+	2
M01009	F01009	+	+	3
M01010	F01010	+	+	3
M01011	F01011	+	+	1
M01012	F01012	+	+	2
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.4
S.D.				1.4
(N)				(12)

+, confirmed

-, not confirmed

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

Appendix 37-2. Results of observations about reproductive performance

2-IBE (15 mg/kg)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M02013	F02013	+	+	1
M02014	F02014	+	+	7
M02015	F02015	+	+	3
M02016	F02016	+	+	4
M02017	F02017	+	+	3
M02018	F02018	+	+	3
M02019	F02019	+	+	4
M02020	F02020	+	+	2
M02021	F02021	+	+	2
M02022	F02022	+	+	2
M02023	F02023	+	-	4
M02024	F02024	+	+	4
Total		+: 12, -: 0	+: 11, -: 1	
Mean				3.3
S.D.				1.5
(N)				(12)

+, confirmed

-, not confirmed

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

Appendix 37-3. Results of observations about reproductive performance

2-IBE (50 mg/kg)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M03025	F03025	+	+	4
M03026	F03026	+	+	1
M03027	F03027	+	+	2
M03028	F03028	+	+	4
M03029	F03029	+	+	1
M03030	F03030	+	+	4
M03031	F03031	+	+	3
M03032	F03032	+	+	1
M03033	F03033	+	+	2
M03034	F03034	+	+	2
M03035	F03035	+	+	1
M03036	F03036	+	+	2
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.3
S.D.				1.2
(N)				(12)

+, confirmed

-, not confirmed

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

Appendix 37-4. Results of observations about reproductive performance

2-IBE (150 mg/kg)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M04037	F04037	+	+	4
M04038	F04038	+	+	2
M04039	F04039	+	+	2
M04040	F04040	+	+	3
M04041	F04041	+	+	2
M04042	F04042	+	+	4
M04043	F04043	+	+	4
M04044	F04044	+	+	4
M04045	F04045	+	+	2
M04046	F04046	+	+	3
M04047	F04047	+	+	1
M04048	F04048	+	+	3
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.8
S.D.				1.0
(N)				(12)

+, confirmed

-, not confirmed

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

Appendix 38-1. Observation of offspring (F₁)

Control (vehicle: water for injection)																					
Dam No.	Gestation length	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring				External abnormalities ^{b)}			
						Number of offspring	Sex ratio			Dead offspring				4 days		Sex ratio	Viability index (%)	(Number)	(%)		
							Live	Male	Female					Total							
F01001	23	13	13	100.0	+	13	7	6	13	0.54	0	100.0	100.0	100.0	7	6	0.54	100.0	0	0.0	
F01002	22	17	16	94.1	+	16	9	7	16	0.56	0	100.0	100.0	100.0	9	7	0.56	100.0	0	0.0	
F01003	23	17	17	100.0	+	14	9	5	14	0.64	0	82.4	82.4	100.0	9	5	0.64	100.0	0	0.0	
F01004	22	17	16	94.1	+	16	5	11	16	0.31	0	100.0	100.0	100.0	5	11	0.31	100.0	0	0.0	
F01005	22	15	14	93.3	+	14	5	9	14	0.36	0	100.0	100.0	100.0	5	9	0.36	100.0	0	0.0	
F01006	22	18	18	100.0	+	17	11	6	17	0.65	0	94.4	94.4	100.0	11	6	0.65	100.0	0	0.0	
F01007	22	16	15	93.8	+	15	8	7	15	0.53	0	100.0	100.0	100.0	8	7	0.53	100.0	0	0.0	
F01008	22	18	17	94.4	+	14	6	8	14	0.43	0	82.4	82.4	100.0	5	7	0.42	85.7	0	0.0	
F01009	22	16	16	100.0	+	16	7	9	16	0.44	0	100.0	100.0	100.0	7	9	0.44	100.0	0	0.0	
F01010	22	15	14	93.3	+	14	5	9	14	0.36	0	100.0	100.0	100.0	5	9	0.36	100.0	0	0.0	
F01011	22	17	16	94.1	+	16	10	6	16	0.63	0	100.0	100.0	100.0	10	6	0.63	100.0	0	0.0	
F01012	23	17	17	100.0	+	16	7	9	16	0.44	0	94.1	94.1	100.0	7	8	0.47	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		196	189			181	89	92	181		0				88	90			0		
Mean	22.3	16.3	15.8	96.4		15.1	7.4	7.7	15.1	0.49	0.0	96.1	96.1	100.0	7.3	7.5	0.49	98.3		0.0	
S.D.	0.5	1.4	1.5	3.2		1.2	2.0	1.8	1.2	0.12	0.0	6.8	6.8	0.0	2.1	1.7	0.12	4.3		0.0	
%					100.0																

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

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

Appendix 38-2. Observation of offspring (F₁)

2-IBE 15 mg/kg																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implan- tation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring				External abnormalities ^{b)}		
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio	Viability index (%)	External abnormalities ^{b)}		
							Male	Female	Total									(Number)	(%)	
F02013	23	14	14	100.0	+	14	5	9	14	0.36	0	100.0	100.0	100.0	5	9	0.36	100.0	0	0.0
F02014	^{c)}	17	17	100.0	+	15	9	6	15	0.60	0	88.2	88.2	100.0	9	6	0.60	100.0	0	0.0
F02015	22	13	13	100.0	+	12	5	7	12	0.42	0	92.3	92.3	100.0	5	7	0.42	100.0	0	0.0
F02016	22	15	15	100.0	+	15	7	5	12	0.58	3	100.0	80.0	80.0	7	5	0.58	100.0	0	0.0
F02017	22	17	17	100.0	+	17	8	9	17	0.47	0	100.0	100.0	100.0	8	8	0.50	94.1	0	0.0
F02018	22	14	13	92.9	+	13	8	5	13	0.62	0	100.0	100.0	100.0	8	5	0.62	100.0	0	0.0
F02019	22	15	15	100.0	+	15	7	8	15	0.47	0	100.0	100.0	100.0	7	8	0.47	100.0	0	0.0
F02020	22	21	19	90.5	+	14	7	7	14	0.50	0	73.7	73.7	100.0	5	5	0.50	71.4	0	0.0
F02021	22	16	16	100.0	+	15	9	4	13	0.69	2	93.8	81.3	86.7	9	4	0.69	100.0	0	0.0
F02022	23	6	6	100.0	+	6	4	2	6	0.67	0	100.0	100.0	100.0	4	2	0.67	100.0	0	0.0
F02023	Not pregnant																			
F02024	22	16	16	100.0	+	15	8	7	15	0.53	0	93.8	93.8	100.0	8	7	0.53	100.0	0	0.0
Number of dams	10	11	11	11	11 ^{a)}	11			11	11	11	11	11			11	11		11	11
Total		164	161			151	77	69	146		5			75	66				0	
Mean	22.2	14.9	14.6	98.5		13.7	7.0	6.3	13.3	0.54	0.5	94.7	91.8	97.0	6.8	6.0	0.54	96.9		0.0
S.D.	0.4	3.6	3.4	3.4		2.9	1.7	2.1	2.8	0.10	1.0	8.1	9.6	6.9	1.8	2.0	0.10	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	AN	KW	KW	AN	KW	KW	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	KW		AN

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

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

c): Failure of the copulation day.

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

Appendix 38-3. Observation of offspring (F₁)

2-IBE 50 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 (%)	External abnormalities ^{b)}		
							Male	Female	Total									(Number)	(%)	
F03025	22	17	17	100.0	+	17	9	8	17	0.53	0	100.0	100.0	100.0	9	8	0.53	100.0	0	0.0
F03026	22	13	13	100.0	+	12	6	6	12	0.50	0	92.3	92.3	100.0	6	6	0.50	100.0	0	0.0
F03027	22	20	17	85.0	+	14	7	7	14	0.50	0	82.4	82.4	100.0	7	6	0.54	92.9	0	0.0
F03028	23	15	15	100.0	+	15	6	9	15	0.40	0	100.0	100.0	100.0	6	9	0.40	100.0	0	0.0
F03029	23	16	16	100.0	+	15	8	7	15	0.53	0	93.8	93.8	100.0	8	7	0.53	100.0	0	0.0
F03030	22	12	12	100.0	+	12	5	6	11	0.45	1	100.0	91.7	91.7	5	6	0.45	100.0	0	0.0
F03031	22	15	15	100.0	+	14	7	6	13	0.54	1	93.3	86.7	92.9	7	6	0.54	100.0	0	0.0
F03032	22	17	17	100.0	+	17	9	8	17	0.53	0	100.0	100.0	100.0	9	8	0.53	100.0	0	0.0
F03033	22	18	17	94.4	+	16	6	9	15	0.40	1	94.1	88.2	93.8	6	9	0.40	100.0	0	0.0
F03034	22	22	21	95.5	+	21	9	11	20	0.45	1	100.0	95.2	95.2	8	10	0.44	90.0	0	0.0
F03035	22	16	16	100.0	+	13	5	8	13	0.38	0	81.3	81.3	100.0	5	8	0.38	100.0	0	0.0
F03036	23	16	16	100.0	+	16	10	6	16	0.63	0	100.0	100.0	100.0	10	6	0.63	100.0	0	0.0
Number of dams	12	12	12	12	12 ^{a)}	12			12	12	12	12	12	12			12	12	12	12
Total		197	192			182	87	91	178		4				86	89			0	
Mean	22.3	16.4	16.0	97.9		15.2	7.3	7.6	14.8	0.49	0.3	94.8	92.6	97.8	7.2	7.4	0.49	98.6		0.0
S.D.	0.5	2.7	2.3	4.5		2.5	1.7	1.6	2.5	0.07	0.5	6.8	6.8	3.3	1.6	1.4	0.08	3.4		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	KW	AN	KW	KW	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	KW		AN

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

+: Dams with live offspring, -: dams without live offspring

a): Number of dams with live offspring.

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

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

Appendix 38-4. Observation of offspring (F₁)

2-IBE 150 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 (%)	abnormalities		
Male	Female	Total	Male	Female											(Number)	(%)				
F04037	22	17	17	100.0	+	16	9	7	16	0.56	0	94.1	94.1	100.0	1	0	1.00	6.3	0	0.0
F04038	22	16	16	100.0	+	16	10	6	16	0.63	0	100.0	100.0	100.0	10	6	0.63	100.0	0	0.0
F04039	22	14	14	100.0	+	12	8	4	12	0.67	0	85.7	85.7	100.0	8	4	0.67	100.0	0	0.0
F04040	22	14	13	92.9	+	13	6	7	13	0.46	0	100.0	100.0	100.0	6	7	0.46	100.0	0	0.0
F04041	22	15	14	93.3	+	14	6	8	14	0.43	0	100.0	100.0	100.0	6	8	0.43	100.0	0	0.0
F04042	22	18	17	94.4	+	17	9	8	17	0.53	0	100.0	100.0	100.0	9	8	0.53	100.0	0	0.0
F04043	22	17	16	94.1	+	15	3	12	15	0.20	0	93.8	93.8	100.0	3	11	0.21	93.3	0	0.0
F04044	22	15	15	100.0	+	12	5	7	12	0.42	0	80.0	80.0	100.0	4	6	0.40	83.3	0	0.0
F04045	23	17	17	100.0	+	14	7	7	14	0.50	0	82.4	82.4	100.0	7	7	0.50	100.0	0	0.0
F04046	22	16	15	93.8	+	14	2	11	13	0.15	1	93.3	86.7	92.9	2	11	0.15	100.0	0	0.0
F04047	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
F04048	23	16	15	93.8	+	12	5	7	12	0.42	0	80.0	80.0	100.0	5	7	0.42	100.0	0	0.0
Number of dams	12	12	12	12	12 ^{a)}	12			12	12	12	12	12	12			12	12	12	12
Total		190	184			169	77	91	168		1			68	82			0		
Mean	22.2	15.8	15.3	96.9		14.1	6.4	7.6	14.0	0.46	0.1	91.9	91.3	99.4	5.7	6.8	0.49	90.2		0.0
S.D.	0.4	1.3	1.3	3.3		1.7	2.4	2.1	1.7	0.15	0.3	7.9	8.0	2.0	2.8	2.9	0.22	26.9		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	KW	AN	KW	KW	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	KW	AN	AN

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

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

NS: Not significantly different from the control group.

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

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

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

NA: Not analyzed.

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

Appendix 39-1. 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	7.0	(7)	10.9	(7)	6.8	(6)	10.7	(6)
F01002	6.4	(9)	10.6	(9)	6.1	(7)	9.5	(7)
F01003	6.8	(9)	10.9	(9)	6.5	(5)	10.3	(5)
F01004	6.3	(5)	9.0	(5)	6.3	(11)	8.8	(11)
F01005	5.5	(5)	9.8	(5)	5.2	(9)	9.0	(9)
F01006	6.3	(11)	8.1	(11)	6.2	(6)	8.1	(6)
F01007	6.7	(8)	11.3	(8)	6.6	(7)	10.0	(7)
F01008	6.4	(6)	7.4	(5)	6.2	(8)	7.4	(7)
F01009	5.9	(7)	9.7	(7)	5.7	(9)	9.5	(9)
F01010	6.8	(5)	10.2	(5)	6.1	(9)	10.9	(9)
F01011	6.3	(10)	10.7	(10)	6.1	(6)	10.3	(6)
F01012	7.0	(7)	11.4	(7)	6.7	(9)	11.3	(8)
Number of dams	12		12		12		12	
Mean	6.5		10.0		6.2		9.7	
S.D.	0.4		1.3		0.4		1.2	

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring

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

Appendix 39-2. Body weights of offspring (F₁) before weaning

2-IBE 15 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F02013	7.3	(5)	11.3	(5)	7.2	(9)	11.6	(9)
F02014	6.5	(9)	10.1	(9)	6.2	(6)	10.0	(6)
F02015	7.4	(5)	10.6	(5)	7.2	(7)	10.3	(7)
F02016	6.7	(7)	11.1	(7)	6.4	(5)	11.6	(5)
F02017	6.2	(8)	9.2	(8)	5.8	(9)	9.3	(8)
F02018	7.3	(8)	10.1	(8)	7.1	(5)	10.7	(5)
F02019	6.8	(7)	10.7	(7)	6.5	(8)	9.7	(8)
F02020	6.1	(7)	11.8	(5)	6.0	(7)	11.8	(5)
F02021	7.5	(9)	11.7	(9)	6.7	(4)	11.7	(4)
F02022	8.7	(4)	16.0	(4)	8.2	(2)	15.7	(2)
F02023	Not pregnant							
F02024	6.5	(8)	10.4	(8)	6.3	(7)	9.8	(7)
Number of dams	11		11		11		11	
Mean	7.0		11.2		6.7		11.1	
S.D.	0.7		1.8		0.7		1.8	
Significance	NS		NS		NS		NS	
Statistical method	AN		AN		AN		AN	

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

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

Appendix 39-3. Body weights of offspring (F₁) before weaning

2-IBE 50 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F03025	6.0	(9)	9.1	(9)	5.5	(8)	9.3	(8)
F03026	6.6	(6)	11.0	(6)	6.4	(6)	10.6	(6)
F03027	7.0	(7)	10.0	(7)	6.6	(7)	9.7	(6)
F03028	7.1	(6)	11.7	(6)	6.7	(9)	11.2	(9)
F03029	7.1	(8)	10.8	(8)	6.7	(7)	10.8	(7)
F03030	6.7	(5)	11.2	(5)	6.4	(6)	10.8	(6)
F03031	6.4	(7)	10.2	(7)	6.2	(6)	10.1	(6)
F03032	6.3	(9)	10.0	(9)	5.8	(8)	9.3	(8)
F03033	6.5	(6)	11.0	(6)	6.6	(9)	10.1	(9)
F03034	5.4	(9)	8.5	(8)	5.0	(11)	7.7	(10)
F03035	6.2	(5)	10.8	(5)	6.0	(8)	10.2	(8)
F03036	6.0	(10)	9.0	(10)	5.8	(6)	9.7	(6)
Number of dams	12		12		12		12	
Mean	6.4		10.3		6.1		10.0	
S.D.	0.5		1.0		0.5		0.9	
Significance	NS		NS		NS		NS	
Statistical method	AN		AN		AN		AN	

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring

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

NS: Not significantly different from the control group.

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

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

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol by oral administration in rats

Appendix 39-4. Body weights of offspring (F₁) before weaning

2-IBE 150 mg/kg

Dam No.	Days after birth					
	Male body weight			Female body weight		
	0		4	0		4
F04037	6.3	(9)	9.9 (1)	6.2	(7)	Total litter loss
F04038	6.5	(10)	10.2 (10)	6.3	(6)	9.7 (6)
F04039	6.8	(8)	10.5 (8)	6.6	(4)	11.1 (4)
F04040	6.6	(6)	11.0 (6)	6.5	(7)	11.0 (7)
F04041	6.6	(6)	11.1 (6)	6.4	(8)	10.5 (8)
F04042	6.1	(9)	8.8 (9)	5.5	(8)	7.8 (8)
F04043	6.5	(3)	10.3 (3)	6.4	(12)	10.2 (11)
F04044	4.7	(5)	8.0 (4)	4.8	(7)	8.3 (6)
F04045	6.8	(7)	10.8 (7)	6.5	(7)	10.3 (7)
F04046	6.7	(2)	9.6 (2)	5.9	(11)	9.6 (11)
F04047	5.1	(7)	9.8 (7)	5.0	(7)	9.4 (7)
F04048	7.5	(5)	12.7 (5)	7.1	(7)	12.4 (7)
Number of dams	12		12	12		11
Mean	6.4		10.2	6.1		10.0
S.D.	0.8		1.2	0.7		1.3
Significance	NS		NS	NS		NS
Statistical method	AN		AN	AN		AN

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol by oral administration in rats

Appendix 40-1. 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	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
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	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01005	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01006	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F01007	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01008	Number of offspring	14	14	14	14	13
	General appearance, No abnormality	14	14	14	13	12
	General appearance, Death	0	0	0	1	1
F01009	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
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	16	15
	General appearance, No abnormality	16	16	16	15	15
	General appearance, Death	0	0	0	1	0
Number of offspring		181	181	181	181	179
General appearance, No abnormality		181	181	181	179	178
General appearance, Death					2	1
Number of offspring						

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol by oral administration in rats

Appendix 40-2. General conditions in offspring (F₁) before weaning

2-IBE 15 mg/kg						
Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F02013	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02014	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02015	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02016	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02017	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
F02018	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F02019	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02020	Number of offspring	14	14	14	12	10
	General appearance, No abnormality	14	14	12	10	10
	General appearance, Death	0	0	2	2	0
F02021	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F02022	Number of offspring	6	6	6	6	6
	General appearance, No abnormality	6	6	6	6	6
F02023	Not pregnant					
F02024	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
Number of offspring		146	146	146	143	141
General appearance, No abnormality		146	146	143	141	141
General appearance, Death				3	2	
Number of offspring						

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol by oral administration in rats

Appendix 40-3. General conditions in offspring (F₁) before weaning

2-IBE 50 mg/kg						
Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F03025	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F03026	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F03027	Number of offspring	14	14	13	13	13
	General appearance, No abnormality	14	13	13	13	13
	General appearance, Death	0	1	0	0	0
F03028	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03029	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03030	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F03031	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03032	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F03033	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03034	Number of offspring	20	20	20	19	18
	General appearance, No abnormality	20	20	19	18	18
	General appearance, Death	0	0	1	1	0
F03035	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03036	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
Number of offspring		178	178	177	176	175
General appearance, No abnormality		178	177	176	175	175
General appearance, Death			1	1	1	
Number of offspring						

Combined repeat dose and reproductive/developmental toxicity screening test of 2-isobutoxyethanol by oral administration in rats

Appendix 41-4. General conditions in offspring (F₁) before weaning

2-IBE 150 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
F04037	Number of offspring	16	16	9	1	1
	General appearance, No abnormality	16	9	1	1	1
	General appearance, Death	0	7	8	0	0
F04038	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F04039	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F04040	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F04041	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04042	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F04043	Number of offspring	15	15	14	14	14
	General appearance, No abnormality	15	14	14	14	14
	General appearance, Death	0	1	0	0	0
F04044	Number of offspring	12	12	10	10	10
	General appearance, No abnormality	12	10	10	10	10
	General appearance, Death	0	2	0	0	0
F04045	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04046	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F04047	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04048	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
Number of offspring		168	168	158	150	150
General appearance, No abnormality		168	158	150	150	150
General appearance, Death			10	8		
Number of offspring						

信頼性保証書

表題 2-イソブトキシエタノールのラットを用いる反復投与毒性・生殖発生毒性併合試験

試験番号 R-12-014

この試験に関する信頼性保証部門による査察および監査状況等は下記のとおりであった。

査察・監査項目	査察・監査年月日	運営管理者および試験責任者への報告年月日
試験計画書	2012 年 9 月 12 日	2012 年 9 月 12 日
試験計画書変更書		
R-12-014-No.1	2012 年 11 月 8 日	2012 年 11 月 8 日
R-12-014-No.2	2013 年 1 月 9 日	2013 年 1 月 9 日
R-12-014-No.3	2013 年 3 月 21 日	2013 年 3 月 21 日
R-12-014-No.4	2013 年 4 月 1 日	2013 年 4 月 1 日
動物の受入れおよび検疫	2012 年 9 月 19 日	2012 年 9 月 19 日
群分け、検体調製および含量試験	2012 年 10 月 1 日	2012 年 10 月 1 日
体重測定、給餌量測定、投与および一般状態の観察	2012 年 10 月 2 日	2012 年 10 月 2 日
性周期観察	2012 年 10 月 3 日	2012 年 10 月 3 日
詳細な症状観察および機能検査	2012 年 10 月 9 日	2012 年 10 月 9 日
交尾確認	2012 年 10 月 17 日	2012 年 10 月 17 日
尿検査	2012 年 11 月 7、8 日	2012 年 11 月 8 日
分娩状態および出生児の観察	2012 年 11 月 8 日	2012 年 11 月 8 日
機能検査	2012 年 11 月 9、12 日	2012 年 11 月 12 日
出生児剖検、採血、血液学検査、血液生化学検査、雌雄動物剖検、器官重量測定および固定	2012 年 11 月 13 日	2012 年 11 月 13 日
病理組織学検査(標本作製:切り出し)	2012 年 12 月 3 日	2012 年 12 月 3 日
報告書草案および生データ	2013 年 3 月 25、26、28、29 日、 4 月 1～5、8～12 日	2013 年 4 月 12 日
最終報告書	2014 年 1 月 14 日	2014 年 1 月 14 日

試験は、「新規化学物質等に係る試験を実施する試験施設に関する基準について」(平成 23 年 3 月 31 日、薬食発 0331 第 8 号、平成 23・03・29 製局第 6 号、環保企発第 110331010 号)を遵守して実施され、また、この報告書は試験に使用された方法および手順を正確に記載し、記載された結果は試験の生データを正確に反映していることを保証する。

2014 年 1 月 14 日

一般財団法人食品薬品安全センター 奏
信頼性保証部門責任者