試験番号 R-12-006

最終報告書

β-Cyclodextrin, 2-hydroxypropyl ethers 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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試験番号	R-12-006
被験物質	β-Cyclodextrin, 2-hydroxypropyl ethers
試験項目	反復投与毒性ならびに生殖発生毒性試験
試験開始日	2012 年 11 月 19 日
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試験終了日	試験責任者の捺印日
試資料保管場所	秦野研究所資料保存室
被験物質保管場所	秦野研究所被験物質保存庫
保管期間	試験終了後 10 年間 その後の保管については試験委託者と協議する。
運営管理者	一般財団法人食品薬品安全センター　秦野研究所 所長 [redacted]

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

2014 年 1 月 14 日　　試験責任者 [redacted]

試験従事者

試験責任者	[redacted]
試験担当主任者	
試験担当者 投与観察 動物飼育管理 （検疫を含む） 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	[redacted]

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信頼性保証書

要約

今回、β-Cyclodextrin, 2-hydroxypropyl ethers 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。被験物質を日局注射用水に溶解して 0、100、300 ならびに 1000 mg/kg の用量で、各群とも雌雄各 12 匹の Crl:CD(SD)ラットに強制経口投与した。雄は 42 日間投与した後に剖検し、雌は交配前 2 週間および交配期間、妊娠期間を通して哺育 4 日までの 41～48 日間投与し、出生児は哺育 4 日、母動物は哺育 5 日に剖検した。

また、0 および 1000 mg/kg の用量に非交配雌(10 匹/群)を設け、42 日間投与した後に半数を剖検し、残りの半数と 0 および 1000 mg/kg 群の雄 5 匹は、42 日間投与した後に 14 日間飼育して剖検した。

1. 反復投与毒性および回復性

投与期間中の一般状態、詳細な症状観察、体重推移、摂餌量、機能検査および尿検査では、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。投与期間終了時の血液生化学検査では、1000 mg/kg 群の非交配雌で ALT が高値を示し、肝臓および腎臓の重量が増加したが、血液学検査および病理組織学検査においては、被験物質投与の影響を示唆する変化ならびに所見は認められなかった。

回復観察中の一般状態、詳細な症状観察、体重推移、摂餌量および尿検査、ならびに回復観察終了時の血液学検査、血液生化学検査および剖検においては、被験物質投与の影響を示唆する変化は認められなかった。

2. 生殖発生毒性

親動物の性周期、交配成績、出産率、妊娠期間、分娩状態、哺育状態、黄体数、着床数および着床率に、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。また、出生児の生存率、体重および形態にも被験物質投与の影響は認められなかった。

3. 無毒性量

1000 mg/kg 群の非交配雌で投与終了時の ALT が高値を示し、肝臓および腎臓の重量が増加したことから雌動物の反復投与毒性に対する無毒性量(NOAEL)は 300 mg/kg/day、雄動物では影響が認められなかったことから無毒性量は 1000 mg/kg/day 以上と判断された。また、1000 mg/kg までの用量は、親動物の生殖能力および新生児の発育に影響を及ぼさなかったことから、生殖発生毒性に対する無毒性量は 1000 mg/kg/day 以上と判断された。

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β-Cyclodextrin, 2-hydroxypropyl ethers 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、環保企発第 110331009 号環境省総合環境政策局長通知)に準拠し、「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成 23 年 3 月 31 日付け、薬食発 0331 第 8 号厚生労働省医薬食品局長、平成 23・03・29 製局第 6 号経済産業省製造産業局長、環保企発第 110331010 号環境省総合環境政策局長通知)を遵守して実施した。

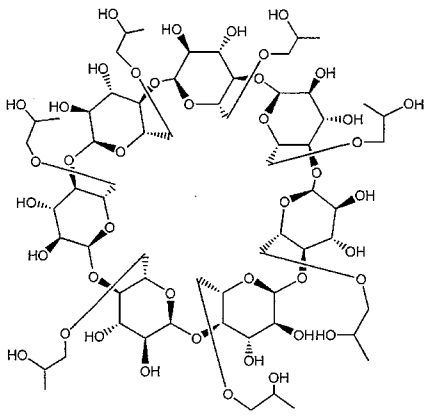
動物愛護

全ての実験操作は、「動物の愛護及び管理に関する法律」(昭和 48 年 10 月 1 日 法律第 105 号、平成 24 年 9 月 5 日 一部改正)、「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」(平成 18 年 4 月 28 日、環境省告示第 88 号)および「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」(平成 18 年 6 月 1 日、科発第 0601001 号)を遵守し、「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:1120250A)。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β-Cyclodextrin, 2-hydroxypropyl ethers(別名:2-ヒドロキシプロピル-β-シクロデキストリン、CAS No. 128446-35-5、分子式:$C_{63}H_{112}O_{42}$、分子量:1541.54、性状:白色の粉末、融点:278℃)、ロット番号:TLN0205 および TLJ0205(TLN0205 と同一ロットの追加入手分)、含量:99.7%、Annex A-1、A-2、以下、B-CH)は、[redacted]より購入し(被験物質入手:2012 年 7 月 3 日および 2012 年 11 月 9 日)、使用時まで室温、遮光、密閉(実測値 17.1～25.5℃)で保管した。B-CH 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:G-12-007)。

2. 動物および飼育方法

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

動物入荷日　:2012 年 11 月 26 日

入荷時体重　:雄 271.8～299.7 g、雌 178.4～211.5 g

検疫終了日　:2012 年 12 月 10 日

検疫終了時体重　:雄 374.3～439.4 g、雌 213.6～282.5 g

検疫・馴化期間中、雄動物の 1 例(馴化番号 40)で一時的に痩せが観察されたが、その後回復し、検疫期間中の一般状態、詳細な症状観察および体重推移に試験実施に影響を及ぼすと判断される異常は認められなかった。なお、雌動物では、規則的な性周期の回帰が認められない 8 匹を除外し、検疫終了時の体重を基に体重別層化無作為抽出法により群分けを行った。群分けした動物には一連の動物番号を割り当て、フェルトペンで尾に動物番号を標識し、色彩の異なった動物カードに試験番号および動物番号を記入して飼育ケージに掛けた。群分けから棄却した雄動物 7 匹、雌動物 15 匹(性周期の結果により除外した例を含む)は全て余剰動物とし、雄 5 匹は微生物モニタリングに使用し、その他の動物は他の目的に転用予定がなかったため、安楽死させた。

動物は許容温度 21.0～25.0℃、許容湿度 40.0～75.0%、換気設定約 15 回/時間、明暗サイクル 12 時間(7 時～19 時)点灯、12 時間(19 時～7 時)消灯に設定された飼育室内で、金属製金網床ケージ(220w×270d×190h mm)に 1 匹ずつ(交配時は 2 匹)収容し、固型飼料(CE-2、日本クレア)と水道水(秦野市水道局給水)を自由に摂取させて飼育した(剖検前の絶食に関しては剖検の項を参照)。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 22.0～25.0℃、湿度は 48.5～69.5%であった。また、供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを確認した。

3. 投与検体

1)調製

被験物質を秤量し、媒体(日局注射用水、製造元:光製薬、製造番号:C23VS1)を加え溶解させ、20 w/v%液を調製した。さらに 20 w/v%液を媒体によって希釈し、6 ならびに 2 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 2～12℃)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 0.5 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:G-12-007)。

3)含量試験

初回調製検体(調製日:2012 年 12 月 10 日)について、2、6 および 20 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 94.4～98.7%であり、各測定値のばらつきはそれぞれ平均値の 95.9～102.9%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「β-Cyclodextrin, 2-hydroxypropyl ethers 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-12-005)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)、100、300 および 1000 mg/kg の B-CH 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、1000 mg/kg までの投与群に、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。

従って、限度量の 1000 mg/kg を本試験の最高用量に設定し、中用量には 300 mg/kg を、最低用量には 100 mg/kg を設定した。

本試験では、雄動物は交配前 2 週間、交配期間を通して剖検前日まで(総投与回数 42 回)、雌動物は交配前 2 週間、交配期間、妊娠期間を通して分娩後の哺育 4 日まで(総投与回数 41～48 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 04 分～12 時 05 分)に投与した。投与容量は 5 mL/kg とし、雌雄とも最新の測定日の体重を基に投与液量を算出した。なお、対照群には媒体である日局注射用水を同様に投与した。投与経路は化審法ガイドラインに拠り、

ラット用胃管による強制経口投与とした。

本試験の群構成および動物番号を以下に示した。

群	投与物質	投与量 (mg/kg)	濃度 (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	B-CH	100	2	5	M02013～M02024	F02013～F02024
中用量群	B-CH	300	6	5	M03025～M03036	F03025～F03036
高用量群	B-CH	1000	20	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)	B-CH	1000	20	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(F_0)

①一般状態の観察

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

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 09 分～14 時 40 分)に行った。

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

④機能検査

各群の動物番号の若い雄 5 例とサテライト群の動物番号の若い 5 例については、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。分娩例については投与期間が近接し、出来るだけ分娩から日数が経過した各群の 5 例を選び、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(Chatillon、Columbus Instruments)を用いて握力を測定した。各動物の前肢および後肢の握力をそれぞれ 5 回測定し、最高値および最低値を除外した 3 回の握力値の平均値を求めた。

(3) 自発運動測定

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(投与開始日)、4、7、14、21、28、35、42 日、回復 1、7、14 日および剖検日に測定した。雌動物は投与 1、4、7、14 日、妊娠 0、7、14、20 日、哺育 0、4 日および剖検日に測定し、未交尾例は投与 21、28、35、42、49 日および剖検日に測定した。

⑥摂餌量測定

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

⑦尿検査

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

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

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

全例の雌について、検疫 3 日から性周期を観察し、群分け後、投与開始以降も引き続きサテライト群を除く全例の腟スメア標本を作製し、各動物の同居後、交尾が確認されるまで性周期を観察した。また、群ごとの平均発情回帰日数(個体ごとの発情期から発情期までの日数の平均)および投与開始後に 4 あ

るいは 5 日間隔の性周期がそれ以外の性周期に変化した動物の頻度を群毎に算出した。なお、規則的に 4～5 日の間で性周期が回帰している動物は正常と判断した。

⑨交配

投与 15 日の 16 時 23 分より同群内の雌雄を 1 対 1 で同居させた。翌朝より毎朝、腟栓を確認し、同居中の雌の腟スメア標本を作製して鏡検した。腟内に腟栓あるいは腟スメア標本中に精子が確認された動物を交尾成立動物とし、この日を妊娠 0 日と起算して個別飼育に戻した。交配結果および妊娠の成否により、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数、交尾率〔(交尾動物数/交配に用いた動物数)×100, %〕、妊娠率〔(妊娠動物数/交尾した雌動物数)×100, %〕を算出した。

⑩妊娠・分娩・哺育状態の観察

交尾が確認された全例を自然分娩させた。分娩の確認は、妊娠 21 日相当日から分娩が確認されるまで毎日、午前と午後に行い、15 時までに分娩が完了した例について、その日を哺育 0 日(分娩日)とした。分娩状態の直接観察は観察可能な動物について行い、直接観察できなかった動物についても、分娩後の一般状態および産児の状態から異常の有無を判断した。分娩後は、哺育状態を哺育 1～4 日の間、毎日観察した。分娩例については、妊娠期間(妊娠 0 日から分娩日までの日数)を求めた。また、剖検時には、妊娠黄体数と着床数を数え、着床率〔(着床数/妊娠黄体数)×100, %〕を算出した。

⑪採血

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

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

⑫血液学検査

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

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

項目	測定法	使用機器
平均赤血球容積(MCV)	計算(HCT×1000/RBC)	血液自動分析装置 XT-2000iV(ｼｽﾒｯｸｽ)
血小板数(PLT)	電気抵抗検出法	同上
ヘマトクリット値(HCT)	同上	同上
平均赤血球血色素量(MCH)	計算(HGB×1000/RBC)	同上
平均赤血球血色素濃度(MCHC)	計算(HGB×100/HCT)	同上
活性化部分ﾄﾛﾝﾎﾞﾌﾟﾗｽﾁﾝ時間(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)
ﾌﾟﾛﾄﾛﾝﾋﾞﾝ時間(PT)	同上	同上

⑬血液生化学検査

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

項目	測定法	使用機器
総蛋白濃度(TP)	ﾋﾞｳﾚｯﾄ法	自動分析装置 JCA-BM6010(日本電子)
ｱﾙﾌﾞﾐﾝ濃度(rALB)	BCG法	同上
ｸﾞﾙｺｰｽ濃度(Glc)	ﾍｷｿｷﾅｰｾﾞ・G-6-PDH法	同上
総ｺﾚｽﾃﾛｰﾙ濃度(TC)	ｺﾚｽﾃﾛｰﾙｵｷｼﾀﾞｰｾﾞ・HMMPS法	同上
ﾄﾘｸﾞﾘｾﾗｲﾄﾞ濃度(TG)	GPO・HMMPS法、ｸﾞﾘｾﾘﾝ消去法	同上
ﾘﾝ脂質濃度(PL)	ｺﾘﾝｵｷｼﾀﾞｰｾﾞ・DAOS法	同上
尿素窒素濃度(BUN)	ｳﾚｱｰｾﾞ・GlDH法,ｳﾚｱｰｾﾞ律速系	同上
ｸﾚｱﾁﾆﾝ濃度(cre)	Jaffé法	同上
γ-ｸﾞﾙﾀﾐﾙﾄﾗﾝｽﾍﾟﾌﾟﾁﾀﾞｰｾﾞ活性(γ-GTP)	IFCC法	同上
ｱﾙｶﾘﾌｫｽﾌｧﾀｰｾﾞ活性(ALP)	GSCC法	同上
ｱｽﾊﾟﾗｷﾞﾝ酸ｱﾐﾉﾄﾗﾝｽﾌｪﾗｰｾﾞ活性(AST)	IFCC法	同上
ｱﾗﾆﾝｱﾐﾉﾄﾗﾝｽﾌｪﾗｰｾﾞ活性(ALT)	同上	同上
乳酸脱水素酵素活性(LDH)	JSCC標準化対応法	同上
ｶﾙｼｳﾑ濃度(Ca)	OCPC法	同上
総ﾋﾞﾘﾙﾋﾞﾝ濃度(tbil)	酵素法	同上
無機ﾘﾝ濃度(IP)	ﾓﾘﾌﾞﾃﾞﾝ酸直接法	同上
胆汁酸濃度(TBA)	酵素サイクリング法	同上
A/G比	計算(rALB/(TP- rALB))	同上
ﾅﾄﾘｳﾑｲｵﾝ濃度(Na)	ｲｵﾝ電極法	全自動電解質分析装置 EA05(ｴｲｱﾝﾄﾞﾃｨｰ)
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
交尾が確認されなかった例(未交尾)	投与52日の翌日	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)および精嚢(凝固腺を含む)、卵巣、子宮の重量を測定した。また、全例の脳、脊髄、下垂体、眼球(ハーダー腺)、顎下腺および舌下腺、気管、甲状腺および上皮小体、胸腺、心臓、肺および気管支、肝臓、腎臓、脾臓、膵臓、副腎、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、下顎リンパ節、腸間膜リンパ節、精巣、精巣上体、前立腺、精嚢および凝固腺、卵巣、子宮、腟、膀胱、大腿骨および大腿骨骨髄、骨格筋、坐骨神経、乳腺、および病変部を採取し、保存した。肺／気管支は 15 cm 水柱以下の圧力で、気管内に 10%中性緩衝ホルマリン溶液 5 mL 以下を注入し固定してから摘出して同固定液に保存した。精巣および精巣上体はブアン液に固定(長期保存は 10%中性緩衝ホルマリン溶液)し、その他の器官・組織は 10%中性緩衝ホルマリン溶液に固定した。

なお、未交尾例の器官重量値は評価対象から除外した。

⑮病理組織学検査

剖検した動物のうち、雄およびサテライト群の投与終了時剖検では対照群ならびに高用量群の動物番号が若い各 5 例、雌の投与終了時剖検では分娩例について哺育 5 日に投与期間が近接した対照群ならびに高用量群の各 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)標本を作製し、病理組織学検査を実施した。また、剖検時に異常がみられた器官・組織に関しても同様に HE 標本を作製し、病理組織学検査を実施した。

2)出生児(F_1)

①出生児の観察

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

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様性について検定(有意水準:5%)を行った。分散が一様であった場合には、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様でなかった場合には、Kruskal-Wallis の順位検定(有意水準:5%)を行い、群間に有意性が認められた場合には、Dunnett 型の検定法により多重比較を行った(有意水準:5%)。

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

2013 年 1 月 14 日、18:07～18:13 に東京電力からの送電停止による停電が発生し、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、温湿度は許容範囲内であったことから、試験への影響はないと判断した。

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

試験成績

1. 親動物

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

雄では 100 mg/kg 群の 1 例(動物番号 M02023)において、投与 36 日から鼻周囲の汚れおよび紅涙が、投与 37 日から自発運動の低下が、さらに投与 40 日から排便量の減少が剖検日まで継続して観察された。その他の動物に異常は観察されなかった。

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

雄では、一般状態の観察で異常が認められた 1 例(動物番号 M02023)に自発運動の低下、紅涙、被毛の汚れおよび歩行異常が投与 42 日に観察されたが、その他の動物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。

雌では、投与期間ならびに回復期間を通して、被験物質投与の影響を示唆する変化は認められなかった。

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

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

非交配雌を含む雌においても、投与期間ならびに回復期間を通して、被験物質投与の影響を示唆する体重の変化は認められなかった。また、妊娠中および分娩後の体重推移に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。

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

雄では、投与期間および回復期間を通して被験物質投与の影響を示唆する摂餌量の変化は認め得なかった。

交配雌では、300 mg/kg 群の投与 7～8 日の摂餌量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。非交配雌では、投与期間および回復期間を通して被験物質投与の影響を示唆する摂餌量の変化は認め得なかった。また、妊娠中および分娩後の摂餌量に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。

5)機能検査

①刺激に対する感覚運動反応 (Table 15～Table 16, Appendix 15-1～Appendix 16-6)

投与最終週に実施したプライエル反応、瞳孔反射、視覚定位、驚愕反応、後肢引込み反射、眼瞼反射、正向反射の検査では、非交配雌を含む雌雄いずれの群の検査対象動物においても異常は認められなかった。

②握力測定 (Table 17～Table 19, Appendix 17-1～Appendix 19-2)

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

分娩雌では、300 mg/kg 群の後肢の握力が対照群に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。非交配雌では、被験物質投与の影響を示唆する握力の変化は認められなかった。

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

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

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

投与最終週および回復 13 日に実施した尿検査では、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。

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

①雄動物

投与期間終了時の雄では、いずれの検査項目について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。

回復期間終了時の雄では、1000 mg/kg 群の網状赤血球比率が対照群と比較して有意に低下したが、その差はわずかであり、それ以外の検査項目に有意差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、いずれの検査項目について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。

投与期間終了時の非交配雌では、1000 mg/kg 群の血色素量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たが、その差はわずかであり、赤血球数を含むその他の検査項目に対照群との差は認められなかった。

回復期間終了時の非交配雌では、1000 mg/kg 群のプロトロンビン時間が対照群より有意に遅延したが、その差はわずかであり、活性化部分トロンボプラスチン時間を含むその他の検査項目に対照群との差は認められなかった。

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

①雄動物

投与期間終了時の雄では、1000 mg/kg 群のトリグリセライド濃度が対照群より有意に低下した。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。

回復期間終了時の雄では、いずれの検査項目について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。

②雌動物

投与期間終了時の分娩雌では、いずれの検査項目について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。

投与期間終了時の非交配雌では、1000 mg/kg 群の ALT が対照群と比較して有意に増加した。その他、1000 mg/kg 群のγ-GTP とカルシウム濃度が対照群と比較して有意な高値を示したが、その差はわずかであった。

回復期間終了時の非交配雌では、1000 mg/kg 群の総蛋白(平均 5.9 g/dL)、胆汁酸(平均 7.3 μmol/L)およびカルシウム(平均 9.0mg/dL)の各濃度が対照群と比較して有意に低下したが、いずれも背景データの範囲内(下表参照)であった。

非交配雌(回復終了時)	試験数*	サンプル数	平均	平均±2SD
血中総蛋白濃度	4	20	6.0	5.5-6.4
血中胆汁酸濃度	4	20	14.4	1.2-27.6
血中カルシウム濃度	4	20	9.3	8.9-9.8

*: 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

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

①雄動物

投与期間終了時の雄では、いずれの器官重量に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。

回復期間終了時の雄では、1000 mg/kg 群の胸腺は絶対重量と相対重量が、心臓は絶対重量のみが対照群と比較して有意に低下した。その他の器官重量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、いずれの器官重量に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。

投与期間終了時の非交配雌では、1000 mg/kg 群の肝臓は絶対重量と相対重量が、腎臓は絶対重量のみが対照群と比較して有意に増加した。その他、1000 mg/kg 群の副腎の相対重量が対照群と比較して有意に低下した。

回復期間終了時の非交配雌では、1000 mg/kg 群の心臓および腎臓(右)は絶対重量が対照群と比較して有意に低下したが、相対重量には対照群との差はなかった。

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

①雄の投与期間終了時剖検例

肝臓に暗赤色点の散在および精巣上体(左側)尾部に黄白色結節が 100 mg/kg 群に各 1 例観察された。また、同群の一般状態に変化がみられた 1 例(動物番号 M02023)では、両眼および鼻周囲の汚れがみられ、胸腺も小型化を呈していた。

②雄の回復観察例

対照群および 1000 mg/kg 群に異常は認められなかった。

③分娩雌の投与終了時剖検例

腺胃粘膜に暗色を呈していた陥凹部が、対照群に 2 例、100 mg/kg 群に 1 例、1000 mg/kg 群に 2 例に、腺胃粘膜に赤色斑が 1000 mg/kg 群の 1 例に、それぞれ認められた。また、脾臓が一部萎縮し、周囲脂肪組織と癒着をしていた例が、1000 mg/kg 群に 1 例観察された。

④未交尾例

交尾が確認されなかった 300 mg/kg 群の 1 例(動物番号 F03034)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

非交配雌の対照群および 1000 mg/kg 群に異常は認められなかった。

⑥サテライト群の回復観察例

非交配雌の対照群および 1000 mg/kg 群に異常は認められなかった。

11)病理組織学検査 (Table 33～Table 34-2, Appendix 33～Appendix 34-2)

①雄の投与期間終了時剖検例

投与終了時剖検例のうち、対照群および 1000 mg/kg 群の 5 例について病理組織学検査を実施した。また、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以下の通りである。

肝臓では、門脈周囲性に肝細胞の脂肪化が対照群および 1000 mg/kg 群に各 4 例、小肉芽腫が両群の全例に、それぞれ観察されたが両群間に程度の差はなかった。剖検時に異常がみられた 100 mg/kg 群の 1 例の肝臓では、門脈周囲性に肝細胞の脂肪化、小肉芽腫および限局性ではあったが壊死巣の散在が認められた。対照群では、小葉中心性の肝細胞肥大および肝細胞の空胞変性が 1 例に観察された。

脾臓では、髄外造血像および褐色色素沈着が対照群および 1000 mg/kg 群の全例に観察されたが、両群間の程度には差はなかった。

腎臓では、皮質に好塩基性尿細管が対照群に 4 例および 1000 mg/kg 群に 3 例、皮髄境界部あるいは乳頭部に鉱質沈着が両群に各 1 例観察されたが、両群間の程度に差はなかった。

肺では、肺胞に泡沫細胞の集簇が、対照群の 1 例および 1000 mg/kg 群の 3 例に観察されたが、程度および頻度に有意差はなかった。

副腎では、球状帯細胞の肥大および束状帯細胞の空胞化が、1000 mg/kg 群に各 1 例観察されたが、ごく軽度な変化であった。

精巣上体では、剖検時に異常のあった 100 mg/kg 群の 1 例に精子肉芽腫が観察された。

前立腺では、間質にリンパ球浸潤が、対照群および 1000 mg/kg 群の各 2 例に観察されたが、程度には差はなかった。

剖検時に異常のあった 100 mg/kg 群の胸腺では、中等度の萎縮が観察された。

また、対照群では甲状腺に鰓後体遺残、心筋に限局性の変性/線維化、片側精巣に精細管の委縮、ハーダー腺の間質にリンパ球浸潤が観察された。

その他の組織学検査対象器官・組織には、病理組織学的変化は観察されなかった。

②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 1000 mg/kg 群の 5 例について、病理組織学検査を実施した。また、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以

下の通りである。

肝臓では、門脈周囲性に肝細胞の脂肪化が対照群に 4 例および 1000 mg/kg 群に 2 例、小肉芽腫が対照群に 1 例および 1000 mg/kg 群に 3 例観察されたが、程度および頻度には差はなかった。

胃では、腺胃にびらんが対照群に 2 例および 1000 mg/kg 群に 1 例観察されたが、程度には差はなかった。剖検時に異常がみられた 100 mg/kg 投与群の 1 例では、腺胃粘膜に出血が認められた。対照群では、腺胃の粘膜固有層に炎症細胞浸潤および水腫が 1 例に、腺胃粘膜に出血が観察された。

脾臓では、髄外造血像および褐色色素沈着が対照群および 1000 mg/kg 群の全例に観察されたが、両群間の程度には差はなかった。また、剖検時に異常がみられた 1000 mg/kg 群の 1 例(動物番号 F04045)に被膜の線維化が観察された。

腎臓では、皮質に好塩基性尿細管が対照群および 1000 mg/kg 群の各 1 例、間質にリンパ球浸潤が両群の各 2 例、それぞれ認められたが、程度には差がなかった。また、皮髄境界部にごく軽度な鉱質沈着が 1000 mg/kg 群に 1 例観察された。対照群では、硝子円柱が観察された。

肺では、肺胞に泡沫細胞の集簇が対照群および 1000 mg/kg 群に各 2 例観察されたが、程度に差はなかった。

甲状腺では異所性胸腺組織、胸腺では出血が 1000 mg/kg 群に各 1 例、副腎では束状帯細胞の肥大が同群に 2 例、それぞれ観察されたがいずれもごく軽度な変化であった。

また、対照群ではハーダー腺の間質にリンパ球浸潤が観察された。

その他の組織学検査対象器官・組織には、病理組織学的変化は観察されなかった。

③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 1000 mg/kg 群 5 例の病理組織所見は以下の通りである。

肝臓では、門脈周囲性に肝細胞の脂肪化が対照群に 3 例および 1000 mg/kg 群に 2 例、小肉芽腫が対照群に 3 例および 1000 mg/kg 群に 5 例観察されたが、程度および頻度には差はなかった。また、肝細胞核の大小不同、小葉中心性の肝細胞肥大が 1000 mg/kg 群に各 1 例観察されたが、いずれもごく軽度な変化であった。

脾臓では、髄外造血像および褐色色素沈着が対照群および 1000 mg/kg 群の全例に観察されたが、両群間の程度には差はなかった。

腎臓では、皮質に好塩基性尿細管が対照群に 1 例および 1000 mg/kg 群の 3 例に、間質へのリンパ球浸潤が対照群の 2 例および 1000 mg/kg 群の 1 例に、それぞれ観察されたが両群間の程度および頻度に差はなかった。対照群では、髄質に嚢胞が、皮髄境界部に鉱質沈着が観察された。

肺では、肺胞に泡沫細胞の集簇が対照群および 1000 mg/kg 群の各 1 例に観察されたが、いずれもごく軽度な変化であった。

対照群では、甲状腺に鰓後体遺残、卵巣に閉鎖卵胞の増加が観察された。

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

2. 生殖能力

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

4 あるいは 5 日間隔の性周期が投与開始後にそれ以外の性周期に変化した動物は、いずれの群にも認められなった。300 mg/kg 群の 1 組では、2 週間の交配期間中に交尾は確認されなかったが、その他の動物では交尾が確認され、交尾が確認された雌は全て妊娠が確認された。その他、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なかった。

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

各群の出産率はいずれも 100%を示した。分娩例の妊娠期間には、被験物質投与の影響を示唆する変化は認められなかった。

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 37, Appendix 37-1～Appendix 37-4)

黄体数、着床数および着床率に、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。

3. 出生児

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

産児数、出産生児数、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 38, Appendix 38-1～Appendix 38-4)

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 39～Table 40, Appendix 39-1～Appendix 39-4)

出生児の一般状態に被験物質投与の影響を示唆する変化はみられなかった。また、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β-Cyclodextrin, 2-hydroxypropyl ethers を経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

1. 反復投与毒性および回復性

投与期間中の一般状態観察では、100 mg/kg 群の雄 1 例に自発運動の低下や排便量の減少が観察されたが、300 mg/kg 以上の群で一般状態の異常が雌雄ともに認められていないことから、被験物質投与による影響ではないと判断した。その他、詳細な症状観察、体重推移、摂餌量、機能検査、尿検査、血液学検査において、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。

投与終了時の血液生化学検査では、ALT の上昇(平均 92 U/L)、肝臓の絶対重量(平均 8210.2 mg)および相対重量(平均 27.858 mg/g)の増加、さらには腎臓の絶対重量(平均 1961.8 mg)の増加が 1000 mg/kg 群の非交配雌でみられ、これらの値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被験物質投与の影響と判断した。しかし、肝臓および腎臓の病理組織学検査では、被験物質投与の影響を示唆する所見は認められなかった。

非交配雌(投与終了時)	試験数*	サンプル数	平均	平均±2SD
ALT	4	20	28	19-36
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
腎臓の絶対重量	4	20	1805.7	1766.4-1844.9

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

回復観察中の一般状態、詳細な症状観察、体重推移、摂餌量および尿検査では、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。また、回復観察後の 1000 mg/kg 群の雄では、胸腺の絶対重量(平均 259.4 mg)および相対重量(平均 0.479 mg/g)と、心臓の絶対重量(平均 1468.0 mg)が有意に低下したが、いずれも背景データの範囲内(下表参照)であったことから被験物質投与の影響ではないと判断した。回復観察後の血液学検査、血液生化学検査および剖検では、被験物質投与の影響を示唆する変化は認められなかった。

雄(回復終了時)	試験数*	サンプル数	平均	平均±2SD
胸腺の絶対重量	4	20	294.8	200.6-389.1
胸腺の相対重量	4	20	0.590	0.476-0.703
心臓の絶対重量	4	20	1458.6	1321.5-1595.7

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

2. 生殖発生毒性

性周期、交配成績、出産率、妊娠期間、分娩状態、哺育状態、黄体数、着床数および着床率に、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ことから、1000 mg/kg までの用量は、親動物の生殖能力に影響を及ぼさないと考えられる。また、出生児の生存率、体重および形態に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、1000 mg/kg までの用量は、新生児の発育にも影響を及ぼさないと考えられる。

3. 無毒性量

1000 mg/kg 群の非交配雌で投与終了時の ALT が高値を示し、肝臓および腎臓の重量が増加したことから雌動物の反復投与毒性に対する無毒性量(NOAEL)は 300 mg/kg/day、雄動物では 1000 mg/kg までの用量に影響が認められなかったことから、無毒性量は 1000 mg/kg/day 以上と判断された。また、1000 mg/kg までの用量は、親動物の生殖能力および新生児の発育に影響を及ぼさなかったことから、生殖発生毒性に対する無毒性量は 1000 mg/kg/day 以上と判断された。

Annex A-1

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　御中

2012年7月3日

株式会社　ワコーケミカル

[redacted]

Code No. 324-84233

2-ヒドロキシプロピル-β-シクロデキストリン

規格／等級

Lot No.　TLN0205

数量　100g

検査項目	検査成績	規格値
外観	白色の粉末	白～淡黄色、結晶性粉末～粉末
含量	99.7%	98.0%以上
検査年月日	2012/04/23	

判定	合格	検査責任者	[redacted]

成績書発行番号 9861461

Annex A-2

2012年11月6日

財団法人食品薬品安全センター
[redacted]

和光純[redacted]
東京営[redacted]

同一バルク証明

毎々格別の御引立てを賜り厚く御礼申し上げます。
さて掲題の件、貴社に販売させて頂きました下記製品は2ロットとも同一バルクから小分けされた製品である事を証明致します。

<記>

（対象品目）
コード：324-84233
品　名：2-ヒドロキシプロピル-β-シクロデキストリン
容　量：100g

（対象ロット）
ロット：TLN0205
ロット：TLJ0205

以上

Annex B

試験番号	R－12－006

含 量 試 験 結 果

被験物質：β-Cyclodextrin, 2-hydroxypropyl ethers　　調製年月日：2012年12月10日
ロット番号：TLN0205　　測定年月日：2012年12月10日
媒　　体：日局注射用水

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
1	20.0	18.91	19.72	94.6	98.7	95.9
2		19.97		99.9		101.3
3		20.29		101.5		102.9
4	60.0	59.70	58.74	99.5	97.9	101.6
5		57.22		95.4		97.4
6		59.32		98.9		101.0
7	200	190.0	188.8	95.0	94.4	100.6
8		190.9		95.5		101.1
9		185.5		92.8		98.3

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

電子天秤(LA230S)　ザルトリウス

② 測定条件

測定方法　臭化カリウム錠剤法

波数範囲　4000～400 cm^{-1}

③ 測定方法

被験物質1～2 mgをとり、めのう製乳鉢で粉末とし、これに赤外吸収スペクトル用臭化カリウム(島津製作所)0.10～0.20 gを加え、湿気を吸わないように注意し、速やかによくすり混ぜた後、錠剤成型器に入れて加圧製錠する。同様にして対照臭化カリウム錠剤を製する。

2. 投与検体中の被験物質濃度測定法

① 試薬

日局注射用水(以下、水)　光製薬

② 使用機器

電子天秤(R200D)　ザルトリウス

紫外可視分光光度計(UV-1700)　島津製作所

③ 標準溶液の調製

被験物質約1 gを精密に量り、水に溶解して正確に50 mLとし、標準溶液(約20 mg/mL)とする。この標準溶液2.5、5および10 mLを正確にとり、水を加えて正確にそれぞれ20 mLとし、標準溶液(約2.5、5および10 mg/mL、各濃度n=1)を調製する。

④ 試料溶液の調製

2 w/v%の投与液については、5 mLを正確に採り、水で希釈して10 mLとして試料溶液(約10 mg/mL、希釈係数 2)を調製する。6 w/v%の投与液については、2 mLを正確に採り、水で希釈して10 mLとして試料溶液(約12 mg/mL、希釈係数 5)を調製する。また、20 w/v%の投与検体については、1 mLを正確にとり、水で希釈して20 mLとし、試料溶液(約10 mg/mL、希釈係数 20)を調製する。試料溶液は、投与検体の採取からn=3で調製する。

⑤ 検量線の作成および投与検体中被験物質濃度の算出

試料溶液および標準溶液につき、水を対照として紫外可視分光光度計により、波長205 nmにおける吸光度をn=1で測定する。標準溶液から得られたB-CHの吸光度と調製濃度を基に検量線を作成し、この検量線を用いて試料溶液中B-CHの濃度を求める。さらに、希釈係数を乗じて投与検体中のB-CH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。

⑥ 数値の取り扱い

SOP/CHE/001に従い、調製濃度は有効数字4桁目を四捨五入して有効数字3桁で、測定濃度および平均測定濃度は有効数字5桁目を切り捨てて有効数字4桁で表示し、含量、平均含量およびばらつきは小数点以下第2位を四捨五入して少数点以下第1位まで表示する。

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

Table 1-1. General conditions of male rats

Group	Number of males and general conditions	Days of administration																																																	
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
B-CH 100 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
B-CH 300 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
B-CH 1000 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration. Post: after administration.

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

Group	Number of males and general conditions	Days of administration																																	
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
B-CH 100 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
	Nose, Smudge of perinasal area	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	1	1	1	1	1	1	1	1	1	1
	Eye, Eyeball, Bulbi, Globe, Reddish tear	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	1	1	1	1	1	1	1	1	1	1
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1
	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	1	0	1	0	1	0	1
B-CH 300 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
B-CH 1000 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	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

Pre: Before administration. Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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
B-CH 1000 mg/kg	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

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

Table 2-1. General conditions of female rats

Group	Number of females and general conditions	Days of administration																																																	
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	6	6	3	3	1	1	1	1	1	1	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	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	6	6	3	3	1	1	1	1	1	1	0	0	0	0	0	0	0	0
B-CH 100 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	1	1	1	1	0	0	0	0	0	0	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	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B-CH 300 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	10	10	7	7	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	10	10	7	7	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
B-CH 1000 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	5	5	4	4	0	0	0	0	0	0	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	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	5	5	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

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

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		44		45		46		47		48		49		50	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
B-CH 300 mg/kg	Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	General appearance, No abnormality	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Pre: Before administration, Post: after administration.

Group	Number of females and general conditions	Days of administration				
		51		52		53
		Pre	Post	Pre	Post	Pre
B-CH 300 mg/kg	Number of females	1	1	1	1	1
	General appearance, No abnormality	1	1	1	1	1

Pre: Before administration, Post: after administration.

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

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

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

Pre: Before administration, Post: after administration.

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

Group	Number of females and general conditions	Days of administration																																	
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
B-CH 1000 mg/kg	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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
B-CH 1000 mg/kg	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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
B-CH 100 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
B-CH 300 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	11	11	11	11	11	11
B-CH 1000 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

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

Group	Number of dams and general conditions	Days of pregnancy																	
		14		15		16		17		18		19		20		21		22	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5
B-CH 100 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4
B-CH 300 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6	6
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6	6
B-CH 1000 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6

Pre: Before administration, Post: after administration.

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

Table 4. General conditions in dams during lactation

Group	Number of dams and general conditions	Days of lactation										
		0		1		2		3		4		5
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of dams	7	7	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	7	7	12	12	12	12	12	12	12	12	12
B-CH 100 mg/kg	Number of dams	7	7	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	7	7	12	12	12	12	12	12	12	12	12
B-CH 300 mg/kg	Number of dams	5	5	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	5	5	11	11	11	11	11	11	11	11	11
B-CH 1000 mg/kg	Number of dams	5	5	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	5	5	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

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

Table 5. Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery [a]	
				8	15	24	30	36	42	7	14
[Locomotor in home-cage]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Decrease in locomotor activity	B-CH 100 mg/kg	12	0	0	0	0	0	0	1		
	B-CH 300 mg/kg	12	0	0	0	0	0	0	0		
	B-CH 1000 mg/kg	12	0	0	0	0	0	0	0	0	0
[Lacrimation]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Reddish tear	B-CH 100 mg/kg	12	0	0	0	0	0	1	1		
	B-CH 300 mg/kg	12	0	0	0	0	0	0	0		
	B-CH 1000 mg/kg	12	0	0	0	0	0	0	0	0	0
[Fur]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Soiled fur	B-CH 100 mg/kg	12	0	0	0	0	0	0	1		
	B-CH 300 mg/kg	12	0	0	0	0	0	0	0		
	B-CH 1000 mg/kg	12	0	0	0	0	0	0	0	0	0
[Gait]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Abnormal gait	B-CH 100 mg/kg	12	0	0	0	0	0	1	1		
	B-CH 300 mg/kg	12	0	0	0	0	0	0	0		
	B-CH 1000 mg/kg	12	0	0	0	0	0	0	0	0	0

[a] the recovery test was performed in 5 animals for each of the 0 and 250 mg/kg groups
[b] Values represent number of animals with the findings.

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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	6 [b]	3	1	1	3	2	0	2	5
	B-CH 100 mg/kg	12	2	1	2	2	3	2	2		
	B-CH 300 mg/kg	12	0	1	1	2	0	2	2		
	B-CH 1000 mg/kg	12	2	0	0	1	0	1	2	0	3
[Defecation] (frequency/30sec)	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
	B-CH 100 mg/kg	12	0	0	0	0	0	0	0		
	B-CH 300 mg/kg	12	0	0	0	0	0	0	2		
	B-CH 1000 mg/kg	12	1	0	0	0	0	0	0	0	0

[a] The recovery test was performed in 5 animals for each of the 0 and 1000 mg/kg groups.
[b] Values represent total score of each group.

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

Table 6-1. Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment							The lactation period
				8	15	24	30	36	42	49	
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	12	0 [a]	0	1	0	0	0			5
	B-CH 100 mg/kg	12	0	0	0	0	0	0			0
	B-CH 300 mg/kg	12	2	0	0	0	0	0	0 (1)	0 (1)	0 (11)
	B-CH 1000 mg/kg	12	1	0	0	1	0	0			1

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

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

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery [a]	
				8	15	24	30	36	42	7	14
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	10	0 [b]	0	0	0	1	0	0	0	0
	B-CH 1000 mg/kg	10	0	0	0	0	0	0	0	0	0

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

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

Table 7-1. Body weights of male rats

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of males	12	12	12	12
Days of administration				
1	412.2 ± 15.0	407.4 ± 15.4	410.7 ± 13.3	410.0 ± 15.4
4	423.4 ± 14.2	418.3 ± 19.1	420.6 ± 16.0	415.2 ± 16.1
7	435.8 ± 15.9	430.8 ± 22.6	434.8 ± 17.4	423.8 ± 19.4
14	462.6 ± 15.8	459.7 ± 28.1	463.2 ± 24.5	447.3 ± 18.4
21	483.5 ± 16.0	478.9 ± 32.7	479.5 ± 26.8	473.7 ± 16.6
28	509.3 ± 17.8	506.6 ± 34.9	503.8 ± 33.0	503.3 ± 17.2
35	529.8 ± 18.7	526.5 ± 38.4	526.1 ± 37.8	525.8 ± 16.2
42	544.1 ± 20.4	526.8 ± 54.0	539.3 ± 39.3	537.9 ± 16.4

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of males	5	5
Days of recovery		
1	548.6 ± 13.9	543.1 ± 20.2
7	562.4 ± 15.0	559.3 ± 20.1
14	580.9 ± 17.5	569.9 ± 19.2

Each value shows mean (g) ± S.D.

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

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

Table 8-1. Body weights of female rats

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of females	12	12	12	12
Days of administration				
1	247.9 ± 12.7	253.6 ± 11.5	247.8 ± 9.8	249.9 ± 12.4
4	254.9 ± 13.7	256.9 ± 11.5	252.9 ± 9.2	255.0 ± 12.4
7	260.6 ± 17.9	266.9 ± 13.0	257.8 ± 11.3	261.5 ± 15.8
14	269.0 ± 19.0	277.8 ± 13.2	266.5 ± 10.0	272.0 ± 16.8

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females	10	10
Days of administration		
1	251.0 ± 14.3	253.5 ± 15.1
4	260.6 ± 15.3	260.9 ± 14.4
7	265.5 ± 14.6	263.7 ± 14.1
14	272.5 ± 13.6	272.3 ± 20.3
21	284.3 ± 14.9	283.3 ± 23.3
28	292.1 ± 15.6	293.6 ± 24.3
35	298.2 ± 15.1	298.8 ± 24.3
42	300.9 ± 15.7	303.8 ± 26.4

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females	5	5
Days of recovery		
1	308.7 ± 13.6	300.4 ± 32.0
7	316.8 ± 12.8	308.5 ± 30.8
14	319.4 ± 18.4	308.6 ± 27.1

Each value shows mean (g) ± S.D.

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

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

Table 9. Body weights of dams during pregnancy

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of dams	12	12	11	12
Days of pregnancy				
0	273.9 ± 14.4	276.4 ± 13.8	273.4 ± 9.4	278.2 ± 16.9
7	314.7 ± 21.4	311.9 ± 18.1	307.5 ± 13.6	313.5 ± 18.5
14	351.2 ± 25.6	347.7 ± 18.5	341.6 ± 14.8	351.8 ± 22.5
20	433.5 ± 32.0	433.5 ± 25.0	423.4 ± 22.5	434.6 ± 28.9

Each value shows mean ± S.D. (g).

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

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

Table 10. Body weights of dams during lactation

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of dams	12	12	11	12
Days of lactation				
0	330.1 ± 26.5	329.2 ± 16.8	324.0 ± 26.6	332.1 ± 22.4
4	340.3 ± 21.4	340.2 ± 19.4	329.3 ± 22.7	341.1 ± 20.9

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

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

Table 11-1. Food consumption of male rats

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of males	12	12	12	12
Days of administration				
1	30.6 ± 2.6	33.2 ± 3.9	32.4 ± 3.0	28.7 ± 3.4
7	29.8 ± 1.7	30.9 ± 3.6	31.0 ± 3.4	27.8 ± 2.6
14	27.7 ± 1.5	29.9 ± 4.3	28.6 ± 3.6	27.7 ± 2.0
29	30.6 ± 3.1	30.8 ± 3.2	31.2 ± 2.2	32.0 ± 2.2
35	31.5 ± 2.5	29.0 ± 6.7	31.4 ± 3.4	30.3 ± 2.6
41	29.8 ± 1.5	29.5 ± 6.9	30.6 ± 2.7	30.8 ± 2.2

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of males	5	5
Days of recovery		
6	31.2 ± 1.4	31.5 ± 2.6
12	32.2 ± 1.3	31.8 ± 2.4

Each value shows mean (g) ± S.D.

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

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

Table 12-1. Food consumption of female rats

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of females	12	12	12	12
Days of administration				
1	20.7 ± 3.9	22.6 ± 3.0	19.9 ± 2.9	22.2 ± 2.8
7	22.6 ± 2.3	18.7 ± 2.8 **	20.2 ± 2.3	21.2 ± 3.5
14	21.1 ± 3.9	21.4 ± 2.9	19.0 ± 3.4	21.3 ± 3.8

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females	10	10
Days of administration		
1	22.2 ± 3.4	20.3 ± 2.9
7	21.5 ± 3.0	23.2 ± 2.0
14	21.7 ± 2.5	22.2 ± 2.5
21	21.6 ± 3.3	21.1 ± 3.1
29	21.0 ± 2.9	19.9 ± 3.3
35	21.7 ± 2.3	22.8 ± 2.8
41	19.7 ± 4.1	20.5 ± 1.7

Each value shows mean (g) ± S.D.

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

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females	5	5
Days of recovery		
6	21.4 ± 1.7	22.2 ± 1.7
12	20.9 ± 3.3	21.7 ± 1.9

Each value shows mean (g) ± S.D.

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

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

Table 13. Food consumption in dams during pregnancy

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of dams	12	12	11	12
Days of pregnancy				
0	22.9 ± 3.6	20.3 ± 2.4	20.5 ± 2.0	21.8 ± 2.3
7	27.9 ± 3.5	27.2 ± 3.4	25.7 ± 2.7	28.0 ± 2.7
14	27.3 ± 3.2	25.2 ± 3.3	26.0 ± 2.9	27.6 ± 3.7
20	23.4 ± 3.2	25.0 ± 3.5	22.5 ± 2.5	22.8 ± 5.1

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

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

Table 14. Food consumption in dams during lactation

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of dams	12	12	11	12
Days of lactation				
3	42.1 ± 6.3	42.9 ± 3.8	39.1 ± 5.3	43.4 ± 3.2

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

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

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

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Male				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100

Values represent % of animals showing normal responses.

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

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

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Female, dam				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
Female, satellite groups				
Number of animals	5			5
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Preyer's reaction	100			100
Withdrawal reflex	100			100
Eyelid reflex	100			100

Values represent % of animals showing normal responses.

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

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

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of males	5	5	5	5
Administration period				
Forelimb	0.887 ± 0.153	1.017 ± 0.049	0.929 ± 0.055	1.051 ± 0.126
Hindlimb	0.377 ± 0.143	0.396 ± 0.037	0.486 ± 0.087	0.469 ± 0.072

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

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

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of females	5	5	5	5
Administration period				
Forelimb	0.943 ± 0.120	0.901 ± 0.041	0.944 ± 0.174	0.950 ± 0.084
Hindlimb	0.516 ± 0.136	0.521 ± 0.120	0.333 ± 0.029 *	0.437 ± 0.086

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females	5	5
Administration period		
Forelimb	1.038 ± 0.013	1.025 ± 0.052
Hindlimb	0.413 ± 0.136	0.419 ± 0.060

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

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

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of males	5	5	5	5
Administration period				
Ambulation (counts)				
5min	1185 ± 98	1109 ± 167	1238 ± 92	1186 ± 446
10min	1058 ± 196	1030 ± 265	1114 ± 216	1154 ± 460
15min	981 ± 175	941 ± 200	1058 ± 137	1097 ± 439
20min	673 ± 251	759 ± 178	970 ± 180	936 ± 448
Total	3896 ± 629	3839 ± 676	4381 ± 600	4372 ± 1735
Rearing (counts)				
5min	34 ± 11	34 ± 12	44 ± 4	32 ± 8
10min	31 ± 9	27 ± 11	30 ± 9	35 ± 8
15min	26 ± 8	21 ± 6	29 ± 9	25 ± 9
20min	15 ± 8	15 ± 5	19 ± 9	18 ± 7
Total	105 ± 32	96 ± 31	122 ± 23	110 ± 17

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

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

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of females	5	5	5	5
Administration period				
Ambulation (counts)				
5min	1309 ± 324	1039 ± 267	1075 ± 64	1162 ± 126
10min	1192 ± 337	909 ± 203	832 ± 173	889 ± 88
15min	1004 ± 326	747 ± 220	757 ± 283	788 ± 118
20min	735 ± 271	512 ± 174	546 ± 274	625 ± 305
Total	4241 ± 1134	3207 ± 682	3209 ± 563	3465 ± 274
Rearing (counts)				
5min	32 ± 7	33 ± 8	32 ± 9	29 ± 5
10min	22 ± 9	24 ± 8	27 ± 22	23 ± 8
15min	16 ± 7	11 ± 4	13 ± 11	13 ± 9
20min	8 ± 6	7 ± 4	9 ± 9	10 ± 10
Total	79 ± 20	75 ± 9	81 ± 46	75 ± 24

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females	5	5
Administration period		
Ambulation (counts)		
5min	1163 ± 55	1107 ± 237
10min	1170 ± 104	988 ± 189
15min	1137 ± 136	1003 ± 344
20min	1004 ± 145	912 ± 281
Total	4474 ± 365	4010 ± 998
Rearing (counts)		
5min	38 ± 6	36 ± 11
10min	41 ± 18	32 ± 11
15min	39 ± 11	36 ± 23
20min	25 ± 13	23 ± 14
Total	144 ± 36	127 ± 49

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

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

Table 23-1. Urinalysis in male rats

Group	Number of males	Quality[a)]																		
		Color	Turbidity	pH				Protein			Glucose	Ketone			Bilirubin	Occult blood		Urobilinogen		
		Light yellow	-	6.5	7.0	7.5	8.0	±	+	2+	-	-	±	+	-	-	±	±	+	2+
Control (vehicle: water for injection)	5	5	5	0	3	1	1	1	4	0	5	1	1	3	5	5	0	2	3	0
B-CH 100 mg/kg	5	5	5	0	1	2	2	1	3	1	5	1	4	0	5	5	0	4	1	0
B-CH 300 mg/kg	5	5	5	0	5	0	0	1	4	0	5	2	3	0	5	4	1	5	0	0
B-CH 100 mg/kg	5	5	5	2	3	0	0	0	2	3	5	1	0	4	5	5	0	2	2	1

Group	Number of males	Urinary sediments[a)]						Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells								
		-	-	-	-	±	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	1	4	5	15.4 ±4.4	1.066 ±0.009	108.6 ±9.0	220.4 ±20.6	125.0 ±17.6	1.67 ±0.45	3.36 ±0.79	1.89 ±0.41
B-CH 100 mg/kg	5	5	5	5	1	4	5	19.2 ±5.9	1.050 ±0.012	76.9 ±33.5	183.8 ±37.0	81.9 ±39.3	1.40 ±0.46	3.39 ±0.54	1.50 ±0.62
B-CH 300 mg/kg	5	5	5	5	0	5	5	23.8 ±11.4	1.050 ±0.016	91.9 ±30.6	183.4 ±49.2	97.4 ±34.2	1.93 ±0.19	3.97 ±0.67	2.08 ±0.42
B-CH 100 mg/kg	5	5	5	5	0	5	5	15.2 ±4.2	1.063 ±0.010	110.5 ±25.4	224.4 ±18.0	126.0 ±23.1	1.63 ±0.44	3.37 ±0.77	1.86 ±0.40

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative ; ±: 0.03≦and<0.06 mg/dL
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

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

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

Group	Number of males	Quality[a]																
		Color	Turbidity	pH			Protein			Glucose	Ketone			Bilirubin	Occult blood	Urobilinogen		
		Light yellow	-	7.0	7.5	8.0	±	+	2+	-	-	±	+	-	-	±	+	2+
Control (vehicle: water for injection)	5	5	5	2	3	0	1	3	1	5	1	1	3	5	5	2	2	1
B-CH 1000 mg/kg	5	5	5	3	0	2	1	4	0	5	1	2	2	5	5	2	3	0

Group	Number of males	Urinary sediments[a]						Urine volume[b]	Specific gravity[b]	Electrolyte, density[b] (mEq/L)			Electrolyte, gross volume[b] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells								
		-	-	-	-	±	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	1	4	5	22.1 ±5.1	1.054 ±0.009	96.3 ±19.6	208.6 ±28.3	116.2 ±19.6	2.11 ±0.52	4.51 ±0.46	2.52 ±0.38
B-CH 1000 mg/kg	5	5	5	5	1	4	5	19.1 ±2.5	1.054 ±0.016	87.4 ±34.1	188.1 ±55.5	100.6 ±48.2	1.63 ±0.56	3.55 ±0.99	1.87 ±0.79

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

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

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

Group	Number of females	Quality[a)]																
		Color	Turbidity	pH				Protein			Glucose	Ketone			Bilirubin	Occult blood	Urobilinogen	
		Light yellow	-	6.0	6.5	7.0	8.0	-	±	+	-	-	±	+	-	-	±	+
Control (vehicle: water for injection)	5	5	5	1	1	2	1	4	1	0	5	3	2	0	5	5	5	0
B-CH 100 mg/kg	5	5	5	0	1	4	0	3	0	2	5	4	0	1	5	5	4	1

Group	Number of females	Urinary sediments[a)]						Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells								
		-	-	-	-	±	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	3	2	5	13.8 ±2.5	1.048 ±0.010	81.4 ±20.8	184.5 ±25.0	99.0 ±25.2	1.09 ±0.15	2.51 ±0.23	1.33 ±0.20
B-CH 100 mg/kg	5	5	5	5	2	3	5	13.9 ±3.6	1.055 ±0.017	107.9 ±42.7	190.6 ±37.5	114.0 ±53.8	1.39 ±0.27	2.56 ±0.27	1.46 ±0.36

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, -: negative ; ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

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

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

Group	Number of females	Quality[a]														
		Color	Turbidity	pH			Protein			Glucose	Ketone		Bilirubin	Occult blood	Urobilinogen	
		Light yellow	-	6.5	7.0	8.0	-	±	+	-	-	±	-	-	±	+
Control (vehicle: water for injection)	5	5	5	2	3	0	1	3	1	5	5	0	5	5	3	2
B-CH 1000 mg/kg	5	5	5	2	2	1	1	2	2	5	2	3	5	5	2	3

Group	Number of females	Urinary sediments[a]							Urine volume[b]	Specific gravity[b]	Electrolyte, density[b] (mEq/L)			Electrolyte, gross volume[b] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells									
		-	-	-	-	±	-	±	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	3	2	4	1	13.0 ±0.9	1.052 ±0.007	96.9 ±18.8	188.6 ±37.2	104.7 ±31.1	1.26 ±0.21	2.45 ±0.48	1.36 ±0.41
B-CH 1000 mg/kg	5	5	5	5	1	4	4	1	16.4 ±7.4	1.044 ±0.016	77.3 ±27.6	159.3 ±68.1	82.8 ±40.8	1.14 ±0.20	2.32 ±0.73	1.20 ±0.50

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, -: negative ; ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

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

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

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of males	5	5	5	5
RBC ($\times 10^4/\mu$ L)	853 ± 19	882 ± 35	859 ± 17	850 ± 20
Hemoglobin (g/dL)	15.6 ± 0.4	15.7 ± 0.3	15.7 ± 0.2	15.5 ± 0.6
Hematocrit (%)	43.6 ± 0.9	43.4 ± 1.1	43.7 ± 1.3	43.7 ± 2.0
MCV (fL)	51.1 ± 0.5	49.3 ± 2.5	50.9 ± 1.4	51.3 ± 1.6
MCH (pg)	18.2 ± 0.4	17.8 ± 0.8	18.3 ± 0.4	18.2 ± 0.5
MCHC (g/dL)	35.7 ± 0.5	36.1 ± 0.3	35.9 ± 0.6	35.5 ± 0.4
Platelet ($\times 10^4/\mu$ L)	111.3 ± 15.0	109.3 ± 13.4	104.9 ± 5.3	101.7 ± 5.2
PT (sec)	19.9 ± 4.9	22.8 ± 2.8	16.2 ± 3.1	14.4 ± 0.7
APTT (sec)	25.6 ± 1.5	27.0 ± 2.5	24.7 ± 3.0	22.1 ± 1.0
WBC ($\times 10^2/\mu$ L)	86.5 ± 39.4	89.1 ± 27.0	69.6 ± 23.1	66.3 ± 19.0
Differental leukocyte count (%)				
Neutrophil	17.9 ± 7.6	17.6 ± 7.2	22.7 ± 7.3	17.4 ± 4.3
Eosinophil	1.4 ± 0.3	1.6 ± 0.4	1.5 ± 0.7	1.5 ± 0.4
Basophil	0.0 ± 0.0	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.1
Monocyte	4.6 ± 1.8	4.0 ± 0.8	4.2 ± 1.1	3.5 ± 0.3
Lymphocyte	76.0 ± 9.4	76.8 ± 6.6	71.7 ± 8.0	77.6 ± 4.7
Reticulocyte count (%)	3.72 ± 0.54	3.41 ± 0.66	3.16 ± 0.71	3.32 ± 0.32

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of males	5	5
RBC ($\times 10^4/\mu$ L)	793 ± 37	796 ± 39
Hemoglobin (g/dL)	13.7 ± 0.9	13.9 ± 0.7
Hematocrit (%)	40.5 ± 2.1	41.1 ± 1.9
MCV (fL)	51.1 ± 0.8	51.6 ± 1.9
MCH (pg)	17.2 ± 0.5	17.4 ± 0.6
MCHC (g/dL)	33.7 ± 0.7	33.8 ± 0.5
Platelet ($\times 10^4/\mu$ L)	110.7 ± 15.8	105.2 ± 8.4
PT (sec)	16.9 ± 2.2	16.7 ± 2.3
APTT (sec)	25.6 ± 1.1	26.1 ± 1.8
WBC ($\times 10^2/\mu$ L)	102.7 ± 23.6	95.5 ± 11.9
Differental leukocyte count (%)		
Neutrophil	20.6 ± 5.1	14.0 ± 4.0
Eosinophil	1.1 ± 0.6	1.1 ± 0.3
Basophil	0.0 ± 0.0	0.0 ± 0.1
Monocyte	4.1 ± 1.1	3.6 ± 1.5
Lymphocyte	74.1 ± 6.0	81.2 ± 5.0
Reticulocyte count (%)	4.32 ± 0.63	3.37 ± 0.39 *

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

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

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of females	5	5	5	5
RBC ($\times 10^4/\mu$ L)	686 ± 38	680 ± 57	668 ± 41	656 ± 60
Hemoglobin (g/dL)	13.7 ± 0.8	13.5 ± 0.9	13.0 ± 0.8	13.1 ± 1.2
Hematocrit (%)	40.1 ± 1.6	39.8 ± 2.5	38.3 ± 2.4	39.1 ± 3.0
MCV (fL)	58.5 ± 2.4	58.7 ± 2.6	57.4 ± 2.4	59.8 ± 1.7
MCH (pg)	20.0 ± 0.7	19.9 ± 0.8	19.4 ± 0.4	20.1 ± 0.4
MCHC (g/dL)	34.2 ± 1.0	33.9 ± 0.6	33.9 ± 0.8	33.6 ± 0.5
Platelet ($\times 10^4/\mu$ L)	111.9 ± 9.6	116.3 ± 5.6	122.8 ± 18.5	125.9 ± 7.7
PT (sec)	12.4 ± 0.3	12.7 ± 0.6	12.5 ± 0.5	12.3 ± 0.2
APTT (sec)	20.4 ± 0.8	20.2 ± 0.6	19.6 ± 0.8	20.2 ± 1.1
WBC ($\times 10^2/\mu$ L)	139.6 ± 32.0	126.4 ± 22.4	119.1 ± 25.8	119.4 ± 23.9
Differental leukocyte count (%)				
Neutrophil	35.1 ± 9.5	41.6 ± 13.5	37.2 ± 4.4	37.6 ± 8.3
Eosinophil	0.7 ± 0.3	0.8 ± 0.3	0.8 ± 0.6	0.7 ± 0.3
Basophil	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Monocyte	3.5 ± 1.2	3.3 ± 0.7	3.6 ± 0.7	3.1 ± 0.8
Lymphocyte	60.7 ± 9.3	54.3 ± 13.7	58.4 ± 4.1	58.6 ± 8.0
Reticulocyte count (%)	8.21 ± 1.24	7.02 ± 1.69	7.43 ± 3.46	9.11 ± 3.68

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females	5	5
RBC ($\times 10^4/\mu$ L)	806 ± 30	778 ± 32
Hemoglobin (g/dL)	15.3 ± 0.6	14.4 ± 0.2 *
Hematocrit (%)	41.9 ± 1.2	40.2 ± 0.9 *
MCV (fL)	52.0 ± 1.3	51.7 ± 1.6
MCH (pg)	18.9 ± 0.5	18.5 ± 0.6
MCHC (g/dL)	36.4 ± 0.5	35.9 ± 0.6
Platelet ($\times 10^4/\mu$ L)	109.1 ± 17.2	114.6 ± 7.2
PT (sec)	11.7 ± 0.3	11.9 ± 0.6
APTT (sec)	20.8 ± 0.8	20.3 ± 1.1
WBC ($\times 10^2/\mu$ L)	53.9 ± 14.7	53.3 ± 24.1
Differental leukocyte count (%)		
Neutrophil	14.9 ± 4.5	14.0 ± 4.1
Eosinophil	1.8 ± 0.3	2.4 ± 1.2
Basophil	0.0 ± 0.0	0.0 ± 0.0
Monocyte	3.2 ± 0.9	3.8 ± 1.4
Lymphocyte	80.1 ± 5.3	79.7 ± 6.2
Reticulocyte count (%)	3.65 ± 1.18	2.86 ± 0.59

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

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

Group	Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females	5	5
RBC ($\times 10^4/\mu$ L)	759 ± 30	774 ± 47
Hemoglobin (g/dL)	14.2 ± 0.4	14.1 ± 1.0
Hematocrit (%)	41.4 ± 1.7	41.3 ± 2.5
MCV (fL)	54.5 ± 1.1	53.4 ± 1.8
MCH (pg)	18.7 ± 0.3	18.3 ± 0.5
MCHC (g/dL)	34.3 ± 0.6	34.2 ± 0.7
Platelet ($\times 10^4/\mu$ L)	98.7 ± 4.3	95.5 ± 15.6
PT (sec)	11.3 ± 0.4	11.9 ± 0.5 *
APTT (sec)	21.5 ± 1.1	19.8 ± 2.1
WBC ($\times 10^2/\mu$ L)	38.9 ± 11.9	34.3 ± 10.5
Differental leukocyte count (%)		
Neutrophil	14.7 ± 2.5	16.7 ± 3.9
Eosinophil	2.1 ± 1.1	1.5 ± 0.4
Basophil	0.0 ± 0.0	0.0 ± 0.0
Monocyte	3.2 ± 1.1	2.8 ± 1.0
Lymphocyte	80.0 ± 3.5	78.9 ± 4.6
Reticulocyte count (%)	3.14 ± 0.27	3.32 ± 0.58

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

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

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

Group		Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of males		5	5	5	5
Total protein	g/dL	5.6 ± 0.3	5.6 ± 0.2	6.0 ± 0.2	5.6 ± 0.3
Albumin	g/dL	3.6 ± 0.1	3.7 ± 0.1	3.7 ± 0.1	3.6 ± 0.2
A/G		1.86 ± 0.18	1.92 ± 0.24	1.69 ± 0.10	1.84 ± 0.27
Glucose	mg/dL	143 ± 19	148 ± 19	136 ± 12	137 ± 12
Total cholesterol	mg/dL	44 ± 3	37 ± 5	49 ± 17	49 ± 8
Triglyceride	mg/dL	54 ± 21	37 ± 15	37 ± 10	24 ± 5 *
Phospholipid	mg/dL	80 ± 4	71 ± 5	83 ± 19	78 ± 6
AST	U/L	65 ± 8	68 ± 8	67 ± 5	71 ± 14
ALT	U/L	31 ± 5	32 ± 2	37 ± 6	39 ± 7
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0
LDH	U/L	122 ± 89	163 ± 45	242 ± 111	221 ± 83
Bile acid	μmol/L	15.9 ± 8.1	7.7 ± 5.1	6.1 ± 1.4	5.5 ± 1.3
BUN	mg/dL	18 ± 2	15 ± 2	18 ± 2	16 ± 2
Creatinine	mg/dL	0.5 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.1
Total bilirubin	mg/dL	0.06 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.06 ± 0.02
ALP	U/L	345 ± 48	336 ± 59	308 ± 39	343 ± 53
Inorganic phosphorus	mg/dL	5.7 ± 0.3	6.2 ± 0.5	6.1 ± 0.2	5.4 ± 0.3
Ca	mg/dL	9.0 ± 0.5	9.3 ± 0.5	9.6 ± 0.2	9.0 ± 0.3
Na	mEq/L	143.9 ± 0.6	144.3 ± 1.1	143.9 ± 0.4	144.2 ± 0.8
K	mEq/L	3.82 ± 0.19	3.97 ± 0.37	3.97 ± 0.12	3.95 ± 0.22
Cl	mEq/L	107.1 ± 1.1	106.9 ± 1.8	106.4 ± 0.9	106.9 ± 1.5

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of males		5	5
Total protein	g/dL	5.7 ± 0.1	5.6 ± 0.3
Albumin	g/dL	3.7 ± 0.2	3.6 ± 0.2
A/G		1.91 ± 0.18	1.90 ± 0.07
Glucose	mg/dL	141 ± 13	141 ± 7
Total cholesterol	mg/dL	44 ± 5	47 ± 6
Triglyceride	mg/dL	41 ± 11	30 ± 12
Phospholipid	mg/dL	76 ± 5	76 ± 9
AST	U/L	65 ± 6	66 ± 7
ALT	U/L	27 ± 4	28 ± 2
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	206 ± 75	233 ± 86
Bile acid	μmol/L	24.1 ± 17.7	10.4 ± 2.4
BUN	mg/dL	15 ± 2	15 ± 2
Creatinine	mg/dL	0.5 ± 0.0	0.5 ± 0.0
Total bilirubin	mg/dL	0.05 ± 0.02	0.05 ± 0.01
ALP	U/L	230 ± 35	232 ± 43
Inorganic phosphorus	mg/dL	6.5 ± 1.0	6.3 ± 0.5
Ca	mg/dL	9.4 ± 0.2	9.3 ± 0.3
Na	mEq/L	143.8 ± 0.9	144.2 ± 0.7
K	mEq/L	3.86 ± 0.37	3.68 ± 0.24
Cl	mEq/L	107.1 ± 2.1	107.4 ± 1.3

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of females		5	5	5	5
Total protein	g/dL	6.1 ± 0.1	5.9 ± 0.3	5.9 ± 0.4	5.9 ± 0.2
Albumin	g/dL	4.2 ± 0.1	4.0 ± 0.2	4.0 ± 0.2	4.1 ± 0.2
A/G		2.17 ± 0.15	2.18 ± 0.14	2.25 ± 0.30	2.25 ± 0.15
Glucose	mg/dL	147 ± 6	135 ± 20	141 ± 14	132 ± 13
Total cholesterol	mg/dL	61 ± 4	64 ± 9	57 ± 4	57 ± 13
Triglyceride	mg/dL	62 ± 25	44 ± 19	48 ± 10	45 ± 23
Phospholipid	mg/dL	130 ± 15	128 ± 16	113 ± 6	115 ± 21
AST	U/L	76 ± 20	79 ± 15	76 ± 18	76 ± 13
ALT	U/L	45 ± 7	43 ± 7	53 ± 17	50 ± 14
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0
LDH	U/L	68 ± 32	88 ± 56	97 ± 47	62 ± 25
Bile acid	μmol/L	17.9 ± 4.2	11.7 ± 1.6	14.9 ± 8.1	11.2 ± 3.4
BUN	mg/dL	15 ± 2	16 ± 3	15 ± 4	14 ± 2
Creatinine	mg/dL	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.0	0.6 ± 0.1
Total bilirubin	mg/dL	0.10 ± 0.01	0.09 ± 0.03	0.08 ± 0.01	0.08 ± 0.01
ALP	U/L	160 ± 53	198 ± 57	214 ± 40	178 ± 102
Inorganic phosphorus	mg/dL	6.4 ± 1.0	6.7 ± 0.6	6.3 ± 0.7	6.2 ± 0.3
Ca	mg/dL	9.7 ± 0.3	9.7 ± 0.3	9.4 ± 0.2	9.7 ± 0.3
Na	mEq/L	140.4 ± 1.0	141.7 ± 0.6	141.9 ± 1.4	142.4 ± 2.0
K	mEq/L	4.03 ± 0.25	3.82 ± 0.20	3.94 ± 0.26	3.92 ± 0.56
Cl	mEq/L	104.5 ± 2.1	105.8 ± 1.6	106.7 ± 1.0	107.6 ± 2.5

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females		5	5
Total protein	g/dL	6.0 ± 0.2	6.3 ± 0.5
Albumin	g/dL	4.2 ± 0.2	4.4 ± 0.4
A/G		2.26 ± 0.26	2.38 ± 0.22
Glucose	mg/dL	120 ± 16	138 ± 15
Total cholesterol	mg/dL	63 ± 5	62 ± 7
Triglyceride	mg/dL	14 ± 2	18 ± 6
Phospholipid	mg/dL	117 ± 8	123 ± 14
AST	U/L	66 ± 10	143 ± 96
ALT	U/L	29 ± 11	92 ± 50 *
γ-GTP	U/L	0 ± 0	1 ± 1 *
LDH	U/L	64 ± 21	115 ± 73
Bile acid	μmol/L	19.2 ± 8.7	12.3 ± 5.9
BUN	mg/dL	18 ± 2	17 ± 2
Creatinine	mg/dL	0.6 ± 0.1	0.7 ± 0.1
Total bilirubin	mg/dL	0.08 ± 0.02	0.09 ± 0.03
ALP	U/L	197 ± 36	187 ± 33
Inorganic phosphorus	mg/dL	4.4 ± 0.4	4.2 ± 0.5
Ca	mg/dL	9.1 ± 0.2	9.6 ± 0.3 *
Na	mEq/L	142.9 ± 1.0	142.9 ± 0.7
K	mEq/L	3.67 ± 0.12	3.60 ± 0.18
Cl	mEq/L	107.5 ± 0.9	106.7 ± 1.0

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: water for injection)	B-CH 1000 mg/kg
Number of females		5	5
Total protein	g/dL	6.3 ± 0.5	5.9 ± 0.2 *
Albumin	g/dL	4.4 ± 0.3	4.1 ± 0.2
A/G		2.37 ± 0.08	2.35 ± 0.28
Glucose	mg/dL	119 ± 10	131 ± 17
Total cholesterol	mg/dL	69 ± 15	56 ± 6
Triglyceride	mg/dL	21 ± 16	16 ± 6
Phospholipid	mg/dL	128 ± 28	105 ± 10
AST	U/L	63 ± 6	73 ± 19
ALT	U/L	29 ± 10	35 ± 17
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	88 ± 39	117 ± 59
Bile acid	μmol/L	12.2 ± 2.6	7.3 ± 2.8 *
BUN	mg/dL	19 ± 2	17 ± 2
Creatinine	mg/dL	0.7 ± 0.1	0.6 ± 0.1
Total bilirubin	mg/dL	0.08 ± 0.02	0.09 ± 0.03
ALP	U/L	120 ± 15	129 ± 19
Inorganic phosphorus	mg/dL	4.1 ± 0.4	3.4 ± 0.8
Ca	mg/dL	9.6 ± 0.5	9.0 ± 0.1 *
Na	mEq/L	143.6 ± 1.5	144.3 ± 0.7
K	mEq/L	3.39 ± 0.22	3.12 ± 0.20
Cl	mEq/L	108.6 ± 1.7	109.8 ± 1.0

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of males		7	12	12	7
Body weight	(g)	507.7 ± 24.1	496.6 ± 49.7	507.6 ± 36.5	502.0 ± 11.8
Brain	(mg)	2043.1 ± 77.1	2025.1 ± 96.0	2011.6 ± 109.5	2055.3 ± 72.6
	(mg/g)	4.028 ± 0.146	4.110 ± 0.392	3.984 ± 0.376	4.095 ± 0.137
Thymus	(mg)	265.6 ± 43.0	324.2 ± 116.3	279.8 ± 98.0	288.0 ± 59.9
	(mg/g)	0.524 ± 0.087	0.650 ± 0.237	0.549 ± 0.179	0.574 ± 0.118
Heart	(mg)	1533.9 ± 170.8	1490.6 ± 168.6	1472.8 ± 103.0	1440.3 ± 129.1
	(mg/g)	3.025 ± 0.360	3.005 ± 0.230	2.904 ± 0.109	2.870 ± 0.264
Liver	(mg)	13950.9 ± 2322.1	13379.1 ± 2459.9	14063.8 ± 1779.3	13431.2 ± 790.4
	(mg/g)	27.392 ± 3.552	26.765 ± 2.735	27.670 ± 2.302	26.766 ± 1.643
Kidney (R)	(mg)	1677.0 ± 131.6	1676.7 ± 152.7	1686.7 ± 164.1	1637.6 ± 150.7
	(mg/g)	3.305 ± 0.239	3.396 ± 0.353	3.328 ± 0.284	3.264 ± 0.309
Kidney (L)	(mg)	1695.3 ± 228.6	1684.2 ± 198.1	1671.3 ± 145.7	1622.4 ± 98.0
	(mg/g)	3.339 ± 0.427	3.402 ± 0.349	3.299 ± 0.270	3.232 ± 0.186
Kidneys	(mg)	3372.3 ± 354.5	3360.9 ± 345.2	3358.0 ± 304.8	3260.0 ± 245.5
	(mg/g)	6.644 ± 0.653	6.798 ± 0.685	6.628 ± 0.543	6.496 ± 0.493
Spleen	(mg)	796.7 ± 109.3	824.9 ± 130.8	869.6 ± 125.7	812.6 ± 114.0
	(mg/g)	1.573 ± 0.237	1.667 ± 0.260	1.720 ± 0.269	1.620 ± 0.236
Testis (R)	(mg)	1649.1 ± 90.7	1668.9 ± 96.3	1721.1 ± 175.2	1718.2 ± 126.6
	(mg/g)	3.251 ± 0.170	3.403 ± 0.489	3.396 ± 0.326	3.425 ± 0.281
Testis (L)	(mg)	1662.9 ± 88.4	1659.3 ± 102.2	1709.5 ± 172.1	1712.6 ± 129.2
	(mg/g)	3.277 ± 0.130	3.382 ± 0.478	3.374 ± 0.330	3.414 ± 0.287
Testes	(mg)	3312.0 ± 172.4	3328.2 ± 192.9	3430.6 ± 343.9	3430.8 ± 253.8
	(mg/g)	6.527 ± 0.287	6.785 ± 0.962	6.770 ± 0.649	6.840 ± 0.564
Epididymis (R)	(mg)	636.7 ± 45.0	645.0 ± 42.8	653.1 ± 63.8	641.8 ± 43.2
	(mg/g)	1.255 ± 0.085	1.312 ± 0.160	1.293 ± 0.156	1.280 ± 0.098
Epididymis (L)	(mg)	641.6 ± 44.6	633.9 ± 48.9	638.0 ± 76.2	641.5 ± 45.5
	(mg/g)	1.264 ± 0.067	1.285 ± 0.127	1.262 ± 0.174	1.279 ± 0.109
Epididymides	(mg)	1278.3 ± 86.9	1278.8 ± 85.5	1291.1 ± 136.3	1283.3 ± 86.0
	(mg/g)	2.519 ± 0.147	2.597 ± 0.280	2.555 ± 0.324	2.559 ± 0.203

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

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

Group		Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of males		7	12	12	7
Prostate, ventral	(mg)	586.3 ± 98.6	636.4 ± 121.0	603.8 ± 128.6	547.9 ± 127.3
	(mg/g)	1.155 ± 0.188	1.286 ± 0.233	1.195 ± 0.260	1.089 ± 0.241
Seminal vesicles	(mg)	1840.7 ± 405.7	1747.6 ± 306.3	1772.0 ± 239.8	1764.4 ± 201.8
	(mg/g)	3.617 ± 0.739	3.539 ± 0.646	3.500 ± 0.459	3.511 ± 0.352
Thyroid gland	(mg)	17.9 ± 3.8	19.9 ± 3.3	16.8 ± 3.5	19.9 ± 3.3
	(mg/g)	0.035 ± 0.008	0.040 ± 0.008	0.033 ± 0.008	0.040 ± 0.007
Adrenal gland (R)	(mg)	27.1 ± 2.8	26.4 ± 4.3	27.4 ± 5.5	28.9 ± 3.8
	(mg/g)	0.054 ± 0.006	0.054 ± 0.012	0.054 ± 0.010	0.058 ± 0.007
Adrenal gland (L)	(mg)	28.5 ± 3.5	28.3 ± 6.0	29.2 ± 5.8	29.8 ± 4.1
	(mg/g)	0.056 ± 0.007	0.058 ± 0.017	0.058 ± 0.011	0.059 ± 0.008
Adrenal glands	(mg)	55.6 ± 5.7	54.7 ± 10.1	56.6 ± 11.2	58.7 ± 7.7
	(mg/g)	0.110 ± 0.011	0.112 ± 0.028	0.112 ± 0.020	0.117 ± 0.015

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: water for injection)			B-CH 1000 mg/kg			
Number of males		5			5			
Body weight	(g)	550.3	±	18.5	543.6	±	17.2	
Brain	(mg)	2061.4	±	110.6	2104.1	±	31.2	
	(mg/g)	3.748	±	0.203	3.873	±	0.110	
Thymus	(mg)	355.9	±	47.5	259.4	±	68.4	*
	(mg/g)	0.646	±	0.076	0.479	±	0.132	*
Heart	(mg)	1555.0	±	56.4	1468.0	±	49.6	*
	(mg/g)	2.827	±	0.109	2.704	±	0.161	
Liver	(mg)	14882.7	±	1734.9	14532.5	±	763.7	
	(mg/g)	27.044	±	2.991	26.731	±	1.024	
Kidney (R)	(mg)	1631.2	±	80.4	1640.5	±	97.8	
	(mg/g)	2.966	±	0.160	3.023	±	0.246	
Kidney (L)	(mg)	1621.8	±	37.9	1667.3	±	118.1	
	(mg/g)	2.950	±	0.119	3.072	±	0.276	
Kidneys	(mg)	3253.0	±	116.0	3307.8	±	206.5	
	(mg/g)	5.916	±	0.268	6.095	±	0.508	
Spleen	(mg)	931.4	±	65.5	923.8	±	77.8	
	(mg/g)	1.692	±	0.106	1.702	±	0.174	
Testis (R)	(mg)	1661.0	±	79.9	1700.2	±	111.7	
	(mg/g)	3.024	±	0.237	3.125	±	0.123	
Testis (L)	(mg)	1679.2	±	73.7	1679.9	±	119.6	
	(mg/g)	3.057	±	0.227	3.088	±	0.149	
Testes	(mg)	3340.2	±	152.2	3380.1	±	229.7	
	(mg/g)	6.082	±	0.462	6.213	±	0.268	
Epididymis (R)	(mg)	689.4	±	89.8	677.4	±	60.9	
	(mg/g)	1.253	±	0.164	1.246	±	0.106	
Epididymis (L)	(mg)	671.8	±	96.1	669.8	±	55.8	
	(mg/g)	1.221	±	0.174	1.232	±	0.098	
Epididymides	(mg)	1361.2	±	185.2	1347.2	±	115.6	
	(mg/g)	2.475	±	0.336	2.478	±	0.200	

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

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

Group		Control (vehicle: water for injection)			B-CH 1000 mg/kg		
Number of males		5			5		
Prostate, ventral	(mg)	613.7	±	163.3	728.1	±	133.4
	(mg/g)	1.121	±	0.312	1.340	±	0.249
Seminal vesicles	(mg)	1615.1	±	77.6	1899.3	±	375.8
	(mg/g)	2.940	±	0.225	3.484	±	0.620
Thyroid gland	(mg)	20.9	±	3.9	19.5	±	2.7
	(mg/g)	0.038	±	0.008	0.036	±	0.004
Adrenal gland (R)	(mg)	26.0	±	2.4	27.4	±	6.7
	(mg/g)	0.047	±	0.005	0.051	±	0.012
Adrenal gland (L)	(mg)	27.2	±	3.8	29.4	±	6.9
	(mg/g)	0.049	±	0.007	0.054	±	0.013
Adrenal glands	(mg)	53.2	±	6.0	56.8	±	13.4
	(mg/g)	0.097	±	0.011	0.104	±	0.024

Each value shows mean ± S.D.

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

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

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

Group		Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of females		12	12	11	12
Body weight	(g)	308.5 ± 15.8	313.8 ± 19.0	303.6 ± 16.6	308.6 ± 17.0
Brain	(mg)	1872.6 ± 48.8	1887.1 ± 69.3	1882.6 ± 55.2	1886.3 ± 44.1
	(mg/g)	6.083 ± 0.337	6.030 ± 0.370	6.220 ± 0.427	6.128 ± 0.341
Thymus	(mg)	202.0 ± 67.7	231.4 ± 64.3	209.6 ± 85.9	199.1 ± 47.5
	(mg/g)	0.655 ± 0.221	0.740 ± 0.216	0.682 ± 0.252	0.644 ± 0.142
Heart	(mg)	986.7 ± 63.4	1024.7 ± 89.7	985.4 ± 47.2	1005.4 ± 74.0
	(mg/g)	3.202 ± 0.204	3.268 ± 0.248	3.251 ± 0.170	3.258 ± 0.146
Liver	(mg)	10088.1 ± 816.0	10367.1 ± 512.0	10032.5 ± 517.7	10173.7 ± 606.2
	(mg/g)	32.698 ± 2.045	33.126 ± 2.293	33.151 ± 2.732	32.993 ± 1.552
Kidney (R)	(mg)	977.1 ± 83.6	1039.5 ± 65.3	999.8 ± 74.4	1037.9 ± 89.7
	(mg/g)	3.172 ± 0.285	3.322 ± 0.267	3.296 ± 0.218	3.364 ± 0.239
Kidney (L)	(mg)	977.3 ± 88.9	1020.9 ± 82.7	970.9 ± 68.2	1001.5 ± 82.7
	(mg/g)	3.175 ± 0.333	3.260 ± 0.278	3.201 ± 0.201	3.248 ± 0.246
Kidneys	(mg)	1954.4 ± 164.8	2060.4 ± 145.8	1970.8 ± 137.7	2039.3 ± 166.8
	(mg/g)	6.348 ± 0.596	6.581 ± 0.535	6.498 ± 0.401	6.613 ± 0.464
Spleen	(mg)	646.7 ± 76.5	710.7 ± 81.5	725.9 ± 121.0	787.4 ± 312.1
	(mg/g)	2.097 ± 0.233	2.274 ± 0.305	2.393 ± 0.386	2.568 ± 1.094
Ovary (R)	(mg)	48.8 ± 6.9	52.0 ± 9.7	47.8 ± 7.3	49.7 ± 9.4
	(mg/g)	0.158 ± 0.021	0.165 ± 0.025	0.158 ± 0.027	0.161 ± 0.027
Ovary (L)	(mg)	50.9 ± 8.7	52.1 ± 6.7	51.5 ± 7.2	47.8 ± 4.7
	(mg/g)	0.164 ± 0.024	0.167 ± 0.029	0.170 ± 0.025	0.155 ± 0.015
Ovaries	(mg)	99.6 ± 12.0	104.1 ± 8.4	99.3 ± 8.6	97.5 ± 12.0
	(mg/g)	0.323 ± 0.032	0.332 ± 0.030	0.329 ± 0.037	0.316 ± 0.034
Uterus	(mg)	535.8 ± 58.0	592.8 ± 66.0	555.5 ± 59.5	614.8 ± 100.3
	(mg/g)	1.735 ± 0.147	1.895 ± 0.240	1.833 ± 0.213	1.990 ± 0.288
Thyroid gland	(mg)	14.1 ± 3.1	14.7 ± 3.2	14.3 ± 3.3	14.9 ± 2.1
	(mg/g)	0.046 ± 0.010	0.047 ± 0.012	0.047 ± 0.010	0.048 ± 0.007
Adrenal gland (R)	(mg)	38.4 ± 4.6	38.8 ± 4.7	37.9 ± 4.7	41.8 ± 7.2
	(mg/g)	0.125 ± 0.016	0.124 ± 0.017	0.125 ± 0.015	0.136 ± 0.022
Adrenal gland (L)	(mg)	40.4 ± 4.4	41.4 ± 5.6	40.5 ± 4.6	46.1 ± 7.8
	(mg/g)	0.131 ± 0.016	0.133 ± 0.021	0.134 ± 0.016	0.149 ± 0.023
Adrenal glands	(mg)	78.8 ± 8.5	80.2 ± 10.1	78.5 ± 9.1	87.9 ± 14.9
	(mg/g)	0.256 ± 0.030	0.257 ± 0.037	0.259 ± 0.030	0.285 ± 0.045

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

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

Group		Control (vehicle: water for injection)				B-CH 1000 mg/kg			
Number of females		5				5			
Body weight	(g)	277.7	±	13.0		294.6	±	20.6	
Brain	(mg)	1846.0	±	65.6		1932.2	±	68.9	
	(mg/g)	6.656	±	0.326		6.587	±	0.564	
Thymus	(mg)	279.2	±	25.7		259.7	±	46.1	
	(mg/g)	1.006	±	0.092		0.879	±	0.114	
Heart	(mg)	916.1	±	14.6		947.8	±	94.0	
	(mg/g)	3.304	±	0.159		3.216	±	0.207	
Liver	(mg)	7216.1	±	455.6		8210.2	±	638.3	*
	(mg/g)	25.970	±	0.486		27.858	±	0.411	**
Kidney (R)	(mg)	918.0	±	45.4		995.6	±	60.4	
	(mg/g)	3.311	±	0.224		3.384	±	0.138	
Kidney (L)	(mg)	901.1	±	21.3		966.1	±	51.9	*
	(mg/g)	3.251	±	0.169		3.289	±	0.234	
Kidneys	(mg)	1819.2	±	66.4		1961.8	±	106.2	*
	(mg/g)	6.562	±	0.386		6.672	±	0.363	
Spleen	(mg)	565.1	±	62.7		617.8	±	78.9	
	(mg/g)	2.037	±	0.219		2.100	±	0.255	
Ovary (R)	(mg)	39.3	±	4.3		49.8	±	11.2	
	(mg/g)	0.142	±	0.019		0.168	±	0.036	
Ovary (L)	(mg)	44.5	±	5.0		46.1	±	9.0	
	(mg/g)	0.161	±	0.019		0.156	±	0.030	
Ovaries	(mg)	83.8	±	8.9		95.8	±	19.8	
	(mg/g)	0.303	±	0.038		0.325	±	0.064	
Uterus	(mg)	503.5	±	168.0		481.5	±	50.9	
	(mg/g)	1.806	±	0.562		1.639	±	0.189	
Thyroid gland	(mg)	14.7	±	1.5		14.6	±	1.8	
	(mg/g)	0.053	±	0.004		0.050	±	0.007	
Adrenal gland (R)	(mg)	36.9	±	1.8		33.8	±	4.4	
	(mg/g)	0.133	±	0.008		0.114	±	0.009	**
Adrenal gland (L)	(mg)	37.1	±	1.5		34.7	±	3.5	
	(mg/g)	0.134	±	0.006		0.118	±	0.008	**
Adrenal glands	(mg)	74.0	±	2.5		68.5	±	7.7	
	(mg/g)	0.267	±	0.013		0.232	±	0.016	**

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

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

Group		Control (vehicle: water for injection)			B-CH 1000 mg/kg			
Number of females		5			5			
Body weight	(g)	301.1	±	17.2	290.2	±	26.7	
Brain	(mg)	1886.3	±	33.4	1917.7	±	64.3	
	(mg/g)	6.279	±	0.298	6.645	±	0.550	
Thymus	(mg)	303.8	±	56.7	281.1	±	65.3	
	(mg/g)	1.016	±	0.222	0.973	±	0.236	
Heart	(mg)	935.9	±	22.4	853.0	±	48.7	**
	(mg/g)	3.118	±	0.205	2.957	±	0.296	
Liver	(mg)	7475.5	±	462.4	6917.7	±	463.4	
	(mg/g)	24.845	±	1.187	23.919	±	1.676	
Kidney (R)	(mg)	919.6	±	28.6	855.0	±	49.4	*
	(mg/g)	3.064	±	0.218	2.956	±	0.183	
Kidney (L)	(mg)	903.6	±	90.6	841.1	±	54.7	
	(mg/g)	3.003	±	0.269	2.911	±	0.248	
Kidneys	(mg)	1823.2	±	109.2	1696.1	±	102.1	
	(mg/g)	6.066	±	0.407	5.868	±	0.430	
Spleen	(mg)	581.5	±	56.7	546.4	±	46.9	
	(mg/g)	1.930	±	0.113	1.889	±	0.157	
Ovary (R)	(mg)	43.8	±	7.3	40.3	±	3.7	
	(mg/g)	0.146	±	0.031	0.140	±	0.014	
Ovary (L)	(mg)	42.4	±	4.7	40.1	±	2.9	
	(mg/g)	0.141	±	0.011	0.139	±	0.012	
Ovaries	(mg)	86.2	±	7.4	80.4	±	5.1	
	(mg/g)	0.287	±	0.031	0.278	±	0.022	
Uterus	(mg)	680.0	±	207.5	887.1	±	206.4	
	(mg/g)	2.276	±	0.734	3.039	±	0.579	
Thyroid gland	(mg)	12.4	±	1.7	14.2	±	3.4	
	(mg/g)	0.041	±	0.007	0.048	±	0.008	
Adrenal gland (R)	(mg)	30.3	±	3.6	28.9	±	3.4	
	(mg/g)	0.101	±	0.015	0.100	±	0.013	
Adrenal gland (L)	(mg)	32.2	±	2.6	30.9	±	4.9	
	(mg/g)	0.107	±	0.013	0.107	±	0.018	
Adrenal glands	(mg)	62.6	±	5.9	59.7	±	8.0	
	(mg/g)	0.209	±	0.027	0.207	±	0.030	

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

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

Group	Control (vehicle: water for injection)		B-CH 100 mg/kg		B-CH 300 mg/kg		B-CH 1000 mg/kg	
Findings / Grade	-	P	-	P	-	P	-	P
Epididymis								
Nodule, yellowish white, caudal, unilateral	7	0	11	1	12	0	7	0
Liver								
Dark colored spot, scattered	7	0	11	1	12	0	7	0
Skin								
Soiled fur, eyelid/perinasal area	7	0	11	1	12	0	7	0
Thymus								
Small	7	0	11	1	12	0	7	0

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

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

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

	Group	Control (vehicle: water for injection)		B-CH 1000 mg/kg	
Findings	Grade	-	P	-	P
All organs and tissues					
		5	0	5	0

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

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

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

Group	Control (vehicle: water for injection)		B-CH 100 mg/kg		B-CH 300 mg/kg		B-CH 1000 mg/kg	
Findings / Grade	-	P	-	P	-	P	-	P
Glandular stomach								
Recessed area, mucosa, dark	10	2	11	1	11	0	10	2
Reddish area, mucosa	12	0	12	0	11	0	11	1
Spleen								
Adhesion with adipose tissue	12	0	12	0	11	0	11	1
Atrophy, partially	12	0	12	0	11	0	11	1

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

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

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

Group	Control (vehicle: water for injection)		B-CH 1000 mg/kg	
Findings / Grade	-	P	-	P
All organs and tissues				
	5	0	5	0

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

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

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

Findings	Group Grade	Control (vehicle: water for injection) -	 P	B-CH 1000 mg/kg -	 P
All organs and tissues					
		5	0	5	0

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

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

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

Group	Corn oil (vehicle: water for injection)							B-CH 100 mg/kg							B-CH 300 mg/kg							B-CH 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5						2	0						12	0						12	5						2
Spinal cord	5						2	0						12	0						12	5						2
Pituitary gland	5						2	0						12	0						12	5						2
Submandibular gland	5						2	0						12	0						12	5						2
Sublingual gland	5						2	0						12	0						12	5						2
Lymph node, submandibular	5						2	0						12	0						12	5						2
Thyroid gland																												
Ultimobranchial body	4					1	2	0					0	12	0					0	12	5					0	2
Parathyroid gland	5						2	0						12	0						12	5						2
Thymus																												
Atrophy	5	0	0	0	0		2	0	0	0	1	0		11	0	0	0	0	0		12	5	0	0	0	0		2
Heart																												
Degeneration/fibrosis, myocardial, focal	3	2	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		2
Trachea	5						2	0						12	0						12	5						2
Lung																												
Accumulation, foam cell, alveolus	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	2	3	0	0	0		2
Bronchus	5						2	0						12	0						12	5						2
Liver																												
Degeneration, vacuolar, hepatocyte, centrilobular	4	1	0	0	0		2	1	0	0	0	0		11	0	0	0	0	0		12	5	0	0	0	0		2
Fatty change, hepatocyte, periportal	1	4	0	0	0		2	0	1	0	0	0		11	0	0	0	0	0		12	1	4	0	0	0		2
Hypertrophy, hepatocyte, centrilobular	4	1	0	0	0		2	1	0	0	0	0		11	0	0	0	0	0		12	5	0	0	0	0		2
Microgranuloma	0	5	0	0	0		2	0	1	0	0	0		11	0	0	0	0	0		12	0	5	0	0	0		2
Necrosis, focal, scattered	5	0	0	0	0		2	0	0	1	0	0		11	0	0	0	0	0		12	5	0	0	0	0		2
Pancreas	5						2	0						12	0						12	5						2
Stomach	5						2	0						12	0						12	5						2
Duodenum	5						2	0						12	0						12	5						2
Jejunum	5						2	0						12	0						12	5						2
Ileum	5						2	0						12	0						12	5						2
Cecum	5						2	0						12	0						12	5						2
Colon	5						2	0						12	0						12	5						2
Rectum	5						2	0						12	0						12	5						2
Lymph node, mesenteric	5						2	0						12	0						12	5						2

- : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Not significantly different from control.

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

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

Group	Corn oil (vehicle: water for injection)							B-CH 100 mg/kg							B-CH 300 mg/kg							B-CH 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Spleen																												
Deposit, pigment, brown	0	0	5	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	0	1	2	2	0		2
Hematopoiesis, extramedullary	0	1	1	3	0		2	0	0	0	0	0		12	0	0	0	0	0		12	0	1	3	1	0		2
Kidney																												
Basophilic tubule, cortex	1	4	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	2	3	0	0	0		2
Mineralization, cortico-medullary junction/ medulla	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Urinary bladder	5						2	0						12	0						12	5						2
Adrenal gland																												
Hypertrophy, zona glomerulosa	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Vacuolation, zona fasciculata	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Testis																												
Atrophy, seminiferous tubule, unilateral	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		2
Epididymis																												
Granuloma, spermatic, caudal, unilateral	5					0	2	0					1	11	0					0	12	5					0	2
Prostate																												
Cellular infiltration, lymphocyte, interstitial	3	2	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	3	1	1	0	0		2
Seminal vesicle	5						2	0						12	0						12	5						2
Coagulating gland	5						2	0						12	0						12	5						2
Eyeball	5						2	0						12	0						12	5						2
Harderian gland																												
Cellular infiltration, lymphocyte, interstitial	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		2
Sciatic nerve	5						2	0						12	0						12	5						2
Skeletal muscle	5						2	0						12	0						12	5						2
Femur	5						2	0						12	0						12	5						2
Marrow, femur	5						2	0						12	0						12	5						2

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

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

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

Group	Control (vehicle: water for injection)							B-CH 100 mg/kg							B-CH 300 mg/kg							B-CH 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5						7	0						12	0						11	5						7
Spinal cord	5						7	0						12	0						11	5						7
Pituitary gland	5						7	0						12	0						11	5						7
Submandibular gland	5						7	0						12	0						11	5						7
Sublingual gland	5						7	0						12	0						11	5						7
Lymph node, submandibular	5						7	0						12	0						11	5						7
Thyroid gland																												
Ectopic thymic tissue	5					0	7	0					0	12	0					0	11	4					1	7
Parathyroid gland	5						7	0						12	0						11	5						7
Thymus																												
Hemorrhage	5	0	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	4	1	0	0	0		7
Heart	5						7	0						12	0						11	5						7
Trachea	5						7	0						12	0						11	5						7
Lung																												
Accumulation, foam cell, alveolus	3	2	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	3	2	0	0	0		7
Bronchus	5						7	0						12	0						11	5						7
Liver																												
Fatty change, hepatocyte, periportal	1	4	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	3	2	0	0	0		7
Microgranuloma	4	1	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	2	3	0	0	0		7
Pancreas	5						7	0						12	0						11	5						7
Stomach																												
Cellular infiltration, inflammatory, submucosa, glandular stomach	5	1	0	0	0		6	1	0	0	0	0		11	0	0	0	0	0		11	7	0	0	0	0		5
Edema, submucosa, glandular stomach	5	1	0	0	0		6	1	0	0	0	0		11	0	0	0	0	0		11	7	0	0	0	0		5
Erosion, glandular stomach	4	2	0	0	0		6	1	0	0	0	0		11	0	0	0	0	0		11	6	1	0	0	0		5
Hemorrhage, mucosa, glandular stomach	5	1	0	0	0		6	0	1	0	0	0		11	0	0	0	0	0		11	7	0	0	0	0		5
Duodenum	5						7	0						12	0						11	5						7
Jejunum	5						7	0						12	0						11	5						7

- : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Not significantly different from control.

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

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

Group	Control (vehicle: water for injection)							B-CH 100 mg/kg							B-CH 300 mg/kg							B-CH 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Ileum	5						7	0						12	0						11	5						7
Cecum	5						7	0						12	0						11	5						7
Colon	5						7	0						12	0						11	5						7
Rectum	5						7	0						12	0						11	5						7
Lymph node, mesenteric	5						7	0						12	0						11	5						7
Spleen																												
Deposit, pigment, brown	0	0	5	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	0	0	5	0	0		7
Fibrosis, capsule	5	0	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	4	0	1	0	0		7
Hematopoiesis, extramedullary	0	0	0	5	0		7	0	0	0	0	0		12	0	0	0	0	0		11	0	0	0	5	0		7
Kidney																												
Basophilic tubule, cortex	4	1	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	4	1	0	0	0		7
Cast, hyalin	4	1	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	5	0	0	0	0		7
Cellular infiltration, lymphocyte, interstitial	3	2	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	3	2	0	0	0		7
Mineralization, cortico-medullary junction	5	0	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	4	1	0	0	0		7
Urinary bladder	5						7	0						12	0						11	5						7
Adrenal gland																												
Hypertrophy, zona fasciculata	5	0	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	3	2	0	0	0		7
Ovary	5						7	0						12	0						11	5						7
Uterus	5						7	0						12	0						11	5						7
Vagina	5						7	0						12	0						11	5						7
Eyeball	5						7	0						12	0						11	5						7
Harderian gland																												
Cellular infiltration, lymphocyte, interstitial	4	1	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	5	0	0	0	0		7
Sciatic nerve	5						7	0						12	0						11	5						7
Skeletal muscle	5						7	0						12	0						11	5						7
Femur	5						7	0						12	0						11	5						7
Marrow, femur	5						7	0						12	0						11	5						7

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

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

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

Group	Corn oil (veicle: water for injection)							B-CH 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5							5						
Spinal cord	5							5						
Pituitary gland	5							5						
Submandibular gland	5							5						
Sublingual gland	5							5						
Lymph node, submandibular	5							5						
Thyroid gland														
Ultimobranchial body	4					1		5					0	
Parathyroid gland	5							5						
Thymus	5							5						
Heart	5							5						
Trachea	5							5						
Lung														
Accumulation, foam cell, alveolus	4	1	0	0	0			4	1	0	0	0		
Bronchus	5							5						
Liver														
Anisonucleosis, hepatocyte	5	0	0	0	0			4	1	0	0	0		
Fatty change, hepatocyte, periportal	2	3	0	0	0			3	2	0	0	0		
Hypertrophy, hepatocyte, centrilobular	5	0	0	0	0			4	1	0	0	0		
Microgranuloma	2	3	0	0	0			0	5	0	0	0		
Pancreas	5							5						

- : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Not significantly different from control.

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

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

Group	Corn oil (veicle: water for injection)							B-CH 1000 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
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	4	1	0			0	1	2	2	0		
Hematopoiesis, extramedullary	0	3	2	0	0			0	4	1	0	0		
Kidney														
Basophilic tubule, cortex	4	1	0	0	0			2	3	0	0	0		
Cellular infiltration, lymphocyte, interstitial	3	2	0	0	0			4	1	0	0	0		
Cyst, medulla	4					1		5					0	
Mineralization, cortico-medullary junction	4	1	0	0	0			5	0	0	0	0		
Urinary bladder	5							5						
Adrenal gland	5							5						
Ovary														
Increase, atretic follicle	4	1	0	0	0			5	0	0	0	0		
Uterus	5							5						
Vagina	5							5						
Eyeball	5							5						
Harderian gland	5							5						
Sciatic nerve	5							5						
Skeletal muscle	5							5						
Femur	5							5						
Marrow, femur	5							5						

- : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Not significantly different from control.

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

Table 35. Results of observations about estrous cycle

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of animals examined	12	12	12	12
Pre-treatment period				
Number of animals showing type of cycle				
4-day cycle	11	10	10	11
5-day cycle	1	2	2	1
Mean length of estrous cycle in days; Mean±S.D. (N)	4.1 ± 0.3 (12)	4.2 ± 0.4 (12)	4.2 ± 0.4 (12)	4.1 ± 0.3 (12)
Treatment period				
Number of animals showing each type of cycle				
4-day cycle	12	10	10	11
4/5-day cycle	0	1	2	0
5-day cycle	0	1	0	1
Mean length of estrous cycle in days; Mean±S.D. (N)	4.0 ± 0.0 (12)	4.1 ± 0.3 (12)	4.1 ± 0.2 (12)	4.1 ± 0.3 (12)
Frequency of animals that show abnormal estrous cycles after the treatment	0 / 12	0 / 12	0 / 12	0 / 12
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.1 ± 0.3 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (11)	1.0 ± 0.0 (12)

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

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

Table 36. Results of observations about reproductive performance

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of mated pairs [A]	12	12	12	12
Number of copulated pairs [B]	12	12	11	12
Copulation index [(B/A)×100,%]	100.0	100.0	91.7	100.0
Number of fertile males [C]	12	12	11	12
Fertility index [(C/B)×100,%]	100.0	100.0	100.0	100.0
Pairing days until copulation ;Mean±S.D.(N)	2.9 ± 1.6 (12)	1.6 ± 0.9 (12)	2.6 ± 1.1 (11)	2.4 ± 1.3 (12)

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

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

Table 37. Observation of offspring (F_1)

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of dams	12	12	11	12
Gestation length (days)				
Mean ± S.D. per dam	22.0 ± 0.0	21.9 ± 0.3	22.0 ± 0.0	21.9 ± 0.3
Number of corpora lutea				
Total	186	189	175	190
Mean ± S.D. per dam	15.5 ± 2.0	15.8 ± 1.7	15.9 ± 1.5	15.8 ± 1.6
Number of implantation scars				
Total	185	188	174	188
Mean ± S.D. per dam	15.4 ± 2.1	15.7 ± 1.8	15.8 ± 1.4	15.7 ± 1.6
Implantation index (%) [a]	99.4 ± 2.0	99.4 ± 2.0	99.5 ± 1.7	99.0 ± 2.3
Delivery index (dams,%) [b]	100.0	100.0	100.0	100.0
Number of offspring at birth				
Total	177	184	165	174
Mean ± S.D. per dam	14.8 ± 1.9	15.3 ± 1.8	15.0 ± 1.5	14.5 ± 2.3
Number of live offspring at birth				
Male	98	87	81	93
Female	77	95	83	76
Total	175	182	164	169
Mean ± S.D. per dam	14.6 ± 1.6	15.2 ± 1.6	14.9 ± 1.6	14.1 ± 2.4
Sex ratio [c]				
Mean ± S.D. per dam	0.56 ± 0.17	0.48 ± 0.11	0.49 ± 0.08	0.55 ± 0.15
Number of dead offspring				
Total	2	2	1	5
Mean ± S.D. per dam	0.2 ± 0.6	0.2 ± 0.4	0.1 ± 0.3	0.4 ± 0.7
Delivery index (offspring) [d]				
Mean% ± S.D. per dam	95.9 ± 5.6	97.8 ± 3.2	94.9 ± 6.1	92.2 ± 9.2
Birth index [e]				
Mean% ± S.D. per dam	95.1 ± 6.4	96.9 ± 3.3	94.3 ± 5.8	89.5 ± 9.8
Live birth index [f]				
Mean% ± S.D. per dam	99.1 ± 3.0	99.0 ± 2.2	99.4 ± 2.1	97.1 ± 4.6
Number of offspring on day 4				
Male	97	87	81	93
Female	77	95	82	76
Sex ratio [c]				
Mean ± S.D. per dam	0.56 ± 0.17	0.48 ± 0.11	0.50 ± 0.08	0.55 ± 0.15
Viability index [g]				
Mean% ± S.D. per dam	99.5 ± 1.8	100.0 ± 0.0	99.4 ± 1.9	100.0 ± 0.0
Number of external abnormalities [h]	0	0	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

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

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

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

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

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

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

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

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

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

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

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

Group	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Number of dams	12	12	11	12
Male				
Days after birth				
0	6.7 ± 0.4	6.6 ± 0.3	6.5 ± 0.4	6.9 ± 0.5
4	10.6 ± 1.0	10.6 ± 1.0	10.0 ± 1.1	11.0 ± 1.5
Number of dams	11	12	11	12
Female				
Days after birth				
0	6.4 ± 0.3	6.2 ± 0.3	6.2 ± 0.4	6.6 ± 0.5
4	10.1 ± 1.0	9.9 ± 0.9	9.7 ± 1.2	10.5 ± 1.3

Each value shows mean ± S.D. per dam. (g).
Significantly different from the control group (*: P<0.05, **: P<0.01).

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

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

Group	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
Control (vehicle: water for injection)	Number of offspring	175	175	174	174	174
	General appearance, No abnormality	175	174	174	174	174
	General appearance, Death		1			
B-CH 100 mg/kg	Number of offspring	182	182	182	182	182
	General appearance, No abnormality	182	182	182	182	182
B-CH 300 mg/kg	Number of offspring	164	164	164	164	163
	General appearance, No abnormality	164	164	164	163	163
	General appearance, Death				1	
B-CH 1000 mg/kg	Number of offspring	169	169	169	169	169
	General appearance, No abnormality	169	169	169	169	169

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

Table 40. Morphological observations of offspring (F_1)

Dose	Control (vehicle: water for injection)	B-CH 100 mg/kg	B-CH 300 mg/kg	B-CH 1000 mg/kg
Dead offspring				
Number of dead offspring [a)]	3	2	2	5
Number of missing offspring	0	0	0	0
Number of dead offspring examined [b)]	3 (3)	2 (0)	2 (1)	5 (2)
Number of dead offspring with external changes	0	0	0	0
Number of dead offspring with visceral changes	0	0	0	0
Live offspring				
Number of live offspring examined (postnatal day 0)	175	182	164	169
Number of live offsping with external changes	0	0	0	0
Number of live offspring examined (postnatal day 4)	174	182	163	169
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 bacause of their autolysis.

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

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

Control (vehicle: water for injection)

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

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

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

Control (vehicle: water for injection)

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

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

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

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

B-CH 100 mg/kg

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

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

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

B-CH 100 mg/kg

Male No.	Days of administration																																																	
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,b	a,b	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c	a,b,c,d	a,b,c	a,b,c,d	a,b,c	a,b,c,d	a,b,c	a,b,c,d	
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	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
a	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	1	1	1	1	1	1	1	1	1	1	
b	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	1	1	1	1	1	1	1	1	1	1	
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	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	0	0	0	1	0	1	0	1	0	1	

Pre: Before administration. Post: after administration.
-: General appearance. No abnormality.
a: Nose. Smudge of perinasal area.
b: Eye. Eyeball. Bulbi. Globe. Reddish tear.
c: Behavior. Decrease in locomotor activity.
d: Excretion. Decrease in amount of feces.

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

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

B-CH 300 mg/kg

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

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

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

B-CH 300 mg/kg

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

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

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

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

B-CH 1000 mg/kg

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

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

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

B-CH 1000 mg/kg

Male No.	Days of administration																																	
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
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	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	12	7

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

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

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

Control (vehicle: water for injection)

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

-: General appearance, No abnormality.

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

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

B-CH 1000 mg/kg

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

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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	11	11	6	6	3	3	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	12	12	11	11	6	6	3	3	1	1	1	1	1	1

Pre: Before administration, Post: after administration.

-: General appearance. No abnormality.

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

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

B-CH 100 mg/kg

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

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

B-CH 300 mg/kg

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

Female No.	Days of administration																									
	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
F03025	-	-	-	-	-	-	-	-	-	-	-	-														
F03026	-	-	-	-	-	-	-	-	-	-																
F03027	-	-	-	-	-	-																				
F03028	-	-	-	-	-	-	-	-																		
F03029	-	-	-	-	-	-	-	-	-	-	-	-														
F03030	-	-	-	-	-	-	-	-																		
F03031	-	-	-	-	-	-	-	-	-	-																
F03032	-	-	-	-	-	-	-	-																		
F03033	-	-	-	-	-	-	-	-	-	-	-	-														
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-																				
F03036	-	-	-	-	-	-	-	-	-	-																
Number of females	12	12	12	12	12	12	10	10	7	7	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
-	12	12	12	12	12	12	10	10	7	7	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1

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

Appendix 2-1-3 (continued). General conditions of female rats

B-CH 300 mg/kg

Female No.	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
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Female No.	Days of administration																									
	38		39		40		41		42		43		44		45		46		47		48		49		50	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

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

B-CH 300 mg/kg

Female No.	Days of administration					
	51		52		53	
	Pre	Post	Pre	Post	Pre	Post
F03034	-	-	-	-	-	
Number of females	1	1	1	1	1	
-	1	1	1	1	1	

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

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

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

B-CH 1000 mg/kg

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

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

Control (vehicle: water for injection)

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

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

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

Control (vehicle: water for injection)

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

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

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

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

B-CH 1000 mg/kg

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

B-CH 1000 mg/kg

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

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

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

B-CH 1000 mg/kg

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

-: General appearance, No abnormality.

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

Appendix 3-1. General conditions in dams during pregnancy

Control (vehicle: water for injection)

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

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

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

Control (vehicle: water for injection)

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

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

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

Appendix 3-2. General conditions in dams during pregnancy

B-CH 100 mg/kg

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

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

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

B-CH 100 mg/kg

Dam No.	Days of pregnancy																	
	14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4

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

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

Appendix 3-3. General conditions in dams during pregnancy

B-CH 300 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11

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

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

B-CH 300 mg/kg

Dam No.	Days of pregnancy																	
	14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6	6
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6	6

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

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

Appendix 3-4. General conditions in dams during pregnancy

B-CH 1000 mg/kg

Dam No.	Days of pregnancy																											
	0		1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

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

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

B-CH 1000 mg/kg

Dam No.	Days of pregnancy																	
	14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6

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

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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	7	7	12	12	12	12	12	12	12	12	12
-	7	7	12	12	12	12	12	12	12	12	12

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

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

Appendix 4-2. General conditions in dams during lactation

B-CH 100 mg/kg

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

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

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

Appendix 4-3. General conditions in dams during lactation

B-CH 300 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	#	#	-	-	-	-	-	-	-	-	-
F03035	#	#	-	-	-	-	-	-	-	-	-
F03036	#	#	-	-	-	-	-	-	-	-	-
Number of dams	5	5	11	11	11	11	11	11	11	11	11
-	5	5	11	11	11	11	11	11	11	11	11

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

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

Appendix 4-4. General conditions in dams during lactation

B-CH 1000 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F04037	#	#	-	-	-	-	-	-	-	-	-
F04038	#	#	-	-	-	-	-	-	-	-	-
F04039	#	#	-	-	-	-	-	-	-	-	-
F04040	#	#	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-
F04043	#	#	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	-	-	-	-	-	-	-
F04045	#	#	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-
F04048	#	#	-	-	-	-	-	-	-	-	-
Number of dams	5	5	12	12	12	12	12	12	12	12	12
-	5	5	12	12	12	12	12	12	12	12	12

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

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

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

Control (vehicle: water for injection)

Male No.	Cage-side observation [a]									Observations made while handling [b]																	Open-field observations [c]								
	Locomotor in home-cage									Lacrimation									Fur									Gait								
	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
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		
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		
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		
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		
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		
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		
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		
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
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
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
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
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
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	4:0	4:0	4:0	4:0	4:0	4:0	4:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	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)

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

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

Lacrimation [2, normal; 4, reddish tear]

Fur [2, normal; 1, soiled fur]

Gait [2, normal; 1, abnormal gait]

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

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

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

Control (vehicle: water for injection)

Male No.	Open-field observations [c]																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M01001	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01002	2	1	0	1	1	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	1	0	0	1	0	0			0	0	0	0	0	0	0		
M01007	2	0	1	0	0	1	0			0	0	0	0	0	0	0		
M01008	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
M01009	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M01010	0	0	0	0	1	1	0	1	3	0	0	0	0	0	0	0	0	0
M01011	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
M01012	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	6	3	1	1	3	2	0	2	5	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 (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

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

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

B-CH 100 mg/kg

Male No.	Cage-side observation [a]							Observations made while handling [b]																			Open-field observations [c]						
	Locomotor in home-cage							Lacrimation							Fur							Gait						
	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
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
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
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
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
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
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
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
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
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
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
M02023	2	2	2	2	2	2	1	2	2	2	2	2	4	4	2	2	2	2	2	2	1	2	2	2	2	2	1	1
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
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:1	4:0	4:0	4:0	4:0	4:0	4:1	4:1	1:0	1:0	1:0	1:0	1:0	1:0	1:1	1:0	1:0	1:0	1:0	1:0	1:1	1:1
(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)

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

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

Lacrimation [2, normal; 4, reddish tear]

Fur [2, normal; 1, soiled fur]

Gait [2, normal; 1, abnormal gait]

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

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

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

B-CH 100 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	1	1	1	1	1	1	0	0	0	0	0	0	0
M02015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02016	1	0	1	1	1	1	1	0	0	0	0	0	0	0
M02017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02018	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02020	0	0	0	0	1	0	0	0	0	0	0	0	0	0
M02021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02024	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	2	1	2	2	3	2	2	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 8 of treatment; [c] 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 (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

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

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

B-CH 300 mg/kg

Male No.	Cage-side observation [a)]							Observations made while handling [b)]																Open-field observations [c)]						
	Locomotor in home-cage							Lacrimation							Fur							Gait						
	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
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
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
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
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
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
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
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
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
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
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
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
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
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	4:0	4:0	4:0	4:0	4:0	4:0	4:0	1:0	1:0	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)

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

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

Lacrimation [2, normal; 4, reddish tear]

Fur [2, normal; 1, soiled fur]

Gait [2, normal; 1, abnormal gait]

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

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

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

B-CH 300 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	1	1	1	0	1	1	0	0	0	0	0	0	0
M03026	0	0	0	0	0	1	0	0	0	0	0	0	0	2
M03027	0	0	0	0	0	0	1	0	0	0	0	0	0	0
M03028	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M03029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03030	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03031	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0
M03034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03035	0	0	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	0	1	1	2	0	2	2	0	0	0	0	0	0	2
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

B-CH 1000 mg/kg

Male No.	Cage-side observation [a]									Observations made while handling [b]																					Open-field observations [c]								
	Locomotor in home-cage									Lacrimation									Fur									Gait								
	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
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		
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		
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		
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		
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		
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		
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		
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
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
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
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
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
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	4:0	4:0	4:0	4:0	4:0	4:0	4:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	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)

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

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

Lacrimation [2, normal; 4, reddish tear]

Fur [2, normal; 1, soiled fur]

Gait [2, normal; 1, abnormal gait]

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

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

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

B-CH 1000 mg/kg

Male No.	Open-field observations [c]																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M04037	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04038	1	0	0	0	0	0	0			1	0	0	0	0	0	0		
M04039	1	0	0	0	0	1	1			0	0	0	0	0	0	0		
M04040	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04041	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04042	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04043	0	0	0	0	0	0	1			0	0	0	0	0	0	0		
M04044	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04045	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04046	0	0	0	1	0	0	0	0	3	0	0	0	0	0	0	0	0	0
M04047	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04048	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	2	0	0	1	0	1	2	0	3	1	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 (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, grooming, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

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

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

Control (vehicle: water for injection)

Female No.	Open-field observations [c]						
	Urination						
	Pre [a]	T8 [b]	T15	T24	T30	T36	L [c]
F01001	0	0	0	0	0	0	0
F01002	0	0	0	0	0	0	2
F01003	0	0	0	0	0	0	0
F01004	0	0	0	0	0	0	0
F01005	0	0	0	0	0	0	0
F01006	0	0	0	0	0	0	0
F01007	0	0	0	0	0	0	0
F01008	0	0	0	0	0	0	0
F01009	0	0	1	0	0	0	0
F01010	0	0	0	0	0	0	3
F01011	0	0	0	0	0	0	0
F01012	0	0	0	0	0	0	0
Total score	0	0	1	0	0	0	5
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

B-CH 100 mg/kg

Female No.	Open-field observations [c]						
	Urination						
	Pre [a]	T8 [b]	T15	T24	T30	T36	L [c]
F02013	0	0	0	0	0	0	0
F02014	0	0	0	0	0	0	0
F02015	0	0	0	0	0	0	0
F02016	0	0	0	0	0	0	0
F02017	0	0	0	0	0	0	0
F02018	0	0	0	0	0	0	0
F02019	0	0	0	0	0	0	0
F02020	0	0	0	0	0	0	0
F02021	0	0	0	0	0	0	0
F02022	0	0	0	0	0	0	0
F02023	0	0	0	0	0	0	0
F02024	0	0	0	0	0	0	0
Total score	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

B-CH 300 mg/kg

Female No.	Open-field observations [c]								
	Urination								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]
F03025	0	0	0	0	0	0			0
F03026	0	0	0	0	0	0			0
F03027	0	0	0	0	0	0			0
F03028	0	0	0	0	0	0			0
F03029	0	0	0	0	0	0			0
F03030	0	0	0	0	0	0			0
F03031	0	0	0	0	0	0			0
F03032	1	0	0	0	0	0			0
F03033	0	0	0	0	0	0			0
F03034	0	0	0	0	0	0	0	0	
F03035	0	0	0	0	0	0			0
F03036	1	0	0	0	0	0			0
Total score	2	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

B-CH 1000 mg/kg

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

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

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

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

Control (vehicle: water for injection)

Female No.	Open-field observations [c]								
	Urination								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14
F05049	0	0	0	0	0	0	0		
F05050	0	0	0	0	0	0	0		
F05051	0	0	0	0	0	0	0		
F05052	0	0	0	0	0	0	0		
F05053	0	0	0	0	0	0	0		
F05054	0	0	0	0	1	0	0	0	0
F05055	0	0	0	0	0	0	0	0	0
F05056	0	0	0	0	0	0	0	0	0
F05057	0	0	0	0	0	0	0	0	0
F05058	0	0	0	0	0	0	0	0	0
Total score	0	0	0	0	1	0	0	0	0
(N)	(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 (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex, pinna reflex, defecation).

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

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

B-CH 1000 mg/kg

Female No.	Open-field observations [c)]								
	Urination								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14
F06059	0	0	0	0	0	0	0		
F06060	0	0	0	0	0	0	0		
F06061	0	0	0	0	0	0	0		
F06062	0	0	0	0	0	0	0		
F06063	0	0	0	0	0	0	0		
F06064	0	0	0	0	0	0	0	0	0
F06065	0	0	0	0	0	0	0	0	0
F06066	0	0	0	0	0	0	0	0	0
F06067	0	0	0	0	0	0	0	0	0
F06068	0	0	0	0	0	0	0	0	0
Total score	0	0	0	0	0	0	0	0	0
(N)	(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 (posture in home-cage, locomoter activity in home-cage, vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, handling behavir, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex, pinna reflex, defecation).

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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	413.9	430.3	443.6	472.7	492.0	521.3	541.2	544.8
M01002	420.4	433.1	447.2	483.3	503.7	529.6	554.5	559.9
M01003	420.7	435.5	449.0	469.4	499.2	530.3	560.1	584.1
M01004	388.5	400.0	407.9	434.9	459.2	478.3	499.6	509.0
M01005	430.4	437.6	443.3	445.2	467.4	489.8	524.0	528.9
M01006	396.3	409.8	421.1	452.7	475.5	501.3	518.0	527.6
M01007	389.5	402.0	411.6	448.4	469.8	497.5	520.7	533.5
M01008	424.1	421.4	443.6	466.9	475.5	499.1	521.0	541.7
M01009	409.3	417.9	425.7	452.7	468.8	497.0	506.5	528.8
M01010	414.4	419.8	437.1	468.4	495.8	528.4	544.7	561.2
M01011	405.0	427.3	439.8	470.0	488.1	511.1	524.8	547.3
M01012	433.4	445.5	460.2	486.9	506.7	527.4	542.7	562.2
Number of males	12	12	12	12	12	12	12	12
Mean	412.2	423.4	435.8	462.6	483.5	509.3	529.8	544.1
S.D.	15.0	14.2	15.9	15.8	16.0	17.8	18.7	20.4

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

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

B-CH 100 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M02013	428.6	444.8	463.2	503.8	527.1	560.1	576.8	587.3
M02014	412.5	426.5	442.2	473.2	492.9	513.5	534.5	540.2
M02015	405.3	419.0	432.2	459.7	479.2	502.7	512.4	513.4
M02016	395.2	397.5	403.4	426.9	453.3	480.6	496.4	497.7
M02017	391.4	406.8	426.4	460.2	474.9	494.8	518.1	526.8
M02018	377.2	378.9	386.4	407.8	408.8	437.9	454.8	470.6
M02019	420.2	431.7	446.1	481.2	508.4	545.1	565.3	588.5
M02020	422.8	437.7	455.8	490.1	514.4	554.2	587.9	606.1
M02021	420.0	429.1	435.2	449.5	466.6	484.1	499.5	514.2
M02022	418.1	433.0	448.5	483.4	501.8	519.6	546.6	559.0
M02023	397.1	407.0	416.4	441.2	467.0	502.5	528.5	416.9
M02024	400.9	407.5	414.0	439.2	452.2	484.3	497.0	501.1
Number of males	12	12	12	12	12	12	12	12
Mean	407.4	418.3	430.8	459.7	478.9	506.6	526.5	526.8
S.D.	15.4	19.1	22.6	28.1	32.7	34.9	38.4	54.0
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	KW	KW	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

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

B-CH 300 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M03025	421.5	434.5	450.5	480.1	500.7	521.4	549.6	567.6
M03026	408.0	422.2	434.3	469.9	490.1	525.2	554.0	557.1
M03027	423.4	442.1	459.8	497.5	518.1	549.7	578.4	587.7
M03028	407.4	406.6	419.2	443.3	451.0	454.8	469.8	477.0
M03029	397.0	400.9	418.7	442.9	457.0	473.6	488.1	500.4
M03030	425.8	440.3	454.6	483.1	497.7	524.2	553.5	568.5
M03031	408.1	417.0	430.5	461.4	471.8	490.5	514.7	529.9
M03032	391.2	406.8	415.0	436.3	466.9	490.3	510.8	518.8
M03033	434.3	444.9	462.7	508.8	526.5	562.5	588.1	610.5
M03034	409.8	415.8	427.3	444.9	443.2	485.6	500.5	520.7
M03035	408.8	413.1	425.6	451.7	471.0	499.0	515.6	529.6
M03036	393.4	402.9	419.4	437.9	459.5	469.3	490.2	503.7
Number of males	12	12	12	12	12	12	12	12
Mean	410.7	420.6	434.8	463.2	479.5	503.8	526.1	539.3
S.D.	13.3	16.0	17.4	24.5	26.8	33.0	37.8	39.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	KW	KW	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

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

B-CH 1000 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M04037	393.8	396.9	408.3	427.6	452.1	481.5	502.7	514.9
M04038	423.6	424.7	431.6	451.9	492.4	525.3	550.8	549.6
M04039	431.0	432.5	444.4	467.6	483.8	516.1	531.2	532.3
M04040	400.6	403.9	405.3	424.5	456.0	484.9	515.8	532.0
M04041	420.2	429.2	434.7	439.0	465.6	500.8	518.5	514.3
M04042	432.2	440.6	451.8	477.6	494.7	512.6	537.4	550.9
M04043	413.9	410.2	421.3	445.3	469.1	501.3	522.3	541.9
M04044	382.3	393.0	388.0	417.9	446.8	474.1	499.7	523.9
M04045	405.1	418.9	435.8	466.1	489.2	509.9	527.6	539.4
M04046	395.5	395.8	407.9	440.4	466.7	492.2	516.3	530.2
M04047	411.5	428.9	443.3	457.9	489.8	526.9	545.4	566.0
M04048	410.7	407.3	413.5	452.0	477.8	513.8	541.8	558.9
Number of males	12	12	12	12	12	12	12	12
Mean	410.0	415.2	423.8	447.3	473.7	503.3	525.8	537.9
S.D.	15.4	16.1	19.4	18.4	16.6	17.2	16.2	16.4
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	KW	KW	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 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	545.6	558.3	576.2
M01009	527.2	540.6	558.6
M01010	559.7	571.6	582.3
M01011	548.0	560.9	580.0
M01012	562.3	580.4	607.5
Number of males	5	5	5
Mean	548.6	562.4	580.9
S.D.	13.9	15.0	17.5

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

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

B-CH 1000 mg/kg

Male No.	Days of recovery		
	1	7	14
M04044	522.5	541.4	568.0
M04045	530.2	548.3	573.2
M04046	534.0	544.7	539.9
M04047	569.4	582.0	575.4
M04048	559.3	580.3	592.9
Number of males	5	5	5
Mean	543.1	559.3	569.9
S.D.	20.2	20.1	19.2
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 β-Cyclodextrin, 2-hydroxypropyl ethers 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	231.9	232.1	235.9	249.5	
F01002	258.9	264.5	268.1	268.6	
F01003	232.2	244.6	251.9	261.0	
F01004	243.4	248.6	246.1	246.9	269.4
F01005	253.0	263.2	273.3	277.2	
F01006	251.9	255.1	252.0	257.1	
F01007	240.4	260.4	266.4	272.9	
F01008	233.7	230.1	229.8	247.9	
F01009	262.3	266.0	274.6	283.3	
F01010	262.0	270.8	282.6	291.4	
F01011	238.5	254.1	259.4	263.2	
F01012	266.4	269.6	286.7	309.4	
Number of females	12	12	12	12	
Mean	247.9	254.9	260.6	269.0	
S.D.	12.7	13.7	17.9	19.0	

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

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

B-CH 100 mg/kg

Female No.	Days of administration			
	1	4	7	14
F02013	226.9	231.5	236.4	249.6
F02014	248.4	253.6	267.5	279.6
F02015	243.4	243.1	256.1	259.6
F02016	266.8	264.2	270.8	280.5
F02017	252.4	255.8	259.9	268.2
F02018	264.2	272.3	284.1	289.5
F02019	249.7	261.0	263.0	278.4
F02020	260.5	271.0	277.6	285.8
F02021	250.9	254.0	262.7	278.9
F02022	269.4	265.8	283.8	298.6
F02023	254.2	257.2	268.4	280.9
F02024	256.1	252.7	272.0	283.7
Number of females	12	12	12	12
Mean	253.6	256.9	266.9	277.8
S.D.	11.5	11.5	13.0	13.2
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

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

B-CH 300 mg/kg

Female No.	Days of administration								
	1	4	7	14	21	28	35	42	49
F03025	238.7	245.1	244.6	265.8					
F03026	242.1	246.5	247.9	248.6					
F03027	263.4	255.9	266.8	277.1					
F03028	239.7	253.1	259.8	269.9					
F03029	247.2	248.0	248.2	256.1					
F03030	247.4	254.4	262.0	271.4					
F03031	252.2	258.9	261.4	265.4					
F03032	256.5	265.6	274.0	278.1					
F03033	248.7	254.9	262.5	264.1					
F03034	236.8	242.4	245.2	257.5	281.9	292.2	280.9	282.3	295.7
F03035	236.3	239.8	245.3	261.3					
F03036	264.6	270.3	275.7	283.2					
Number of females	12	12	12	12					
Mean	247.8	252.9	257.8	266.5					
S.D.	9.8	9.2	11.3	10.0					
Significance	NS	NS	NS	NS	---	---	---	---	---
Statistical method	AN	AN	AN	AN	NA	NA	NA	NA	NA

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

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

B-CH 1000 mg/kg

Female No.	Days of administration			
	1	4	7	14
F04037	248.8	250.0	258.1	261.5
F04038	263.3	276.8	289.9	296.4
F04039	234.7	248.1	255.2	258.3
F04040	254.3	258.1	257.4	264.6
F04041	271.7	269.7	289.8	297.5
F04042	236.5	244.2	248.5	251.4
F04043	239.0	250.7	248.3	265.2
F04044	264.4	272.6	275.7	298.1
F04045	241.2	238.0	249.3	258.2
F04046	257.2	256.6	260.4	274.3
F04047	249.7	254.2	263.1	277.7
F04048	237.4	241.4	242.2	261.2
Number of females	12	12	12	12
Mean	249.9	255.0	261.5	272.0
S.D.	12.4	12.4	15.8	16.8
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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	224.7	240.1	251.0	260.3	269.5	277.7	280.2	278.0
F05050	258.9	264.4	274.7	265.2	285.6	284.0	297.2	300.9
F05051	254.8	259.7	261.5	263.8	269.7	271.8	275.0	279.3
F05052	258.5	271.3	277.6	286.7	293.8	306.5	310.6	310.5
F05053	255.7	272.9	270.6	278.9	284.5	298.0	301.9	297.7
F05054	268.8	282.4	286.3	286.8	300.0	311.1	314.8	314.8
F05055	261.0	271.7	276.7	291.6	310.7	316.7	322.5	328.3
F05056	246.7	250.2	260.9	270.1	276.7	282.0	298.5	305.4
F05057	253.1	259.1	259.2	273.4	289.3	295.0	295.1	305.5
F05058	227.6	234.2	236.9	248.6	263.0	278.3	286.4	288.6
Number of females	10	10	10	10	10	10	10	10
Mean	251.0	260.6	265.5	272.5	284.3	292.1	298.2	300.9
S.D.	14.3	15.3	14.6	13.6	14.9	15.6	15.1	15.7

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

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

B-CH 1000 mg/kg

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F06059	266.4	279.3	277.1	301.8	312.1	320.3	329.1	338.3
F06060	257.0	263.0	271.0	282.8	290.0	296.7	302.2	304.9
F06061	256.7	262.9	261.5	275.1	282.9	304.8	303.1	301.6
F06062	253.9	254.5	255.2	261.3	270.6	278.7	283.6	285.5
F06063	270.8	266.2	271.0	286.3	300.5	303.2	308.5	324.0
F06064	225.9	235.7	240.8	236.8	236.2	247.5	260.3	263.4
F06065	274.5	283.5	289.5	297.4	315.9	334.0	342.3	348.5
F06066	238.0	246.7	254.9	259.8	279.7	290.8	297.2	299.1
F06067	246.4	265.7	265.0	266.8	276.0	281.8	284.0	290.6
F06068	245.1	251.9	251.2	254.6	269.0	277.7	277.9	281.6
Number of females	10	10	10	10	10	10	10	10
Mean	253.5	260.9	263.7	272.3	283.3	293.6	298.8	303.8
S.D.	15.1	14.4	14.1	20.3	23.3	24.3	24.3	26.4
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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	318.4	320.1	326.2
F05055	326.8	336.9	345.5
F05056	304.6	309.2	313.9
F05057	299.9	314.3	316.3
F05058	293.6	303.4	295.3
Number of females	5	5	5
Mean	308.7	316.8	319.4
S.D.	13.6	12.8	18.4

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

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

B-CH 1000 mg/kg

Female No.	Days of recovery		
	1	7	14
F06064	268.3	276.2	283.0
F06065	353.1	358.6	350.8
F06066	303.1	310.8	318.4
F06067	291.8	303.1	290.1
F06068	285.9	293.9	300.6
Number of females	5	5	5
Mean	300.4	308.5	308.6
S.D.	32.0	30.8	27.1
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 9-1. Body weights of dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	255.8	292.9	334.6	424.4
F01002	275.1	318.7	356.0	436.9
F01003	265.3	296.0	327.2	417.9
F01004	281.1	322.7	370.2	451.2
F01005	278.9	308.8	341.5	424.0
F01006	267.3	308.1	338.1	417.3
F01007	279.1	320.8	358.8	441.3
F01008	245.7	276.8	310.3	384.2
F01009	288.9	338.0	381.3	448.5
F01010	290.2	345.2	386.8	496.0
F01011	266.0	302.0	325.1	387.7
F01012	293.3	345.8	385.0	472.5
Number of dams	12	12	12	12
Mean	273.9	314.7	351.2	433.5
S.D.	14.4	21.4	25.6	32.0

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

Appendix 9-2. Body weights of dams during pregnancy

B-CH 100 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	244.4	279.1	317.2	392.4
F02014	280.7	322.8	352.1	438.8
F02015	261.8	284.5	323.9	415.1
F02016	275.3	307.2	335.3	416.1
F02017	274.4	292.1	325.6	400.8
F02018	291.1	323.9	362.1	461.4
F02019	269.5	317.6	363.1	460.8
F02020	294.0	320.5	362.4	457.2
F02021	277.0	324.4	361.0	441.1
F02022	292.0	334.7	363.0	439.3
F02023	277.2	306.9	338.0	415.3
F02024	278.8	329.0	368.5	464.2
Number of dams	12	12	12	12
Mean	276.4	311.9	347.7	433.5
S.D.	13.8	18.1	18.5	25.0
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 9-3. Body weights of dams during pregnancy

B-CH 300 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03025	275.2	303.2	337.3	406.3
F03026	265.4	294.6	327.1	421.5
F03027	277.0	312.4	351.4	437.6
F03028	270.1	308.0	333.7	402.8
F03029	263.6	293.2	328.8	405.6
F03030	268.5	301.1	331.0	409.9
F03031	277.8	309.7	345.9	436.7
F03032	287.2	324.3	356.4	432.6
F03033	275.2	313.3	359.6	454.2
F03035	258.7	288.8	321.2	390.5
F03036	288.9	334.4	365.3	460.2
Number of dams	11	11	11	11
Mean	273.4	307.5	341.6	423.4
S.D.	9.4	13.6	14.8	22.5
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 9-4. Body weights of dams during pregnancy

B-CH 1000 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	279.4	314.0	357.3	455.3
F04038	306.5	335.3	378.6	467.1
F04039	263.7	295.9	336.1	413.7
F04040	276.7	308.2	341.8	438.4
F04041	287.8	345.0	389.5	484.6
F04042	258.1	294.1	334.7	403.2
F04043	266.0	291.5	318.4	389.2
F04044	308.1	339.4	387.4	461.9
F04045	254.6	295.1	335.9	418.1
F04046	281.3	312.0	341.8	430.4
F04047	281.2	321.4	352.4	410.0
F04048	274.6	309.7	347.3	443.8
Number of dams	12	12	12	12
Mean	278.2	313.5	351.8	434.6
S.D.	16.9	18.5	22.5	28.9
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 10-1. Body weights of dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation	
	0	4
F01001	300.1	319.3
F01002	342.1	357.6
F01003	307.7	322.1
F01004	362.7	375.3
F01005	335.2	325.1
F01006	320.3	335.2
F01007	336.4	355.7
F01008	280.2	305.3
F01009	362.6	354.5
F01010	348.4	363.4
F01011	309.9	324.1
F01012	355.9	346.5
Number of dams	12	12
Mean	330.1	340.3
S.D.	26.5	21.4

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

Appendix 10-2. Body weights of dams during lactation

B-CH 100 mg/kg

Dam No.	Days of lactation	
	0	4
F02013	315.6	312.4
F02014	326.8	342.7
F02015	289.4	324.2
F02016	320.9	322.2
F02017	312.9	308.1
F02018	343.3	352.9
F02019	336.0	351.2
F02020	343.0	359.6
F02021	342.5	368.0
F02022	342.0	351.4
F02023	342.7	336.1
F02024	335.1	353.5
Number of dams	12	12
Mean	329.2	340.2
S.D.	16.8	19.4
Significance	NS	NS
Statistical method	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 10-3. Body weights of dams during lactation

B-CH 300 mg/kg

Dam No.	Days of lactation	
	0	4
F03025	301.2	330.2
F03026	300.4	328.9
F03027	339.7	335.9
F03028	300.1	277.1
F03029	299.5	331.6
F03030	304.0	304.0
F03031	352.5	345.3
F03032	332.1	340.7
F03033	333.4	352.6
F03035	320.5	319.3
F03036	380.6	356.2
Number of dams	11	11
Mean	324.0	329.3
S.D.	26.6	22.7
Significance	NS	NS
Statistical method	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 10-4. Body weights of dams during lactation

B-CH 1000 mg/kg

Dam No.	Days of lactation	
	0	4
F04037	349.2	341.7
F04038	379.8	377.0
F04039	321.9	332.6
F04040	328.1	341.7
F04041	359.4	379.4
F04042	308.8	332.9
F04043	324.7	326.3
F04044	339.0	363.5
F04045	307.0	316.4
F04046	307.3	324.5
F04047	319.9	326.5
F04048	340.2	330.8
Number of dams	12	12
Mean	332.1	341.1
S.D.	22.4	20.9
Significance	NS	NS
Statistical method	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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	36.2	30.9	29.1	29.0	30.8	28.7
M01002	28.1	29.3	28.2	31.5	28.1	28.8
M01003	29.1	28.3	27.3	32.9	33.5	28.5
M01004	30.9	30.5	27.6	25.9	31.1	31.9
M01005	32.7	25.9	25.6	30.6	33.4	32.1
M01006	26.9	28.6	27.0	33.4	27.7	28.6
M01007	29.8	30.6	29.2	27.9	31.1	29.6
M01008	29.2	29.7	28.8	32.8	35.4	28.9
M01009	29.1	29.6	26.3	29.7	34.6	28.7
M01010	29.1	31.1	30.6	36.6	33.2	32.7
M01011	33.3	30.8	26.5	26.1	29.0	29.5
M01012	32.2	32.6	26.7	30.3	29.9	29.5
Number of males	12	12	12	12	12	12
Mean	30.6	29.8	27.7	30.6	31.5	29.8
S.D.	2.6	1.7	1.5	3.1	2.5	1.5

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

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

B-CH 100 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02013	34.7	32.5	35.6	34.7	33.4	34.6
M02014	37.7	34.2	30.0	27.6	31.0	29.9
M02015	32.2	30.8	29.3	29.7	30.1	29.2
M02016	29.2	27.6	25.9	29.8	27.7	27.4
M02017	40.3	34.2	35.3	32.3	31.0	35.5
M02018	26.7	24.1	22.9	25.4	22.7	24.3
M02019	35.6	33.4	32.9	35.4	35.4	37.5
M02020	34.8	33.1	32.7	33.5	34.6	32.6
M02021	34.8	25.3	23.5	26.3	27.4	29.7
M02022	33.7	33.5	33.3	33.0	35.0	32.5
M02023	30.0	28.9	28.4	31.0	11.3	10.7
M02024	29.1	33.2	28.6	31.1	27.9	30.6
Number of males	12	12	12	12	12	12
Mean	33.2	30.9	29.9	30.8	29.0	29.5
S.D.	3.9	3.6	4.3	3.2	6.7	6.9
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	KW	AN	KW	KW

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

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

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

B-CH 300 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03025	36.9	31.5	30.9	32.3	35.2	35.1
M03026	35.1	32.8	33.6	32.1	27.5	30.2
M03027	35.5	36.6	31.8	34.4	36.5	34.7
M03028	30.9	28.5	25.0	30.1	31.6	29.4
M03029	27.5	29.9	22.9	27.9	27.9	27.8
M03030	35.4	31.2	29.4	32.0	34.5	30.2
M03031	29.8	29.0	29.4	32.9	31.8	28.3
M03032	29.1	28.0	27.1	31.1	31.2	28.5
M03033	34.1	38.0	33.8	34.4	35.8	34.8
M03034	31.9	29.8	27.6	28.0	29.1	30.1
M03035	30.5	29.2	27.7	29.7	27.3	29.6
M03036	31.5	26.9	24.0	29.0	28.1	28.8
Number of males	12	12	12	12	12	12
Mean	32.4	31.0	28.6	31.2	31.4	30.6
S.D.	3.0	3.4	3.6	2.2	3.4	2.7
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	KW	AN	KW	KW

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

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

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

B-CH 1000 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04037	26.3	26.3	25.1	29.0	30.3	29.1
M04038	29.5	25.5	31.0	35.9	33.4	29.2
M04039	31.8	25.9	26.8	30.6	30.2	26.6
M04040	27.6	24.5	26.5	30.5	33.1	30.2
M04041	28.5	28.7	24.8	31.9	26.7	29.4
M04042	31.1	31.1	28.8	35.5	31.3	30.0
M04043	29.1	27.8	27.0	31.7	30.2	31.9
M04044	29.2	25.3	26.6	29.5	26.1	32.9
M04045	33.2	28.0	29.5	32.4	28.6	31.8
M04046	26.1	29.3	30.2	33.8	29.7	33.3
M04047	31.6	33.5	29.4	32.7	34.9	34.6
M04048	20.6	27.5	27.1	30.5	28.7	30.7
Number of males	12	12	12	12	12	12
Mean	28.7	27.8	27.7	32.0	30.3	30.8
S.D.	3.4	2.6	2.0	2.2	2.6	2.2
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	KW	AN	KW	KW

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

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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	32.2	32.4
M01009	29.7	34.2
M01010	31.9	31.7
M01011	29.6	30.7
M01012	32.5	31.9
Number of males	5	5
Mean	31.2	32.2
S.D.	1.4	1.3

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

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

B-CH 1000 mg/kg

Male No.	Days of recovery	
	6	12
M04044	31.5	34.2
M04045	28.0	30.8
M04046	34.5	34.3
M04047	33.2	30.9
M04048	30.1	28.7
Number of males	5	5
Mean	31.5	31.8
S.D.	2.6	2.4
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 β-Cyclodextrin, 2-hydroxypropyl ethers 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	18.3	19.9	15.7
F01002	17.1	25.8	21.2
F01003	19.5	21.5	19.8
F01004	14.9	20.0	18.7
F01005	24.1	21.3	22.7
F01006	20.5	22.2	18.0
F01007	23.9	22.7	24.3
F01008	17.9	21.2	16.3
F01009	17.2	26.0	26.3
F01010	24.2	24.6	21.1
F01011	22.9	20.4	20.8
F01012	28.3	25.3	28.5
Number of females	12	12	12
Mean	20.7	22.6	21.1
S.D.	3.9	2.3	3.9

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

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

B-CH 100 mg/kg

Female No.	Days of administration		
	1	7	14
F02013	17.2	20.2	15.8
F02014	22.9	19.0	21.2
F02015	22.4	16.0	17.6
F02016	24.3	13.7	20.0
F02017	22.7	19.2	19.9
F02018	22.3	21.4	24.2
F02019	16.8	20.9	19.2
F02020	21.8	23.2	23.8
F02021	23.7	18.5	22.2
F02022	27.2	19.2	25.1
F02023	26.1	18.7	24.7
F02024	23.6	14.5	22.7
Number of females	12	12	12
Mean	22.6	18.7	21.4
S.D.	3.0	2.8	2.9
Significance	NS	**	NS
Statistical method	AN	DU	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

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

B-CH 300 mg/kg

Female No.	Days of administration						
	1	7	14	29	35	41	48
F03025	23.6	19.8	16.7				
F03026	15.9	22.4	18.4				
F03027	23.0	16.5	20.4				
F03028	20.9	20.5	21.5				
F03029	20.4	19.0	13.9				
F03030	22.3	21.9	18.3				
F03031	17.8	22.4	21.5				
F03032	21.7	23.1	23.8				
F03033	15.2	21.3	15.7				
F03034	21.7	17.2	13.8	12.6	18.5	16.5	24.0
F03035	19.1	16.9	22.3				
F03036	16.7	21.1	22.2				
Number of females	12	12	12				
Mean	19.9	20.2	19.0				
S.D.	2.9	2.3	3.4				
Significance	NS	NS	NS	---	---	---	---
Statistical method	AN	DU	AN	NA	NA	NA	NA

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

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

B-CH 1000 mg/kg

Female No.	Days of administration		
	1	7	14
F04037	19.8	24.0	24.8
F04038	25.6	26.1	26.3
F04039	25.2	21.7	24.3
F04040	20.1	20.9	14.7
F04041	25.6	17.5	25.3
F04042	21.3	19.3	18.7
F04043	19.4	22.3	21.3
F04044	24.4	24.0	21.1
F04045	23.0	12.8	20.3
F04046	23.7	22.7	18.1
F04047	17.0	21.4	24.4
F04048	21.5	21.2	16.3
Number of females	12	12	12
Mean	22.2	21.2	21.3
S.D.	2.8	3.5	3.8
Significance	NS	NS	NS
Statistical method	AN	DU	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 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	19.6	20.0	22.6	19.7	17.9	20.2	10.9
F05050	21.8	18.4	19.2	23.0	20.3	23.0	21.0
F05051	23.4	21.7	17.6	18.5	20.3	22.9	21.3
F05052	26.9	25.7	24.1	23.9	23.8	23.6	19.7
F05053	23.7	22.8	19.9	22.2	18.6	23.0	15.6
F05054	18.4	25.3	22.8	17.9	17.0	21.4	18.6
F05055	25.6	22.5	23.0	25.5	25.9	21.0	22.1
F05056	24.3	15.7	23.5	27.1	24.3	16.1	26.4
F05057	22.9	20.3	18.8	20.1	22.2	22.4	20.3
F05058	15.8	22.9	25.0	17.9	19.8	23.8	21.3
Number of females	10	10	10	10	10	10	10
Mean	22.2	21.5	21.7	21.6	21.0	21.7	19.7
S.D.	3.4	3.0	2.5	3.3	2.9	2.3	4.1

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

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

B-CH 1000 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06059	18.8	24.5	24.2	19.4	25.2	17.6	21.6
F06060	24.8	24.5	18.4	25.5	23.5	21.8	20.5
F06061	21.0	21.5	24.8	25.1	21.3	25.6	19.9
F06062	16.4	19.7	20.8	16.4	15.9	19.4	18.0
F06063	22.0	22.7	17.9	24.1	23.6	21.4	24.0
F06064	20.7	21.0	21.2	22.2	17.7	22.0	21.1
F06065	19.8	25.8	24.4	20.8	18.9	26.3	20.9
F06066	17.6	23.6	23.6	18.2	17.9	24.9	20.0
F06067	24.4	25.6	24.0	18.9	16.4	24.9	18.4
F06068	17.2	23.2	22.6	20.0	18.5	23.9	20.8
Number of females	10	10	10	10	10	10	10
Mean	20.3	23.2	22.2	21.1	19.9	22.8	20.5
S.D.	2.9	2.0	2.5	3.1	3.3	2.8	1.7
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	AW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of β-Cyclodextrin, 2-hydroxypropyl ethers 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	19.8	19.5
F05055	20.3	19.8
F05056	22.5	25.3
F05057	20.5	16.8
F05058	23.8	23.1
Number of females	5	5
Mean	21.4	20.9
S.D.	1.7	3.3

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

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

B-CH 1000 mg/kg

Female No.	Days of recovery	
	6	12
F06064	19.8	21.6
F06065	24.3	24.7
F06066	21.6	21.5
F06067	23.3	19.4
F06068	22.2	21.1
Number of females	5	5
Mean	22.2	21.7
S.D.	1.7	1.9
Significance	NS	NS
Statistical method	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 13-1. Food consumption in dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	21.9	23.1	26.8	21.5
F01002	26.0	28.3	26.2	26.8
F01003	20.4	27.7	25.4	21.8
F01004	23.8	29.9	31.4	26.9
F01005	17.7	25.8	23.9	24.7
F01006	22.9	27.5	25.5	20.3
F01007	19.7	28.9	29.8	22.3
F01008	21.4	26.4	23.4	20.8
F01009	25.0	31.7	31.0	20.2
F01010	24.7	33.0	33.3	26.5
F01011	20.0	21.4	24.5	19.6
F01012	31.2	31.6	26.8	29.1
Number of dams	12	12	12	12
Mean	22.9	27.9	27.3	23.4
S.D.	3.6	3.5	3.2	3.2

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

Appendix 13-2. Food consumption in dams during pregnancy

B-CH 100 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	16.9	23.4	22.0	22.1
F02014	22.5	30.7	21.9	23.9
F02015	19.3	23.4	25.0	22.5
F02016	17.9	26.3	22.8	19.4
F02017	18.6	23.7	22.0	21.1
F02018	23.6	24.0	27.8	26.3
F02019	18.1	29.3	28.3	30.1
F02020	20.7	23.8	29.4	28.6
F02021	22.4	30.3	23.0	27.3
F02022	19.4	30.1	31.0	28.2
F02023	20.3	29.5	22.5	27.8
F02024	24.4	31.7	27.2	22.6
Number of dams	12	12	12	12
Mean	20.3	27.2	25.2	25.0
S.D.	2.4	3.4	3.3	3.5
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 13-3. Food consumption in dams during pregnancy

B-CH 300 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03025	20.1	25.3	25.2	23.4
F03026	24.1	22.8	23.1	25.9
F03027	16.5	27.0	25.8	23.1
F03028	20.3	28.9	24.7	19.2
F03029	21.2	24.8	26.4	20.7
F03030	18.9	26.1	21.6	19.0
F03031	22.4	20.3	26.1	23.8
F03032	22.0	26.5	25.9	19.4
F03033	20.4	29.0	31.8	23.4
F03035	19.1	23.5	25.3	24.1
F03036	20.4	28.4	30.4	25.6
Number of dams	11	11	11	11
Mean	20.5	25.7	26.0	22.5
S.D.	2.0	2.7	2.9	2.5
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 13-4. Food consumption in dams during pregnancy

B-CH 1000 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	23.8	29.1	29.6	21.7
F04038	15.9	30.1	30.5	21.0
F04039	23.6	24.5	28.1	22.9
F04040	21.7	27.6	26.6	22.0
F04041	23.1	32.0	35.0	34.0
F04042	20.3	26.3	24.7	22.8
F04043	21.7	24.9	24.0	26.4
F04044	22.9	30.4	30.4	14.9
F04045	20.3	23.7	21.8	14.7
F04046	21.8	30.7	28.3	23.4
F04047	22.8	29.3	23.7	22.6
F04048	24.1	27.0	28.8	26.9
Number of dams	12	12	12	12
Mean	21.8	28.0	27.6	22.8
S.D.	2.3	2.7	3.7	5.1
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 14-1. Food consumption in dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation
	3
F01001	40.7
F01002	52.8
F01003	37.7
F01004	52.8
F01005	34.7
F01006	33.1
F01007	47.7
F01008	41.2
F01009	42.0
F01010	43.5
F01011	38.3
F01012	41.2
Number of dams	12
Mean	42.1
S.D.	6.3

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

Appendix 14-2. Food consumption in dams during lactation

B-CH 100 mg/kg

Dam No.	Days of lactation
	3
F02013	41.7
F02014	50.7
F02015	47.3
F02016	39.1
F02017	39.1
F02018	42.8
F02019	42.9
F02020	44.1
F02021	46.1
F02022	43.7
F02023	38.2
F02024	39.6
Number of dams	12
Mean	42.9
S.D.	3.8
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 14-3. Food consumption in dams during lactation

B-CH 300 mg/kg

Dam No.	Days of lactation
	3
F03025	45.9
F03026	41.3
F03027	43.6
F03028	28.2
F03029	43.6
F03030	32.6
F03031	37.9
F03032	40.9
F03033	41.9
F03035	35.5
F03036	39.1
Number of dams	11
Mean	39.1
S.D.	5.3
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 14-4. Food consumption in dams during lactation

B-CH 1000 mg/kg

Dam No.	Days of lactation
	3
F04037	41.6
F04038	42.0
F04039	41.1
F04040	45.5
F04041	48.4
F04042	44.5
F04043	37.2
F04044	41.7
F04045	44.6
F04046	48.9
F04047	43.2
F04048	42.5
Number of dams	12
Mean	43.4
S.D.	3.2
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

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

Control (vehicle: water for injection)

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

2 or +, normal

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

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

B-CH 100 mg/kg

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

2 or +, normal

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

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

B-CH 300 mg/kg

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

2 or +, normal

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

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

B-CH 1000 mg/kg

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M04037	2	2	2	2	+	+	+
M04038	2	2	2	2	+	+	+
M04039	2	2	2	2	+	+	+
M04040	2	2	2	2	+	+	+
M04041	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

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

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

Control (vehicle: water for injection)
Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F01003	2	2	2	2	+	+	+
F01005	2	2	2	2	+	+	+
F01007	2	2	2	2	+	+	+
F01010	2	2	2	2	+	+	+
F01012	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

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

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

B-CH 100 mg/kg
Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F02014	2	2	2	2	+	+	+
F02015	2	2	2	2	+	+	+
F02016	2	2	2	2	+	+	+
F02019	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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

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

B-CH 300 mg/kg
Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F03027	2	2	2	2	+	+	+
F03028	2	2	2	2	+	+	+
F03030	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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 16-4. Functional findings of female rats at the last week of the dosing period

B-CH 1000 mg/kg
Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F04038	2	2	2	2	+	+	+
F04041	2	2	2	2	+	+	+
F04043	2	2	2	2	+	+	+
F04045	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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 16-5. Functional findings of female rats at the last week of the dosing period

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

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

2 or +, normal

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

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

B-CH 1000 mg/kg
Female, satellite groups

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F06059	2	2	2	2	+	+	+
F06060	2	2	2	2	+	+	+
F06061	2	2	2	2	+	+	+
F06062	2	2	2	2	+	+	+
F06063	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

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

Appendix 17-1. Assessment of grip strength of male rats at the last week of the dosing period

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M01001	0.791	0.210
M01002	0.732	0.536
M01003	0.993	0.267
M01004	0.822	0.505
M01005	1.098	0.367
Number of males	5	5
Mean	0.887	0.377
S.D.	0.153	0.143

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

Appendix 17-2. Assessment of grip strength of male rats at the last week of the dosing period

B-CH 100 mg/kg

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M02013	1.057	0.359
M02014	1.072	0.408
M02015	1.022	0.452
M02016	0.972	0.397
M02017	0.964	0.366
Number of males	5	5
Mean	1.017	0.396
S.D.	0.049	0.037

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

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

Appendix 17-3. Assessment of grip strength of male rats at the last week of the dosing period

B-CH 300 mg/kg

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M03025	0.883	0.531
M03026	0.877	0.610
M03027	0.911	0.473
M03028	0.996	0.393
M03029	0.978	0.422
Number of males	5	5
Mean	0.929	0.486
S.D.	0.055	0.087

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

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

Appendix 17-4. Assessment of grip strength of male rats at the last week of the dosing period

B-CH 1000 mg/kg

Male No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
M04037	0.946	0.416
M04038	1.176	0.474
M04039	0.992	0.449
M04040	1.198	0.590
M04041	0.943	0.415
Number of males	5	5
Mean	1.051	0.469
S.D.	0.126	0.072

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

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

Appendix 18-1. Assessment of grip strength of female rats at the last week of the dosing period

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F01003	1.045	0.482
F01005	0.743	0.360
F01007	0.939	0.733
F01010	0.959	0.476
F01012	1.027	0.527
Number of females	5	5
Mean	0.943	0.516
S.D.	0.120	0.136

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

Appendix 18-2. Assessment of grip strength of female rats at the last week of the dosing period

B-CH 100 mg/kg

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F02014	0.952	0.512
F02015	0.902	0.608
F02016	0.920	0.346
F02019	0.841	0.654
F02021	0.890	0.483
Number of females	5	5
Mean	0.901	0.521
S.D.	0.041	0.120

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

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

Appendix 18-3. Assessment of grip strength of female rats at the last week of the dosing period

B-CH 300 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F03027	0.799	0.332
F03028	0.809	0.309
F03030	1.129	0.301
F03032	1.138	0.371
F03035	0.847	0.353
Number of females	5	5
Mean	0.944	0.333 *
S.D.	0.174	0.029

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

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

Appendix 18-4. Assessment of grip strength of female rats at the last week of the dosing period

B-CH 1000 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
F04038	1.036	0.466
F04041	0.954	0.563
F04043	0.916	0.362
F04045	1.015	0.352
F04047	0.827	0.442
Number of females	5	5
Mean	0.950	0.437
S.D.	0.084	0.086

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

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

Appendix 19-1. Assessment of grip strength of female rats at the last week of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F05049	1.059	0.358
F05050	1.041	0.391
F05051	1.032	0.226
F05052	1.024	0.544
F05053	1.032	0.548
Number of females	5	5
Mean	1.038	0.413
S.D.	0.013	0.136

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

Appendix 19-2. Assessment of grip strength of female rats at the last week of the dosing period, satellite group

B-CH 1000 mg/kg

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F06059	0.940	0.439
F06060	1.057	0.468
F06061	1.042	0.321
F06062	1.016	0.404
F06063	1.070	0.463
Number of females	5	5
Mean	1.025	0.419
S.D.	0.052	0.060

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

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

Appendix 20-1. Motor activity of male rats at the last week of the dosing period

Control (vehicle: water for injection)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1181	973	989	881	4024	38	34	31	20	123
M01002	1278	1101	970	885	4234	49	33	24	20	126
M01003	1198	1248	1181	771	4398	36	41	34	22	133
M01004	1246	1203	1059	510	4018	28	29	26	5	88
M01005	1023	763	705	316	2807	20	17	14	6	57
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1185	1058	981	673	3896	34	31	26	15	105
S.D.	98	196	175	251	629	11	9	8	8	32

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

Appendix 20-2. Motor activity of male rats at the last week of the dosing period

B-CH 100 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02013	1081	1047	991	950	4069	42	36	24	23	125
M02014	886	692	657	744	2979	23	9	11	13	56
M02015	1105	853	823	490	3271	37	29	26	14	106
M02016	1118	1349	1085	887	4439	20	25	17	10	72
M02017	1355	1210	1148	722	4435	46	36	25	15	122
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1109	1030	941	759	3839	34	27	21	15	96
S.D.	167	265	200	178	676	12	11	6	5	31

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

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

Appendix 20-3. Motor activity of male rats at the last week of the dosing period

B-CH 300 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03025	1311	1392	1208	1237	5148	39	35	34	31	139
M03026	1205	1128	1064	979	4376	44	30	19	22	115
M03027	1360	1188	1166	1006	4720	50	32	39	20	141
M03028	1158	1067	981	882	4088	43	38	34	16	131
M03029	1158	796	872	747	3573	43	15	20	7	85
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1238	1114	1058	970	4381	44	30	29	19	122
S.D.	92	216	137	180	600	4	9	9	9	23

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

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

Appendix 20-4. Motor activity of male rats at the last week of the dosing period

B-CH 1000 mg/kg

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04037	1873	1932	1847	1665	7317	26	30	19	11	86
M04038	1320	1026	1105	748	4199	43	26	40	22	131
M04039	1098	959	880	589	3526	39	31	22	11	103
M04040	701	724	746	618	2789	27	44	24	20	115
M04041	937	1128	905	1058	4028	26	43	20	27	116
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1186	1154	1097	936	4372	32	35	25	18	110
S.D.	446	460	439	448	1735	8	8	9	7	17

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

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

Appendix 21-1. Motor activity of female rats at the last week of the dosing period

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01003	1212	999	1006	541	3758	22	14	18	9	63
F01005	1880	1782	1460	1032	6154	35	14	9	3	61
F01007	1086	993	595	515	3189	42	34	12	13	101
F01010	1143	1019	1138	557	3857	29	24	16	1	70
F01012	1224	1167	823	1031	4245	33	26	27	13	99
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1309	1192	1004	735	4241	32	22	16	8	79
S.D.	324	337	326	271	1134	7	9	7	6	20

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

Appendix 21-2. Motor activity of female rats at the last week of the dosing period

B-CH 100 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02014	1276	929	705	523	3433	37	11	10	2	60
F02015	1065	916	713	615	3309	38	24	11	10	83
F02016	678	593	419	402	2092	20	32	17	7	76
F02019	1304	945	970	732	3951	40	26	8	7	81
F02021	870	1161	930	290	3251	28	26	8	11	73
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1039	909	747	512	3207	33	24	11	7	75
S.D.	267	203	220	174	682	8	8	4	4	9

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

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

Appendix 21-3. Motor activity of female rats at the last week of the dosing period

B-CH 300 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03027	1156	923	339	144	2562	36	27	4	0	67
F03028	1048	684	852	693	3277	27	10	10	14	61
F03030	1084	608	607	413	2712	21	8	2	2	33
F03032	985	983	1027	849	3844	43	63	29	21	156
F03035	1102	960	960	630	3652	35	29	18	7	89
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1075	832	757	546	3209	32	27	13	9	81
S.D.	64	173	283	274	563	9	22	11	9	46

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

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

Appendix 21-4. Motor activity of female rats at the last week of the dosing period

B-CH 1000 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04038	1154	882	887	595	3518	32	35	14	20	101
F04041	1275	915	671	225	3086	36	14	8	0	58
F04043	1132	969	663	531	3295	26	17	3	5	51
F04045	1279	937	807	710	3733	27	20	15	3	65
F04047	971	743	914	1066	3694	25	27	26	21	99
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1162	889	788	625	3465	29	23	13	10	75
S.D.	126	88	118	305	274	5	8	9	10	24

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

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

Appendix 22-1. Motor activity of female rats at the last week of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05049	1121	1161	1030	758	4070	48	44	37	7	136
F05050	1157	1172	1089	1020	4438	39	23	31	26	119
F05051	1101	1096	1026	1049	4272	33	48	35	31	147
F05052	1232	1079	1189	1046	4546	35	25	33	21	114
F05053	1205	1342	1350	1145	5042	36	66	59	42	203
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1163	1170	1137	1004	4474	38	41	39	25	144
S.D.	55	104	136	145	365	6	18	11	13	36

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

Appendix 22-2. Motor activity of female rats at the last week of the dosing period, satellite grou

B-CH 1000 mg/kg

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06059	1318	1122	1204	851	4495	33	23	44	10	110
F06060	793	798	635	694	2920	47	38	21	43	149
F06061	1368	1248	1496	1366	5478	48	48	72	33	201
F06062	1013	870	859	973	3715	29	24	17	13	83
F06063	1045	900	821	677	3443	22	28	24	16	90
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1107	988	1003	912	4010	36	32	36	23	127
S.D.	237	189	344	281	998	11	11	23	14	49

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

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

Appendix 23-1-1. 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	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M01003	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
M01004	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
M01005	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
M01001	14.2	1.070	122.7	218.4	137.8	1.74	3.10	1.96
M01002	11.7	1.070	105.9	206.1	124.0	1.24	2.41	1.45
M01003	16.6	1.071	111.7	236.8 §	142.8	1.85	3.93	2.37
M01004	12.1	1.068	100.3	245.0 §	122.7	1.21	2.96	1.48
M01005	22.4	1.049	102.4	195.6 §	97.5	2.29	4.38	2.18
Number of males	5	5	5	5	5	5	5	5
Mean	15.4	1.066	108.6	220.4	125.0	1.67	3.36	1.89
±S.D.	4.4	0.009	9.0	20.6	17.6	0.45	0.79	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.
Turbidity, -: negative
Protein, ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative ; ±: 0.03≦and<0.06 mg/dL
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few

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

Appendix 23-1-2. Urinalysis in male rats

B-CH 100 mg/kg

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02013	Light yellow	-	7.0	2+	-	±	-	-	±	-	-	-	±	-
M02014	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
M02015	Light yellow	-	8.0	+	-	±	-	-	+	-	-	-	±	-
M02016	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M02017	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
M02013	20.7	1.039	45.7	146.5	37.7	0.95	3.03	0.78
M02014	15.3	1.059	61.7	198.1	63.2	0.94	3.03	0.97
M02015	12.9	1.066	133.7	237.1 §	144.2	1.72	3.06	1.86
M02016	19.0	1.049	73.9	185.6	83.0	1.40	3.53	1.58
M02017	28.2	1.038	69.7	151.7	81.3	1.97	4.28	2.29
Number of males	5	5	5	5	5	5	5	5
Mean	19.2	1.050	76.9	183.8	81.9	1.40	3.39	1.50
±S.D.	5.9	0.012	33.5	37.0	39.3	0.46	0.54	0.62

§, 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
Protein, ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative ; ±: 0.03≦and<0.06 mg/dL
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few

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

Appendix 23-1-3. Urinalysis in male rats

B-CH 300 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	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M03028	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
M03029	Light yellow	-	7.0	+	-	±	-	±	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M03025	21.2	1.057	101.1	199.7	117.7	2.14	4.23	2.50
M03026	16.7	1.054	96.3	180.0	83.9	1.61	3.01	1.40
M03027	22.7	1.049	85.8	177.9	88.5	1.95	4.04	2.01
M03028	43.5	1.024	45.8	111.2 §	53.7	1.99	4.84	2.34
M03029	15.1	1.065	130.3	248.0 §	143.1	1.97	3.74	2.16
Number of males	5	5	5	5	5	5	5	5
Mean	23.8	1.050	91.9	183.4	97.4	1.93	3.97	2.08
±S.D.	11.4	0.016	30.6	49.2	34.2	0.19	0.67	0.42

§, 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
Protein, ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative ; ±: 0.03≦and<0.06 mg/dL
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few

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

Appendix 23-1-4. Urinalysis in male rats

B-CH 100 mg/kg

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

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M04037	11.3	1.073	117.1	229.6 §	133.3	1.32	2.59	1.51
M04038	19.6	1.058	121.0	222.3 §	128.7	2.37	4.36	2.52
M04039	15.9	1.057	104.8	209.5 §	104.7	1.67	3.33	1.66
M04040	18.8	1.053	70.8	208.1 §	103.8	1.33	3.91	1.95
M04041	10.5	1.076	139.0	252.4 §	159.5	1.46	2.65	1.67
Number of males	5	5	5	5	5	5	5	5
Mean	15.2	1.063	110.5	224.4	126.0	1.63	3.37	1.86
±S.D.	4.2	0.010	25.4	18.0	23.1	0.44	0.77	0.40

§, 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
Protein, ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative ; ±: 0.03≦and<0.06 mg/dL
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few

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

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

Control (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	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	+	-	+	-	-	2+	-	-	-	±	-
M01010	Light yellow	-	7.5	2+	-	+	-	-	+	-	-	-	±	-
M01011	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	-	-
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	23.3	1.052	83.3	218.5 §	109.4	1.94	5.09	2.55
M01009	20.8	1.054	82.8	203.6	111.5	1.72	4.23	2.32
M01010	17.2	1.063	92.8	235.9 §	115.0	1.60	4.06	1.98
M01011	30.3	1.041	92.3	162.4	96.1	2.80	4.92	2.91
M01012	19.1	1.062	130.4	222.7	148.8	2.49	4.25	2.84
Number of males	5	5	5	5	5	5	5	5
Mean	22.1	1.054	96.3	208.6	116.2	2.11	4.51	2.52
±S.D.	5.1	0.009	19.6	28.3	19.6	0.52	0.46	0.38

§, 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
Protein, ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few

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

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

B-CH 1000 mg/kg

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04044	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
M04045	Light yellow	-	8.0	+	-	±	-	-	+	-	-	-	±	-
M04046	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
M04047	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	-	-
M04048	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
M04044	18.1	1.067	129.7	223.6	150.9	2.35	4.05	2.73
M04045	15.4	1.072	111.8	240.3	143.9	1.72	3.70	2.22
M04046	19.7	1.043	52.3	141.6 §	46.5	1.03	2.79	0.92
M04047	20.3	1.035	55.4	115.9	56.7	1.12	2.35	1.15
M04048	22.1	1.052	87.8	218.9 §	104.8	1.94	4.84	2.32
Number of males	5	5	5	5	5	5	5	5
Mean	19.1	1.054	87.4	188.1	100.6	1.63	3.55	1.87
±S.D.	2.5	0.016	34.1	55.5	48.2	0.56	0.99	0.79

§, 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
Protein, ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few

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

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

Control (vehicle: water for injection)

Female No.	Quality									Urinary sediments				
	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	-	6.0	-	-	±	-	-	±	-	-	-	-	-
F05053	Light yellow	-	6.5	±	-	±	-	-	±	-	-	-	-	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05049	15.1	1.042	60.4	161.8	84.0	0.91	2.44	1.27
F05050	13.1	1.046	77.5	177.1	77.2	1.02	2.32	1.01
F05051	11.5	1.061	113.4	221.5 §	134.0	1.30	2.55	1.54
F05052	17.6	1.037	67.2	164.7 §	82.4	1.18	2.90	1.45
F05053	11.9	1.055	88.5	197.4	117.2	1.05	2.35	1.39
Number of females	5	5	5	5	5	5	5	5
Mean	13.8	1.048	81.4	184.5	99.0	1.09	2.51	1.33
±S.D.	2.5	0.010	20.8	25.0	25.2	0.15	0.23	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.
Turbidity, -: negative
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL
Red blood cells, White blood cells, Casts and Epithelial cells, -: not observed
Crystals, -: not observed; ±: a few

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

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

B-CH 100 mg/kg

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06059	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	±	-
F06060	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	-	-
F06061	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	±	-
F06062	Light yellow	-	7.0	+	-	-	-	-	±	-	-	-	±	-
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	10.1	1.080	173.3	239.9	202.0	1.75	2.42	2.04
F06060	19.0	1.035	57.0	138.7 §	63.5	1.08	2.64	1.21
F06061	14.2	1.045	89.0	174.4 §	81.4	1.26	2.48	1.16
F06062	11.0	1.060	115.3	205.2	121.5	1.27	2.26	1.34
F06063	15.3	1.055	104.8	195.0	101.7	1.60	2.98	1.56
Number of females	5	5	5	5	5	5	5	5
Mean	13.9	1.055	107.9	190.6	114.0	1.39	2.56	1.46
±S.D.	3.6	0.017	42.7	37.5	53.8	0.27	0.27	0.36

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

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

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

Control (vehicle: water for injection)

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

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05054	14.1	1.055	91.4	204.3	128.0	1.29	2.88	1.80
F05055	13.4	1.052	105.4	204.5 §	111.8	1.41	2.74	1.50
F05056	12.3	1.059	110.3	190.1	101.4	1.36	2.34	1.25
F05057	12.0	1.056	111.0	219.4 §	129.1	1.33	2.63	1.55
F05058	13.4	1.040	66.3	124.8	53.1	0.89	1.67	0.71
Number of females	5	5	5	5	5	5	5	5
Mean	13.0	1.052	96.9	188.6	104.7	1.26	2.45	1.36
±S.D.	0.9	0.007	18.8	37.2	31.1	0.21	0.48	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.
Turbidity, -: negative
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and＜10 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

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

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

B-CH 1000 mg/kg

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06064	Light yellow	-	6.5	±	-	±	-	-	+	-	-	-	-	±
F06065	Light yellow	-	8.0	-	-	-	-	-	±	-	-	-	±	-
F06066	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	±	-
F06067	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F06068	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06064	10.3	1.062	114.7	215.2	106.0	1.18	2.22	1.09
F06065	29.2	1.020	41.0	65.0 §	27.6	1.20	1.90	0.81
F06066	14.9	1.052	86.8	207.4 §	112.2	1.29	3.09	1.67
F06067	12.7	1.037	62.2	108.8 §	50.8	0.79	1.38	0.65
F06068	15.1	1.049	81.9	199.9	117.2	1.24	3.02	1.77
Number of females	5	5	5	5	5	5	5	5
Mean	16.4	1.044	77.3	159.3	82.8	1.14	2.32	1.20
±S.D.	7.4	0.016	27.6	68.1	40.8	0.20	0.73	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.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, -: negative ; ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL
Glucose, -: negative
Ketone, -: negative ; ±: 5≦and<10 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

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

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

Control (vehicle: water for injection)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	(×10⁴/μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(×10⁴/μL)	(sec)	(sec)
M01001	875	16.2	44.9	51.3	18.5	36.1	98.8	27.1	27.1
M01002	837	15.5	42.6	50.9	18.5	36.4	106.6	16.8	23.4
M01003	870	15.5	44.1	50.7	17.8	35.1	97.8	14.9	25.3
M01004	854	15.3	43.2	50.6	17.9	35.4	121.0	18.2	26.9
M01005	831	15.4	43.1	51.9	18.5	35.7	132.5	22.5	25.4 §
Number of males	5	5	5	5	5	5	5	5	5
Mean	853	15.6	43.6	51.1	18.2	35.7	111.3	19.9	25.6
S.D.	19	0.4	0.9	0.5	0.4	0.5	15.0	4.9	1.5

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	(×10²/μL)	(%)	(%)	(%)	(%)	(%)	(%)
M01001	150.0	16.2	1.1	0.1	3.9	78.7	4.58
M01002	92.6	8.6	1.6	0.0	3.5	86.3	3.39
M01003	80.6	21.0	1.6	0.0	4.7	72.7	3.38
M01004	61.5	14.9	1.1	0.0	3.3	80.7	3.93
M01005	48.0	28.9	1.7	0.0	7.7	61.7	3.30
Number of males	5	5	5	5	5	5	5
Mean	86.5	17.9	1.4	0.0	4.6	76.0	3.72
S.D.	39.4	7.6	0.3	0.0	1.8	9.4	0.54

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

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

B-CH 100 mg/kg

Male No.	RBC ($\times 10^4/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu L$)	PT (sec)	APTT (sec)
M02013	860	15.9	44.2	51.4	18.5	36.0	106.0	21.9	23.3
M02014	892	15.1	41.5	46.5	16.9	36.4	116.5	25.6	28.1
M02015	926	15.8	43.7	47.2	17.1	36.2	122.0	23.4	27.6
M02016	836	15.7	43.6	52.2	18.8	36.0	87.7	24.7	30.0
M02017	898	15.8	44.2	49.2	17.6	35.7	114.5	18.4	26.0
Number of males	5	5	5	5	5	5	5	5	5
Mean	882	15.7	43.4	49.3	17.8	36.1	109.3	22.8	27.0
S.D.	35	0.3	1.1	2.5	0.8	0.3	13.4	2.8	2.5

Male No.	WBC ($\times 10^2/\mu L$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M02013	116.5	13.2	2.3	0.1	5.2	79.2	4.03
M02014	119.2	13.8	1.3	0.0	4.2	80.7	3.97
M02015	73.3	12.7	1.4	0.0	3.4	82.5	2.63
M02016	76.5	29.9	1.3	0.0	3.0	65.8	3.64
M02017	60.1	18.6	1.5	0.2	4.0	75.7	2.77
Number of males	5	5	5	5	5	5	5
Mean	89.1	17.6	1.6	0.1	4.0	76.8	3.41
S.D.	27.0	7.2	0.4	0.1	0.8	6.6	0.66

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

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

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

B-CH 300 mg/kg

Male No.	RBC ($\times 10^4/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu L$)	PT (sec)	APTT (sec)
M03025	846	15.4	42.4	50.1	18.2	36.3	109.2	13.9	21.3
M03026	884	15.7	44.1	49.9	17.8	35.6	105.4	13.2	23.2
M03027	842	15.7	43.2	51.3	18.6	36.3	96.0	20.9	25.4
M03028	864	15.6	43.2	50.0	18.1	36.1	105.3	17.3	29.3
M03029	857	16.0	45.7	53.3	18.7	35.0	108.8	15.7	24.5
Number of males	5	5	5	5	5	5	5	5	5
Mean	859	15.7	43.7	50.9	18.3	35.9	104.9	16.2	24.7
S.D.	17	0.2	1.3	1.4	0.4	0.6	5.3	3.1	3.0

Male No.	WBC ($\times 10^2/\mu L$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M03025	92.4	16.7	1.1	0.0	4.1	78.1	3.20
M03026	91.2	31.1	2.1	0.0	4.4	62.4	1.92
M03027	71.1	15.7	1.7	0.0	2.7	79.9	3.58
M03028	39.8	29.9	2.0	0.0	3.8	64.3	3.44
M03029	53.3	20.1	0.4	0.0	5.8	73.7	3.65
Number of males	5	5	5	5	5	5	5
Mean	69.6	22.7	1.5	0.0	4.2	71.7	3.16
S.D.	23.1	7.3	0.7	0.0	1.1	8.0	0.71

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

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

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

B-CH 1000 mg/kg

Male No.	RBC ($\times 10^4/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu L$)	PT (sec)	APTT (sec)
M04037	861	16.3	46.0	53.4	18.9	35.4	100.2	13.5	22.0
M04038	819	14.8	41.0	50.1	18.1	36.1	104.6	14.6	22.0
M04039	842	15.3	43.5	51.7	18.2	35.2	94.8	14.9	23.8
M04040	865	15.9	45.1	52.1	18.4	35.3	100.5	14.0	21.1
M04041	865	15.1	42.7	49.4	17.5	35.4	108.6	15.1	21.7
Number of males	5	5	5	5	5	5	5	5	5
Mean	850	15.5	43.7	51.3	18.2	35.5	101.7	14.4	22.1
S.D.	20	0.6	2.0	1.6	0.5	0.4	5.2	0.7	1.0

Male No.	WBC ($\times 10^2/\mu L$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M04037	85.1	12.5	0.9	0.1	3.5	83.0	3.54
M04038	53.8	15.2	1.9	0.0	3.0	79.9	3.06
M04039	55.6	17.8	1.4	0.2	3.6	77.0	2.95
M04040	88.8	17.1	1.5	0.0	3.7	77.7	3.31
M04041	48.4	24.2	1.7	0.0	3.9	70.2	3.73
Number of males	5	5	5	5	5	5	5
Mean	66.3	17.4	1.5	0.1	3.5	77.6	3.32
S.D.	19.0	4.3	0.4	0.1	0.3	4.7	0.32

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

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

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

Control (vehicle: water for injection)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	(×10⁴/μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(×10⁴/μL)	(sec)	(sec)
M01008	816	14.2	41.4	50.7	17.4	34.3	123.0	19.0	26.3
M01009	815	14.1	42.2	51.8	17.3	33.4	106.1	14.5	24.0 §
M01010	803	13.6	40.3	50.2	16.9	33.7	129.4	19.4	26.8
M01011	802	14.4	41.8	52.1	18.0	34.4	89.4	15.4	25.4
M01012	728	12.1	37.0	50.8	16.6	32.7	105.6	16.0	25.5
Number of males	5	5	5	5	5	5	5	5	5
Mean	793	13.7	40.5	51.1	17.2	33.7	110.7	16.9	25.6
S.D.	37	0.9	2.1	0.8	0.5	0.7	15.8	2.2	1.1

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	(×10²/μL)	(%)	(%)	(%)	(%)	(%)	(%)
M01008	95.4	28.6	0.5	0.0	6.0	64.9	5.35
M01009	119.9	16.6	0.7	0.0	3.9	78.8	3.73
M01010	113.9	19.2	1.4	0.0	3.2	76.2	4.07
M01011	64.5	16.4	1.2	0.0	3.3	79.1	3.99
M01012	119.7	22.3	1.9	0.0	4.2	71.6	4.48
Number of males	5	5	5	5	5	5	5
Mean	102.7	20.6	1.1	0.0	4.1	74.1	4.32
S.D.	23.6	5.1	0.6	0.0	1.1	6.0	0.63

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

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

B-CH 1000 mg/kg

Male No.	RBC ($\times 10^4/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu L$)	PT (sec)	APTT (sec)
M04044	766	13.6	40.6	53.0	17.8	33.5	102.4	14.1	24.5
M04045	808	14.3	41.5	51.4	17.7	34.5	118.8	19.8	25.8
M04046	859	14.5	42.8	49.8	16.9	33.9	98.1	15.9	27.1
M04047	764	12.8	38.1	49.9	16.8	33.6	99.5	15.4	24.4
M04048	784	14.1	42.3	54.0	18.0	33.3	107.4	18.3	28.6
Number of males	5	5	5	5	5	5	5	5	5
Mean	796	13.9	41.1	51.6	17.4	33.8	105.2	16.7	26.1
S.D.	39	0.7	1.9	1.9	0.6	0.5	8.4	2.3	1.8

Male No.	WBC ($\times 10^2/\mu L$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
M04044	102.8	15.5	1.0	0.1	3.7	79.7	3.57
M04045	81.8	12.4	1.0	0.0	4.3	82.3	2.94
M04046	106.6	7.8	1.5	0.0	1.5	89.2	3.24
M04047	102.9	16.7	1.3	0.1	3.0	78.9	3.94
M04048	83.5	17.8	0.8	0.0	5.6	75.8	3.17
Number of males	5	5	5	5	5	5	5
Mean	95.5	14.0	1.1	0.0	3.6	81.2	3.37 *
S.D.	11.9	4.0	0.3	0.1	1.5	5.0	0.39

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

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

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

Control (vehicle: water for injection)

Female No.	RBC ($\times 10^4/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu L$)	PT (sec)	APTT (sec)
F01003	748	14.8	41.5	55.5	19.8	35.7	125.1	12.2	21.2
F01005	682	14.1	40.6	59.5	20.7	34.7	106.6	12.6	20.1
F01007	661	13.7	41.0	62.0	20.7	33.4	99.7	12.8	19.9
F01010	649	12.6	37.4	57.6	19.4	33.7	115.6	12.3	21.2
F01012	692	13.4	40.0	57.8	19.4	33.5	112.7	12.3	19.4
Number of females	5	5	5	5	5	5	5	5	5
Mean	686	13.7	40.1	58.5	20.0	34.2	111.9	12.4	20.4
S.D.	38	0.8	1.6	2.4	0.7	1.0	9.6	0.3	0.8

Female No.	WBC ($\times 10^2/\mu L$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F01003	183.8	30.8	0.6	0.1	3.6	64.9	10.14
F01005	133.6	20.4	1.2	0.0	3.5	74.9	6.99
F01007	105.9	39.1	0.7	0.0	2.6	57.6	8.09
F01010	115.6	43.8	0.4	0.0	2.2	53.6	7.30
F01012	159.2	41.3	0.8	0.0	5.4	52.5	8.52
Number of females	5	5	5	5	5	5	5
Mean	139.6	35.1	0.7	0.0	3.5	60.7	8.21
S.D.	32.0	9.5	0.3	0.0	1.2	9.3	1.24

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

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

B-CH 100 mg/kg

Female No.	RBC ($\times 10^4/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu L$)	PT (sec)	APTT (sec)
F02014	647	12.9	37.7	58.3	19.9	34.2	123.6	12.5	19.6
F02015	740	13.8	40.3	54.5	18.6	34.2	115.3	12.4	20.0
F02016	610	12.4	37.4	61.3	20.3	33.2	116.6	12.3	19.8
F02019	664	13.8	40.0	60.2	20.8	34.5	108.1	12.6	20.8
F02021	738	14.6	43.7	59.2	19.8	33.4	118.0	13.8	20.8
Number of females	5	5	5	5	5	5	5	5	5
Mean	680	13.5	39.8	58.7	19.9	33.9	116.3	12.7	20.2
S.D.	57	0.9	2.5	2.6	0.8	0.6	5.6	0.6	0.6

Female No.	WBC ($\times 10^2/\mu L$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F02014	114.9	35.2	0.5	0.0	3.0	61.3	7.17
F02015	124.2	62.3	0.5	0.0	3.5	33.7	7.29
F02016	110.6	25.9	1.0	0.0	2.5	70.6	9.57
F02019	116.6	44.8	1.1	0.0	2.9	51.2	5.14
F02021	165.5	39.9	0.9	0.1	4.4	54.7	5.91
Number of females	5	5	5	5	5	5	5
Mean	126.4	41.6	0.8	0.0	3.3	54.3	7.02
S.D.	22.4	13.5	0.3	0.0	0.7	13.7	1.69

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

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

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

B-CH 300 mg/kg

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	(×10⁴/μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(×10⁴/μL)	(sec)	(sec)
F03027	720	14.2	42.1	58.5	19.7	33.7	133.3	13.0	20.3 §
F03028	681	12.9	36.8	54.0	18.9	35.1	110.6	11.8	18.6
F03030	648	12.4	36.5	56.3	19.1	34.0	148.8	12.8	20.0
F03032	610	12.1	36.8	60.3	19.8	32.9	118.8	12.6	20.3
F03035	679	13.4	39.4	58.0	19.7	34.0	102.3	12.1	18.9
Number of females	5	5	5	5	5	5	5	5	5
Mean	668	13.0	38.3	57.4	19.4	33.9	122.8	12.5	19.6
S.D.	41	0.8	2.4	2.4	0.4	0.8	18.5	0.5	0.8

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	(×10²/μL)	(%)	(%)	(%)	(%)	(%)	(%)
F03027	129.6	30.2	1.4	0.0	3.8	64.6	7.93
F03028	115.9	39.9	0.3	0.0	3.8	56.0	2.11
F03030	125.2	41.8	0.5	0.0	3.7	54.0	8.03
F03032	147.2	37.0	0.4	0.1	2.4	60.1	11.77
F03035	77.7	37.0	1.5	0.0	4.2	57.3	7.32
Number of females	5	5	5	5	5	5	5
Mean	119.1	37.2	0.8	0.0	3.6	58.4	7.43
S.D.	25.8	4.4	0.6	0.0	0.7	4.1	3.46

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

Appendix 26-1-4. Hematological findings of female rats at the end of the dosing period

B-CH 1000 mg/kg

Female No.	RBC ($\times 10^4/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu L$)	PT (sec)	APTT (sec)
F04038	660	13.7	40.9	62.0	20.8	33.5	122.7	12.4	21.0
F04041	712	14.0	41.2	57.9	19.7	34.0	121.2	12.3	20.3
F04043	717	14.2	41.7	58.2	19.8	34.1	138.0	12.5	18.8
F04045	585	11.7	35.3	60.3	20.0	33.1	128.9	11.9	19.5
F04047	604	12.1	36.5	60.4	20.0	33.2	118.8	12.5	21.4
Number of females	5	5	5	5	5	5	5	5	5
Mean	656	13.1	39.1	59.8	20.1	33.6	125.9	12.3	20.2
S.D.	60	1.2	3.0	1.7	0.4	0.5	7.7	0.2	1.1

Female No.	WBC ($\times 10^2/\mu L$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F04038	123.0	31.1	0.4	0.0	3.0	65.5	9.73
F04041	153.3	40.2	0.7	0.0	4.0	55.1	5.86
F04043	88.8	26.8	1.2	0.0	3.3	68.7	7.89
F04045	125.1	45.1	0.7	0.0	1.8	52.4	15.18
F04047	106.9	44.7	0.7	0.0	3.5	51.1	6.88
Number of females	5	5	5	5	5	5	5
Mean	119.4	37.6	0.7	0.0	3.1	58.6	9.11
S.D.	23.9	8.3	0.3	0.0	0.8	8.0	3.68

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

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

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

Control (vehicle: water for injection)

Female No.	RBC ($\times 10^4/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu L$)	PT (sec)	APTT (sec)
F05049	839	16.3	44.0	52.4	19.4	37.0	121.8	11.2	20.8
F05050	781	14.8	41.6	53.3	19.0	35.6	126.7	11.7	21.5
F05051	785	15.2	41.3	52.6	19.4	36.8	89.7	12.0	20.9
F05052	787	14.8	40.8	51.8	18.8	36.3	115.6	12.0	19.5
F05053	838	15.2	41.8	49.9	18.1	36.4	91.9	11.7	21.1
Number of females	5	5	5	5	5	5	5	5	5
Mean	806	15.3	41.9	52.0	18.9	36.4	109.1	11.7	20.8
S.D.	30	0.6	1.2	1.3	0.5	0.5	17.2	0.3	0.8

Female No.	WBC ($\times 10^2/\mu L$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F05049	79.5	12.8	2.0	0.1	3.1	82.0	4.95
F05050	43.3	10.4	2.1	0.0	1.8	85.7	4.61
F05051	45.9	19.7	1.5	0.0	3.9	74.9	3.81
F05052	49.1	19.8	2.0	0.0	4.1	74.1	2.40
F05053	51.7	11.7	1.5	0.0	2.9	83.9	2.48
Number of females	5	5	5	5	5	5	5
Mean	53.9	14.9	1.8	0.0	3.2	80.1	3.65
S.D.	14.7	4.5	0.3	0.0	0.9	5.3	1.18

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

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

B-CH 1000 mg/kg

Female No.	RBC ($\times 10^4/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu L$)	PT (sec)	APTT (sec)
F06059	730	14.2	39.0	53.4	19.5	36.4	120.4	11.7	19.3
F06060	764	14.3	40.0	52.4	18.7	35.8	116.8	12.8	21.8
F06061	791	14.4	40.9	51.7	18.2	35.2	109.3	12.0	20.2
F06062	811	14.5	39.7	49.0	17.9	36.5	104.9	11.2	21.1
F06063	796	14.6	41.3	51.9	18.3	35.4	121.5	11.8	19.3
Number of females	5	5	5	5	5	5	5	5	5
Mean	778	14.4 *	40.2 *	51.7	18.5	35.9	114.6	11.9	20.3
S.D.	32	0.2	0.9	1.6	0.6	0.6	7.2	0.6	1.1

Female No.	WBC ($\times 10^2/\mu L$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)
F06059	33.8	16.6	2.4	0.0	4.1	76.9	3.23
F06060	49.8	15.1	3.0	0.0	3.2	78.7	2.79
F06061	40.4	17.4	4.2	0.0	5.9	72.5	2.05
F06062	47.6	13.6	1.3	0.0	3.8	81.3	2.64
F06063	95.0	7.2	1.3	0.1	2.2	89.2	3.59
Number of females	5	5	5	5	5	5	5
Mean	53.3	14.0	2.4	0.0	3.8	79.7	2.86
S.D.	24.1	4.1	1.2	0.0	1.4	6.2	0.59

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

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

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

Control (vehicle: water for injection)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	(×10⁴/μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(×10⁴/μL)	(sec)	(sec)
F05054	762	14.3	41.1	53.9	18.8	34.8	95.4	11.1	22.1
F05055	729	13.9	40.4	55.4	19.1	34.4	98.2	11.6	22.5
F05056	754	13.9	39.9	52.9	18.4	34.8	102.6	10.9	21.5
F05057	743	13.9	41.1	55.3	18.7	33.8	93.6	11.0	21.8 §
F05058	809	14.9	44.3	54.8	18.4	33.6	103.5	11.7	19.7
Number of females	5	5	5	5	5	5	5	5	5
Mean	759	14.2	41.4	54.5	18.7	34.3	98.7	11.3	21.5
S.D.	30	0.4	1.7	1.1	0.3	0.6	4.3	0.4	1.1

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	(×10²/μL)	(%)	(%)	(%)	(%)	(%)	(%)
F05054	44.1	14.0	1.6	0.0	2.5	81.9	3.36
F05055	48.2	16.1	1.0	0.0	4.1	78.8	3.15
F05056	49.2	11.2	3.3	0.0	3.0	82.5	3.45
F05057	22.0	17.8	3.2	0.0	4.5	74.5	2.94
F05058	30.9	14.3	1.3	0.0	1.9	82.5	2.82
Number of females	5	5	5	5	5	5	5
Mean	38.9	14.7	2.1	0.0	3.2	80.0	3.14
S.D.	11.9	2.5	1.1	0.0	1.1	3.5	0.27

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

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

B-CH 1000 mg/kg

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	(×10⁴/μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(×10⁴/μL)	(sec)	(sec)
F06064	781	13.7	39.4	50.4	17.5	34.8	94.2	12.2	22.1
F06065	819	15.2	44.3	54.1	18.6	34.3	101.9	11.2	18.6
F06066	718	13.2	39.8	55.4	18.4	33.2	72.6	12.0	21.3
F06067	818	15.3	43.7	53.4	18.7	35.0	115.5	11.8	20.0 §
F06068	734	13.3	39.4	53.7	18.1	33.8	93.1	12.4	17.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	774	14.1	41.3	53.4	18.3	34.2	95.5	11.9 *	19.8
S.D.	47	1.0	2.5	1.8	0.5	0.7	15.6	0.5	2.1

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	(×10²/μL)	(%)	(%)	(%)	(%)	(%)	(%)
F06064	52.6	16.3	1.9	0.0	4.0	77.8	4.30
F06065	27.4	19.7	1.5	0.0	1.8	77.0	3.03
F06066	29.8	21.5	2.0	0.0	3.7	72.8	3.06
F06067	33.9	13.8	0.9	0.0	2.1	83.2	3.35
F06068	27.8	12.3	1.4	0.0	2.5	83.8	2.86
Number of females	5	5	5	5	5	5	5
Mean	34.3	16.7	1.5	0.0	2.8	78.9	3.32
S.D.	10.5	3.9	0.4	0.0	1.0	4.6	0.58

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

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

Control (vehicle: water for injection)

Male No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Triglyceride	Phospholipid	AST	ALT	γ-GTP	LDH	Bile acid	BUN	Creatinine	Total bilirubin	ALP
	g/dL	g/dL		mg/dL	mg/dL	mg/dL	mg/dL	U/L	U/L	U/L	U/L	μmol/L	mg/dL	mg/dL	mg/dL	U/L
M01001	5.9	3.8	1.81	166	40	78	85	69	37	0	279	27.8	15	0.5	0.07	344
M01002	5.6	3.6	1.80	118	47	40	77	67	27	0	110	15.3	16	0.6	0.08	413
M01003	5.8	3.6	1.64	148	47	68	83	55	26	0	83	6.4	19	0.5	0.05	343
M01004	5.3	3.5	1.94	153	43	26	76	60	33	0	63	18.9	19	0.6	0.05	348
M01005	5.3	3.6	2.12	132	43	60	77	76	32	0	77	11.2	20	0.5	0.07	276
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.6	1.86	143	44	54	80	65	31	0	122	15.9	18	0.5	0.06	345
S.D.	0.3	0.1	0.18	19	3	21	4	8	5	0	89	8.1	2	0.1	0.01	48

Control (vehicle: water for injection)

Male No.	Inorganic phosphorus	Ca	Na	K	Cl
	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
M01001	6.0	9.8	143.3	3.86	105.7
M01002	5.7	8.5	144.1	3.96	106.5
M01003	5.8	9.1	143.7	3.95	107.1
M01004	5.2	8.6	143.8	3.82	108.2
M01005	5.8	9.2	144.8	3.50	108.2
Number of males	5	5	5	5	5
Mean	5.7	9.0	143.9	3.82	107.1
S.D.	0.3	0.5	0.6	0.19	1.1

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

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

B-CH 100 mg/kg

Male No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Triglyceride	Phospholipid	AST	ALT	γ-GTP	LDH	Bile acid	BUN	Creatinine	Total bilirubin	ALP
	g/dL	g/dL		mg/dL	mg/dL	mg/dL	mg/dL	U/L	U/L	U/L	U/L	μmol/L	mg/dL	mg/dL	mg/dL	U/L
M02013	5.7	3.7	1.85	176	35	51	76	63	30	0	127	5.8	13	0.7	0.07	421
M02014	5.9	3.8	1.81	159	31	54	70	61	31	0	234	4.2	13	0.5	0.05	309
M02015	5.6	3.5	1.67	133	44	25	70	70	34	0	176	6.4	17	0.6	0.05	287
M02016	5.6	3.7	1.95	133	34	20	63	64	32	0	125	5.3	14	0.5	0.05	290
M02017	5.3	3.7	2.31	138	40	37	75	81	34	0	151	16.7	17	0.5	0.05	374
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.7	1.92	148	37	37	71	68	32	0	163	7.7	15	0.6	0.05	336
S.D.	0.2	0.1	0.24	19	5	15	5	8	2	0	45	5.1	2	0.1	0.01	59
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	KW	DU	KW	AN	AN	AN	AN	KW	AN	AN	AN	AN

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

B-CH 100 mg/kg

Male No.	Inorganic phosphorus	Ca	Na	K	Cl
	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
M02013	6.5	10.1	143.6	4.62	106.0
M02014	6.8	9.3	143.0	3.83	104.2
M02015	5.6	9.0	145.7	3.81	108.4
M02016	6.2	9.3	144.8	3.83	107.2
M02017	5.7	8.9	144.5	3.75	108.7
Number of males	5	5	5	5	5
Mean	6.2	9.3	144.3	3.97	106.9
S.D.	0.5	0.5	1.1	0.37	1.8
Significance	NS	NS	NS	NS	NS
Statistical method	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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

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

B-CH 300 mg/kg

Male No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Triglyceride	Phospholipid	AST	ALT	γ-GTP	LDH	Bile acid	BUN	Creatinine	Total bilirubin	ALP
	g/dL	g/dL		mg/dL	mg/dL	mg/dL	mg/dL	U/L	U/L	U/L	U/L	μmol/L	mg/dL	mg/dL	mg/dL	U/L
M03025	6.1	3.7	1.54	145	76	50	109	62	39	0	324	5.6	17	0.5	0.06	315
M03026	6.2	3.9	1.70	150	53	44	98	64	30	0	318	8.5	16	0.6	0.06	271
M03027	5.9	3.7	1.68	137	38	27	68	74	39	0	300	5.9	16	0.6	0.07	284
M03028	5.9	3.8	1.81	128	35	38	69	63	33	0	206	4.6	18	0.5	0.05	372
M03029	5.7	3.6	1.71	120	41	26	70	71	45	0	62	5.9	22	0.5	0.06	300
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.0	3.7	1.69	136	49	37	83	67	37	0	242	6.1	18	0.5	0.06	308
S.D.	0.2	0.1	0.10	12	17	10	19	5	6	0	111	1.4	2	0.1	0.01	39
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	KW	DU	KW	AN	AN	AN	AN	KW	AN	AN	AN	AN

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

B-CH 300 mg/kg

Male No.	Inorganic phosphorus	Ca	Na	K	Cl
	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
M03025	6.4	9.7	143.4	3.87	105.5
M03026	6.3	9.7	143.7	4.01	106.0
M03027	6.1	9.4	144.4	4.05	107.1
M03028	5.9	9.3	143.8	3.82	105.7
M03029	6.0	9.8	144.4	4.10	107.6
Number of males	5	5	5	5	5
Mean	6.1	9.6	143.9	3.97	106.4
S.D.	0.2	0.2	0.4	0.12	0.9
Significance	NS	NS	NS	NS	NS
Statistical method	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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 27-1-4. Biochemical findings of male rats at the end of the dosing period

B-CH 1000 mg/kg

Male No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Triglyceride	Phospholipid	AST	ALT	γ-GTP	LDH	Bile acid	BUN	Creatinine	Total bilirubin	ALP
	g/dL	g/dL		mg/dL	mg/dL	mg/dL	mg/dL	U/L	U/L	U/L	U/L	μmol/L	mg/dL	mg/dL	mg/dL	U/L
M04037	5.8	3.6	1.64	154	55	20	83	66	38	0	265	7.3	17	0.6	0.04	390
M04038	5.9	3.8	1.81	134	43	28	75	80	44	0	301	4.7	13	0.6	0.08	404
M04039	5.6	3.7	1.95	136	46	19	77	55	30	0	118	4.2	18	0.6	0.05	287
M04040	5.2	3.6	2.25	139	41	31	70	89	47	0	275	6.5	16	0.5	0.06	336
M04041	5.4	3.3	1.57	120	58	21	84	64	36	0	146	5.0	17	0.5	0.07	298
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.6	1.84	137	49	24	78	71	39	0	221	5.5	16	0.6	0.06	343
S.D.	0.3	0.2	0.27	12	8	5	6	14	7	0	83	1.3	2	0.1	0.02	53
Significance	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	KW	DU	KW	AN	AN	AN	AN	KW	AN	AN	AN	AN

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

B-CH 1000 mg/kg

Male No.	Inorganic phosphorus	Ca	Na	K	Cl
	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
M04037	5.9	9.0	143.7	4.07	104.5
M04038	5.3	9.4	143.6	3.98	106.7
M04039	5.1	8.9	143.6	4.22	106.8
M04040	5.2	9.1	145.3	3.87	108.3
M04041	5.4	8.5	144.9	3.63	108.2
Number of males	5	5	5	5	5
Mean	5.4	9.0	144.2	3.95	106.9
S.D.	0.3	0.3	0.8	0.22	1.5
Significance	NS	NS	NS	NS	NS
Statistical method	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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Triglyceride	Phospholipid	AST	ALT	γ-GTP	LDH	Bile acid	BUN	Creatinine	Total bilirubin	ALP
	g/dL	g/dL		mg/dL	mg/dL	mg/dL	mg/dL	U/L	U/L	U/L	U/L	μmol/L	mg/dL	mg/dL	mg/dL	U/L
M01008	5.8	3.8	1.90	145	38	35	70	68	26	0	110	51.3	16	0.5	0.07	221
M01009	5.8	4.0	2.22	142	48	47	79	73	27	0	315	27.4	12	0.5	0.07	286
M01010	5.7	3.7	1.85	159	40	49	73	57	23	0	182	12.4	15	0.5	0.05	204
M01011	5.6	3.6	1.80	132	51	48	83	63	27	0	228	4.9	16	0.5	0.02	201
M01012	5.6	3.6	1.80	125	45	24	76	64	33	0	195	24.3	15	0.5	0.06	237
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.7	1.91	141	44	41	76	65	27	0	206	24.1	15	0.5	0.05	230
S.D.	0.1	0.2	0.18	13	5	11	5	6	4	0	75	17.7	2	0.0	0.02	35

Control (vehicle: water for injection)

Male No.	Inorganic phosphorus	Ca	Na	K	Cl
	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
M01008	8.1	9.8	142.5	4.50	103.8
M01009	6.0	9.5	143.7	3.84	106.9
M01010	6.8	9.4	143.8	3.71	107.9
M01011	6.3	9.3	144.9	3.61	109.4
M01012	5.4	9.2	143.9	3.65	107.7
Number of males	5	5	5	5	5
Mean	6.5	9.4	143.8	3.86	107.1
S.D.	1.0	0.2	0.9	0.37	2.1

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

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

B-CH 1000 mg/kg

Male No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Triglyceride	Phospholipid	AST	ALT	γ-GTP	LDH	Bile acid	BUN	Creatinine	Total bilirubin	ALP
	g/dL	g/dL		mg/dL	mg/dL	mg/dL	mg/dL	U/L	U/L	U/L	U/L	μmol/L	mg/dL	mg/dL	mg/dL	U/L
M04044	5.9	3.9	1.95	142	53	44	86	70	29	0	284	9.4	16	0.6	0.05	265
M04045	5.4	3.5	1.84	137	39	22	65	68	27	0	272	13.7	15	0.5	0.06	275
M04046	5.1	3.4	2.00	153	43	26	70	58	25	0	205	11.8	13	0.5	0.04	243
M04047	5.7	3.7	1.85	137	52	16	76	74	30	0	310	9.0	12	0.5	0.07	174
M04048	5.7	3.7	1.85	135	49	42	84	60	27	0	96	7.9	17	0.5	0.04	203
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.6	1.90	141	47	30	76	66	28	0	233	10.4	15	0.5	0.05	232
S.D.	0.3	0.2	0.07	7	6	12	9	7	2	0	86	2.4	2	0.0	0.01	43
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
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.

B-CH 1000 mg/kg

Male No.	Inorganic phosphorus	Ca	Na	K	Cl
	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
M04044	6.6	9.5	143.0	3.99	105.9
M04045	7.0	9.5	144.2	3.89	106.3
M04046	5.9	8.8	145.0	3.45	107.9
M04047	6.1	9.1	144.4	3.56	109.2
M04048	6.0	9.5	144.4	3.52	107.9
Number of males	5	5	5	5	5
Mean	6.3	9.3	144.2	3.68	107.4
S.D.	0.5	0.3	0.7	0.24	1.3
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F01003	6.2	4.1	1.95	151	61	40	123	72	46	0	71	13.2	15	0.5	0.11	130
F01005	6.2	4.2	2.10	151	54	42	112	57	36	0	50	13.7	12	0.5	0.09	111
F01007	6.0	4.2	2.33	148	62	84	140	62	41	0	46	19.3	17	0.6	0.11	176
F01010	6.2	4.3	2.26	146	65	93	149	81	56	0	123	21.3	14	0.6	0.10	139
F01012	6.1	4.2	2.21	137	61	51	124	107	46	0	49	22.1	15	0.6	0.09	244
Number of females	5.0	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	4.2	2.17	147	61	62	130	76	45	0	68	17.9	15	0.6	0.10	160
S.D.	0.1	0.1	0.15	6	4	25	15	20	7	0	32	4.2	2	0.1	0.01	53

Control (vehicle: water for injection)

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F01003	6.5	9.5	139.5	4.14	101.3
F01005	5.5	10.2	140.0	4.42	105.4
F01007	7.4	9.4	140.8	3.87	104.1
F01010	5.3	9.7	139.8	3.87	104.8
F01012	7.2	9.5	142.0	3.86	107.1
Number of females	5	5	5	5	5
Mean	6.4	9.7	140.4	4.03	104.5
S.D.	1.0	0.3	1.0	0.25	2.1

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

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

B-CH 100 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F02014	5.7	4.0	2.35	139	53	32	104	79	54	0	101	10.4	13	0.5	0.06	159
F02015	6.0	4.0	2.00	145	72	41	146	93	46	0	68	10.0	21	0.7	0.06	210
F02016	6.2	4.2	2.10	149	57	37	121	55	39	0	46	11.5	13	0.5	0.07	125
F02019	5.4	3.7	2.18	101	74	32	137	77	36	0	46	12.9	16	0.5	0.12	225
F02021	6.2	4.3	2.26	143	66	78	132	89	40	0	180	13.8	18	0.7	0.12	271
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.0	2.18	135	64	44	128	79	43	0	88	11.7	16	0.6	0.09	198
S.D.	0.3	0.2	0.14	20	9	19	16	15	7	0	56	1.6	3	0.1	0.03	57
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

B-CH 100 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F02014	6.5	9.5	140.6	3.73	106.5
F02015	7.7	9.7	141.6	4.08	105.4
F02016	6.4	9.8	142.2	3.97	106.7
F02019	6.0	9.3	142.0	3.60	107.2
F02021	6.7	10.1	141.9	3.73	103.2
Number of females	5	5	5	5	5
Mean	6.7	9.7	141.7	3.82	105.8
S.D.	0.6	0.3	0.6	0.20	1.6
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 28-1-3. Biochemical findings of female rats at the end of the dosing period

B-CH 300 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F03027	6.1	4.0	1.90	119	59	35	112	70	42	0	162	21.5	18	0.5	0.08	247
F03028	5.3	3.8	2.53	141	58	60	112	59	46	0	44	9.4	10	0.5	0.07	245
F03030	5.8	4.1	2.41	142	56	54	111	65	43	0	62	25.2	19	0.5	0.10	153
F03032	5.9	3.9	1.95	157	62	49	122	85	52	0	119	6.0	12	0.5	0.07	232
F03035	6.2	4.4	2.44	145	51	44	107	103	82	0	97	12.6	16	0.6	0.07	193
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.0	2.25	141	57	48	113	76	53	0	97	14.9	15	0.5	0.08	214
S.D.	0.4	0.2	0.30	14	4	10	6	18	17	0	47	8.1	4	0.0	0.01	40
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

B-CH 300 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F03027	6.7	9.4	140.2	3.68	107.5
F03028	7.2	9.5	143.8	4.21	105.5
F03030	6.1	9.2	142.6	4.11	107.9
F03032	5.4	9.4	141.9	3.64	106.3
F03035	5.9	9.7	140.8	4.04	106.2
Number of females	5	5	5	5	5
Mean	6.3	9.4	141.9	3.94	106.7
S.D.	0.7	0.2	1.4	0.26	1.0
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

B-CH 1000 mg/kg

Female No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Triglyceride	Phospholipid	AST	ALT	γ-GTP	LDH	Bile acid	BUN	Creatinine	Total bilirubin	ALP
	g/dL	g/dL		mg/dL	mg/dL	mg/dL	mg/dL	U/L	U/L	U/L	U/L	μmol/L	mg/dL	mg/dL	mg/dL	U/L
F04038	6.0	4.2	2.33	138	47	58	102	65	46	1	59	10.6	12	0.5	0.09	100
F04041	6.0	4.1	2.16	144	50	76	113	80	70	0	39	16.9	14	0.5	0.08	118
F04043	5.6	3.8	2.11	110	51	14	92	67	31	0	47	10.7	14	0.6	0.07	158
F04045	6.0	4.1	2.16	137	78	39	148	96	56	0	59	10.2	17	0.6	0.08	354
F04047	5.9	4.2	2.47	131	57	36	119	71	46	0	104	7.8	14	0.6	0.07	160
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.1	2.25	132	57	45	115	76	50	0	62	11.2	14	0.6	0.08	178
S.D.	0.2	0.2	0.15	13	13	23	21	13	14	0	25	3.4	2	0.1	0.01	102
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	AN	KW	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

B-CH 1000 mg/kg

Female No.	Inorganic phosphorus	Ca	Na	K	Cl
	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
F04038	5.7	9.6	140.0	4.65	105.3
F04041	6.3	10.0	140.5	4.01	104.7
F04043	6.6	9.4	144.3	4.12	110.2
F04045	6.1	9.4	143.8	3.67	109.5
F04047	6.3	9.9	143.3	3.13	108.5
Number of females	5	5	5	5	5
Mean	6.2	9.7	142.4	3.92	107.6
S.D.	0.3	0.3	2.0	0.56	2.5
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Control (vehicle: water for injection)

Female No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Triglyceride	Phospholipid	AST	ALT	γ-GTP	LDH	Bile acid	BUN	Creatinine	Total bilirubin	ALP
	g/dL	g/dL		mg/dL	mg/dL	mg/dL	mg/dL	U/L	U/L	U/L	U/L	μmol/L	mg/dL	mg/dL	mg/dL	U/L
F05049	6.1	4.2	2.21	113	62	13	113	79	49	0	69	29.4	18	0.6	0.07	147
F05050	6.3	4.5	2.50	145	56	15	110	52	21	0	44	14.2	15	0.6	0.07	240
F05051	5.7	4.1	2.56	115	66	14	119	65	24	0	42	9.5	16	0.6	0.10	207
F05052	5.9	3.9	1.95	103	63	12	113	65	25	0	71	27.3	19	0.5	0.06	215
F05053	6.2	4.2	2.10	123	69	18	131	69	27	0	92	15.4	21	0.7	0.08	176
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.0	4.2	2.26	120	63	14	117	66	29	0	64	19.2	18	0.6	0.08	197
S.D.	0.2	0.2	0.26	16	5	2	8	10	11	0	21	8.7	2	0.1	0.02	36

Control (vehicle: water for injection)

Female No.	Inorganic phosphorus	Ca	Na	K	Cl
	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
F05049	4.0	9.1	143.2	3.74	108.1
F05050	4.6	9.1	144.4	3.47	107.6
F05051	4.1	9.0	141.8	3.75	106.2
F05052	4.2	9.4	142.7	3.71	108.5
F05053	5.0	9.1	142.6	3.68	106.9
Number of females	5	5	5	5	5
Mean	4.4	9.1	142.9	3.67	107.5
S.D.	0.4	0.2	1.0	0.12	0.9

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

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

B-CH 1000 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06059	6.1	4.2	2.21	128	59	15	113	97	85	1	86	6.5	15	0.7	0.08	151
F06060	6.2	4.4	2.44	134	68	17	132	58	29	1	50	11.9	19	0.6	0.08	175
F06061	6.6	4.8	2.67	120	66	12	133	291	141	0	210	16.1	16	0.6	0.14	226
F06062	6.9	4.9	2.45	154	67	28	134	186	142	0	175	20.1	20	0.7	0.08	164
F06063	5.6	3.8	2.11	153	52	18	104	84	61	1	54	7.0	16	0.7	0.07	218
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.3	4.4	2.38	138	62	18	123	143	92	1	115	12.3	17	0.7	0.09	187
S.D.	0.5	0.4	0.22	15	7	6	14	96	50	1	73	5.9	2	0.1	0.03	33
Significance	NS	NS	NS	NS	NS	NS	NS	NS	*	*	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	AW	AW	TT	AW	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

B-CH 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06059	4.6	9.5	141.9	3.82	106.4
F06060	3.4	9.1	142.7	3.44	106.9
F06061	4.1	10.0	143.9	3.67	108.3
F06062	4.2	9.8	143.3	3.70	105.9
F06063	4.8	9.5	142.9	3.39	105.8
Number of females	5	5	5	5	5
Mean	4.2	9.6	142.9	3.60	106.7
S.D.	0.5	0.3	0.7	0.18	1.0
Significance	NS	*	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 28-3-1. Biochemical findings of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05054	6.6	4.6	2.30	127	92	49	172	58	23	0	155	13.7	19	0.7	0.07	128
F05055	6.6	4.6	2.30	118	58	16	117	56	21	0	73	10.7	18	0.6	0.09	124
F05056	6.3	4.4	2.32	115	68	13	117	70	42	0	77	9.3	18	0.6	0.06	139
F05057	6.6	4.7	2.47	130	73	15	137	68	36	0	56	15.9	23	0.8	0.10	106
F05058	5.5	3.9	2.44	105	53	12	97	62	22	0	77	11.2	18	0.6	0.07	105
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.3	4.4	2.37	119	69	21	128	63	29	0	88	12.2	19	0.7	0.08	120
S.D.	0.5	0.3	0.08	10	15	16	28	6	10	0	39	2.6	2	0.1	0.02	15

Control (vehicle: water for injection)

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05054	3.9	10.2	144.6	3.25	108.1
F05055	4.7	9.6	142.5	3.49	108.3
F05056	4.0	9.3	143.2	3.47	107.9
F05057	3.6	9.8	142.2	3.65	107.0
F05058	4.1	9.0	145.7	3.08	111.5
Number of females	5	5	5	5	5
Mean	4.1	9.6	143.6	3.39	108.6
S.D.	0.4	0.5	1.5	0.22	1.7

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

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

B-CH 1000 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06064	5.7	3.9	2.17	135	48	13	99	106	63	0	149	6.2	16	0.7	0.13	139
F06065	6.0	4.2	2.33	141	61	18	103	65	22	0	200	5.5	15	0.7	0.06	119
F06066	5.7	4.1	2.56	122	50	25	101	65	30	0	102	6.2	19	0.6	0.09	124
F06067	5.9	4.3	2.69	151	58	14	101	73	34	0	88	6.2	15	0.6	0.07	107
F06068	6.0	4.0	2.00	106	62	11	123	58	24	0	48	12.2	18	0.6	0.08	156
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.1	2.35	131	56	16	105	73	35	0	117	7.3	17	0.6	0.09	129
S.D.	0.2	0.2	0.28	17	6	6	10	19	17	0	59	2.8	2	0.1	0.03	19
Significance	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS
Statistical method	AW	TT	AW	TT	TT	TT	TT	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.

B-CH 1000 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06064	4.7	8.9	143.4	3.22	108.8
F06065	2.5	9.1	143.7	3.40	109.1
F06066	3.0	9.1	144.8	3.06	109.5
F06067	3.3	8.9	144.4	2.86	110.6
F06068	3.6	9.0	145.0	3.06	111.0
Number of females	5	5	5	5	5
Mean	3.4	9.0	144.3	3.12	109.8
S.D.	0.8	0.1	0.7	0.20	1.0
Significance	NS	*	NS	NS	NS
Statistical method	TT	AW	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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	507.0	2122.3	4.186	262.1	0.517	1563.5	3.084	14445.5	28.492	1565.9	3.089	1581.3	3.119	3147.2	6.207	954.5	1.883
M01002	526.2	2152.9	4.091	287.7	0.547	1491.4	2.834	12936.4	24.585	1680.6	3.194	1717.8	3.265	3398.4	6.458	718.3	1.365
M01003	550.6	2050.9	3.725	274.7	0.499	1638.2	2.975	18260.9	33.165	1790.6	3.252	1793.8	3.258	3584.4	6.510	742.5	1.349
M01004	478.4	1923.0	4.020	304.3	0.636	1726.0	3.608	12178.9	25.458	1636.6	3.421	1562.9	3.267	3199.5	6.688	822.7	1.720
M01005	489.1	2007.8	4.105	201.4	0.412	1297.0	2.652	12058.7	24.655	1504.6	3.076	1474.1	3.014	2978.7	6.090	624.7	1.277
M01006	499.8	2002.7	4.007	215.1	0.430	1327.1	2.655	12188.7	24.387	1666.8	3.335	1582.5	3.166	3249.3	6.501	848.1	1.697
M01007	502.8	2042.2	4.062	314.2	0.625	1694.2	3.370	15587.1	31.001	1894.1	3.767	2154.7	4.285	4048.8	8.053	865.8	1.722
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	507.7	2043.1	4.028	265.6	0.524	1533.9	3.025	13950.9	27.392	1677.0	3.305	1695.3	3.339	3372.3	6.644	796.7	1.573
S.D.	24.1	77.1	0.146	43.0	0.087	170.8	0.360	2322.1	3.552	131.6	0.239	228.6	0.427	354.5	0.653	109.3	0.237

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

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	1618.1	3.192	1571.0	3.099	3189.1	6.290	606.6	1.196	598.2	1.180	1204.8	2.376
M01002	1572.7	2.989	1642.1	3.121	3214.8	6.109	576.6	1.096	622.7	1.183	1199.3	2.279
M01003	1770.3	3.215	1825.6	3.316	3595.9	6.531	713.6	1.296	730.4	1.327	1444.0	2.623
M01004	1503.2	3.142	1564.2	3.270	3067.4	6.412	639.1	1.336	635.5	1.328	1274.6	2.664
M01005	1715.6	3.508	1685.1	3.445	3400.7	6.953	610.8	1.249	618.7	1.265	1229.5	2.514
M01006	1684.3	3.370	1698.5	3.398	3382.8	6.768	641.3	1.283	617.9	1.236	1259.2	2.519
M01007	1679.2	3.340	1654.1	3.290	3333.3	6.629	668.6	1.330	668.0	1.329	1336.6	2.658
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1649.1	3.251	1662.9	3.277	3312.0	6.527	636.7	1.255	641.6	1.264	1278.3	2.519
S.D.	90.7	0.170	88.4	0.130	172.4	0.287	45.0	0.085	44.6	0.067	86.9	0.147

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	540.0	1.065	1257.9	2.481	18.0	0.036	26.6	0.052	29.1	0.057	55.7	0.110
M01002	453.9	0.863	2058.4	3.912	17.6	0.033	28.3	0.054	28.8	0.055	57.1	0.109
M01003	679.2	1.234	2123.1	3.856	18.8	0.034	28.1	0.051	29.3	0.053	57.4	0.104
M01004	538.7	1.126	1455.4	3.042	19.4	0.041	24.7	0.052	21.2	0.044	45.9	0.096
M01005	519.6	1.062	1551.8	3.173	14.1	0.029	32.2	0.066	32.4	0.066	64.6	0.132
M01006	645.6	1.292	2186.3	4.374	12.9	0.026	26.4	0.053	30.6	0.061	57.0	0.114
M01007	726.8	1.446	2252.3	4.480	24.6	0.049	23.7	0.047	28.0	0.056	51.7	0.103
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	586.3	1.155	1840.7	3.617	17.9	0.035	27.1	0.054	28.5	0.056	55.6	0.110
S.D.	98.6	0.188	405.7	0.739	3.8	0.008	2.8	0.006	3.5	0.007	5.7	0.011

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

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

B-CH 100 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)
M02013	557.9	1992.7	3.572	260.1	0.466	1646.8	2.952	15787.6	28.298	1629.4	2.921	1751.1	3.139	3380.5	6.059	733.5	1.315
M02014	509.9	1945.0	3.814	476.7	0.935	1534.6	3.010	15513.3	30.424	1985.0	3.893	2055.7	4.032	4040.7	7.924	857.2	1.681
M02015	484.6	2032.0	4.193	377.4	0.779	1530.2	3.158	13569.2	28.001	1502.7	3.101	1475.5	3.045	2978.2	6.146	734.0	1.515
M02016	472.0	2021.0	4.282	258.4	0.547	1534.2	3.250	11439.6	24.236	1717.4	3.639	1728.4	3.662	3445.8	7.300	1091.4	2.312
M02017	491.2	1940.4	3.950	306.3	0.624	1453.1	2.958	11888.2	24.202	1550.6	3.157	1449.1	2.950	2999.7	6.107	695.8	1.417
M02018	443.0	2024.9	4.571	363.5	0.821	1170.5	2.642	11501.6	25.963	1708.0	3.856	1585.9	3.580	3293.9	7.435	726.8	1.641
M02019	544.7	2097.8	3.851	329.6	0.605	1714.3	3.147	17021.9	31.250	1680.4	3.085	1764.8	3.240	3445.2	6.325	839.9	1.542
M02020	579.4	2296.9	3.964	393.7	0.679	1662.9	2.870	16206.6	27.971	1794.0	3.096	1889.5	3.261	3683.5	6.357	917.4	1.583
M02021	482.2	1972.1	4.090	190.6	0.395	1309.1	2.715	11526.8	23.905	1645.0	3.411	1654.9	3.432	3299.9	6.843	847.3	1.757
M02022	523.4	1967.7	3.759	338.9	0.647	1469.9	2.808	14772.0	28.223	1683.4	3.216	1637.2	3.128	3320.6	6.344	972.0	1.857
M02023	404.3	2024.5	5.007	88.0	0.218	1259.6	3.116	9041.1	22.362	1403.0	3.470	1368.7	3.385	2771.7	6.856	622.4	1.539
M02024	466.1	1986.5	4.262	507.6	1.089	1602.5	3.438	12281.3	26.349	1821.0	3.907	1849.9	3.969	3670.9	7.876	860.6	1.846
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	496.6	2025.1	4.110	324.2	0.650	1490.6	3.005	13379.1	26.765	1676.7	3.396	1684.2	3.402	3360.9	6.798	824.9	1.667
S.D.	49.7	96.0	0.392	116.3	0.237	168.6	0.230	2459.9	2.735	152.7	0.353	198.1	0.349	345.2	0.685	130.8	0.260
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	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

B-CH 100 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	1586.9	2.844	1565.0	2.805	3151.9	5.650	612.3	1.098	662.6	1.188	1274.9	2.285
M02014	1591.6	3.121	1592.2	3.123	3183.8	6.244	636.8	1.249	651.4	1.278	1288.2	2.526
M02015	1531.7	3.161	1546.5	3.191	3078.2	6.352	620.6	1.281	594.6	1.227	1215.2	2.508
M02016	1648.3	3.492	1637.7	3.470	3286.0	6.962	649.8	1.377	639.5	1.355	1289.3	2.732
M02017	1739.6	3.542	1725.1	3.512	3464.7	7.054	630.0	1.283	624.0	1.270	1254.0	2.553
M02018	1792.6	4.047	1841.5	4.157	3634.1	8.203	675.5	1.525	586.5	1.324	1262.0	2.849
M02019	1585.5	2.911	1529.5	2.808	3115.0	5.719	625.0	1.147	620.0	1.138	1245.0	2.286
M02020	1612.1	2.782	1624.7	2.804	3236.8	5.586	599.1	1.034	590.6	1.019	1189.7	2.053
M02021	1852.3	3.841	1800.6	3.734	3652.9	7.575	683.1	1.417	701.0	1.454	1384.1	2.870
M02022	1651.5	3.155	1644.5	3.142	3296.0	6.297	756.0	1.444	739.6	1.413	1495.6	2.857
M02023	1738.7	4.301	1635.5	4.045	3374.2	8.346	615.5	1.522	576.6	1.426	1192.1	2.949
M02024	1695.8	3.638	1768.4	3.794	3464.2	7.432	636.1	1.365	619.9	1.330	1256.0	2.695
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1668.9	3.403	1659.3	3.382	3328.2	6.785	645.0	1.312	633.9	1.285	1278.8	2.597
S.D.	96.3	0.489	102.2	0.478	192.9	0.962	42.8	0.160	48.9	0.127	85.5	0.280
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN	KW	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.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

B-CH 100 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	599.2	1.074	1605.0	2.877	22.5	0.040	21.3	0.038	21.9	0.039	43.2	0.077
M02014	746.5	1.464	2297.2	4.505	24.8	0.049	27.5	0.054	26.1	0.051	53.6	0.105
M02015	558.8	1.153	1572.5	3.245	15.0	0.031	20.4	0.042	22.3	0.046	42.7	0.088
M02016	819.1	1.735	2058.2	4.361	16.7	0.035	27.8	0.059	30.1	0.064	57.9	0.123
M02017	699.6	1.424	2122.1	4.320	19.9	0.041	24.6	0.050	24.8	0.050	49.4	0.101
M02018	604.3	1.364	1757.9	3.968	23.2	0.052	29.9	0.067	34.5	0.078	64.4	0.145
M02019	598.3	1.098	1506.0	2.765	19.3	0.035	25.0	0.046	22.4	0.041	47.4	0.087
M02020	830.0	1.433	1754.5	3.028	19.0	0.033	33.9	0.059	37.8	0.065	71.7	0.124
M02021	683.5	1.417	1954.0	4.052	14.1	0.029	22.0	0.046	27.1	0.056	49.1	0.102
M02022	519.7	0.993	1618.2	3.092	21.2	0.041	27.9	0.053	28.0	0.053	55.9	0.107
M02023	537.1	1.328	1244.7	3.079	19.9	0.049	32.7	0.081	39.6	0.098	72.3	0.179
M02024	440.1	0.944	1480.7	3.177	23.2	0.050	24.1	0.052	25.0	0.054	49.1	0.105
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	636.4	1.286	1747.6	3.539	19.9	0.040	26.4	0.054	28.3	0.058	54.7	0.112
S.D.	121.0	0.233	306.3	0.646	3.3	0.008	4.3	0.012	6.0	0.017	10.1	0.028
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.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-3. Organ weights of male rats at the end of the dosing period

B-CH 300 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M03025	540.6	2210.0	4.088	219.8	0.407	1554.1	2.875	16454.0	30.437	1580.8	2.924	1573.3	2.910	3154.1	5.834	1010.3	1.869
M03026	521.0	2074.4	3.982	317.1	0.609	1551.6	2.978	13749.4	26.390	1661.9	3.190	1688.5	3.241	3350.4	6.431	783.1	1.503
M03027	546.6	1984.6	3.631	487.2	0.891	1504.3	2.752	14253.4	26.076	1619.3	2.962	1619.3	2.962	3238.6	5.925	844.3	1.545
M03028	449.7	2063.6	4.589	168.5	0.375	1308.9	2.911	12189.9	27.107	1532.3	3.407	1460.6	3.248	2992.9	6.655	827.0	1.839
M03029	471.7	1915.8	4.061	219.4	0.465	1451.2	3.077	13582.7	28.795	1707.6	3.620	1704.5	3.614	3412.1	7.234	858.4	1.820
M03030	535.3	1889.7	3.530	184.8	0.345	1430.3	2.672	13224.8	24.705	1618.3	3.023	1648.3	3.079	3266.6	6.102	909.8	1.700
M03031	497.2	2154.4	4.333	383.7	0.772	1449.8	2.916	12732.0	25.607	1893.4	3.808	1890.4	3.802	3783.8	7.610	1158.8	2.331
M03032	491.8	2069.2	4.207	244.6	0.497	1442.1	2.932	13053.2	26.542	1682.4	3.421	1673.6	3.403	3356.0	6.824	834.0	1.696
M03033	575.3	1852.2	3.220	337.5	0.587	1712.3	2.976	18268.4	31.755	2101.1	3.652	1954.8	3.398	4055.9	7.050	813.0	1.413
M03034	489.0	2038.7	4.169	231.9	0.474	1398.6	2.860	15202.6	31.089	1661.1	3.397	1744.5	3.567	3405.6	6.964	641.3	1.311
M03035	497.5	1911.7	3.843	195.7	0.393	1492.3	3.000	13580.8	27.298	1684.5	3.386	1622.7	3.262	3307.2	6.648	846.6	1.702
M03036	475.4	1974.8	4.154	367.9	0.774	1377.9	2.898	12474.7	26.240	1498.0	3.151	1474.6	3.102	2972.6	6.253	908.2	1.910
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	507.6	2011.6	3.984	279.8	0.549	1472.8	2.904	14063.8	27.670	1686.7	3.328	1671.3	3.299	3358.0	6.628	869.6	1.720
S.D.	36.5	109.5	0.376	98.0	0.179	103.0	0.109	1779.3	2.302	164.1	0.284	145.7	0.270	304.8	0.543	125.7	0.269
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	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

B-CH 300 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	1783.6	3.299	1787.2	3.306	3570.8	6.605	653.4	1.209	616.3	1.140	1269.7	2.349
M03026	1617.0	3.104	1620.2	3.110	3237.2	6.213	715.6	1.374	691.1	1.326	1406.7	2.700
M03027	1724.8	3.156	1777.7	3.252	3502.5	6.408	608.4	1.113	639.1	1.169	1247.5	2.282
M03028	1403.1	3.120	1445.2	3.214	2848.3	6.334	629.1	1.399	618.4	1.375	1247.5	2.774
M03029	1636.9	3.470	1593.5	3.378	3230.4	6.848	656.8	1.392	633.8	1.344	1290.6	2.736
M03030	1870.4	3.494	1827.8	3.415	3698.2	6.909	704.8	1.317	717.2	1.340	1422.0	2.656
M03031	2045.4	4.114	2037.2	4.097	4082.6	8.211	744.2	1.497	711.5	1.431	1455.7	2.928
M03032	1657.1	3.369	1566.2	3.185	3223.3	6.554	564.9	1.149	491.3	0.999	1056.2	2.148
M03033	1862.7	3.238	1790.1	3.112	3652.8	6.349	630.0	1.095	623.1	1.083	1253.1	2.178
M03034	1714.0	3.505	1781.3	3.643	3495.3	7.148	543.2	1.111	557.9	1.141	1101.1	2.252
M03035	1499.2	3.013	1468.3	2.951	2967.5	5.965	649.8	1.306	585.6	1.177	1235.4	2.483
M03036	1838.7	3.868	1819.2	3.827	3657.9	7.694	736.5	1.549	770.8	1.621	1507.3	3.171
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1721.1	3.396	1709.5	3.374	3430.6	6.770	653.1	1.293	638.0	1.262	1291.1	2.555
S.D.	175.2	0.326	172.1	0.330	343.9	0.649	63.8	0.156	76.2	0.174	136.3	0.324
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN	KW	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.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

B-CH 300 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	864.9	1.600	2269.9	4.199	18.1	0.033	22.4	0.041	23.0	0.043	45.4	0.084
M03026	647.6	1.243	2050.5	3.936	15.9	0.031	31.8	0.061	35.7	0.069	67.5	0.130
M03027	566.5	1.036	1886.4	3.451	16.6	0.030	32.2	0.059	31.6	0.058	63.8	0.117
M03028	629.2	1.399	1573.8	3.500	9.5	0.021	24.3	0.054	29.5	0.066	53.8	0.120
M03029	619.2	1.313	1905.5	4.040	17.4	0.037	26.1	0.055	27.7	0.059	53.8	0.114
M03030	384.1	0.718	1436.1	2.683	13.3	0.025	21.3	0.040	22.9	0.043	44.2	0.083
M03031	661.6	1.331	1909.8	3.841	16.0	0.032	20.9	0.042	22.7	0.046	43.6	0.088
M03032	535.0	1.088	1660.2	3.376	17.2	0.035	21.7	0.044	23.2	0.047	44.9	0.091
M03033	632.1	1.099	1628.0	2.830	14.8	0.026	37.6	0.065	38.7	0.067	76.3	0.133
M03034	399.4	0.817	1716.2	3.510	18.6	0.038	29.4	0.060	30.6	0.063	60.0	0.123
M03035	598.2	1.202	1711.7	3.441	22.3	0.045	33.7	0.068	37.1	0.075	70.8	0.142
M03036	707.2	1.488	1516.4	3.190	21.8	0.046	27.9	0.059	27.4	0.058	55.3	0.116
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	603.8	1.195	1772.0	3.500	16.8	0.033	27.4	0.054	29.2	0.058	56.6	0.112
S.D.	128.6	0.260	239.8	0.459	3.5	0.008	5.5	0.010	5.8	0.011	11.2	0.020
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.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-4. Organ weights of male rats at the end of the dosing period

B-CH 1000 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	485.2	2112.9	4.355	263.3	0.543	1524.0	3.141	13656.3	28.146	1790.1	3.689	1658.9	3.419	3449.0	7.108	876.6	1.807
M04038	519.9	2112.1	4.063	307.3	0.591	1437.0	2.764	13070.2	25.140	1547.6	2.977	1592.3	3.063	3139.9	6.039	697.3	1.341
M04039	503.2	2079.9	4.133	410.1	0.815	1674.1	3.327	14750.8	29.314	1542.5	3.065	1576.4	3.133	3118.9	6.198	998.7	1.985
M04040	501.1	2013.9	4.019	235.5	0.470	1375.5	2.745	12502.7	24.951	1563.7	3.121	1582.3	3.158	3146.0	6.278	862.7	1.722
M04041	490.6	1925.2	3.924	298.2	0.608	1262.6	2.574	12964.2	26.425	1469.8	2.996	1502.8	3.063	2972.6	6.059	699.2	1.425
M04042	511.8	2123.2	4.148	250.8	0.490	1405.3	2.746	14138.6	27.625	1885.8	3.685	1815.7	3.548	3701.5	7.232	840.4	1.642
M04043	502.2	2019.9	4.022	250.6	0.499	1403.4	2.795	12935.5	25.758	1663.4	3.312	1628.4	3.243	3291.8	6.555	713.6	1.421
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	502.0	2055.3	4.095	288.0	0.574	1440.3	2.870	13431.2	26.766	1637.6	3.264	1622.4	3.232	3260.0	6.496	812.6	1.620
S.D.	11.8	72.6	0.137	59.9	0.118	129.1	0.264	790.4	1.643	150.7	0.309	98.0	0.186	245.5	0.493	114.0	0.236
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	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 29-1-4 (continued). Organ weights of male rats at the end of the dosing period

B-CH 1000 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	1620.2	3.339	1632.0	3.364	3252.2	6.703	652.5	1.345	679.5	1.400	1332.0	2.745
M04038	1629.0	3.133	1668.1	3.209	3297.1	6.342	591.6	1.138	587.9	1.131	1179.5	2.269
M04039	1724.8	3.428	1667.2	3.313	3392.0	6.741	627.0	1.246	646.2	1.284	1273.2	2.530
M04040	1559.9	3.113	1542.9	3.079	3102.8	6.192	601.2	1.200	606.7	1.211	1207.9	2.410
M04041	1920.5	3.915	1940.1	3.955	3860.6	7.869	642.7	1.310	636.4	1.297	1279.1	2.607
M04042	1746.5	3.412	1732.6	3.385	3479.1	6.798	655.0	1.280	614.1	1.200	1269.1	2.480
M04043	1826.5	3.637	1805.6	3.595	3632.1	7.232	722.6	1.439	719.4	1.432	1442.0	2.871
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1718.2	3.425	1712.6	3.414	3430.8	6.840	641.8	1.280	641.5	1.279	1283.3	2.559
S.D.	126.6	0.281	129.2	0.287	253.8	0.564	43.2	0.098	45.5	0.109	86.0	0.203
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN	KW	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.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
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.

B-CH 1000 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	371.3	0.765	1525.1	3.143	24.1	0.050	25.6	0.053	25.9	0.053	51.5	0.106
M04038	592.2	1.139	1941.3	3.734	22.8	0.044	31.3	0.060	31.2	0.060	62.5	0.120
M04039	680.3	1.352	1828.2	3.633	20.6	0.041	27.0	0.054	28.2	0.056	55.2	0.110
M04040	637.1	1.271	1818.9	3.630	14.2	0.028	32.3	0.064	36.3	0.072	68.6	0.137
M04041	501.4	1.022	1481.6	3.020	18.2	0.037	26.4	0.054	26.5	0.054	52.9	0.108
M04042	659.7	1.289	1731.3	3.383	21.1	0.041	24.9	0.049	26.7	0.052	51.6	0.101
M04043	393.3	0.783	2024.6	4.031	18.3	0.036	34.5	0.069	33.9	0.068	68.4	0.136
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	547.9	1.089	1764.4	3.511	19.9	0.040	28.9	0.058	29.8	0.059	58.7	0.117
S.D.	127.3	0.241	201.8	0.352	3.3	0.007	3.8	0.007	4.1	0.008	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.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Control (vehicle: water for injection)

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	541.5	2101.3	3.881	288.5	0.533	1602.4	2.959	13844.0	25.566	1623.2	2.998	1606.2	2.966	3229.4	5.964	902.8	1.667
M01009	526.9	2076.9	3.942	353.1	0.670	1501.0	2.849	13627.9	25.864	1563.8	2.968	1614.1	3.063	3177.9	6.031	906.5	1.720
M01010	555.4	2061.7	3.712	337.7	0.608	1608.8	2.897	17873.1	32.181	1765.6	3.179	1688.7	3.041	3454.3	6.219	1026.5	1.848
M01011	550.5	1882.6	3.420	388.6	0.706	1489.2	2.705	14850.7	26.977	1628.2	2.958	1603.9	2.914	3232.1	5.871	856.8	1.556
M01012	577.2	2184.3	3.784	411.5	0.713	1573.8	2.727	14217.6	24.632	1575.0	2.729	1596.2	2.765	3171.2	5.494	964.4	1.671
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	550.3	2061.4	3.748	355.9	0.646	1555.0	2.827	14882.7	27.044	1631.2	2.966	1621.8	2.950	3253.0	5.916	931.4	1.692
S.D.	18.5	110.6	0.203	47.5	0.076	56.4	0.109	1734.9	2.991	80.4	0.160	37.9	0.119	116.0	0.268	65.5	0.106

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

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	1710.5	3.159	1753.3	3.238	3463.8	6.397	586.9	1.084	586.2	1.083	1173.1	2.166
M01009	1770.8	3.361	1758.7	3.338	3529.5	6.699	733.5	1.392	711.9	1.351	1445.4	2.743
M01010	1647.2	2.966	1665.2	2.998	3312.4	5.964	804.5	1.449	800.6	1.441	1605.1	2.890
M01011	1576.3	2.863	1612.5	2.929	3188.8	5.793	611.2	1.110	567.2	1.030	1178.4	2.141
M01012	1600.2	2.772	1606.4	2.783	3206.6	5.555	710.9	1.232	693.3	1.201	1404.2	2.433
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1661.0	3.024	1679.2	3.057	3340.2	6.082	689.4	1.253	671.8	1.221	1361.2	2.475
S.D.	79.9	0.237	73.7	0.227	152.2	0.462	89.8	0.164	96.1	0.174	185.2	0.336

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	594.9	1.099	1622.8	2.997	21.4	0.040	23.6	0.044	21.1	0.039	44.7	0.083
M01009	661.9	1.256	1734.2	3.291	20.0	0.038	29.0	0.055	31.2	0.059	60.2	0.114
M01010	702.7	1.265	1621.3	2.919	22.2	0.040	25.4	0.046	27.3	0.049	52.7	0.095
M01011	765.5	1.391	1526.8	2.773	25.9	0.047	23.9	0.043	27.0	0.049	50.9	0.092
M01012	343.4	0.595	1570.4	2.721	15.1	0.026	28.1	0.049	29.2	0.051	57.3	0.099
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	613.7	1.121	1615.1	2.940	20.9	0.038	26.0	0.047	27.2	0.049	53.2	0.097
S.D.	163.3	0.312	77.6	0.225	3.9	0.008	2.4	0.005	3.8	0.007	6.0	0.011

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

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

B-CH 1000 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	536.1	2075.1	3.871	357.8	0.667	1537.1	2.867	13847.1	25.829	1533.2	2.860	1611.5	3.006	3144.7	5.866	860.1	1.604
M04045	544.0	2133.9	3.923	288.2	0.530	1474.5	2.710	13826.7	25.417	1741.7	3.202	1840.2	3.383	3581.9	6.584	859.8	1.581
M04046	519.5	2093.2	4.029	242.6	0.467	1477.1	2.843	14323.9	27.572	1742.7	3.355	1735.7	3.341	3478.4	6.696	1039.6	2.001
M04047	553.8	2077.5	3.751	234.2	0.423	1451.5	2.621	15187.4	27.424	1619.1	2.924	1552.9	2.804	3172.0	5.728	893.8	1.614
M04048	564.6	2140.7	3.792	174.2	0.309	1399.6	2.479	15477.4	27.413	1565.6	2.773	1596.4	2.827	3162.0	5.600	965.6	1.710
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	543.6	2104.1	3.873	259.4	0.479	1468.0	2.704	14532.5	26.731	1640.5	3.023	1667.3	3.072	3307.8	6.095	923.8	1.702
S.D.	17.2	31.2	0.110	68.4	0.132	49.6	0.161	763.7	1.024	97.8	0.246	118.1	0.276	206.5	0.508	77.8	0.174
Significance	NS	NS	NS	*	*	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

B-CH 1000 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	1675.5	3.125	1678.6	3.131	3354.1	6.256	763.8	1.425	748.7	1.397	1512.5	2.821
M04045	1692.4	3.111	1703.8	3.132	3396.2	6.243	659.4	1.212	662.2	1.217	1321.6	2.429
M04046	1533.0	2.951	1483.7	2.856	3016.7	5.807	594.4	1.144	598.2	1.151	1192.6	2.296
M04047	1825.6	3.296	1806.3	3.262	3631.9	6.558	680.5	1.229	646.9	1.168	1327.4	2.397
M04048	1774.5	3.143	1726.9	3.059	3501.4	6.202	688.9	1.220	693.0	1.227	1381.9	2.448
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1700.2	3.125	1679.9	3.088	3380.1	6.213	677.4	1.246	669.8	1.232	1347.2	2.478
S.D.	111.7	0.123	119.6	0.149	229.7	0.268	60.9	0.106	55.8	0.098	115.6	0.200
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

B-CH 1000 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	880.0	1.641	1906.0	3.555	22.7	0.042	23.4	0.044	28.3	0.053	51.7	0.096
M04045	856.1	1.574	1746.1	3.210	18.3	0.034	38.5	0.071	39.6	0.073	78.1	0.144
M04046	576.5	1.110	1419.9	2.733	16.5	0.032	22.6	0.044	21.4	0.041	44.0	0.085
M04047	678.7	1.226	2452.9	4.429	18.0	0.033	28.8	0.052	32.1	0.058	60.9	0.110
M04048	649.0	1.149	1971.5	3.492	22.2	0.039	23.5	0.042	25.6	0.045	49.1	0.087
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	728.1	1.340	1899.3	3.484	19.5	0.036	27.4	0.051	29.4	0.054	56.8	0.104
S.D.	133.4	0.249	375.8	0.620	2.7	0.004	6.7	0.012	6.9	0.013	13.4	0.024
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Body	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)
F01001	292.7	1939.1	6.625	122.9	0.420	943.4	3.223	10767.7	36.787	889.7	3.040	988.9	3.379	1878.6	6.418	587.6	2.008
F01002	308.2	1817.7	5.898	186.3	0.604	1042.6	3.383	10244.4	33.239	883.2	2.866	852.6	2.766	1735.8	5.632	736.1	2.388
F01003	302.0	1928.2	6.385	158.1	0.524	977.8	3.238	9807.8	32.476	1078.4	3.571	1034.5	3.425	2112.9	6.996	649.2	2.150
F01004	317.3	1852.8	5.839	255.1	0.804	1116.0	3.517	11064.2	34.870	1179.9	3.719	1199.9	3.782	2379.8	7.500	814.2	2.566
F01005	304.7	1805.5	5.926	388.9	1.276	893.5	2.932	9324.1	30.601	977.4	3.208	909.6	2.985	1887.0	6.193	557.9	1.831
F01006	294.8	1804.4	6.121	218.2	0.740	1032.1	3.501	8983.0	30.472	937.6	3.180	915.1	3.104	1852.7	6.285	640.1	2.171
F01007	327.5	1855.5	5.666	201.0	0.614	969.6	2.961	10122.1	30.907	934.1	2.852	963.3	2.941	1897.4	5.794	660.5	2.017
F01008	280.0	1887.6	6.741	168.5	0.602	931.9	3.328	9410.1	33.608	988.2	3.529	1042.4	3.723	2030.6	7.252	609.0	2.175
F01009	316.6	1891.5	5.974	185.6	0.586	936.6	2.958	10078.3	31.833	937.6	2.961	950.9	3.003	1888.5	5.965	598.4	1.890
F01010	336.7	1938.7	5.758	196.7	0.584	1032.4	3.066	11750.3	34.898	1015.1	3.015	992.3	2.947	2007.4	5.962	702.8	2.087
F01011	303.0	1854.0	6.119	188.6	0.622	939.6	3.101	9227.0	30.452	926.7	3.058	967.4	3.193	1894.1	6.251	656.6	2.167
F01012	318.8	1896.4	5.949	153.8	0.482	1025.3	3.216	10277.6	32.238	977.4	3.066	910.7	2.857	1888.1	5.923	547.9	1.719
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	308.5	1872.6	6.083	202.0	0.655	986.7	3.202	10088.1	32.698	977.1	3.172	977.3	3.175	1954.4	6.348	646.7	2.097
S.D.	15.8	48.8	0.337	67.7	0.221	63.4	0.204	816.0	2.045	83.6	0.285	88.9	0.333	164.8	0.596	76.5	0.233

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

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	48.4	0.165	52.0	0.178	100.4	0.343	521.0	1.780	13.8	0.047	44.6	0.152	42.8	0.146	87.4	0.299
F01002	60.4	0.196	52.0	0.169	112.4	0.365	511.7	1.660	11.3	0.037	39.9	0.129	44.2	0.143	84.1	0.273
F01003	42.6	0.141	49.5	0.164	92.1	0.305	541.8	1.794	14.4	0.048	36.2	0.120	37.9	0.125	74.1	0.245
F01004	54.3	0.171	55.5	0.175	109.8	0.346	658.3	2.075	15.7	0.049	39.7	0.125	45.7	0.144	85.4	0.269
F01005	54.8	0.180	36.4	0.119	91.2	0.299	554.2	1.819	17.4	0.057	31.5	0.103	31.6	0.104	63.1	0.207
F01006	48.5	0.165	41.1	0.139	89.6	0.304	483.8	1.641	13.2	0.045	34.6	0.117	40.2	0.136	74.8	0.254
F01007	39.7	0.121	54.0	0.165	93.7	0.286	556.9	1.700	8.2	0.025	39.1	0.119	40.4	0.123	79.5	0.243
F01008	42.4	0.151	41.8	0.149	84.2	0.301	440.2	1.572	13.7	0.049	40.0	0.143	43.3	0.155	83.3	0.298
F01009	46.2	0.146	65.1	0.206	111.3	0.352	548.6	1.733	19.6	0.062	45.3	0.143	42.5	0.134	87.8	0.277
F01010	54.1	0.161	54.5	0.162	108.6	0.323	545.6	1.620	10.9	0.032	41.4	0.123	39.9	0.119	81.3	0.241
F01011	39.4	0.130	44.7	0.148	84.1	0.278	469.2	1.549	14.3	0.047	30.4	0.100	32.6	0.108	63.0	0.208
F01012	54.7	0.172	63.6	0.199	118.3	0.371	597.8	1.875	16.8	0.053	38.3	0.120	43.1	0.135	81.4	0.255
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	48.8	0.158	50.9	0.164	99.6	0.323	535.8	1.735	14.1	0.046	38.4	0.125	40.4	0.131	78.8	0.256
S.D.	6.9	0.021	8.7	0.024	12.0	0.032	58.0	0.147	3.1	0.010	4.6	0.016	4.4	0.016	8.5	0.030

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

Appendix 30-1-2. Organ weights of female rats at the end of the dosing period

B-CH 100 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	287.0	1906.5	6.643	146.8	0.511	1053.4	3.670	10756.5	37.479	1036.5	3.611	1021.1	3.558	2057.6	7.169	802.4	2.796
F02014	326.8	1880.5	5.754	159.7	0.489	937.7	2.869	10218.2	31.267	1005.5	3.077	1010.6	3.092	2016.1	6.169	841.9	2.576
F02015	290.2	1838.1	6.334	246.8	0.850	891.4	3.072	9895.9	34.100	1007.0	3.470	956.5	3.296	1963.5	6.766	780.8	2.691
F02016	301.4	1820.6	6.040	376.5	1.249	1088.3	3.611	10864.1	36.045	1090.6	3.618	1039.6	3.449	2130.2	7.068	669.8	2.222
F02017	288.9	1810.6	6.267	196.0	0.678	901.5	3.120	9998.6	34.609	945.4	3.272	890.6	3.083	1836.0	6.355	668.3	2.313
F02018	321.6	1948.7	6.059	242.7	0.755	1040.9	3.237	10701.7	33.276	1046.1	3.253	1019.1	3.169	2065.2	6.422	704.5	2.191
F02019	340.6	1990.5	5.844	251.7	0.739	1078.3	3.166	9898.6	29.062	1002.6	2.944	1042.8	3.062	2045.4	6.005	805.6	2.365
F02020	336.7	1797.5	5.339	225.7	0.670	1211.5	3.598	11408.9	33.884	1164.8	3.459	1170.3	3.476	2335.1	6.935	658.7	1.956
F02021	329.4	1830.1	5.556	196.7	0.597	1053.1	3.197	10331.1	31.363	973.2	2.954	931.5	2.828	1904.7	5.782	712.7	2.164
F02022	319.5	1999.2	6.257	171.1	0.536	1063.5	3.329	10283.6	32.187	998.6	3.126	965.3	3.021	1963.9	6.147	599.5	1.876
F02023	302.7	1922.6	6.352	272.3	0.900	998.0	3.297	9552.4	31.557	1136.1	3.753	1159.3	3.830	2295.4	7.583	695.5	2.298
F02024	321.2	1900.5	5.917	291.3	0.907	978.6	3.047	10495.7	32.677	1067.1	3.322	1044.4	3.252	2111.5	6.574	589.2	1.834
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	313.8	1887.1	6.030	231.4	0.740	1024.7	3.268	10367.1	33.126	1039.5	3.322	1020.9	3.260	2060.4	6.581	710.7	2.274
S.D.	19.0	69.3	0.370	64.3	0.216	89.7	0.248	512.0	2.293	65.3	0.267	82.7	0.278	145.8	0.535	81.5	0.305
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	KW	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 30-1-2 (continued). Organ weights of female rats at the end of the dosing period

B-CH 100 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	45.5	0.159	55.8	0.194	101.3	0.353	539.2	1.879	12.8	0.045	40.7	0.142	42.9	0.149	83.6	0.291
F02014	57.9	0.177	53.0	0.162	110.9	0.339	550.2	1.684	11.3	0.035	33.2	0.102	35.4	0.108	68.6	0.210
F02015	45.2	0.156	60.6	0.209	105.8	0.365	520.2	1.793	19.7	0.068	42.1	0.145	49.0	0.169	91.1	0.314
F02016	39.9	0.132	47.0	0.156	86.9	0.288	760.8	2.524	12.9	0.043	42.1	0.140	44.0	0.146	86.1	0.286
F02017	47.3	0.164	65.0	0.225	112.3	0.389	559.4	1.936	15.0	0.052	35.4	0.123	39.1	0.135	74.5	0.258
F02018	36.8	0.114	59.3	0.184	96.1	0.299	551.7	1.715	20.8	0.065	43.2	0.134	47.9	0.149	91.1	0.283
F02019	59.4	0.174	44.9	0.132	104.3	0.306	613.3	1.801	11.7	0.034	42.1	0.124	43.5	0.128	85.6	0.251
F02020	62.0	0.184	46.2	0.137	108.2	0.321	557.8	1.657	10.6	0.031	33.1	0.098	35.8	0.106	68.9	0.205
F02021	63.0	0.191	50.5	0.153	113.5	0.345	607.7	1.845	13.9	0.042	45.0	0.137	46.8	0.142	91.8	0.279
F02022	53.5	0.167	50.9	0.159	104.4	0.327	574.8	1.799	14.3	0.045	36.8	0.115	33.8	0.106	70.6	0.221
F02023	47.2	0.156	45.8	0.151	93.0	0.307	653.7	2.160	15.2	0.050	30.6	0.101	33.8	0.112	64.4	0.213
F02024	66.5	0.207	45.8	0.143	112.3	0.350	625.2	1.946	17.6	0.055	41.1	0.128	45.1	0.140	86.2	0.268
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	52.0	0.165	52.1	0.167	104.1	0.332	592.8	1.895	14.7	0.047	38.8	0.124	41.4	0.133	80.2	0.257
S.D.	9.7	0.025	6.7	0.029	8.4	0.030	66.0	0.240	3.2	0.012	4.7	0.017	5.6	0.021	10.1	0.037
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 30-1-3. Organ weights of female rats at the end of the dosing period

B-CH 300 mg/kg

Female No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
F03025	301.6	1877.8	6.226	211.7	0.702	974.1	3.230	10339.0	34.281	935.1	3.100	980.6	3.251	1915.7	6.352	686.4	2.276
F03026	294.8	1817.0	6.164	254.2	0.862	1045.2	3.545	10123.5	34.340	1067.0	3.619	1025.6	3.479	2092.6	7.098	763.3	2.589
F03027	309.5	1979.3	6.395	266.3	0.860	975.6	3.152	9769.3	31.565	898.7	2.904	830.6	2.684	1729.3	5.587	847.0	2.737
F03028	267.8	1921.1	7.174	98.6	0.368	929.7	3.472	10521.8	39.290	912.9	3.409	863.8	3.226	1776.7	6.634	588.5	2.198
F03029	312.7	1918.8	6.136	213.9	0.684	968.6	3.098	9631.4	30.801	1057.3	3.381	1011.1	3.233	2068.4	6.615	750.6	2.400
F03030	298.7	1860.3	6.228	111.6	0.374	947.6	3.172	9418.0	31.530	962.0	3.221	961.4	3.219	1923.4	6.439	734.4	2.459
F03031	315.1	1898.6	6.025	148.7	0.472	982.4	3.118	9729.6	30.878	941.2	2.987	964.4	3.061	1905.6	6.048	776.0	2.463
F03032	322.4	1833.4	5.687	274.6	0.852	1000.8	3.104	10999.9	34.119	1099.3	3.410	1023.4	3.174	2122.7	6.584	817.3	2.535
F03033	297.0	1808.0	6.088	165.8	0.558	1039.1	3.499	10583.0	35.633	1030.5	3.470	985.2	3.317	2015.7	6.787	919.0	3.094
F03034	295.5 a)	1824.2 a)	6.173 a)	235.9 a)	0.798 a)	877.0 a)	2.968 a)	10512.6 a)	35.576 a)	1057.2 a)	3.578 a)	1019.2 a)	3.449 a)	2076.4 a)	7.027 a)	502.0 a)	1.699 a)
F03035	292.1	1945.9	6.662	164.6	0.564	915.5	3.134	9446.1	32.339	995.0	3.406	976.7	3.344	1971.7	6.750	548.6	1.878
F03036	327.8	1847.9	5.637	395.9	1.208	1060.5	3.235	9796.3	29.885	1099.2	3.353	1057.4	3.226	2156.6	6.579	553.8	1.689
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	303.6	1882.6	6.220	209.6	0.682	985.4	3.251	10032.5	33.151	999.8	3.296	970.9	3.201	1970.8	6.498	725.9	2.393
S.D.	16.6	55.2	0.427	85.9	0.252	47.2	0.170	517.7	2.732	74.4	0.218	68.2	0.201	137.7	0.401	121.0	0.386
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	KW	KW

a) Excluded from data analysis (not copulated).
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 30-1-3 (continued). Organ weights of female rats at the end of the dosing period

B-CH 300 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	44.0	0.146	50.0	0.166	94.0	0.312	550.7	1.826	13.7	0.045	36.5	0.121	35.3	0.117	71.8	0.238
F03026	40.0	0.136	55.1	0.187	95.1	0.323	438.1	1.486	15.8	0.054	39.0	0.132	45.4	0.154	84.4	0.286
F03027	53.0	0.171	57.9	0.187	110.9	0.358	525.7	1.699	17.4	0.056	36.2	0.117	39.2	0.127	75.4	0.244
F03028	54.6	0.204	48.4	0.181	103.0	0.385	594.1	2.218	8.3	0.031	36.8	0.137	41.4	0.155	78.2	0.292
F03029	41.2	0.132	51.9	0.166	93.1	0.298	545.4	1.744	16.9	0.054	38.3	0.122	42.2	0.135	80.5	0.257
F03030	37.3	0.125	52.8	0.177	90.1	0.302	570.4	1.910	13.8	0.046	30.9	0.103	34.3	0.115	65.2	0.218
F03031	51.4	0.163	44.2	0.140	95.6	0.303	598.0	1.898	9.1	0.029	37.7	0.120	38.8	0.123	76.5	0.243
F03032	42.7	0.132	62.7	0.194	105.4	0.327	592.2	1.837	19.1	0.059	50.5	0.157	50.8	0.158	101.3	0.314
F03033	59.8	0.201	56.9	0.192	116.7	0.393	635.0	2.138	12.8	0.043	39.0	0.131	41.7	0.140	80.7	0.272
F03034	41.6 a)	0.141 a)	39.2 a)	0.133 a)	80.8 a)	0.273 a)	964.9 a)	3.265 a)	9.0 a)	0.030 a)	27.8 a)	0.094 a)	26.1 a)	0.088 a)	53.9 a)	0.182 a)
F03035	47.1	0.161	50.8	0.174	97.9	0.335	466.7	1.598	14.0	0.048	37.0	0.127	38.8	0.133	75.8	0.260
F03036	55.0	0.168	36.0	0.110	91.0	0.278	594.3	1.813	15.9	0.049	35.3	0.108	38.0	0.116	73.3	0.224
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	47.8	0.158	51.5	0.170	99.3	0.329	555.5	1.833	14.3	0.047	37.9	0.125	40.5	0.134	78.5	0.259
S.D.	7.3	0.027	7.2	0.025	8.6	0.037	59.5	0.213	3.3	0.010	4.7	0.015	4.6	0.016	9.1	0.030
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

a) Excluded from data analysis (not copulated).
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 30-1-4. Organ weights of female rats at the end of the dosing period

B-CH 1000 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04037	318.2	1914.2	6.016	236.7	0.744	1000.3	3.144	10276.5	32.296	1005.8	3.161	994.6	3.126	2000.4	6.287	669.6	2.104
F04038	336.8	1827.3	5.425	309.3	0.918	1108.0	3.290	10739.0	31.885	1044.3	3.101	1034.6	3.072	2078.9	6.173	812.9	2.414
F04039	299.4	1864.2	6.226	214.2	0.715	928.8	3.102	10035.3	33.518	1099.5	3.672	1028.7	3.436	2128.2	7.108	595.5	1.989
F04040	299.5	1929.1	6.441	135.8	0.453	897.0	2.995	9737.1	32.511	982.6	3.281	1011.5	3.377	1994.1	6.658	676.0	2.257
F04041	345.1	1901.9	5.511	167.7	0.486	1167.8	3.384	11399.8	33.033	1221.7	3.540	1112.4	3.223	2334.1	6.764	713.1	2.066
F04042	295.0	1866.1	6.326	253.0	0.858	990.1	3.356	9845.7	33.375	1035.0	3.508	966.0	3.275	2001.0	6.783	703.9	2.386
F04043	297.1	1948.5	6.558	188.8	0.635	967.2	3.255	9127.3	30.721	1003.1	3.376	1006.8	3.389	2009.9	6.765	629.1	2.117
F04044	316.0	1947.6	6.163	183.8	0.582	1017.6	3.220	10241.4	32.409	1157.6	3.663	1103.2	3.491	2260.8	7.154	733.7	2.322
F04045	293.5	1853.4	6.315	168.7	0.575	1030.6	3.511	10730.5	36.560	1058.7	3.607	1021.5	3.480	2080.2	7.088	1763.1	6.007
F04046	297.1	1816.4	6.114	193.7	0.652	1013.8	3.412	10294.1	34.649	953.4	3.209	950.7	3.200	1904.1	6.409	731.6	2.462
F04047	302.9	1900.7	6.275	171.1	0.565	993.5	3.280	9489.9	31.330	887.6	2.930	786.2	2.596	1673.8	5.526	712.1	2.351
F04048	302.4	1866.2	6.171	166.4	0.550	950.6	3.144	10167.6	33.623	1005.0	3.323	1001.4	3.312	2006.4	6.635	708.2	2.342
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	308.6	1886.3	6.128	199.1	0.644	1005.4	3.258	10173.7	32.993	1037.9	3.364	1001.5	3.248	2039.3	6.613	787.4	2.568
S.D.	17.0	44.1	0.341	47.5	0.142	74.0	0.146	606.2	1.552	89.7	0.239	82.7	0.246	166.8	0.464	312.1	1.094
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	KW	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 30-1-4 (continued). Organ weights of female rats at the end of the dosing period

B-CH 1000 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04037	47.4	0.149	45.1	0.142	92.5	0.291	685.2	2.153	15.2	0.048	47.7	0.150	53.4	0.168	101.1	0.318
F04038	46.0	0.137	44.6	0.132	90.6	0.269	754.7	2.241	15.0	0.045	30.0	0.089	35.6	0.106	65.6	0.195
F04039	62.2	0.208	46.5	0.155	108.7	0.363	531.0	1.774	18.5	0.062	42.3	0.141	41.6	0.139	83.9	0.280
F04040	49.2	0.164	49.7	0.166	98.9	0.330	573.5	1.915	13.6	0.045	41.7	0.139	46.4	0.155	88.1	0.294
F04041	69.5	0.201	54.7	0.159	124.2	0.360	728.9	2.112	16.4	0.048	52.1	0.151	57.1	0.165	109.2	0.316
F04042	38.5	0.131	45.3	0.154	83.8	0.284	706.7	2.396	14.8	0.050	39.7	0.135	43.2	0.146	82.9	0.281
F04043	52.9	0.178	40.5	0.136	93.4	0.314	622.2	2.094	15.3	0.051	31.0	0.104	32.8	0.110	63.8	0.215
F04044	51.8	0.164	48.3	0.153	100.1	0.317	468.9	1.484	15.3	0.048	51.9	0.164	56.7	0.179	108.6	0.344
F04045	38.8	0.132	42.4	0.144	81.2	0.277	585.4	1.995	10.8	0.037	42.2	0.144	48.1	0.164	90.3	0.308
F04046	54.3	0.183	51.5	0.173	105.8	0.356	499.1	1.680	17.4	0.059	41.3	0.139	44.2	0.149	85.5	0.288
F04047	39.1	0.129	48.9	0.161	88.0	0.291	509.9	1.683	14.5	0.048	35.2	0.116	41.6	0.137	76.8	0.254
F04048	46.2	0.153	56.0	0.185	102.2	0.338	711.8	2.354	11.8	0.039	46.8	0.155	52.3	0.173	99.1	0.328
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	49.7	0.161	47.8	0.155	97.5	0.316	614.8	1.990	14.9	0.048	41.8	0.136	46.1	0.149	87.9	0.285
S.D.	9.4	0.027	4.7	0.015	12.0	0.034	100.3	0.288	2.1	0.007	7.2	0.022	7.8	0.023	14.9	0.045
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

Appendix 30-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Body	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)
F05049	265.1	1759.7	6.638	305.3	1.152	902.2	3.403	6865.6	25.898	849.3	3.204	868.3	3.275	1717.6	6.479	581.1	2.192
F05050	285.0	1885.3	6.615	275.0	0.965	898.6	3.153	7408.7	25.995	907.7	3.185	904.1	3.172	1811.8	6.357	594.3	2.085
F05051	262.4	1885.3	7.185	237.5	0.905	925.8	3.528	6610.8	25.194	970.1	3.697	924.5	3.523	1894.6	7.220	538.3	2.051
F05052	291.2	1907.5	6.550	286.2	0.983	924.0	3.173	7677.8	26.366	918.3	3.154	895.3	3.075	1813.6	6.228	638.8	2.194
F05053	284.8	1792.4	6.294	291.9	1.025	930.0	3.265	7517.7	26.396	944.8	3.317	913.5	3.208	1858.3	6.525	473.0	1.661
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	277.7	1846.0	6.656	279.2	1.006	916.1	3.304	7216.1	25.970	918.0	3.311	901.1	3.251	1819.2	6.562	565.1	2.037
S.D.	13.0	65.6	0.326	25.7	0.092	14.6	0.159	455.6	0.486	45.4	0.224	21.3	0.169	66.4	0.386	62.7	0.219

Appendix 30-2-1 (continued). Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	38.4	0.145	42.7	0.161	81.1	0.306	420.2	1.585	12.5	0.047	37.2	0.140	34.6	0.131	71.8	0.271
F05050	33.1	0.116	37.4	0.131	70.5	0.247	797.9	2.800	14.5	0.051	35.9	0.126	38.4	0.135	74.3	0.261
F05051	44.0	0.168	46.3	0.176	90.3	0.344	402.4	1.534	15.0	0.057	36.8	0.140	37.9	0.144	74.7	0.285
F05052	38.4	0.132	45.4	0.156	83.8	0.288	487.1	1.673	16.7	0.057	39.7	0.136	38.0	0.130	77.7	0.267
F05053	42.5	0.149	50.9	0.179	93.4	0.328	409.8	1.439	14.6	0.051	34.8	0.122	36.7	0.129	71.5	0.251
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	39.3	0.142	44.5	0.161	83.8	0.303	503.5	1.806	14.7	0.053	36.9	0.133	37.1	0.134	74.0	0.267
S.D.	4.3	0.019	5.0	0.019	8.9	0.038	168.0	0.562	1.5	0.004	1.8	0.008	1.5	0.006	2.5	0.013

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

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

B-CH 1000 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	322.2	1918.0	5.953	335.5	1.041	1015.2	3.151	9093.6	28.223	1080.9	3.355	1040.7	3.230	2121.6	6.585	595.8	1.849
F06060	290.8	1855.9	6.382	270.5	0.930	854.8	2.939	8009.0	27.541	933.2	3.209	909.7	3.128	1842.9	6.337	673.9	2.317
F06061	290.1	2041.2	7.036	222.1	0.766	998.2	3.441	8234.0	28.383	1017.1	3.506	986.5	3.401	2003.6	6.907	531.8	1.833
F06062	266.1	1944.5	7.307	234.3	0.880	837.1	3.146	7328.4	27.540	941.9	3.540	967.6	3.636	1909.5	7.176	564.5	2.121
F06063	303.8	1901.5	6.259	236.0	0.777	1033.7	3.403	8385.8	27.603	1005.0	3.308	926.2	3.049	1931.2	6.357	722.8	2.379
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	294.6	1932.2	6.587	259.7	0.879	947.8	3.216	8210.2	27.858	995.6	3.384	966.1	3.289	1961.8	6.672	617.8	2.100
S.D.	20.6	68.9	0.564	46.1	0.114	94.0	0.207	638.3	0.411	60.4	0.138	51.9	0.234	106.2	0.363	78.9	0.255
Significance	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

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 30-2-2 (continued). Organ weights of female rats at the end of the dosing period, satellite group

B-CH 1000 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	50.3	0.156	44.4	0.138	94.7	0.294	457.6	1.420	12.7	0.039	38.7	0.120	36.3	0.113	75.0	0.233
F06060	48.6	0.167	51.1	0.176	99.7	0.343	495.4	1.704	14.1	0.048	30.3	0.104	32.8	0.113	63.1	0.217
F06061	65.0	0.224	57.3	0.198	122.3	0.422	423.5	1.460	14.8	0.051	31.7	0.109	33.1	0.114	64.8	0.223
F06062	33.6	0.126	33.1	0.124	66.7	0.251	471.0	1.770	14.0	0.053	29.8	0.112	31.4	0.118	61.2	0.230
F06063	51.4	0.169	44.4	0.146	95.8	0.315	559.8	1.843	17.5	0.058	38.3	0.126	40.1	0.132	78.4	0.258
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	49.8	0.168	46.1	0.156	95.8	0.325	481.5	1.639	14.6	0.050	33.8	0.114	34.7	0.118	68.5	0.232
S.D.	11.2	0.036	9.0	0.030	19.8	0.064	50.9	0.189	1.8	0.007	4.4	0.009	3.5	0.008	7.7	0.016
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	**	NS	**
Statistical method	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 30-3-1. Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	305.0	1935.4	6.346	329.1	1.079	957.0	3.138	7498.3	24.585	948.1	3.109	1023.5	3.356	1971.6	6.464	636.2	2.086
F05055	327.3	1907.0	5.826	260.8	0.797	912.2	2.787	7743.3	23.658	881.1	2.692	888.2	2.714	1769.3	5.406	645.4	1.972
F05056	296.9	1859.7	6.264	352.4	1.187	961.0	3.237	7737.8	26.062	914.4	3.080	925.5	3.117	1839.9	6.197	568.5	1.915
F05057	296.0	1863.9	6.297	227.0	0.767	917.1	3.098	7728.9	26.111	947.7	3.202	910.4	3.076	1858.1	6.277	525.0	1.774
F05058	280.1	1865.7	6.661	349.9	1.249	932.3	3.328	6669.2	23.810	906.7	3.237	770.6	2.751	1677.3	5.988	532.5	1.901
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	301.1	1886.3	6.279	303.8	1.016	935.9	3.118	7475.5	24.845	919.6	3.064	903.6	3.003	1823.2	6.066	581.5	1.930
S.D.	17.2	33.4	0.298	56.7	0.222	22.4	0.205	462.4	1.187	28.6	0.218	90.6	0.269	109.2	0.407	56.7	0.113

Appendix 30-3-1 (continued). Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	38.1	0.125	38.4	0.126	76.5	0.251	985.4	3.231	14.5	0.048	25.4	0.083	28.8	0.094	54.2	0.178
F05055	43.8	0.134	49.1	0.150	92.9	0.284	482.0	1.473	10.1	0.031	29.1	0.089	31.0	0.095	60.1	0.184
F05056	40.2	0.135	41.9	0.141	82.1	0.277	581.9	1.960	13.5	0.045	35.1	0.118	35.2	0.119	70.3	0.237
F05057	40.4	0.136	44.9	0.152	85.3	0.288	552.6	1.867	11.8	0.040	31.8	0.107	31.8	0.107	63.6	0.215
F05058	56.4	0.201	37.8	0.135	94.2	0.336	798.2	2.850	12.1	0.043	30.3	0.108	34.3	0.122	64.6	0.231
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	43.8	0.146	42.4	0.141	86.2	0.287	680.0	2.276	12.4	0.041	30.3	0.101	32.2	0.107	62.6	0.209
S.D.	7.3	0.031	4.7	0.011	7.4	0.031	207.5	0.734	1.7	0.007	3.6	0.015	2.6	0.013	5.9	0.027

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

Appendix 30-3-2. Organ weights of female rats at the end of the recovery period

B-CH 1000 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06064	265.2	1911.9	7.209	238.4	0.899	872.0	3.288	6730.8	25.380	785.7	2.963	771.2	2.908	1556.9	5.871	530.4	2.000
F06065	333.7	1986.9	5.954	270.8	0.812	898.8	2.693	7566.2	22.674	915.9	2.745	886.1	2.655	1802.0	5.400	613.6	1.839
F06066	296.3	1833.6	6.188	335.0	1.131	771.7	2.604	6677.1	22.535	829.9	2.801	792.8	2.676	1622.7	5.477	484.2	1.634
F06067	276.4	1881.0	6.805	358.8	1.298	872.9	3.158	7208.0	26.078	866.0	3.133	881.2	3.188	1747.2	6.321	544.6	1.970
F06068	279.4	1975.0	7.069	202.5	0.725	849.5	3.040	6406.4	22.929	877.4	3.140	874.4	3.130	1751.8	6.270	559.0	2.001
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	290.2	1917.7	6.645	281.1	0.973	853.0	2.957	6917.7	23.919	855.0	2.956	841.1	2.911	1696.1	5.868	546.4	1.889
S.D.	26.7	64.3	0.550	65.3	0.236	48.7	0.296	463.4	1.676	49.4	0.183	54.7	0.248	102.1	0.430	46.9	0.157
Significance	NS	NS	NS	NS	NS	**	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 30-3-2 (continued). Organ weights of female rats at the end of the recovery period

B-CH 1000 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06064	39.7	0.150	39.2	0.148	78.9	0.298	560.6	2.114	11.9	0.045	27.2	0.103	28.1	0.106	55.3	0.209
F06065	44.9	0.135	41.9	0.126	86.8	0.260	1082.9	3.245	19.8	0.059	31.6	0.095	33.9	0.102	65.5	0.196
F06066	35.2	0.119	42.0	0.142	77.2	0.261	923.3	3.116	11.2	0.038	24.0	0.081	26.5	0.089	50.5	0.170
F06067	42.5	0.154	41.9	0.152	84.4	0.305	835.0	3.021	14.5	0.052	32.3	0.117	37.9	0.137	70.2	0.254
F06068	39.1	0.140	35.4	0.127	74.5	0.267	1033.7	3.700	13.5	0.048	29.3	0.105	27.9	0.100	57.2	0.205
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	40.3	0.140	40.1	0.139	80.4	0.278	887.1	3.039	14.2	0.048	28.9	0.100	30.9	0.107	59.7	0.207
S.D.	3.7	0.014	2.9	0.012	5.1	0.022	206.4	0.579	3.4	0.008	3.4	0.013	4.9	0.018	8.0	0.030
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

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

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

Findings	Group	Control (vehicle: water for injection)							B-CH 100 mg/kg												B-CH 300 mg/kg												B-CH 1000 mg/kg						
	Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043
Epididymis																																							
Nodule, yellowish white, caudal, unilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver																																							
Dark colored spot, scattered		-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin																																							
Soiled fur, eyelid/perinasal area		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thymus																																							
Small		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

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

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

Findings	Group	Control (vehicle: water for injection)					B-CH 1000 mg/kg				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
All organs											
		-	-	-	-	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

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

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

Findings	Group	Control (vehicle: water for injection)											
	Animal No.	F01 001	F01 002	F01 003	F01 004	F01 005	F01 006	F01 007	F01 008	F01 009	F01 010	F01 011	F01 012
	Fate												
Glandular stomach													
Recessed area, mucosa, dark		-	-	-	-	-	-	P	P	-	-	-	-
Reddish area, mucosa		-	-	-	-	-	-	-	-	-	-	-	-
Spleen													
Adhesion with adipose tissue		-	-	-	-	-	-	-	-	-	-	-	-
Atrophy, partially		-	-	-	-	-	-	-	-	-	-	-	-

Findings	Group	B-CH 100 mg/kg											
	Animal No.	F02 013	F02 014	F02 015	F02 016	F02 017	F02 018	F02 019	F02 020	F02 021	F02 022	F02 023	F02 024
	Fate												
Glandular stomach													
Recessed area, mucosa, dark		-	-	-	-	-	-	-	-	-	-	P	-
Reddish area, mucosa		-	-	-	-	-	-	-	-	-	-	-	-
Spleen													
Adhesion with adipose tissue		-	-	-	-	-	-	-	-	-	-	-	-
Atrophy, partially		-	-	-	-	-	-	-	-	-	-	-	-

Findings	Group	B-CH 300 mg/kg											
	Animal No.	F03 025	F03 026	F03 027	F03 028	F03 029	F03 030	F03 031	F03 032	F03 033	F03 034	F03 035	F03 036
	Fate										NC		
Glandular stomach													
Recessed area, mucosa, dark		-	-	-	-	-	-	-	-	-	-	-	-
Reddish area, mucosa		-	-	-	-	-	-	-	-	-	-	-	-
Spleen													
Adhesion with adipose tissue		-	-	-	-	-	-	-	-	-	-	-	-
Atrophy, partially		-	-	-	-	-	-	-	-	-	-	-	-

Findings	Group	B-CH 1000 mg/kg											
	Animal No.	F04 037	F04 038	F04 039	F04 040	F04 041	F04 042	F04 043	F04 044	F04 045	F04 046	F04 047	F04 048
	Fate												
Glandular stomach													
Recessed area, mucosa, dark		-	-	-	-	-	-	-	-	P	-	-	P
Reddish area, mucosa		-	-	-	-	-	-	-	-	-	P	-	-
Spleen													
Adhesion with adipose tissue		-	-	-	-	-	-	-	-	P	-	-	-
Atrophy, partially		-	-	-	-	-	-	-	-	P	-	-	-

- : No abnormal changes P : Non-graded change

Fate : blanks, Subjected to autopsy on day 5 of lactation; NC, Not copulated.

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

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

Findings	Group	Control (vehicle: water for injection)					B-CH 1000 mg/kg				
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063
All organs											
		-	-	-	-	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

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

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

Findings	Group	Control (vehicle: water for injection)					B-CH 1000 mg/kg				
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 064	F06 065	F06 066	F06 067	F06 068
All organs											
		-	-	-	-	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

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

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

Group	Corn oil (vehicle: water for injection)											
Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M01 008	M01 009	M01 010	M01 011	M01 012
Brain	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Spinal cord	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Submandibular gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Ultimobranchial body	-	-	-	-	P							
Parathyroid gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Thymus	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Atrophy	-	-	-	-	-							
Heart	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Degeneration/fibrosis, myocardial, focal	-	-	-	±	±							
Trachea	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Lung	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Accumulation, foam cell, alveolus	±	-	-	-	-							
Bronchus	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Liver	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Degeneration, vacuolar, hepatocyte, centrilobular	-	-	±	-	-							
Fatty change, hepatocyte, periportal	±	-	±	±	±							
Hypertrophy, hepatocyte, centrilobular	-	-	±	-	-							
Microgranuloma	±	±	±	±	±							
Necrosis, focal, scattered	-	-	-	-	-							
Pancreas	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Stomach	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Duodenum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Jejunum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Ileum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Cecum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Colon	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Rectum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE

Group	B-CH 100 mg/kg											
Animal No.	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024
Brain	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ultimobranchial body												
Parathyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		NE
Atrophy											2+	
Heart	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Degeneration/fibrosis, myocardial, focal												
Trachea	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Accumulation, foam cell, alveolus												
Bronchus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Liver	NE	NE	NE	NE	NE	NE		NE	NE	NE	NE	NE
Degeneration, vacuolar, hepatocyte, centrilobular							-					
Fatty change, hepatocyte, periportal							±					
Hypertrophy, hepatocyte, centrilobular							-					
Microgranuloma							±					
Necrosis, focal, scattered							+					
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	B-CH 300 mg/kg											
Animal No.	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036
Brain	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ultimobranchial body												
Parathyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy												
Heart	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Degeneration/fibrosis, myocardial, focal												
Trachea	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Accumulation, foam cell, alveolus												
Bronchus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Liver	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Degeneration, vacuolar, hepatocyte, centrilobular												
Fatty change, hepatocyte, periportal												
Hypertrophy, hepatocyte, centrilobular												
Microgranuloma												
Necrosis, focal, scattered												
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	B-CH 1000 mg/kg											
Animal No.	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043	M04 044	M04 045	M04 046	M04 047	M04 048
Brain	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Spinal cord	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Submandibular gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Ultimobranchial body	-	-	-	-	-							
Parathyroid gland	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Thymus	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Atrophy	-	-	-	-	-							
Heart	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Degeneration/fibrosis, myocardial, focal	-	-	-	-	-							
Trachea	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Lung	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Accumulation, foam cell, alveolus	-	-	±	±	±							
Bronchus	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Liver	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Degeneration, vacuolar, hepatocyte, centrilobular	-	-	-	-	-							
Fatty change, hepatocyte, periportal	-	±	±	±	±							
Hypertrophy, hepatocyte, centrilobular	-	-	-	-	-							
Microgranuloma	±	±	±	±	±							
Necrosis, focal, scattered	-	-	-	-	-							
Pancreas	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Stomach	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Duodenum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Jejunum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Ileum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Cecum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Colon	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Rectum	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE

-: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P: Non-graded change NE: Not examined M: Missing A: Autolysis

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

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

Group	Corn oil (vehicle: water for injection)											
Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M01 008	M01 009	M01 010	M01 011	M01 012
Findings												
Spleen						NE	NE	NE	NE	NE	NE	NE
Deposit, pigment, brown	+	+	+	+	+							
Hematopoiesis, extramedullary	2+	+	2+	2+	±							
Kidney						NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex	±	±	±	±	-							
Mineralization, cortico-medullary junction~ medulla	±	-	-	-	-							
Urinary bladder						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Adrenal gland						NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona glomerulosa	-	-	-	-	-							
Vacuolation, zona fasciculata	-	-	-	-	-							
Testis						NE	NE	NE	NE	NE	NE	NE
Atrophy, seminiferous tubule, unilateral	-	±	-	-	-							
Epididymis						NE	NE	NE	NE	NE	NE	NE
Granuloma, spermatic, caudal, unilateral	-	-	-	-	-							
Prostate						NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial	-	-	±	±	-							
Seminal vesicle						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Coagulating gland						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Eyeball						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Harderian gland						NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial	-	-	-	±	-							
Sciatic nerve						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Skeletal muscle						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Femur						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Marrow, femur						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							

Group	B-CH 100 mg/kg											
Animal No.	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024
Findings												
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Deposit, pigment, brown												
Hematopoiesis, extramedullary												
Kidney	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex												
Mineralization, cortico-medullary junction~ medulla												
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona glomerulosa												
Vacuolation, zona fasciculata												
Testis	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy, seminiferous tubule, unilateral												
Epididymis	NE	NE	NE	NE	NE	NE	NE		NE	NE	NE	NE
Granuloma, spermatic, caudal, unilateral									P			
Prostate	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial												
Seminal vesicle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Coagulating gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial												
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	B-CH 300 mg/kg											
Animal No.	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036
Findings												
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Deposit, pigment, brown												
Hematopoiesis, extramedullary												
Kidney	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex												
Mineralization, cortico-medullary junction~ medulla												
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona glomerulosa												
Vacuolation, zona fasciculata												
Testis	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy, seminiferous tubule, unilateral												
Epididymis	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Granuloma, spermatic, caudal, unilateral												
Prostate	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial												
Seminal vesicle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Coagulating gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial												
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	B-CH 1000 mg/kg											
Animal No.	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043	M04 044	M04 045	M04 046	M04 047	M04 048
Findings												
Spleen						NE	NE	NE	NE	NE	NE	NE
Deposit, pigment, brown	+	+	2+	2+	±							
Hematopoiesis, extramedullary	2+	+	+	+	±							
Kidney						NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex	-	±	-	±	±							
Mineralization, cortico-medullary junction~ medulla	-	-	-	±	-							
Urinary bladder						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Adrenal gland						NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona glomerulosa	-	-	±	-	-							
Vacuolation, zona fasciculata	-	±	-	-	-							
Testis						NE	NE	NE	NE	NE	NE	NE
Atrophy, seminiferous tubule, unilateral	-	-	-	-	-							
Epididymis						NE	NE	NE	NE	NE	NE	NE
Granuloma, spermatic, caudal, unilateral	-	-	-	-	-							
Prostate						NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial	-	-	-	-	±							
Seminal vesicle						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Coagulating gland						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Eyeball						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Harderian gland						NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial	-	-	-	-	-							
Sciatic nerve						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Skeletal muscle						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Femur						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							
Marrow, femur						NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-							

-: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P: Non-graded change NE: Not examined M: Missing A: Autolysis

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

Appendix 34-1. Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Group	Control (vehicle: water for injection)											
Animal No.	F01 001	F01 002	F01 003	F01 004	F01 005	F01 006	F01 007	F01 008	F01 009	F01 010	F01 011	F01 012
Fate												
Brain	NE	NE		NE		NE		NE	NE		NE	
Spinal cord	NE	NE		NE		NE		NE	NE		NE	
Pituitary gland	NE	NE		NE		NE		NE	NE		NE	
Submandibular gland	NE	NE		NE		NE		NE	NE		NE	
Sublingual gland	NE	NE		NE		NE		NE	NE		NE	
Lymph node, submandibular	NE	NE		NE		NE		NE	NE		NE	
Thyroid gland	NE	NE		NE		NE		NE	NE		NE	
Ectopic thymic tissue												
Parathyroid gland	NE	NE		NE		NE		NE	NE		NE	
Thymus	NE	NE		NE		NE		NE	NE		NE	
Hemorrhage												
Heart	NE	NE		NE		NE		NE	NE		NE	
Trachea	NE	NE		NE		NE		NE	NE		NE	
Lung	NE	NE		NE		NE		NE	NE		NE	
Accumulation, foam cell, alveolus												
Bronchus	NE	NE		NE		NE		NE	NE		NE	
Liver	NE	NE		NE		NE		NE	NE		NE	
Fatty change, hepatocyte, periportal												
Microgranuloma												
Pancreas	NE	NE		NE		NE		NE	NE		NE	
Stomach	NE	NE		NE		NE			NE		NE	
Cellular infiltration, inflammatory, submucosa, glandular stomach												
Edema, submucosa, glandular stomach												
Erosion, glandular stomach												
Hemorrhage, mucosa, glandular stomach												
Duodenum	NE	NE		NE		NE		NE	NE		NE	
Jejunum	NE	NE		NE		NE		NE	NE		NE	

Group	B-CH 100 mg/kg											
Animal No.	F02 013	F02 014	F02 015	F02 016	F02 017	F02 018	F02 019	F02 020	F02 021	F02 022	F02 023	F02 024
Fate												
Brain	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ectopic thymic tissue												
Parathyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hemorrhage												
Heart	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Accumulation, foam cell, alveolus												
Bronchus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Liver	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Fatty change, hepatocyte, periportal												
Microgranuloma												
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach	NE	NE	NE	NE	NE	NE	NE	NE	NE			NE
Cellular infiltration, inflammatory, submucosa, glandular stomach											+	
Edema, submucosa, glandular stomach											+	
Erosion, glandular stomach											+	
Hemorrhage, mucosa, glandular stomach											±	
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	B-CH 300 mg/kg											
Animal No.	F03 025	F03 026	F03 027	F03 028	F03 029	F03 030	F03 031	F03 032	F03 033	F03 034	F03 035	F03 036
Fate										NC		
Brain	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ectopic thymic tissue												
Parathyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hemorrhage												
Heart	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Accumulation, foam cell, alveolus												
Bronchus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Liver	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Fatty change, hepatocyte, periportal												
Microgranuloma												
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, inflammatory, submucosa, glandular stomach												
Edema, submucosa, glandular stomach												
Erosion, glandular stomach												
Hemorrhage, mucosa, glandular stomach												
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	B-CH 1000 mg/kg											
Animal No.	F04 037	F04 038	F04 039	F04 040	F04 041	F04 042	F04 043	F04 044	F04 045	F04 046	F04 047	F04 048
Fate												
Brain	NE		NE	NE		NE		NE		NE		NE
Spinal cord	NE		NE	NE		NE		NE		NE		NE
Pituitary gland	NE		NE	NE		NE		NE		NE		NE
Submandibular gland	NE		NE	NE		NE		NE		NE		NE
Sublingual gland	NE		NE	NE		NE		NE		NE		NE
Lymph node, submandibular	NE		NE	NE		NE		NE		NE		NE
Thyroid gland	NE		NE	NE		NE		NE		NE		NE
Ectopic thymic tissue							P					
Parathyroid gland	NE		NE	NE		NE		NE		NE		NE
Thymus	NE		NE	NE		NE		NE		NE		NE
Hemorrhage		±										
Heart	NE		NE	NE		NE		NE		NE		NE
Trachea	NE		NE	NE		NE		NE		NE		NE
Lung	NE		NE	NE		NE		NE		NE		NE
Accumulation, foam cell, alveolus									±		±	
Bronchus	NE		NE	NE		NE		NE		NE		NE
Liver	NE		NE	NE		NE		NE		NE		NE
Fatty change, hepatocyte, periportal		±			+							
Microgranuloma					±				±		±	
Pancreas	NE		NE	NE		NE		NE		NE		NE
Stomach	NE		NE	NE		NE		NE				
Cellular infiltration, inflammatory, submucosa, glandular stomach					+							
Edema, submucosa, glandular stomach					+							
Erosion, glandular stomach					+						±	
Hemorrhage, mucosa, glandular stomach					+							
Duodenum	NE		NE	NE		NE		NE		NE		NE
Jejunum	NE		NE	NE		NE		NE		NE		NE

-: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P: Non-graded change NE: Not examined M: Missing A: Autolysis NC: Not copulated

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

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

Group	Control (vehicle: water for injection)											
Animal No.	F01 001	F01 002	F01 003	F01 004	F01 005	F01 006	F01 007	F01 008	F01 009	F01 010	F01 011	F01 012
Fate												
Ileum	NE	NE		NE		NE		NE	NE		NE	
Cecum	NE	NE		NE		NE		NE	NE		NE	
Colon	NE	NE		NE		NE		NE	NE		NE	
Rectum	NE	NE		NE		NE		NE	NE		NE	
Lymph node, mesenteric	NE	NE		NE		NE		NE	NE		NE	
Spleen	NE	NE		NE		NE		NE	NE		NE	
Deposit, pigment, brown			+		+		+			+		+
Fibrosis, capsule			-		+		+			-		-
Hematopoiesis, extramedullary			2+		2+		2+			2+		2+
Kidney	NE	NE		NE		NE		NE	NE		NE	
Basophilic tubule, cortex			-		-		-			-		±
Cast, hyalin			-		-		-			±		-
Cellular infiltration, lymphocyte, interstitial			-		±		-			-		±
Mineralization, cortico-medullary junction			-		-		-			-		-
Urinary bladder	NE	NE		NE		NE		NE	NE		NE	
Adrenal gland	NE	NE		NE		NE		NE	NE		NE	
Hypertrophy, zona fasciculata			-		-		-			-		-
Ovary	NE	NE		NE		NE		NE	NE		NE	
Uterus	NE	NE		NE		NE		NE	NE		NE	
Vagina	NE	NE		NE		NE		NE	NE		NE	
Eyeball	NE	NE		NE		NE		NE	NE		NE	
Harderian gland	NE	NE		NE		NE		NE	NE		NE	
Cellular infiltration, lymphocyte, interstitial			-		-		±			-		-
Sciatic nerve	NE	NE		NE		NE		NE	NE		NE	
Skeletal muscle	NE	NE		NE		NE		NE	NE		NE	
Femur	NE	NE		NE		NE		NE	NE		NE	
Marrow, femur	NE	NE		NE		NE		NE	NE		NE	

Group	B-CH 100 mg/kg											
Animal No.	F02 013	F02 014	F02 015	F02 016	F02 017	F02 018	F02 019	F02 020	F02 021	F02 022	F02 023	F02 024
Fate												
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Deposit, pigment, brown												
Fibrosis, capsule												
Hematopoiesis, extramedullary												
Kidney	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex												
Cast, hyalin												
Cellular infiltration, lymphocyte, interstitial												
Mineralization, cortico-medullary junction												
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona fasciculata												
Ovary	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Uterus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Vagina	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial												
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	B-CH 300 mg/kg											
Animal No.	F03 025	F03 026	F03 027	F03 028	F03 029	F03 030	F03 031	F03 032	F03 033	F03 034	F03 035	F03 036
Fate										NC		
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Deposit, pigment, brown												
Fibrosis, capsule												
Hematopoiesis, extramedullary												
Kidney	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex												
Cast, hyalin												
Cellular infiltration, lymphocyte, interstitial												
Mineralization, cortico-medullary junction												
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona fasciculata												
Ovary	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Uterus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Vagina	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial												
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	B-CH 1000 mg/kg										
Animal No.	F04 037	F04 038	F04 039	F04 040	F04 041	F04 042	F04 043	F04 044	F04 045	F04 046	F04 047	F04 048
Fate												
Ileum	NE		NE	NE		NE		NE		NE		NE
Cecum	NE		NE	NE		NE		NE		NE		NE
Colon	NE		NE	NE		NE		NE		NE		NE
Rectum	NE		NE	NE		NE		NE		NE		NE
Lymph node, mesenteric	NE		NE	NE		NE		NE		NE		NE
Spleen	NE		NE	NE		NE		NE		NE		NE
Deposit, pigment, brown		+			+		+		+		+	
Fibrosis, capsule		-			-		-		-		-	
Hematopoiesis, extramedullary		2+			2+		2+		2+		2+	
Kidney	NE		NE	NE		NE		NE		NE		NE
Basophilic tubule, cortex		-			-		-		-		±	
Cast, hyalin		-			-		-		-		-	
Cellular infiltration, lymphocyte, interstitial		±			-		-		-		±	
Mineralization, cortico-medullary junction		±			-		-		-		-	
Urinary bladder	NE		NE	NE		NE		NE		NE		NE
Adrenal gland	NE		NE	NE		NE		NE		NE		NE
Hypertrophy, zona fasciculata		-			±		-		±		-	
Ovary	NE		NE	NE		NE		NE		NE		NE
Uterus	NE		NE	NE		NE		NE		NE		NE
Vagina	NE		NE	NE		NE		NE		NE		NE
Eyeball	NE		NE	NE		NE		NE		NE		NE
Harderian gland	NE		NE	NE		NE		NE		NE		NE
Cellular infiltration, lymphocyte, interstitial		-			-		-		-		-	
Sciatic nerve	NE		NE	NE		NE		NE		NE		NE
Skeletal muscle	NE		NE	NE		NE		NE		NE		NE
Femur	NE		NE	NE		NE		NE		NE		NE
Marrow, femur	NE		NE	NE		NE		NE		NE		NE

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis NC: Not copulated

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

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

Findings	Group	Corn oil (vehicle: water for injection)					B-CH 1000 mg/kg				
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063
Brain		-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-
Thyroid gland											
Ultimobranchial body		-	P	-	-	-	-	-	-	-	-
Parathyroid gland		-	-	-	-	-	-	-	-	-	-
Thymus		-	-	-	-	-	-	-	-	-	-
Heart		-	-	-	-	-	-	-	-	-	-
Trachea		-	-	-	-	-	-	-	-	-	-
Lung											
Accumulation, foam cell, alveolus		-	±	-	-	-	-	-	-	-	±
Bronchus		-	-	-	-	-	-	-	-	-	-
Liver											
Anisonucleosis, hepatocyte		-	-	-	-	-	-	-	±	-	-
Fatty change, hepatocyte, periportal		±	±	±	-	-	±	-	-	-	±
Hypertrophy, hepatocyte, centrilobular		-	-	-	-	-	-	-	±	-	-
Microgranuloma		±	-	±	-	±	±	±	±	±	±
Pancreas		-	-	-	-	-	-	-	-	-	-

- : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis

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

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

Findings	Group	Corn oil (vehicle: water for injection)					B-CH 1000 mg/kg				
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063
Stomach		-	-	-	-	-	-	-	-	-	-
Duodenum		-	-	-	-	-	-	-	-	-	-
Jejunum		-	-	-	-	-	-	-	-	-	-
Ileum		-	-	-	-	-	-	-	-	-	-
Cecum		-	-	-	-	-	-	-	-	-	-
Colon		-	-	-	-	-	-	-	-	-	-
Rectum		-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric		-	-	-	-	-	-	-	-	-	-
Spleen											
Deposit, pigment, brown		+	2+	+	+	+	±	2+	+	+	2+
Hematopoiesis, extramedullary		±	+	±	+	±	+	±	±	±	±
Kidney											
Basophilic tubule, cortex		-	±	-	-	-	±	±	-	-	±
Cellular infiltration, lymphocyte, interstitial		-	±	-	±	-	±	-	-	-	-
Cyst, medulla		-	P	-	-	-	-	-	-	-	-
Mineralization, cortico-medullary junction		-	-	-	±	-	-	-	-	-	-
Urinary bladder		-	-	-	-	-	-	-	-	-	-
Adrenal gland		-	-	-	-	-	-	-	-	-	-
Ovary											
Increase, atretic follicle		-	-	-	-	±	-	-	-	-	-
Uterus		-	-	-	-	-	-	-	-	-	-
Vagina		-	-	-	-	-	-	-	-	-	-
Eyeball		-	-	-	-	-	-	-	-	-	-
Harderian gland		-	-	-	-	-	-	-	-	-	-
Sciatic nerve		-	-	-	-	-	-	-	-	-	-
Skeletal muscle		-	-	-	-	-	-	-	-	-	-
Femur		-	-	-	-	-	-	-	-	-	-
Marrow, femur		-	-	-	-	-	-	-	-	-	-

- : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis

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

Appendix 35-1. Results of observations about estrous cycle

Control (vehicle: water for injection)

Animal No.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F01001	D 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
F01002	D P E D D D E D D P E D D P	4-day	4.0	E D D D E D D P E D D P E D	4-day	4.0	D P PL	1
F01003	D 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
F01004	D 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 E D D P PL	2
F01005	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F01006	D D E D D P E D D P E D D P	4-day	4.0	E D D D E D D P E D D P E D	4-day	4.0	D P PL	1
F01007	D E D D P E D D P E D D D E	4-day	4.0	D D D E D D D E D D D E D D	4-day	4.0	P PL	1
F01008	D D D E D D D E D D P E D D	4-day	4.0	P E D D P E D D P E D D D E	4-day	4.0	D D D PL	1
F01009	D 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
F01010	D P E D D D P E D D D P E D	5-day	5.0	D P P E D D D E D D D E D D	4-day	4.0	P PL	1
F01011	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F01012	D D P E 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
Mean			4.1			4.0		1.1
S.D.			0.3			0.0		0.3
(N)			(12)			(12)		(12)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

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

Appendix 35-2. Results of observations about estrous cycle

B-CH 100 mg/kg

Animal No.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F02013	D D D E E D D P P E D D P P	5-day	5.0	E D D D P E D D P E E D D D	5-day	5.0	E PL	1
F02014	E D D D E D D D 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
F02015	E 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
F02016	E 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
F02017	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F02018	P 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 D E D D	4-day	4.0	P PL	1
F02019	P E D D D E D D D E D D D P	4-day	4.0	E D D D E D D D E E D D D E	4/5-day	4.3	PL	1
F02020	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F02021	E 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
F02022	D D E D D D P E D D D P E D	5-day	5.0	D D E D D P E D D P E D D D	4-day	4.0	P PL	1
F02023	E 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
F02024	E 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
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

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

Appendix 35-3. Results of observations about estrous cycle

B-CH 300 mg/kg

Animal No.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F03025	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F03026	D P E D D D E D D D E D D D	4-day	4.0	E D D P E D D D E D D P E D	4-day	4.0	D P PL	1
F03027	E D D P E D D P E D D D E D	4-day	4.0	D D E D D D E D D D E D D P	4-day	4.0	PL	1
F03028	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03029	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F03030	D 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
F03031	D D E D D D E D D D E D D P	4-day	4.0	E D D P E D D D E D D D E D	4-day	4.0	D P PL	1
F03032	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03033	D P E D D D E D D D E D D D	4-day	4.0	E D D D E D D D E E D D D E	4/5-day	4.3	D D D PL	1
F03034	P E D D D P E D D P E E D D	5-day	5.0	D E D D P E D D P E D D D E	4-day	4.0	D D D D D D D D D D D D D D	
F03035	E D D P E E D D P E E D D P	5-day	5.0	E E D D P E E D D P E D D P	4/5-day	4.5	PL	1
F03036	D 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
Mean			4.2			4.1		1.0
S.D.			0.4			0.2		0.0
(N)			(12)			(12)		(11)

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

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

Appendix 35-4. Results of observations about estrous cycle

B-CH 1000 mg/kg

Animal No.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F04037	D P E D D D E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F04038	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D D E D D	4-day	4.0	P PL	1
F04039	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F04040	D D P 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
F04041	D D D D E D D P E D D D E D	4-day	4.0	D D E D D D E D D D E D D D	4-day	4.0	PL	1
F04042	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F04043	D D P E D D D E E D D D E E	5-day	5.0	D D D P E E D D P E E D D D	5-day	5.0	PL	1
F04044	D D D E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F04045	E D D P E D D D E D D P E D	4-day	4.0	D P E D D P E D D D E D D D	4-day	4.0	PL	1
F04046	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1
F04047	E 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 D	4-day	4.0	PL	1
F04048	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
Mean			4.1			4.1		1.0
S.D.			0.3			0.3		0.0
(N)			(12)			(12)		(12)

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

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

Appendix 36-1. Results of observations about reproductive performance

Control (vehicle: water for injection)

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M01001	F01001	+	+	4
M01002	F01002	+	+	3
M01003	F01003	+	+	2
M01004	F01004	+	+	7
M01005	F01005	+	+	2
M01006	F01006	+	+	3
M01007	F01007	+	+	2
M01008	F01008	+	+	4
M01009	F01009	+	+	3
M01010	F01010	+	+	2
M01011	F01011	+	+	2
M01012	F01012	+	+	1
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.9
S.D.				1.6
(N)				(12)

+, confirmed
-, not confirmed

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

Appendix 36-2. Results of observations about reproductive performance

B-CH 100 mg/kg

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M02013	F02013	+	+	2
M02014	F02014	+	+	1
M02015	F02015	+	+	1
M02016	F02016	+	+	1
M02017	F02017	+	+	4
M02018	F02018	+	+	2
M02019	F02019	+	+	1
M02020	F02020	+	+	2
M02021	F02021	+	+	1
M02022	F02022	+	+	2
M02023	F02023	+	+	1
M02024	F02024	+	+	1
Total		+: 12, -: 0	+: 12, -: 0	
Mean				1.6
S.D.				0.9
(N)				(12)

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

+, confirmed

-, not confirmed

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

Appendix 36-3. Results of observations about reproductive performance

B-CH 300 mg/kg

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M03025	F03025	+	+	4
M03026	F03026	+	+	3
M03027	F03027	+	+	1
M03028	F03028	+	+	2
M03029	F03029	+	+	4
M03030	F03030	+	+	2
M03031	F03031	+	+	3
M03032	F03032	+	+	2
M03033	F03033	+	+	4
M03034	F03034	-		
M03035	F03035	+	+	1
M03036	F03036	+	+	3
Total		+: 12, -: 1	+: 11, -: 0	
Mean				2.6
S.D.				1.1
(N)				(11)

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

+, confirmed

-, not confirmed

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

Appendix 36-4. Results of observations about reproductive performance

B-CH 1000 mg/kg

Male No.	Female No.	Copulation	Conception	Pairing days until copulation
M04037	F04037	+	+	3
M04038	F04038	+	+	2
M04039	F04039	+	+	2
M04040	F04040	+	+	4
M04041	F04041	+	+	1
M04042	F04042	+	+	2
M04043	F04043	+	+	1
M04044	F04044	+	+	4
M04045	F04045	+	+	1
M04046	F04046	+	+	4
M04047	F04047	+	+	1
M04048	F04048	+	+	4
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.4
S.D.				1.3
(N)				(12)

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

+, confirmed

-, not confirmed

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

Appendix 37-1. Observation of offspring (F_1)

Control (vehicle: water for injection)

Dam No.	Gestation length	Number of corpora lutea	Number of implan-tation scars	Implan-tation index	Delivery index (dams)	Number of offspring at birth						Delivery index (offspring)	Birth index	Live birth index	Number of live offspring				External abnormalities [b]	
						Number of offspring	Live			Sex ratio	Dead offspring				4 days		Sex ratio	Viability index		
	(days)			(%)	(%)		Male	Female	Total			(%)	(%)	(%)	Male	Female		(%)	(Number)	(%)
F01001	22	17	17	100.0	+	16	10	6	16	0.63	0	94.1	94.1	100.0	9	6	0.60	93.8	0	0.0
F01002	22	16	16	100.0	+	14	7	7	14	0.50	0	87.5	87.5	100.0	7	7	0.50	100.0	0	0.0
F01003	22	16	16	100.0	+	16	8	8	16	0.50	0	100.0	100.0	100.0	8	8	0.50	100.0	0	0.0
F01004	22	16	16	100.0	+	14	14	0	14	1.00	0	87.5	87.5	100.0	14	0	1.00	100.0	0	0.0
F01005	22	13	13	100.0	+	13	8	5	13	0.62	0	100.0	100.0	100.0	8	5	0.62	100.0	0	0.0
F01006	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
F01007	22	14	14	100.0	+	14	10	4	14	0.71	0	100.0	100.0	100.0	10	4	0.71	100.0	0	0.0
F01008	22	14	13	92.9	+	13	5	8	13	0.38	0	100.0	100.0	100.0	5	8	0.38	100.0	0	0.0
F01009	22	15	15	100.0	+	13	8	5	13	0.62	0	86.7	86.7	100.0	8	5	0.62	100.0	0	0.0
F01010	22	20	20	100.0	+	19	7	10	17	0.41	2	95.0	85.0	89.5	7	10	0.41	100.0	0	0.0
F01011	22	13	13	100.0	+	13	5	8	13	0.38	0	100.0	100.0	100.0	5	8	0.38	100.0	0	0.0
F01012	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
Number of dams	12	12	12	12	12 [a]	12			12	12	12	12	12	12			12	12	12	12
Total		186	185			177	98	77	175		2				97	77			0	
Mean	22.0	15.5	15.4	99.4		14.8	8.2	6.4	14.6	0.56	0.2	95.9	95.1	99.1	8.1	6.4	0.56	99.5		0.0
S.D.	0.0	2.0	2.1	2.0		1.9	2.4	2.6	1.6	0.17	0.6	5.6	6.4	3.0	2.4	2.6	0.17	1.8		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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 37-2. Observation of offspring (F_1)

B-CH 100 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan-tation scars	Implan-tation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities b): (Number)	(%)
F02013	22	13	13	100.0	+	13	6	7	13	0.46	0	100.0	100.0	100.0	6	7	0.46	100.0	0	0.0
F02014	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
F02015	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
F02016	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
F02017	22	17	17	100.0	+	16	5	11	16	0.31	0	94.1	94.1	100.0	5	11	0.31	100.0	0	0.0
F02018	22	17	17	100.0	+	17	7	9	16	0.44	1	100.0	94.1	94.1	7	9	0.44	100.0	0	0.0
F02019	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
F02020	22	18	18	100.0	+	17	7	10	17	0.41	0	94.4	94.4	100.0	7	10	0.41	100.0	0	0.0
F02021	22	14	14	100.0	+	14	4	10	14	0.29	0	100.0	100.0	100.0	4	10	0.29	100.0	0	0.0
F02022	22	15	15	100.0	+	15	9	6	15	0.60	0	100.0	100.0	100.0	9	6	0.60	100.0	0	0.0
F02023	21	14	13	92.9	+	12	7	5	12	0.58	0	92.3	92.3	100.0	7	5	0.58	100.0	0	0.0
F02024	22	18	18	100.0	+	18	9	8	17	0.53	1	100.0	94.4	94.4	9	8	0.53	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		189	188			184	87	95	182		2				87	95			0	
Mean	21.9	15.8	15.7	99.4		15.3	7.3	7.9	15.2	0.48	0.2	97.8	96.9	99.0	7.3	7.9	0.48	100.0		0.0
S.D.	0.3	1.7	1.8	2.0		1.8	1.8	1.8	1.6	0.11	0.4	3.2	3.3	2.2	1.8	1.8	0.11	0.0		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	KW	KW	AN	AN	AN	AN		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
+: Dams with live offspring, -: dams without live offspring.
a): Number of dams with live offspring.
b): Number of external abnormalities in live offspring at birth.
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 37-3. Observation of offspring (F_1)

B-CH 300 mg/kg

Dam No.	Gestation length	Number of corpora lutea	Number of implan-tation scars	Implan-tation index	Delivery index (dams)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring)	Birth index	Live birth index	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index	External abnormalities [b]	
	(days)			(%)	(%)							(%)	(%)	(%)				(%)	(Number)	(%)
F03025	22	14	14	100.0	+	14	6	7	13	0.46	1	100.0	92.9	92.9	6	7	0.46	100.0	0	0.0
F03026	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
F03027	22	17	17	100.0	+	16	10	6	16	0.63	0	94.1	94.1	100.0	10	6	0.63	100.0	0	0.0
F03028	22	18	17	94.4	+	15	8	7	15	0.53	0	88.2	88.2	100.0	8	7	0.53	100.0	0	0.0
F03029	22	14	14	100.0	+	14	8	6	14	0.57	0	100.0	100.0	100.0	8	6	0.57	100.0	0	0.0
F03030	22	15	15	100.0	+	15	6	9	15	0.40	0	100.0	100.0	100.0	6	9	0.40	100.0	0	0.0
F03031	22	17	17	100.0	+	16	8	8	16	0.50	0	94.1	94.1	100.0	8	7	0.53	93.8	0	0.0
F03032	22	16	16	100.0	+	15	9	6	15	0.60	0	93.8	93.8	100.0	9	6	0.60	100.0	0	0.0
F03033	22	18	18	100.0	+	18	7	11	18	0.39	0	100.0	100.0	100.0	7	11	0.39	100.0	0	0.0
F03034	Not copulated																			
F03035	22	14	14	100.0	+	13	6	7	13	0.46	0	92.9	92.9	100.0	6	7	0.46	100.0	0	0.0
F03036	22	16	16	100.0	+	13	6	7	13	0.46	0	81.3	81.3	100.0	6	7	0.46	100.0	0	0.0
Number of dams	11	11	11	11	11 [a]	11			11	11	11	11	11	11			11	11	11	11
Total		175	174			165	81	83	164		1				81	82			0	
Mean	22.0	15.9	15.8	99.5		15.0	7.4	7.5	14.9	0.49	0.1	94.9	94.3	99.4	7.4	7.5	0.50	99.4		0.0
S.D.	0.0	1.5	1.4	1.7		1.5	1.4	1.6	1.6	0.08	0.3	6.1	5.8	2.1	1.4	1.6	0.08	1.9		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	KW	KW	AN	AN	AN	AN		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
+: Dams with live offspring, -: dams without live offspring.
a): Number of dams with live offspring.
b): Number of external abnormalities in live offspring at birth.
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 37-4. Observation of offspring (F_1)

B-CH 1000 mg/kg

Dam No.	Gestation length	Number of corpora lutea	Number of implan-tation scars	Implan-tation index	Delivery index (dams)	Number of offspring at birth						Delivery index (offspring)	Birth index	Live birth index	Number of live offspring				External abnormalities b)	
						Number of offspring	Live			Sex ratio	Dead offspring				4 days		Sex ratio	Viability index		
	(days)			(%)	(%)		Male	Female	Total			(%)	(%)	(%)	Male	Female		(%)	(Number)	(%)
F04037	22	16	16	100.0	+	15	7	8	15	0.47	0	93.8	93.8	100.0	7	8	0.47	100.0	0	0.0
F04038	22	16	15	93.8	+	15	10	5	15	0.67	0	100.0	100.0	100.0	10	5	0.67	100.0	0	0.0
F04039	22	16	16	100.0	+	16	9	6	15	0.60	1	100.0	93.8	93.8	9	6	0.60	100.0	0	0.0
F04040	21	16	16	100.0	+	16	9	7	16	0.56	0	100.0	100.0	100.0	9	7	0.56	100.0	0	0.0
F04041	22	19	19	100.0	+	17	10	7	17	0.59	0	89.5	89.5	100.0	10	7	0.59	100.0	0	0.0
F04042	22	14	14	100.0	+	10	5	5	10	0.50	0	71.4	71.4	100.0	5	5	0.50	100.0	0	0.0
F04043	22	13	13	100.0	+	10	3	6	9	0.33	1	76.9	69.2	90.0	3	6	0.33	100.0	0	0.0
F04044	22	16	16	100.0	+	15	9	6	15	0.60	0	93.8	93.8	100.0	9	6	0.60	100.0	0	0.0
F04045	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
F04046	22	18	17	94.4	+	16	4	11	15	0.27	1	94.1	88.2	93.8	4	11	0.27	100.0	0	0.0
F04047	22	14	14	100.0	+	13	11	2	13	0.85	0	92.9	92.9	100.0	11	2	0.85	100.0	0	0.0
F04048	22	16	16	100.0	+	16	8	6	14	0.57	2	100.0	87.5	87.5	8	6	0.57	100.0	0	0.0
Number of dams	12	12	12	12	12 a)	12			12	12	12	12	12	12			12	12	12	12
Total		190	188			174	93	76	169		5				93	76			0	
Mean	21.9	15.8	15.7	99.0		14.5	7.8	6.3	14.1	0.55	0.4	92.2	89.5	97.1	7.8	6.3	0.55	100.0		0.0
S.D.	0.3	1.6	1.6	2.3		2.3	2.5	2.1	2.4	0.15	0.7	9.2	9.8	4.6	2.5	2.1	0.15	0.0		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	KW	KW	AN	AN	AN	AN		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
+: Dams with live offspring, -: dams without live offspring.
a): Number of dams with live offspring.
b): Number of external abnormalities in live offspring at birth.
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

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

Appendix 38-1. Body weights of offspring (F_1) before weaning

Control (vehicle: water for injection)

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F01001	6.8	(10)	9.3	(9)	6.3	(6)	9.4	(6)
F01002	6.7	(7)	11.0	(7)	6.3	(7)	10.2	(7)
F01003	6.0	(8)	8.8	(8)	5.7	(8)	8.1	(8)
F01004	6.8	(14)	11.8	(14)				
F01005	7.0	(8)	11.7	(8)	6.6	(5)	11.0	(5)
F01006	6.1	(7)	9.4	(7)	6.1	(8)	8.9	(8)
F01007	6.7	(10)	11.4	(10)	6.8	(4)	11.4	(4)
F01008	7.4	(5)	11.0	(5)	6.8	(8)	10.5	(8)
F01009	6.9	(8)	11.4	(8)	6.5	(5)	11.1	(5)
F01010	6.4	(7)	9.9	(7)	6.4	(10)	9.6	(10)
F01011	7.0	(5)	10.5	(5)	6.4	(8)	10.0	(8)
F01012	6.8	(9)	10.4	(9)	6.5	(8)	10.4	(8)
Number of dams	12		12		11		11	
Mean	6.7		10.6		6.4		10.1	
S.D.	0.4		1.0		0.3		1.0	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.

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

Appendix 38-2. Body weights of offspring (F_1) before weaning

B-CH 100 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F02013	7.0	(6)	11.7	(6)	6.8	(7)	10.9	(7)
F02014	6.8	(7)	12.5	(7)	6.4	(7)	11.8	(7)
F02015	6.2	(9)	10.0	(9)	5.9	(8)	9.6	(8)
F02016	7.1	(7)	10.1	(7)	6.1	(8)	9.2	(8)
F02017	6.2	(5)	9.1	(5)	5.8	(11)	8.7	(11)
F02018	6.7	(7)	10.7	(7)	6.4	(9)	10.2	(9)
F02019	6.6	(10)	10.6	(10)	6.0	(6)	10.3	(6)
F02020	6.3	(7)	9.9	(7)	5.8	(10)	9.5	(10)
F02021	6.6	(4)	10.3	(4)	6.4	(10)	10.0	(10)
F02022	6.7	(9)	11.4	(9)	6.5	(6)	10.5	(6)
F02023	6.3	(7)	11.1	(7)	6.2	(5)	10.1	(5)
F02024	6.4	(9)	9.7	(9)	6.0	(8)	8.4	(8)
Number of dams	12		12		12		12	
Mean	6.6		10.6		6.2		9.9	
S.D.	0.3		1.0		0.3		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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 38-3. Body weights of offspring (F_1) before weaning

B-CH 300 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F03025	6.2	(6)	10.6	(6)	6.3	(7)	10.9	(7)
F03026	6.2	(7)	9.2	(7)	5.7	(9)	9.2	(9)
F03027	6.2	(10)	9.7	(10)	5.7	(6)	9.0	(6)
F03028	6.0	(8)	7.7	(8)	5.6	(7)	7.2	(7)
F03029	5.9	(8)	10.0	(8)	6.3	(6)	10.7	(6)
F03030	6.4	(6)	9.8	(6)	6.1	(9)	9.9	(9)
F03031	6.7	(8)	9.9	(8)	6.6	(8)	9.5	(7)
F03032	6.9	(9)	11.4	(9)	6.6	(6)	10.6	(6)
F03033	6.8	(7)	9.6	(7)	6.4	(11)	8.5	(11)
F03034	Not copulated							
F03035	6.8	(6)	11.0	(6)	6.5	(7)	10.9	(7)
F03036	7.3	(6)	11.6	(6)	6.9	(7)	10.8	(7)
Number of dams	11		11		11		11	
Mean	6.5		10.0		6.2		9.7	
S.D.	0.4		1.1		0.4		1.2	
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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 38-4. Body weights of offspring (F_1) before weaning

B-CH 1000 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F04037	7.2	(7)	11.6	(7)	7.1	(8)	10.9	(8)
F04038	6.5	(10)	10.4	(10)	6.3	(5)	11.0	(5)
F04039	6.5	(9)	9.8	(9)	6.1	(6)	9.6	(6)
F04040	6.2	(9)	8.7	(9)	5.9	(7)	7.9	(7)
F04041	6.9	(10)	10.8	(10)	6.4	(7)	10.0	(7)
F04042	7.9	(5)	13.9	(5)	6.9	(5)	12.6	(5)
F04043	7.9	(3)	13.6	(3)	7.5	(6)	12.7	(6)
F04044	6.9	(9)	10.8	(9)	6.2	(6)	10.0	(6)
F04045	6.6	(8)	9.9	(8)	6.4	(7)	9.8	(7)
F04046	6.9	(4)	10.5	(4)	6.6	(11)	9.7	(11)
F04047	6.4	(11)	11.0	(11)	6.4	(2)	10.6	(2)
F04048	7.0	(8)	11.0	(8)	6.9	(6)	11.1	(6)
Number of dams	12		12		12		12	
Mean	6.9		11.0		6.6		10.5	
S.D.	0.5		1.5		0.5		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 β-Cyclodextrin, 2-hydroxypropyl ethers by oral administration in rats

Appendix 39-1. General conditions in offspring (F_1) before weaning

Control (vehicle: water for injection)

Dam No.	Number of offspring and general conditions	Days after birth 0	1	2	3	4
F01001	Number of offspring	16	16	15	15	15
	General appearance, No abnormality	16	15	15	15	15
	General appearance, Death	0	1	0	0	0
F01002	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01003	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01004	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01005	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01006	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01007	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01008	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01009	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01010	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F01011	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01012	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
	Number of offspring	175	175	174	174	174
	General appearance, No abnormality	175	174	174	174	174
	General appearance, Death		1			

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

Appendix 39-2. General conditions in offspring (F_1) before weaning

B-CH 100 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F02013	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F02014	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02015	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F02016	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02017	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02018	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02019	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02020	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F02021	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02022	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02023	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02024	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
	Number of offspring	182	182	182	182	182
	General appearance, No abnormality	182	182	182	182	182

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

Appendix 39-3. General conditions in offspring (F_1) before weaning

B-CH 300 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F03025	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03026	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F03027	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F03028	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03029	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03030	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03031	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
F03032	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03033	Number of offspring	18	18	18	18	18
	General appearance, No abnormality	18	18	18	18	18
F03034	Not copulated					
F03035	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03036	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
	Number of offspring	164	164	164	164	163
	General appearance, No abnormality	164	164	164	163	163
	General appearance, Death				1	

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

Appendix 39-4. General conditions in offspring (F_1) before weaning

B-CH 1000 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth 0	1	2	3	4
F04037	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04038	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04039	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04040	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F04041	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F04042	Number of offspring	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10
F04043	Number of offspring	9	9	9	9	9
	General appearance, No abnormality	9	9	9	9	9
F04044	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04045	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04046	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04047	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F04048	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
	Number of offspring	169	169	169	169	169
	General appearance, No abnormality	169	169	169	169	169

信頼性保証書

表題　　β-Cyclodextrin, 2-hydroxypropyl ethers 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-12-006

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11月19日	2012年11月19日
試験計画書変更書		
R-12-006-No.1	2012年12月 7日	2012年12月 7日
R-12-006-No.2	2013年 1月 9日	2013年 1月 9日
R-12-006-No.3	2013年 3月21日	2013年 3月21日
R-12-006-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11月26日	2012年11月26日
群分け、検体調製および含量試験	2012年12月10日	2012年12月10日
体重測定、給餌量測定、投与および一般状態の観察	2012年12月11日	2012年12月11日
性周期観察	2012年12月12日	2012年12月13日
詳細な症状観察	2012年12月18日	2012年12月18日
交尾確認	2012年12月26日	2012年12月26日
尿検査	2013年 1月16、17日	2013年 1月17日
分娩状態および出生児の観察	2013年 1月17日	2013年 1月17日
機能検査	2013年 1月18、21日	2013年 1月21日
出生児剖検、血液学検査、血液生化学検査、雄動物剖検、器官重量測定および固定	2013年 1月22日	2013年 1月22日
病理組織学検査(標本作製:包埋)	2013年 3月 8日	2013年 3月 8日
報告書草案および生データ	2013年 4月12、15～17日	2013年 4月17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 秦野研究所
信頼性保証部門責任者 [redacted]