最　終　報　告　書

(改訂版)

ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドの
ラットを用いた経口投与による反復投与毒性･生殖発生毒性併合試験

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試験施設
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2. 試験実施概要

2.1 試験番号

R-1102

2.2 試験表題

ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドのラットを用いた経口投与による反復投与毒性･生殖発生毒性併合試験

（Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl) ammonium chloride by oral administration in rats）

2.3 試験目的

本試験は、動物に被験物質を一定期間反復投与したときに現れる被験物質の一般毒性及び生殖発生毒性を明らかにすることを目的とした。

2.4 試験委託者

厚生労働省　医薬食品局　審査管理課　化学物質安全対策室

〒100-8916　東京都千代田区霞が関 1-2-2

2.5 試験受託者

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2.6 試験実施施設

株式会社ボゾリサーチセンター　御殿場研究所

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2.7 被験物質

製造者	:	[redacted]
名称	:	ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリド
英名	:	Benzyl(dimethyl)(octan-1-yl)ammonium chloride
製品名	:	Benzyldimethyloctylammonium chloride
CAS 番号	:	959-55-7
官報公示整理番号	:	1-215、3-2694
入手日	:	2012 年 11 月 6 日

2.8　試験日程

試験開始日　　：　2013 年　1 月 15 日
被験物質出庫日　：　2012 年 12 月 21 日
動物入荷日　　：　2013 年　1 月 16 日
実験開始日（投与開始日）
　　：　2013 年　2 月　5 日
交配開始日　　：　2013 年　2 月 19 日
分娩開始日　　：　2013 年　3 月 13 日
母動物剖検開始日　：　2013 年　3 月 18 日
投与終了剖検日　：　2013 年　3 月 19 日　（雄及び非交配群）
回復開始日　　：　2013 年　3 月 19 日
回復終了剖検日　：　2013 年　4 月　2 日
動物試験終了日　：　2013 年　4 月　2 日
実験終了日（病理組織学検査終了日）
　　：　2013 年　5 月 23 日
試験終了日　　：　2013 年　7 月 11 日

2.9　試験責任者

株式会社ボゾリサーチセンター　御殿場研究所　研究部
[redacted]

2.10　試験担当者

試験主担当者　　：
被験物質保存責任者：
臨床検査責任者　：
化学分析責任者　：
病理検査責任者　：
統計解析責任者　：
[redacted]

2.11　試験成績の信頼性に影響を及ぼしたと思われる環境要因

本試験に関し、試験成績の信頼性に影響を及ぼしたと思われる環境要因はなかった。

2.12　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

1)　高用量群雄における血液学検査及び血液化学検査例数

高用量群の雄 2 例が投与期間中に死亡したことにより、投与期間終了時検査における血液学検査及び血液化学検査用の採血動物は生存動物の若い順に 5 匹実施するところ、死亡動物を含め動物番号の若い順に 5 匹と勘違いしたため、3 例となった。しか

し、高用量群の雄（3 例）、交配群雌（5 例）及び非交配群（4 例）ともにほぼ類似の変化を示しており、検査例数が 2 例少なかったことによる試験成績の信頼性に及ぼす影響は極めて少ないと判断した。

2)　病理組織学検査の上皮小体

対照群の雌 1 例（動物番号 1118）及び 15 mg/kg 投与群の雄 1 例（動物番号 2010）の上皮小体が標本上確認できず、欠臓器となった。しかし、両動物の上皮小体は検査対象外であり、試験の評価上問題はなかった。したがって、試験の信頼性に及ぼす影響はないと判断した。

その他には本試験に関し、試験の信頼性に影響を及ぼす疑いのある環境要因及び試験計画書に従わなかったことはなかった。

2.13　資料保存

株式会社ボゾリサーチセンターの保存方法に従い、試験計画書原本（試験計画書変更書を含む）、記録文書、生データ、報告書類（最終報告書は原本）及び標本（被験物質保存サンプルを含む）は株式会社ボゾリサーチセンター御殿場研究所の資料保存施設に最終報告書提出後 5 年間保存する。期間終了後の保存については、厚生労働省医薬食品局　審査管理課　化学物質安全対策室と株式会社ボゾリサーチセンター間で協議し、その処置を決定する。ただし、長期保存に耐えられない生体試料（尿、血漿、血清）及び膣垢標本については、試験終了までに廃棄した。また、死産児、死亡児及び生後 4 日出生児については、出生率及び生後 4 日生存率に被験物質投与の影響が認められなかったため試験終了までに廃棄した。

2.14　試験責任者の記名・なつ印

[redacted]　2013 年 10 月 15 日 [redacted]

3. 要約

ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドを注射用水で溶解し、15、50 及び 150 mg/kg の投与量で Sprague-Dawley 系 SPF ラットの雄（12 匹/群）には交配前 14 日間に加え交配期間を通して剖検前日まで（42 日間）、雌（12 匹/群）には交配前 14 日間に加え交配期間及び妊娠期間を通して授乳 4 日まで（41~47 日間）、非交配群（対照群及び 150 mg/kg：10 匹/群）には 42 日間強制経口投与し、反復投与毒性及び生殖発生毒性を検討した。更に、対照群及び 150 mg/kg 投与群の一部の動物（各群 4~5 匹）については、42 日間投与した後 14 日間の回復期間を設け、毒性変化の可逆性を検討した。なお、対照群には媒体である注射用水を投与した。

3.1 反復投与毒性

150 mg/kg 投与群の雄 3 例と交配群雌 3 例と非交配群 2 例が投与 5 から 39 日の間に死亡又は安楽死させた。これらの動物は、気管の壊死性炎、気管支の壊死性炎及び肺胞の水腫、細気管支-肺胞の炎症が観察され、死因は呼吸器系の障害と考えられた。

生存動物では、150 mg/kg 投与群の雄及び交配群雌で流涎が一過性にみられ、50 及び 150 mg/kg 投与群の雄で体重増加の抑制、50 mg/kg 投与群の雄及び 150 mg/kg 投与群の雄と交配群雌で投与 2 日に摂餌量の低値が認められた。また、150 mg/kg 投与群の雄及び非交配群で褐色尿、150 mg/kg 投与群の雄、交配群雌及び非交配群でフィブリノーゲン及び総胆汁酸の低値が認められた。150 mg/kg 投与群の雄で肺に細気管支-肺胞の炎症、前胃に扁平上皮細胞の過形成、50 及び 150 mg/kg 投与群の雄、交配群雌及び非交配群で盲腸の大型化が認められた。

回復期間中は 150 mg/kg 投与群の雌であえぎ呼吸が一過性にみられ、同群の雄で回復期間終了時検査に細気管支-肺胞の炎症が観察されたが、その他の変化は消失した。

3.2 生殖発生毒性

雌雄親動物及び児動物のいずれの検査においても、被験物質投与の影響は認められなかった。

これらの結果から、本被験物質の反復投与毒性に対する無影響量及び無毒性量は雄で 15 mg/kg、雌で 50 mg/kg と判断した。また、雌雄親動物の生殖能力に対する無影響量及び無毒性量は雌雄で 150 mg/kg、児動物における無影響量及び無毒性量は 150 mg/kg と判断した。

4. 緒言

厚生労働省　医薬食品局　審査管理課　化学物質安全対策室の委託により、ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドのラットを用いた経口投与による反復投与毒性･生殖発生毒性併合試験を実施したので、その成績を報告する。

なお、本試験は以下の基準を遵守し、ガイドライン等に準拠して、株式会社ボゾリサーチセンターで実施した。また、本試験は動物実験委員会の承認を受けている。

4.1 GLP

- 「新規化学物質等に係る試験を実施する試験施設に関する基準」
  （平成 23 年 3 月 31 日：薬食発 0331 第 8 号、平成 23･03･29 製局第 6 号、環保企発第 110331010 号）

4.2 毒性試験ガイドライン

- 「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：薬食発 0331 第 7 号、平成 23･03･29 製局第 5 号、環保企発第 110331009 号）

4.3 動物の福祉

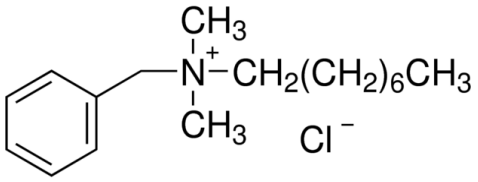
- 「動物の愛護及び管理に関する法律」
  （昭和 48 年 10 月 1 日法律第 105 号）
- 「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」
  （平成 18 年 4 月 28 日環境省告示第 88 号）
- 「動物実験の適正な実施に向けたガイドライン」
  （日本学術会議 平成 18 年 6 月 1 日）

5. 試験材料及び方法

5.1 被験物質及び媒体

5.1.1 被験物質

ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドは[redacted]から以下の情報とともに購入した。また、試験開始前に赤外吸収スペクトルの測定により特性が確認されている（試験番号：A-2513、添付資料 1）。

製造者	:	[redacted]
名称	:	ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリド
英名	:	Benzyl(dimethyl)(octan-1-yl)ammonium chloride
製品名	:	Benzyldimethyloctylammonium chloride
CAS 番号	:	959-55-7
官報公示整理番号	:	1-215、3-2694
構造式又は示性式	:	
分子式	:	$C_{17}H_{30}ClN$
分子量	:	283.88
常温における性状（外観）	:	白色粉末
ロット番号（Batch No）	:	20120927
純度	:	95%以上
入手量	:	1575g（関連試験を含む）
保存条件	:	気密、冷所、防湿
保存方法	:	気密容器に入れ冷蔵庫内（許容値：1~10°C、実測値：3~7.3°C）に保存した。
保存場所	:	御殿場研究所被験物質保存室、第 3 研究棟 2 階被験物質調製室及び生化学部標準物質保存場所
取扱い上の注意	:	作業場の換気を十分に行い、マスク、保護眼鏡、保護手袋等の適切な保護具を着用し、直接の接触を防ぐ。取り扱い後は、手、顔等を良く洗い、うがいをする。
安定性	:	投与期間終了後に株式会社ボゾリサーチセンター御殿

場研究所において、残余被験物質の赤外吸収スペクトルを確認した結果、実験実施前に確認した参照スペクトルとほぼ同様であり安定性に問題はなかった（添付資料 2）。なお、使用天秤の記載、被験物質及び試薬の表示桁数は、試験計画書に記載されていなかったが、特性スペクトル測定時と同様の機器を使用し、同じ数値の取り扱いを行ったため、試験の評価に影響はなかった。

残余被験物質の処理：　被験物質 5 g を保存試料として御殿場研究所の資料保存施設に保存した。動物試験及び分析終了後の残量は全て焼却処分した。

5.1.2　媒体

名称	:	注射用水
規格	:	日本薬局方
製造者	:	株式会社大塚製薬工場
ロット番号	:	2D92、2D93、2F73 及び 2F90
有効期限	:	2017 年 4 月（ロット番号 2D92、2D93） 2017 年 6 月（ロット番号 2F73、2F90）
保存方法	:	室温
保存場所	:	御殿場研究所第 3 研究棟 2 階被験物質調製室

なお、媒体は、本試験に先立って実施した被験液中濃度測定法バリデーション及び安定性試験（試験番号：A-2513）[1]において、注射用水中での被験物質の安定性に良好な結果が得られていることから、注射用水を選択した。

5.2　投与液の調製及び保存方法

5.2.1　対照群投与液の採取

対照群の投与液は被験液調製当日の被験物質を取り扱う前に 1 日使用分ずつ、褐色ガラス瓶に貼付したラベルを確認しながら分注した。

5.2.2　被験液の調製

被験液の調製は先ず、濃度ごとに必要量の被験物質を秤取した。次に、ビーカーに適量（規定量の 6~7 割程度）の注射用水を入れ、スターラーで撹拌しながら被験物質を少量ずつ加え、溶解させた。その後、メスシリンダーに移し、ビーカーを少量の注射用水で数回洗い、その液もメスシリンダーに加え規定量にメスアップし、3、10 及び 30 mg/mL 液（低、中及び高用量群投与液）を調製した。調製は 7 日に 1 回以上の頻度で最大 7 日分を一括して行った。残液はポリ瓶に回収又はペーパータオル等に吸

着させて焼却処分した。

5.2.3　　投与液の保存

投与液は、褐色ガラス瓶に入れて冷所（冷蔵庫内、許容値：1~10°C、実測値：3~9°C）に保存し、安定性の確認された範囲内で投与に使用した。

5.2.4　　被験液の安定性

本被験物質の 1 及び 200 mg/mL 濃度の被験液は、褐色ガラス瓶に入れ冷所（冷蔵庫内、許容値：1~10°C）で 8 日間、その後室温で 24 時間安定であることが株式会社ボゾリサーチセンターで確認されている（試験番号：A-2513、添付資料 3）[1]。

5.2.5　　被験液の濃度確認

初回投与及び投与 6 週の投与に使用する各濃度の被験液(各 10 mL 採取)について、株式会社ボゾリサーチセンター御殿場研究所で HPLC 測定法により濃度確認を実施した。なお、初回投与に使用する被験液については、投与開始前に確認を行った。その結果、各濃度液における表示値に対する被験物質の割合は 97.3~101.0%であり、いずれも許容範囲内（濃度：表示値に対する割合；100.0±10.0%）であった（添付資料 4、5）ことから、被験液の調製に問題はなかったと考えられた。なお、HPLC 測定法バリデーションは株式会社ボゾリサーチセンター御殿場研究所（試験番号：A-2513）[1]で実施された。分析法の概略を以下に示した。

[測定対象物質]

ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリド

[標準物質]

被験物質の一部を標準物質として使用した。

名称	:	ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリド
ロット番号	:	20120927
保存条件	:	気密、冷所（冷蔵庫内、許容値：1~10°C、実測値：3~9°C）、防湿
保存場所	:	御殿場研究所被験物質保存室、第 3 研究棟 2 階被験物質調製室及び生化学部標準物質保存場所

[測定実測試料の調製]

被験液の任意の場所から n=1 で採取し、以下の表に従い、用時調製した溶液をフィルターろ過し、測定実測試料とした。

被験液濃度 (mg/mL)	1 次希釈		2 次希釈		希釈率
	採取量 (mL)	定容量 (mL)	1 次希釈液 採取量 (mL)	定容量 (mL)	
3	1	30	−	−	30
10	1	10	1	10	100
30	1	30	1	10	300

溶媒：精製水

[HPLC システム]

HPLC : 2690 セパレーションモジュール（Waters Corporation）
検出器 : 2487 デュアル λUV/VIS 検出器（Waters Corporation）
データ処理装置 : ミレニアム ^{32} クロマトグラフィーマネジャー（Waters Corporation）

[HPLC 測定条件]

カラム : L-column 2ODS（粒子径 5 μm、細孔径 12 nm、4.6 mmID×150 mm、一般財団法人化学物質評価研究機構）
カラム恒温槽設定温度 : 40°C
移動相 : アセトニトリル／リン酸緩衝液（pH7.0）混液（1：1）
流量 : 1.0 mL/min
検出 : UV（測定波長：220 nm）
分析時間 : 5 min
注入量 : 20 μL
オートサンプラー設定温度 : 10°C

5.3 試験動物種及び系統の選択理由

毒性試験法ガイドラインによりげっ歯類を用いた試験が必要とされていることからラットを選択した。また、この試験に使用された系統のラットは一般毒性試験、生殖発生毒性試験に広く用いられ、かつ、その特性がよく知られており、背景資料が豊富であることから選択した。

5.4 試験動物

Sprague-Dawley 系 SPF ラット〔Crl:CD(SD)、日本チャールス・リバー株式会社、厚木飼育センター〕の雄 62 匹及び雌 83 匹をそれぞれ 8 週齢で入手[注]し、入荷日を馴化 1 日と起算して、3 日間の検疫期間を含む 20 日間の馴化飼育を行った。その間に一般状態の観察（1 回/日）、体重測定（馴化 1、3、8、13 及び 20 日の 5 回）、詳細な一般状態の観察（群分け 4 日前の馴化 16 日に 1 回）を行った。更に、雄は馴化終了日

に陰嚢内の精巣の触診及び陰茎亀頭の観察を行った。また、雌は腟垢を検疫期間終了後群分け日まで採取して性周期（検疫期間終了後 17 日間）を調べた。その結果、雄では精巣の小型化が 1 例（耳標番号：457）みられ、雌では性周期の異常が 4 例（耳標番号：506、533、563 及び 565）、頸部の表皮剥離が 1 例（耳標番号：542）、眼球混濁（左）が 1 例（耳標番号：551）及び胸部の脱毛が 1 例（耳標番号：579）にみられた。それらの異常例を除き、検疫・馴化期間中の一般状態、詳細な一般状態、体重推移、精巣の触診結果及び性周期に異常がなく、性成熟に達した陰茎亀頭であり、健康と思われる雄 48 匹と雌 68 匹を選択し、それぞれ 10 週齢で投与に使用した。投与開始時（10 週齢）の体重範囲は雄で 389~450 g（平均体重：417 g）、雌で 217~289 g（平均体重：247 g）であり、雌雄それぞれ平均体重の±20%以内であった。

なお、動物は検疫・馴化期間中の体重増加量（入荷日~群分け時）により選別後、群分け当日（投与開始の前日）の体重に基づいて、非交配群も含め各群の平均体重ができるだけ均等となるよう各群に割付けた。個体の割付けはコンピュータを用いたブロック配置法及び無作為抽出法の組み合わせ（ブロック配置法で必要な群を構成し、試験群及び群内の個体番号を無作為に割当てた）により行った。供試個体の選択条件を満たして余剰となった雌は、無処置動物として継続飼育した。残りの雌雄動物は群分け当日に試験から除外し､有効利用を目的として動物管理責任者に移管した｡なお、使用しなかった無処置動物は、交配期間終了後に試験から除外し、有効利用を目的として動物管理責任者に移管した。

注： 試験計画書に従い、動物発注数は雄 60 匹及び雌 80 匹であったが、実際には雄 62 匹及び雌 83 匹が納入された。

5.5 飼育条件

動物は、温度 23±3°C（実測値：21~23°C）、相対湿度 50±20%（実測値：39~56%）、換気回数 12~17 回/時間、照明 12 時間/日（07:00~19:00）の動物飼育室（飼育室番号：3112 号室）でブラケット式金属製網ケージ（W254×D350×H170 mm：リードエンジニアリング株式会社）に個別に収容した。なお、交配中は雌雄各 1 匹収容した。また、妊娠 17 日から授乳 4 日までは、床敷（ホワイトフレーク：日本チャールス・リバー株式会社、ロット番号：2012-5）を入れたプラスチック製エコンケージ（W340×D400×H185 mm：日本クレア株式会社）に 1 腹単位で収容した。

飼料は、NMF 固形（放射線滅菌、オリエンタル酵母工業株式会社、ロット番号：120919 及び 121012）をステンレス製給餌器により自由に摂取させた。

飲料水は、御殿場市営水道水を自動給水装置（ブラケット式金属製網ケージでの飼育時）又は給水瓶（プラスチック製エコンケージでの飼育時）により自由に摂取させた。

飼料及び床敷中の混入物質の分析に関しては、使用したロットについて Eurofins Scientific Analytics で実施した分析結果を入手した。また、飲料水については、水道法に準拠した施設全体の水質の分析を定期的（年 4 回）に芝浦セムテック株式会社に

依頼して得られたデータを入手した。これらのデータにより飼料、床敷及び飲料水中の混入物質が試験成績に影響を与える可能性のないことを確認し、分析報告書の写しを保存した。

5.6　動物の識別

動物は、番号が刻印された耳標（雄：439~500、雌：501~583）を入荷時に装着し、個体識別を行った。群分け後は、1000 の位は群（対照群、低、中及び高用量の順）、100 の位は性別（0 番を雄、1 番を雌）、10 と 1 の位は個体番号を示す 4 桁の動物番号を設定した。各飼育ケージに投与量（群）ごとに色分けしたケージラベルを付け、試験番号、投与経路、投与量、性別、動物番号、耳標番号、剖検予定日（雄及び非交配群）、交尾成立日（交配群の雌雄）及び分娩日（交配群雌）を明記した。

5.7　投与経路、投与期間及び投与回数並びに回復期間とそれらの選択理由

投与経路は毒性試験法ガイドラインに準じ、経口投与を選択した。投与期間は交配群雌雄ともに交配前 14 日、更に、雄は交配開始後 28 日（計 42 日）、交配群雌は交配期間及び妊娠期間を通して授乳 4 日まで（計 41~47 日）、非交配群は 42 日であった。投与回数は反復投与試験で一般的に行われている 1 日 1 回とした。回復動物は 42 日の投与期間終了後、被験物質投与に起因した変化の可逆性、持続性並びに遅発性毒性等について観察するため、14 日間の回復期間を設けた。

5.8　投与方法

投与方法はげっ歯類の経口投与に際して一般的な強制経口投与とした。投与容量は 5 mL/kg 体重とし、胃ゾンデを用いて投与液を 09:03~12:22 の間に投与した。ただし、投与時に分娩中であった動物は分娩終了を待って、14:07~15:01 の間に投与したが、50 mg/kg 投与群の 1 例（動物番号：3103）は 17:00 においても分娩が終了していなかったため（分娩遅延）、分娩開始日の投与は行わなかった。対照群には媒体のみを同様に投与した。個体ごとの投与液量（表示単位：0.1 mL）は、直近の体重を基準に算出した。

5.9　投与量及び群構成

投与量は 15、50 及び 150 mg/kg の 3 用量とし、試験群はこれらの用量群に媒体を投与する対照群を加え 4 群構成とした。1 群当たりの動物数は交配を行う交配群として各群で雌雄各 12 匹、交配しない非交配群として対照群及び高用量群で雌各 10 匹とした。なお、対照群及び高用量群における雄の群内番号 8 番以降の各 5 匹（高用量群は投与期間中に 1 匹安楽死させたため、4 匹）並びに非交配群の群内番号 18 番以降の各 5 匹（高用量群は投与期間中に 1 匹死亡し、4 匹）は、最終投与終了日以降、回復動物とした。群構成を表 1-1.及び 1-2.に示した。

表 1-1.群構成表（雄）

試験群	投与量 (mg/kg)	被験液濃度 (mg/mL)	投与容量 (mL/kg)	交配群	
				動物数	動物番号
対照群	0	0	5	12	1001~1012 注 1
低用量群	15	3	5	12	2001~2012
中用量群	50	10	5	12	3001~3012
高用量群	150	30	5	12	4001~4012 注 1

注 1：群内番号 8 番以降の 5 あるいは 4 匹（高用量群で投与期間中に安楽死させたことによる）は、最終投与終了日以降、回復動物とした。

表 1-2.群構成表（雌）

試験群	投与量 (mg/kg)	被験液濃度 (mg/mL)	投与容量 (mL/kg)	交配群		非交配群	
				動物数	動物番号	動物数	動物番号
対照群	0	0	5	12	1101~1112	10	1113~1122 注 2
低用量群	15	3	5	12	2101~2112	−	−
中用量群	50	10	5	12	3101~3112	−	−
高用量群	150	30	5	12	4101~4112	10	4113~4122 注 2

注 2：群内番号 18 番以降の 5 あるいは 4 匹（高用量群で投与期間中に死亡発現による）は、最終投与終了日以降、回復動物とした。

5.10　投与量の設定根拠

本試験の投与量は、先に実施した「ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドのラットを用いた 14 日間反復経口投与毒性試験（投与量設定試験）、株式会社ボゾリサーチセンター、試験番号：N-R033、投与量：10、30、100 及び 300 mg/kg/day」[2]の結果（添付資料 6）を参考に設定した。すなわち、300 mg/kg 投与群で雌雄各 3/5 例が死亡し、100 mg/kg 投与群の雌雄で消化管の拡張がみられたが、組織学的に異常はなかった。10 及び 30 mg/kg 投与群の雌雄で被験物質投与による影響は認められなかった。これらのことから、本試験の投与量は、投与期間が約 3 倍となることを考慮し、肉眼的に消化管の拡張がみられた 100 mg/kg を上回る 150 mg/kg を高用量とし、以下公比 3 で除して、50 及び 15 mg/kg/日をそれぞれ中及び低用量に設定した。

5.11　観察及び検査の方法

試験日の起算は投与開始日を投与 1 日、投与 1 日から 7 日を投与 1 週、回復開始日（投与 42 日の翌日）を回復 1 日、回復 1 日から 7 日を回復 1 週、交尾成立日を妊娠 0 日、分娩終了日（出産日）を授乳 0 日、出生日を生後 0 日とし、以下に示す項目について、それぞれ記載の時期に観察及び検査を実施した。

瀕死に陥った動物並びに動物福祉の見地から安楽死が適当と判断された動物は、体重を測定し、血液及び血液化学検査用試料として可能な範囲内で採血した後、イソフルラン麻酔下で腹大動脈切断により放血し、安楽死させ速やかに病理学検査に供した。死亡動物は発見後体重を測定し、速やかに病理学検査に供した。

5.11.1　一般状態の観察

全個体について、投与期間中は毎日 3 回（投与前、投与直後及び投与 1~3 時間後）、回復期間中は毎日 2 回（午前・午後）、それぞれ生死、身体の外観、姿勢、行動及び排泄物（尿、糞）などの一般状態における異常の有無を観察した。なお、投与 2 週以降の動物のハンドリングを伴った定期的な観察は、詳細な一般状態の観察と兼ねて行った。

5.11.2　詳細な一般状態の観察、機能検査、握力及び自発運動量の測定

詳細な一般状態の観察は全個体について実施した。雄及び非交配群は投与期間中及び回復期間中毎週 1 回、交配群雌は交配前投与期間中毎週 1 回、妊娠期間中及び授乳期間中は指定された日（交尾動物は妊娠 1、7、14 及び 20 日、分娩動物は授乳 4 日）にそれぞれ行った。

機能検査、握力の測定及び自発運動量の測定は、各群の 5 匹（雄の群内番号 8~12 番、交配群雌の各群の分娩順で動物番号が若い順[注 1]、非交配群の群内番号 18~22 番）について行った。投与期間中は交配群雌で授乳 4 日（投与 41~44 日）に、その他は投与 6 週（投与 38 日）[注 2]に、回復期間中は回復 2 週（回復 10 日）[注 2]に行った。

上記の観察、検査及び測定は、動物をランダムに配置し、観察者に対して投与量などの情報を制限（ブラインド化）した状態で行った。ただし、自発運動量の測定はブラインド化を行わなかった。なお、詳細な一般状態の観察及び機能検査の観察・検査結果について、実数データ以外はスコア化した評点法を用いて記録した。

注 1：　交配群雌の検査対象動物を以下に示した。

試験群	動物番号
対照群	1103、1105、1106、1110、1111
低用量群	2104、2106、2107、2111、2112
中用量群	3101、3105、3108、3109、3110
高用量群	4103、4104、4105、4106、4108

注 2：　高用量群において、交配群雄及び非交配群の各 1 例が投与期間中に死亡又は安楽死（動物番号 4010 及び 4118）させたため、各検査時期の検査動物数は各 4 匹であった。

3)　詳細な一般状態の観察

ケージ内観察は姿勢、痙攣、異常行動を、手に持っての観察はケージからの取り出し易さ、被毛・皮膚の状態、眼・鼻の分泌物、眼球突出、眼瞼閉鎖状態、可視粘膜、自律神経機能（流涙、流涎、立毛、瞳孔径、異常呼吸）、ハンドリングに対する反応、ハンドリング時の発声を、オープンフィールド内観察は覚醒状態、痙攣、異常行動、常同行動、歩行、姿勢、身繕い、立ち上がり回数、排泄物（排糞数、排尿）を調べた。

4)　機能検査

検査は聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射、空中正向反射、着地開脚幅とした。

5)　握力測定

機能検査に引き続き、CPU ゲージ MODEL-RX-5（アイコーエンジニアリング株式会社）を用いて前肢及び後肢の握力を測定した。

6)　自発運動量の測定

握力測定に引き続き、実験動物用自発運動センサーNS-AS01（株式会社ニューロサイエンス）を用いて自発運動量を測定した。測定時間は 1 時間とし、10 分間隔及び 0~60 分の測定値を集計した。

5.11.3　　体重測定

全個体について、雄及び非交配群は投与 1、8、15、22、29、36、42 日及び剖検日に、回復動物は更に回復 1、8、14 日及び剖検日に、交配群雌は投与 1、8 及び 15 日、妊娠 0、7、14 及び 20 日、授乳 0 及び 4 日並びに剖検日に体重を測定した。なお、午後の分娩観察時における授乳 0 日の体重測定は 13:22~17:17 の間に実施し、その他の体重測定は測定日の 07:39~11:50 の間（投与期間中は投与前）に行った。剖検日は前日から約 16 時間絶食させた後､相対器官重量算出に備えて体重を 07:24~09:02 の間に、死亡動物は飼育室から搬出する前に、それぞれ体重測定したが、いずれも統計解析から除外した。

5.11.4　　摂餌量測定

雄及び非交配群は投与 2、8、15、30、36 及び 42 日に、回復動物は更に回復 1、8 及び 14 日に、交配群雌は投与 2、8 及び 15 日、妊娠 1、7、14 及び 20 日並びに授乳 2 及び 4 日に残餌量を測定し、前日の給餌量との差から 1 匹当たりの 1 日摂餌量を算出した。給餌量及び残餌量の測定は測定日の 07:56~11:26 の間（投与期間中は投与前）に行った。

5.11.5　　腟垢検査

交配群雌の全個体について、投与開始日から交尾成立まで毎日（午前）腟垢を採取した。交配前投与期間中の標本は、多数の角化上皮細胞から成る腟垢像を発情の指標とし、発情回数及び発情期から次の発情期までの日数（性周期）、観察雌個体数に対する性周期異常を示した個体数の割合を調べた。交配期間中の標本は腟垢内の精子の有無を調べるのに加え、腟垢像を発情前期(P)、発情期(E)、発情後期(M)及び発情休止期(D)に分類した。

非交配群は、投与期間終了時及び回復期間終了時の剖検 6 日前から剖検日まで毎日（午前）腟垢を採取し、鏡検した。鏡検結果は、剖検時における性周期ステージの判別のための参考データとした。なお､P→E→M→D（→P）の順序で周期的変化を示し、4 又は 5 日の周期を繰り返す個体を正常、それ以外を性周期異常とした。

5.11.6　交配方法

交配前投与期間終了後、交配群の同じ投与群の雌雄を 1:1 で終夜同居させ、翌朝、膣栓形成あるいは膣垢中に精子を確認したものを交尾成立とみなした。交配開始日を 0 日と起算して交尾までに要した日数を求めた。同一雌雄による同居期間は最長 6 日間であった。なお、対照群の雌 1 例（動物番号 1104）を投与 12 日に安楽死剖検したため、交配相手の対照群の雄 1 匹（動物番号 1004）は無処置動物（耳標番号 501）と同居させた。また、高用量群の雌雄各 2 匹（動物番号 4003、4010、4101 及び 4107）が死亡又は安楽死剖検したため、雄の動物番号 4001 及び 4007 は、雌の動物番号 4103 及び 4110 とそれぞれ交配させた。無処置動物の雌より得られたデータは雄の交尾率及び授精率の算出に用いた。これら動物の妊娠期間中のデータは統計解析から除外した。

5.11.7　分娩及び哺育観察

1)　母動物の観察

交尾の確認された雌動物は、妊娠 21 日から妊娠 23 日の午前まで 1 日 2 回（午前・午後、妊娠 23 日は午前に 1 回）、分娩の有無並びにその終了を確認するとともに分娩状態の異常の有無（胎盤及び羊膜の処理の有無など）を観察した。交尾成立から分娩終了までを妊娠期間とし、妊娠期間を 0.5 日単位で求めた。ただし、1 日単位で集計した。なお、分娩終了の確認は 17:00 までとした。

分娩が終了した母動物は授乳 4 日まで出生児を哺育させ、哺育状態（児集め、営巣及び授乳など）を観察し、授乳 5 日に病理学検査に供した。

2)　出生児の観察

生後 0 日に出生児数及び死産児数を数え、合わせて出産児数とした。出産児の外表異常[注]の有無を観察して性別を確認した。出生児は体重を個体別に測定した後、母動物に哺育させた。死産児（死産児の外表異常を含む）はブアン液で固定して保存した。

出生児は生後 4 日まで毎日 1 回、死亡児の有無を確認した。死亡児は肉眼による異常の有無を観察した後、ブアン液で固定して保存した。生後 4 日に全生存児の性別を判定し、個体別に体重を測定後、肉眼による異常の有無を観察した後、イソフルラン深麻酔下でブアン液に浸漬し、固定して保存した。

注：　頭部の陥没や裂、顔面の鼻吻や上下顎、口唇のゆがみや裂、眼瞼や耳介の大きさ、形状、左右のバランス、胸胴部のゆがみや大きさ、内部臓器の突出、尾部の長さ、形状、数、欠損、四肢部の長さ、形状、指の数、欠損及び左右のバランスに注意して観察し、正常と異なる場合を異常とした。

5.11.8　尿検査（摂水量測定を含む）

検査は、投与期間終了週（投与 6 週、投与 36~37 日）及び回復期間終了週（回復 2 週、回復 8~9 日）に行った。投与期間中は検査当日の投与後に各群の 5 匹（雄の群内番号 8~12 番、非交配群の群内番号 18~22 番）について、回復期間中は回復動物の全個体について、それぞれ採尿器をセットしたケージに収容し、絶食・自由摂水下で 4 時間尿を、次いで自由摂食・自由摂水下でその後の 20 時間尿を採取した。検査項目を表 2.に示した。採取した最初の 4 時間尿について pH 以下沈渣までの検査と尿量を、その後に得られた 20 時間尿について浸透圧、電解質（ナトリウム、カリウム、塩素）及び尿量の測定を行った。尿量は 4 時間の尿量と 20 時間の尿量を合計して 1 日量を算出した。電解質は 20 時間尿について濃度を測定し、測定濃度と 24 時間の尿量から 1 日当たりの排泄量を算出した。摂水量は採尿器をセットしたケージに収容した状態で前日からの 1 日の摂取量を、給水瓶を用いて測定した。なお、投与 6 週の浸透圧測定時において、動物番号 2008 の試料中の浮遊物によると考えられる過冷却の不良により、測定値が得られなかったため、ろ過後再測定し、ろ過後の測定値を初回値として採用した。

表 2.尿検査の項目、測定法及び使用機器など

検査項目	測定方法
pH	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］[a)]
たん白質	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］[a)]
ケトン体	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］[a)]
グルコース	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］[a)]
潜血	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］[a)]
ビリルビン	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］[a)]
ウロビリノーゲン	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］[a)]
色調	肉眼観察
沈渣	鏡検法
尿量（4 時間量）	目盛付スピッツ管を用いた容量測定（単位：mL）
浸透圧	氷点降下法[b)]（単位：mOsm/kg）
ナトリウム	イオン選択電極法[c)]（単位：mmol/24h）
カリウム	イオン選択電極法[c)]（単位：mmol/24h）
塩素	イオン選択電極法[c)]（単位：mmol/24h）
尿量（20 時間量）	メスシリンダーを用いた容量測定（単位：mL）
摂水量（24 時間量）	重量測定

使用測定機器
a)：尿自動分析装置　クリニテック 500（Siemens Healthcare Diagnostics Inc.）
b)：自動浸透圧測定装置 オートアンドスタット OM-6030（アークレイ株式会社）
c)：臨床化学自動分析装置　TBA-120FR 形（東芝メディカルシステムズ株式会社）

5.11.9　血液学検査

全個体について、剖検前日（最終投与日あるいは回復 14 日）から一夜（約 16~21 時間）絶食させた。そのうちの各群雌雄各 5 匹[注 1]（動物番号が若い順、ただし、交配群雌は分娩順の 5 匹[注 2]）について、イソフルラン麻酔下に開腹し、腹大動脈から

EDTA-2K 加採血瓶（SB-41：シスメックス株式会社）に血液を採取した。得られた血液について、次の表 3.-1)に記載した項目及び方法により検査した。なお、採血した全例について、May-Grünwald-Giemsa 染色法による血液塗抹標本を作製した。また、3.8%クエン酸ナトリウム溶液加試験管（血液 9 容に対し 1 容の割合）に採取した血液を遠心分離（設定：3,100 rpm、1,690×g、12 分間）し、得られた血漿について表 3.-2)に記載の項目及び方法により検査した。なお、動物番号 1104 と 4010 の血液凝固検査は、動物の衰弱により試料採取できなかった。また、動物番号 1104 の血小板数が低値であったため、血液塗抹標本を確認した結果、血小板数は非常に少なく、測定値に問題ないと判断した。

注 1： 高用量群における投与期間終了時検査は雄 3 匹と雌 4 例、回復期間終了時検査は雄 4 例と雌 4 例、交配群雌は各群 5 例であった。

注 2： 交配群雌の検査対象動物を以下に示した。

試験群	動物番号
対照群	1103、1105、1106、1110、1111
低用量群	2104、2106、2107、2111、2112
中用量群	3101、3105、3108、3109、3110
高用量群	4103、4104、4105、4106、4108

表 3.血液学検査の項目、測定法及び使用機器など

1）EDTA-2K 加血液についての検査		
検査項目	測定方法	単位
赤血球数(RBC)	2 角度レーザーフローサイトメトリー法 a)	$10^4/\mu L$
ヘモグロビン量(HGB)	シアンメトヘモグロビン変法 a)	g/dL
ヘマトクリット値(HCT)	赤血球数及び平均赤血球容積から算出 a)	%
平均赤血球容積(MCV)	2 角度レーザーフローサイトメトリー法 a)	fL
平均赤血球血色素量(MCH)	赤血球数及びヘモグロビン量から算出 a)	pg
平均赤血球血色素濃度(MCHC)	ヘモグロビン量及びヘマトクリット値から算出 a)	g/dL
網赤血球率(Retic)	RNA 染色によるレーザーフローサイトメトリー法 a)	%
血小板数(PLT)	2 角度レーザーフローサイトメトリー法 a)	$10^4/\mu L$
白血球数(WBC)	2 角度レーザーフローサイトメトリー法 a)	$10^2/\mu L$
白血球百分率注)	ペルオキシダーゼ染色によるフローサイトメトリー法 +2 角度レーザーフローサイトメトリー法 a)	%
白血球各細胞の絶対数注)	ペルオキシダーゼ染色によるフローサイトメトリー法 +2 角度レーザーフローサイトメトリー法 a)	$10^2/\mu L$
2）クエン酸ナトリウム加血液から分離した血漿についての検査		
検査項目	測定方法	単位
プロトロンビン時間(PT)	クロット法 b)	s
活性化部分トロンボプラスチン時間(APTT)	クロット法 b)	s
フィブリノーゲン量(FIB)	トロンボプラスチン法 b)	mg/dL
使用測定機器 a)：総合血液学検査装置　アドヴィア 120（Siemens Healthcare Diagnostics Inc., Illinois, USA） b)：血液凝固自動分析装置　ACL Elite Pro（Instrumentation Laboratory, MA, USA）		
注）：好中球(Neut.)、好酸球(Eosino.)、好塩基球(Baso.)、リンパ球(Lymph.)、単球(Mono.)及び大型非染色球(LUC)		

5.11.10　血液化学検査

血液学検査用試料と同時に採取した血液を凝固促進剤入り試験管（ベノジェクト II-オートセップ：テルモ株式会社）に採り、遠心分離（設定：3,100 rpm、1,690×g、12 分間）し、得られた血清について表 4.-1)に記載の項目及び方法により検査した。また、ヘパリン加試験管（血液 1 mL 当たり約 20 単位のヘパリン）に採取した血液を遠心分離（設定：3,100 rpm、1,690×g、12 分間）し、得られた血漿について表 4.-2)に記載の項目及び方法により検査した。血清の一部(安楽死動物を除く)は血中ホルモン測定用に約 0.5 mL×3 本をサンプルチューブに分注し、残余の血清と共に−80°C の冷凍庫（許容範囲：−70°C 以下）に保存した。なお、動物番号 1104 の無機リンの測定値が測定上限を超えたため、希釈による再測定を行い、再測定値を採用した。また、動物番号 1104、4114 及び 4010 の採血量（血清分）は、動物の衰弱により約 6 mL から約 1.5~3 mL に変更したが、測定に支障はなかった。更に動物番号 4010 の LDH は測定範囲を超えたが、測定に問題はなく、動物の状態から妥当と判断したため、初回値を採用した。

表 4.血液化学検査の項目、測定法及び使用機器など

1）分離した血清についての検査		
検査項目	測定方法	単位
ALP	Bessey-Lowry 法 a)	IU/L
総胆汁酸（TBA）	3α-ヒドロキシステロイドデヒドロゲナーゼ a)	μmol/L
総コレステロール(T-CHO)	CEH-COD-POD 法 a)	mg/dL
トリグリセライド(TG)	LPL-GK-GPO-POD 法 a)	mg/dL
リン脂質(PL)	PLD-ChOD-POD 法 a)	mg/dL
総ビリルビン(T-BIL)	ビリルビンオキシダーゼ法 a)	mg/dL
グルコース(GLU)	グルコースデヒドロゲナーゼ法 a)	mg/dL
尿素窒素(BUN)	Urease-LEDH 法 a)	mg/dL
クレアチニン(CRNN)	Creatininase-creatinase-sarcosine oxidase-POD 法 a)	mg/dL
ナトリウム(Na)	イオン選択電極法 a)	mmol/L
カリウム(K)	イオン選択電極法 a)	mmol/L
塩素(Cl)	イオン選択電極法 a)	mmol/L
カルシウム(Ca)	OCPC 法 a)	mg/dL
無機リン(P)	モリブデン酸法 a)	mg/dL
総たん白質(TP)	Biuret 法 a)	g/dL
アルブミン(ALB)	BCG 法 a)	g/dL
A/G 比	総たん白質及びアルブミンから算出	
2）ヘパリン加血液から分離した血漿についての検査		
検査項目	測定方法	単位
AST	UV-rate 法 a)	IU/L
ALT	UV-rate 法 a)	IU/L
LDH	UV-rate 法 a)	IU/L
γ-GTP	L-γ-グルタミル-3-カルボキシ-4-ニトロアニリド法 a)	IU/L
使用測定機器 a)：臨床化学自動分析装置　TBA-120FR 形（東芝メディカルシステムズ株式会社）		

5.11.11　血中ホルモン測定

血中ホルモン測定用に約 0.5 mL×3 本をサンプルチューブに分注し、残余の血清と共に−80°C の冷凍庫（許容範囲：−70°C 以下）に保存したが、下垂体－甲状腺系への被験物質投与の影響が認められないことから、検査は実施しなかった。

5.11.12　病理学検査

1)　剖検及び器官重量測定

最終投与翌日及び回復期間終了日に、採血した動物は採血後に、その他の動物はイソフルラン麻酔下で腹大動脈切断により放血致死させ、それぞれ体外表並びに頭部、胸部及び腹部の器官・組織の肉眼検査を行った。安楽死剖検動物は可能な範囲内で採血して放血致死させた後、死亡動物は発見した後、それぞれ速やかに病理学検査に供した。なお、母動物は剖検時に黄体数及び着床痕数を数えた。次いで、全個体について、以下に示す器官の重量を測定した。それら器官重量（絶対重量）と剖検時の体重から体重 100 g 当たりの相対重量を算出した。なお、*印をつけた両側性の器官については左右別々に測定し、その合計値で評価した。また、死亡/安楽死剖検動物についても同様に器官重量を測定したが、剖検日の体重も含め統計解析の対象から除外した。

脳、下垂体、甲状腺*（上皮小体を含む）、副腎*、胸腺、脾臓、心臓、肝臓、腎臓*、精巣*、精巣上体*、前立腺、精嚢（凝固腺を含む）、卵巣*、子宮

2)　病理組織学検査

全ての個体について、以下に示す全検査対象器官/組織をリン酸緩衝 10 vol%ホルマリン液で固定し、保存した。なお、固定時に肺にはリン酸緩衝 10 vol%ホルマリン液を注入した。また、眼球、視神経はリン酸緩衝液で調製した 3 vol%グルタルアルデヒド・2.5 vol%ホルマリン液で固定後、精巣及び精巣上体はブアン液で固定した後、リン酸緩衝 10 vol%ホルマリン液に置換し保存した。次いで、パラフィン包埋した後、切片とし（下線を施した器官・組織は固定・保存のみとした）、ヘマトキシリン・エオジン（H・E）染色標本を作製した。鏡検は血液学及び血液化学検査のために採血を行った動物、投与期間終了時剖検の 150 mg/kg 投与群の雄全例並びに死亡/安楽死剖検動物の全検査対象器官/組織について行った。両側性の器官については両側を摘出し、坐骨神経、眼球、甲状腺、上皮小体、副腎、顎下腺、腎臓、大腿骨（骨髄を含む）及び大腿部骨格筋は片側、精巣、卵巣、精巣上体及び精嚢（凝固腺含む）は両側並びに子宮は両角部を鏡検した。なお、舌下腺及び視神経は H･E 染色標本作製までとし、病理組織学検査は実施しなかった。その結果、150 mg/kg 投与群の雄の前胃及び肺に被験物質投与の影響が疑われたため、中及び低用量群の採血を行った動物並びに回復動物の当該器官についても鏡検した。なお、死亡/安楽死剖検動物のみに変化がみられた器官/組織についても中及び低用量群並びに回復群の病理組織学検査を行った。また、対照群の安楽死動物にみられた肉眼的異常部位の尿道口の組織学検査については、尿

道と合せて評価した。

大脳、小脳（橋を含む）、坐骨神経、脊髄（胸部）、眼球、視神経、ハーダー腺、下垂体、甲状腺、上皮小体、副腎、胸腺、脾臓、顎下リンパ節、腸間膜リンパ節、心臓、胸大動脈、気管、肺（気管支を含む）、舌、喉頭、食道、胃、十二指腸、空腸、回腸（パイエル板を含む）、盲腸、結腸、直腸、顎下腺、舌下腺、肝臓、膵臓、腎臓、膀胱、精巣、卵巣、精巣上体、子宮、腟、前立腺、精嚢（凝固腺を含む）、皮膚（鼠径部）、乳腺（鼠径部）、胸骨（骨髄を含む）、大腿骨（骨髄を含む）、大腿部骨格筋、個体識別部（耳標を装着した耳介）、肉眼的異常部位

5.12　統計解析

5.12.1　　パラメータの算出

以下の式により、性周期異常率、交尾率、授精率、受胎率及び出産率は群ごとに、妊娠期間、着床率、分娩率、死産児率、外表異常率、出生率、生後 4 日生存率、生後 0 及び 4 日の性比は母動物（腹）ごとに算出した。なお、出生児の体重は母動物ごと雌雄別に平均値を求めた。

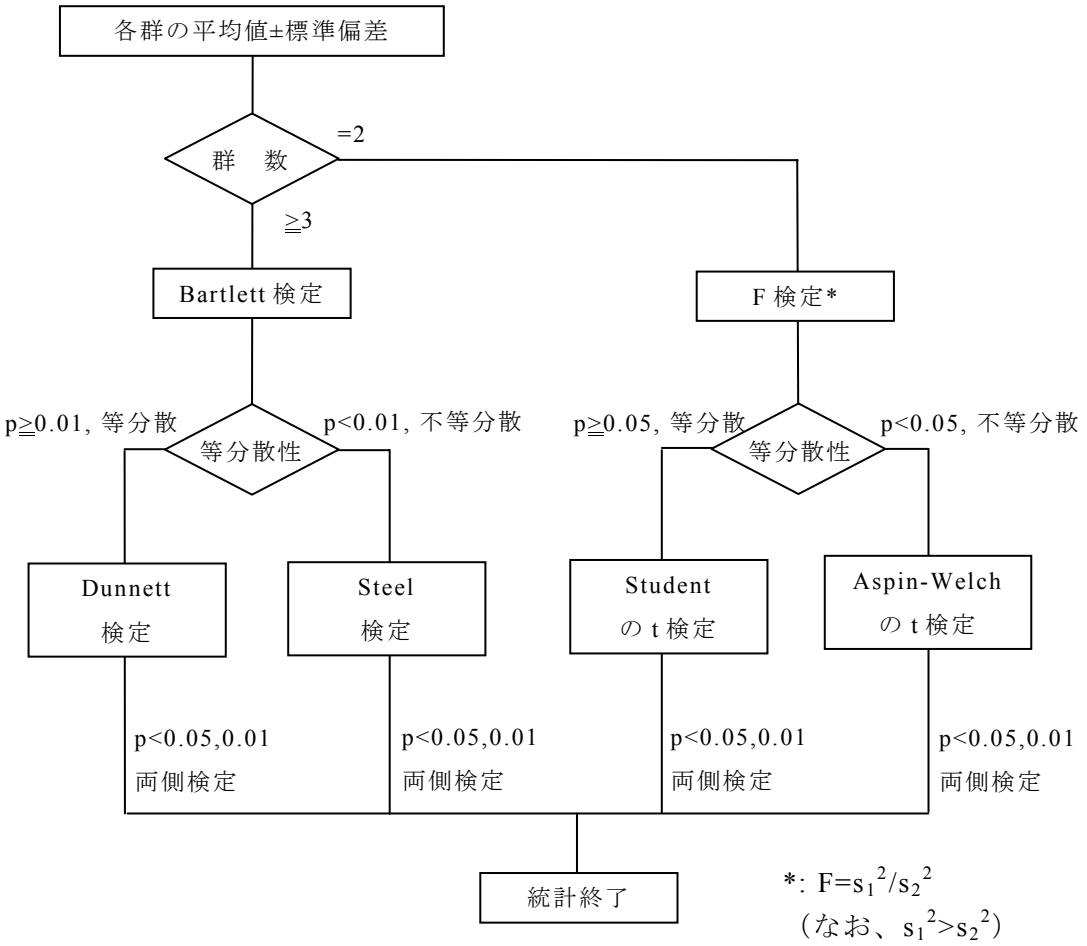
性周期異常率(%) =（性周期異常を示した個体数/観察雌個体数）×100
交尾率(%) =（交尾動物数/同居動物数）×100
授精率(%) =（雌を妊娠させた雄の数/交尾した雄の数）×100
受胎率(%) =（妊娠した雌の数/交尾した雌の数）×100
出産率(%) =（出生児出産雌数/妊娠雌数）×100
妊娠期間(日) = 妊娠 0 日から分娩した日までの日数
着床率(%) =（着床痕数/黄体数）×100
分娩率(%) =（出産児数/着床痕数）×100
死産児率(%) =（死産児数/出産児数）×100
外表異常率(%) =（外表異常児数/出産児数）×100
出生率(%) =（出生児数/出産児数）×100
生後 4 日生存率(%) =（生後 4 日の生存児数/出生児数）×100
生後 0 日（死産児含む）の性比 = 雄出産児数/出産児数
生後 0 日（出生児）の性比 = 雄出生児数/出生児数
生後 4 日の性比 = 生後 4 日の雄生存児数/生後 4 日の生存児数

5.12.2　　検定

対照群と各用量群との差については、以下の手法により統計学的有意性の検定を行った。

体重、体重増加量（雄及び非交配群：投与 1~42 日及び回復 1~14 日、交配群雌：投与 1~15 日、妊娠 0~20 日及び授乳 0~4 日、出生児：生後 0~4 日）、摂餌量、摂水量、

発情期像発現回数、性周期（発情周期）、交尾までに要した日数、妊娠期間、黄体数、着床痕数、生存児数、性比（生後 0 及び 4 日）、オープンフィールド内観察（排糞数、立ち上がり回数）、機能検査（着地開脚幅）、握力及び自発運動量、尿検査の定量的項目、血液学検査、血液化学検査及び器官重量量（含、剖検時体重）は、群ごとに平均値及び標準偏差を求め、次に示す模式図の方法に従って検定した[3][4][5]。



着床率、分娩率、出生率、死産児率、外表異常率及び生後 4 日生存率は、群ごとに平均値及び標準偏差を求め、Steel 検定（有意水準 0.05 及び 0.01、両側）を行った[5]。

性周期異常率、交尾率、授精率、受胎率及び出産率並びに聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射及び空中正向反射の各反応・反射率は、各群の性周期異常を示した個体数、交尾動物数、雌を妊娠させた雄動物数、妊娠雌動物数、出生児出産雌動物数、正常反射のみられた動物数より算出し、期待度数が 5 以下のセルがみられたため、Fisher の直接確率計算法により検定（有意水準 0.05 及び 0.01、両側）を行った[6]。

6. 試験結果

6.1 安楽死及び死亡動物（Appendix 1-10、1-12、1-13、1-16、1-20、1-28、1-30、3-4、3-5、3-8、3-12、3-18、4-4、4-5、4-8、4-12、4-18、6-9、6-10、7-9、7-10、9-39、9-40、9-46、9-52、9-95、9-101、9-103、9-108、9-112）

150 mg/kg 投与群において、雄 3 例、交配群の雌 3 例、非交配群の雌 2 例の計 8 例が死亡又は安楽死させた。これら動物の死亡又は安楽死の原因は呼吸器の障害であった。個体ごとの瀕死/死亡前の一般状態、体重、摂餌量、主な剖検所見及び病理組織学検査所見を下表に示した。

動物番号	瀕死/死亡	発現日	瀕死/死亡前の一般状態、体重、摂餌量、主な剖検所見及び病理組織学検査所見
4003 (雄)	死亡	投与 5 日	投与開始日~投与 5 日の死亡発見日（投与前）にかけて体重減少(−37 g)し、組織学検査で気管の高度の壊死性炎が観察され、呼吸器の障害が死因と判断した。その他に、組織学的に軽微な副腎皮質細胞の肥大、白脾髄及び胸腺の萎縮、大腿骨骨髄の顆粒球造血亢進がみられた。
4004 (雄)	死亡	投与 32 日	投与 29 日~死亡する投与 32 日まで体重減少(−14 g)、投与 31 日にあえぎ呼吸を呈し、投与 32 日の投与前に死亡を発見した。肉眼的に肺の暗赤色巣、組織学的に気管の中等度の壊死性炎、肺気管支の軽度な壊死性炎と肺胞の軽度な水腫が観察され、呼吸器の障害が死因と判断した。その他に、剖検で盲腸の大型化、組織学検査で胸腺の軽微な萎縮がみられた。
4010 (雄)	瀕死	投与 5 日	投与開始日~安楽死される投与 5 日にかけて体重減少(−12 g)、投与 5 日に自発運動の減少、あえぎ呼吸及び体温低下を呈したため、安楽死させた。組織学検査で気管の高度の壊死性炎、肺に細気管支周囲−肺胞に軽度な炎症が観察され、呼吸器の障害が死因と判断した。その他、剖検で盲腸の大型化、組織学的に軽微な副腎皮質細胞の肥大及び胸腺の軽微な萎縮がみられた。
4101 (交配群雌)	死亡	投与 8 日	投与開始日~死亡する投与 8 日まで体重増加の抑制(−4 g)、組織学検査で気管の高度の壊死性炎が観察され、呼吸器の障害が死因と判断した。その他、剖検で盲腸の大型化、組織学検査で軽微な副腎皮質細胞の肥大、白脾髄及び胸腺の萎縮がみられた。
4107 (交配群雌)	死亡	投与 5 日	投与開始日~死亡する投与 5 日まで体重減少(−9 g)、組織学検査で気管に高度な壊死性炎、肺気管支の中等度な壊死性炎と肺胞の軽度な水腫が観察され、呼吸器の障害が死因と判断した。その他、剖検で盲腸の大型化、組織学検査で軽微な副腎皮質細胞の肥大、胸腺の軽微な萎縮がみられた。
4109 (交配群雌)	死亡	投与 32 日 (妊娠 15 日)	妊娠 7 日~妊娠 14 日まで体重増加の抑制(+9 g)、妊娠 14 日に摂餌量の低値、あえぎ呼吸、妊娠 14 日~死亡する妊娠 15 日まで体重減少(−16 g)、肉眼的に肺の暗赤色化、組織学検査で気管の中等度な壊死性炎、肺気管支の軽度な壊死性炎と肺胞の軽度な水腫が観察され、呼吸器の障害が死因と判断した。その他、剖検で盲腸の大型化、組織学検査で胸腺の軽微な萎縮がみられた。

動物番号	瀕死/死亡	発現日	瀕死/死亡前の一般状態、体重、摂餌量、主な剖検所見及び病理組織学検査所見
4114 (非交配群雌)	瀕死	投与 39 日	投与 36 日~投与 39 日にかけて体重減少(−21 g)、投与 38 日にあえぎ呼吸、更に投与 39 日に自発運動の減少及び体温低下を呈したため、安楽死させた。肉眼的に肺の一部暗赤色化、組織学検査で気管に高度な壊死性炎、肺気管支の軽度な壊死性炎と肺胞の軽度な水腫が観察され、呼吸器の障害が死因と判断した。その他、剖検で盲腸の大型化、組織学的に腸間膜リンパ節、顎下リンパ節、白脾髄及び胸腺に軽微な萎縮がみられた。
4118 (非交配群雌)	死亡	投与 12 日	投与 8 日~死亡する投与 12 日まで体重増加の抑制(−3 g)、組織学検査で気管に中等度な壊死性炎が観察され、呼吸器の障害が死因と判断した。その他、剖検で盲腸の大型化がみられた。

その他、対照群の雌 1 例（交配群、動物番号 1104）を安楽死させた。この動物は投与開始日~投与 8 日まで体重増加の抑制(+4 g)、投与 8 日~安楽死させる投与 12 日まで体重減少(−13 g)、摂餌量の低値傾向、投与 11 日に尿道口の腫脹、更に投与 12 日に自発運動の減少及びあえぎ呼吸を呈したため、安楽死させた。血液・血液化学検査で血液濃縮、好中球の増加、AST、LDH、γ-GTP 及び ALP 活性の増加、総胆汁酸の減少、総コレステロール、トリグリセライド、リン脂質、グルコースの増加、BUN 及びクレアチニンの増加、カリウムの増加、塩素の減少、無機リンの増加、総たん白及びアルブミン並びに A/G 比の減少、剖検で腎臓に白色巣及び腎盂拡張、膀胱、尿管及び尿道の拡張、尿道口の腫脹、胸腺の小型化、組織学的に腎臓に腎盂拡張、尿細管の拡張、腎盂腎炎（細菌症と移行上皮の過形成を伴う）及び尿細管の壊死、膀胱の拡張、炎症及び移行上皮のび慢性の過形成、尿道、尿管及び腟に炎症、副腎に限局性出血、大腿骨（骨髄）に骨髄の限局性壊死、心臓に限局性出血、十二指腸、空腸、回腸（パイエル板）、盲腸、結腸、直腸に炎症、肝臓にクッパー細胞の過形成、肺に血栓、膵臓の水腫、顎下リンパ節、腸間膜リンパ節、脾臓、胸腺及びパイエル板にリンパ球の壊死、副腎皮質細胞の肥大、顎下腺に単細胞壊死、腺胃にびらんが認められた。

尿道口の腫脹、膀胱の炎症、腎盂腎炎（細菌症と移行上皮の過形成を伴う）、種々の器官・組織に出血及び炎症性/壊死性変化、かつ肝及び腎機能の低下がみられたことから、尿路の上行性感染による腎盂腎炎から尿毒症（全身状態の悪化）に至った考えられた。なお、本例は対照群であり、偶発的変化である。

6.2　生存動物の一般状態（Table 1-1~1-11、Appendix 1-1~1-34）

1)　投与期間

軟便が 150 mg/kg 投与群の雄 1 例（動物番号 4002）で投与 6 日の投与前にみられたが、一時的変化であり、他の動物に軟便がみられないことから、被験物質投与との関連はないと判断した。

2)　回復期間

あえぎ呼吸が 150 mg/kg 投与群の非交配群 1 例（動物番号 4120）で回復 3 日の詳細な一般状態観察時にみられた。

6.3　詳細な一般状態の観察、機能検査、握力測定及び自発運動量の測定（Fig. 1~5、Table 2-1~2-84、Appendix 2-1~2-258）

6.3.1　ホームケージ内観察（Table 2-1~2-23、Appendix 2-1~2-72）

いずれの動物にも異常はなかった。

6.3.2　手に持っての観察（Table 2-24~2-46、Appendix 2-73~2-144）

流涎が 150 mg/kg 投与群の雄 2 例と交配群の雌 4 例にみられた。

性	動物番号	症状	検査日
雄	4001	流涎	投与 3 週
	4007	流涎	投与 2 週
雌	4102（交配群）	流涎	妊娠 20 日
	4104（交配群）	流涎	妊娠 20 日
	4111（交配群）	流涎	妊娠 14 日
	4112（交配群）	流涎	妊娠 20 日

6.3.3　オープンフィールド内観察（Table 2-47~2-69、Appendix 2-145~2-216）

150 mg/kg 投与群では、雄で立ち上がり回数の有意な低値が投与 1 週に認められたが、軽微な一時的な変動であり、被験物質投与との関連のない偶発的変化と判断した。

その他の被験物質投与群では、対照群との間に有意差は認められなかった。

6.3.4　機能検査（Table 2-70~2-74、Appendix 2-217~2-230）

1)　投与期間終了週検査

いずれの動物にも聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射及び空中正向反射に異常はなかった。

着地開脚幅では、対照群と各被験物質投与群との間に有意差は認められなかった。

2)　回復期間終了週検査

いずれの動物にも聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射及び空中正向反射に異常はなかった。

着地開脚幅では、対照群と 150 mg/kg 投与群との間に有意差は認められなかった。

6.3.5　握力（Table 2-75~2-79、Appendix 2-231~2-244）

1)　投与期間終了週検査

対照群と各被験物質投与群との間に有意差は認められなかった。

2)　回復期間終了週検査

対照群と 150 mg/kg 投与群との間に有意差は認められなかった。

6.3.6　自発運動量（Fig. 1~5、Table 2-80~2-84、Appendix 2-245~2-258）

1)　投与期間終了週検査

対照群と各被験物質投与群との間に有意差は認められなかった。

2)　回復期間終了週検査

150 mg/kg 投与群の雄で投与 20-30 分に有意な低値が認められたが、一時的変化であり、投与期間中に変化がないことから偶発的変化と判断した。雌では対照群と 150 mg/kg 投与群との間に有意差は認められなかった。

6.4　体重（Fig. 6~8、Table 3-1~3-7、Appendix 3-1~3-22）

1)　投与期間

雄では、50 及び 150 mg/kg 投与群で投与 29 日以降に有意な低値が認められ、投与期間中の体重増加量も有意に低かった。15 mg/kg 投与群では対照群と同様な体重推移を示し、有意差は認められなかった。

交配群雌では、各被験物質投与群の交配前、妊娠及び授乳期間を通し、各測定値に有意差は認められなかった。その他、15 mg/kg 投与群では、交配前投与期間中の体重増加量に有意な低値が認められたが、軽微な変動であり用量との関連もないことから偶発的変化と判断した。

非交配群では、対照群と 150 mg/kg 投与群の間に有意差は認められなかった。

2)　回復期間

150 mg/kg 投与群では、雄で回復 1 日に有意な低値が認められたが、その後は対照群を僅かに上回る体重増加を示し、有意差は認められなかった。雌では、対照群と 150 mg/kg 投与群の間に有意差は認められなかった。

6.5　摂餌量（Fig. 9~11、Table 4-1~4-7、Appendix 4-1~4-22）

1)　投与期間

雄では、50 及び 150 mg/kg 投与群で投与 2 日に有意な低値が認められたが、その後は対照群と同等値を示した。15 mg/kg 投与群では対照群と同等度な摂餌量を示し、有意差は認められなかった。

交配群雌では、150 mg/kg 投与群で投与 2 日に有意な低値が認められたが、その後の交配前、妊娠及び授乳期間に有意差は認められなかったことから、毒性学的意義はないと判断した。その他、15 mg/kg 投与群で投与 15 日に有意な低値が認められたが、用量との関連もないことから偶発的変化と判断した。

非交配群では、150 mg/kg 投与群と対照群の間に有意差は認められなかった。

2)　回復期間

150 mg/kg 投与群の雌雄ともに、対照群との間に有意差は認められなかった。

6.6　尿検査（摂水量測定を含む）（Table 5-1~5-16、Appendix 5-1~5-30）

1)　投与期間終了週検査

雄では、褐色尿が 150 mg/kg 投与群の 3/4 例にみられた。

非交配群では、褐色尿が 150 mg/kg 投与群に 1/4 例にみられた。

その他の検査項目では、対照群と比べ雄の各被験物質投与群、非交配群の 150 mg/kg 投与群との間に有意差は認められなかった。

2)　回復期間終了週検査

雌雄ともにいずれの検査項目においても、対照群と 150 mg/kg 投与群との間に有意差は認められなかった。

6.7　血液学検査（Table 6-1~6-10、Appendix 6-1~6-28）

1)　投与期間終了時検査

雄では、対照群と比べ 150 mg/kg 投与群でフィブリノーゲン量に有意な低値が認められた。その他、対照群と比べ 15 mg/kg 投与群でプロトロンビン時間の有意な短縮、50 mg/kg 投与群でプロトロンビン時間の有意な延長がみられたが、用量との関連はないことから、被験物質投与の影響ではないと判断した。

交配群雌では、対照群と比べ 150 mg/kg 投与群でフィブリノーゲン量に有意な低値が認められた。

非交配群では、対照群と比べ 150 mg/kg 投与群で赤血球数及びヘマトクリット値に有意な低値並びにフィブリノーゲン量に有意な低値が認められた。その他、対照群と比べ 150 mg/kg 投与群で網赤血球率の有意な低値が認められた。

2)　回復期間終了時検査

対照群と比べ雄の 150 mg/kg 投与群で平均赤血球容積及び平均赤血球血色素量の有意な高値が認められたが、投与期間終了時検査に異常は認められず、軽微な変化であることから被験物質投与の影響ではないと判断した。

6.8　血液化学検査（Table 7-1~7-10、Appendix 7-1~7-28）

1)　投与期間終了時検査

雄では、対照群と比べ 150 mg/kg 投与群で総胆汁酸の低値が認められた。その他、対照群と比べ 50 mg/kg 投与群でクレアチニンの有意な低値が認められたが、軽微な変化であり被験物質投与の影響ではないと判断した。

交配群雌では、対照群と比べ 150 mg/kg 投与群で総胆汁酸の有意な低値、ナトリウム及び塩素の有意な低値が認められた。その他、対照群と比べ 15 mg/kg 投与群でナトリウムの有意な低値が認められたが、軽微な変化であり明確な用量との関連はないことから偶発的変化と判断した。

非交配群では、対照群と比べて 150 mg/kg 投与群で総胆汁酸の有意な低値が認められた。その他、150 mg/kg 投与群で γ-GTP の有意な低値が認められたが、低下であり被験物質投与の影響ではないと判断した。

2)　回復期間終了時検査

対照群と比べて雄の 150 mg/kg 投与群でリン脂質の有意な低値、非交配群の 150 mg/kg 投与群でナトリウムの有意な低値、A/G 比の有意な高値が認められたが、軽微な変化であり、雄及び非交配群の投与期間終了時検査に異常がないことから偶発的変化と判断した。

6.9　器官重量（Table 8-1~8-10、Appendix 8-1~8-48）

1)　投与期間終了時検査

雄では、被験物質投与の影響はみられなかった。その他、対照群と比べ 50 mg/kg 投与群で脳と前立腺の相対重量に有意な高値、肝臓の絶対重量に有意な低値が認められたが、相対あるいは絶対重量のみの変化であり、用量との関連もないことから、被験物質投与との関連はないと判断した。

交配群雌では、いずれの器官においても対照群と各被験物質投与群との間に有意差は認められなかった。

非交配群では、対照群と比べ 150 mg/kg 投与群で胸腺の絶対及び相対重量に有意な低値が認められた。なお、150 mg/kg 投与群で心臓及び子宮の絶対重量に有意な低値が認められたが、絶対重量のみの変化であり、回復期間終了時検査の対照群とほぼ同等値であることから、偶発的変化と判断した。

2)　回復期間終了時検査

雄及び非交配群ともに、対照群と 150 mg/kg 投与群の間に有意差は認められなかった。

6.10　剖検所見（Table 9-1~9-7、Appendix 9-1~9-116）

瀕死及び死亡動物の剖検所見は「7.1 の項」に記載したため省略する。

1)　投与期間終了時検査

雄では、盲腸及び肺に被験物質投与の影響がみられた。

盲腸　：　大型化が 50 及び 150 mg/kg 投与群でそれぞれ 1/12 及び 4/5 例みられた（組織学的に異常はなかった）。

肺　：　肺の暗赤色巣が 150 mg/kg 投与群で 1/5 例みられた（動物番号 4001、組織学的に軽微な細気管支-肺胞の炎症）。

その他、精巣上体の白色巣が 15 mg/kg 投与群で 1/12 例（動物番号 2009、組織学検査は未実施）、肺の白色化が 50 mg/kg 投与群で 1/12 例（動物番号 3009、組織学検査は未実施）、腺胃部の暗赤色巣が 15 及び 50 mg/kg 投与群で各 1/12 例（動物番号 2003、組織学的に腺胃の軽微なびらん、動物番号 3010、組織学検査は未実施）みられたが、いずれも発現状況から偶発的変化と判断した。

非交配群では、盲腸に被験物質投与の影響がみられた。

盲腸　：　大型化が 150 mg/kg 投与群で 4/4 例みられた（組織学

的に異常はなかった）。

その他、偶発的変化として、対照群で肝臓の横隔膜ヘルニア結節が 1/5 例（動物番号 1117、組織学的にも軽度な肝臓の横隔膜ヘルニア結節）、腺胃部の暗赤色巣が 2/5 例（動物番号 1113、1116、組織学的に腺胃の軽微なびらん）みられた。

交配群雌（授乳 5 日に剖検）では、盲腸に被験物質投与の影響がみられた。

盲腸　　：　大型化が 150 mg/kg 投与群で 4/9 例みられた（組織学的に異常はなかった）。

その他、肝臓の白色巣が 150 mg/kg 投与群で 1/9 例（動物番号 4111、組織学検査は未実施）、肺の暗赤色巣が 15 及び 50 mg/kg 投与群で各 1/12 例（動物番号 2106、組織学的に限局性の軽微な出血、動物番号 3101、組織学的に限局性の軽微な出血と肺胞マクロファージの集簇）、肺の白色巣が 50 mg/kg 投与群で 1/12 例（動物番号 3107、組織学検査は未実施）、腺胃部の暗赤色巣が対照群で 1/11 例（動物番号 1110、組織学的に腺胃の軽微なびらん）、15 mg/kg 投与群で 2/12 例（動物番号 2109、2110、組織学検査は未実施）、50 mg/kg 投与群で 3/12 例（動物番号 3101、3104、3106、組織学検査は未実施）及び 150 mg/kg 投与群で 1/9 例（動物番号 4108、組織学的に腺胃の軽度なびらん）みられたが、いずれも発現状況から偶発的変化と判断した。

2)　回復期間終了時検査

雄では、異常はなかった。

非交配群では、腺胃部の暗赤色巣が対照群で 2/5 例（動物番号 1121、1122、組織学的に腺胃の軽微又は軽度なびらん）及び 150 mg/kg 投与群で 1/4 例（動物番号 4120、組織学的に腺胃の軽微なびらん）みられたが、いずれも発現状況から偶発的変化と判断した。

6.11　病理組織学検査（Table 10-1~10-18、Appendix 9-1~9-116）

瀕死及び死亡動物の病理組織学検査所見は「7.1 の項」に記載したため省略する。

1)　投与期間終了時検査

被験物質投与による影響が肺及び前胃にみられた。

【肺】

細気管支-肺胞の炎症（軽微）が雄の 150 mg/kg 投与群にみられた。

性	雄				交配群雌				非交配群	
投与量（mg/kg）	0	15	50	150	0	15	50	150	0	150
動物数	5	5	5	5	5	5	5	5	5	4
細気管支-肺胞の炎症	0	0	0	1	0	0	0	0	0	0
軽微	0	0	0	1	0	0	0	0	0	0

【前胃】

扁平上皮細胞過形成（軽微又は軽度）が雄の 150 mg/kg 投与群にみられた。

性	雄				交配群雌				非交配群	
投与量（mg/kg）	0	15	50	150	0	15	50	150	0	150
動物数	5	5	5	5	5	0	0	5	5	4
扁平上皮細胞過形成	0	0	0	2	0	/	/	0	0	0
軽微	0	0	0	1	0	/	/	0	0	0
軽度	0	0	0	1	0	/	/	0	0	0

2) 回復期間終了時検査

被験物質投与による影響が肺にみられた。

【肺】

細気管支-肺胞の炎症（軽微）が雄の 150 mg/kg 投与群にみられた。

性	雄		非交配群	
投与量（mg/kg）	0	150	0	150
動物数	5	4	5	4
細気管支-肺胞の炎症	0	1	0	0
軽微	0	1	0	0

6.12 性周期（Table 11、Appendix 10-1~10-4）

50 mg/kg 投与群で性周期が 4 日から 6 日に変わった動物が 1 例みられ、発情期像発現回数の有意な低値が認められた。しかし、用量との関連はなく、性周期異常率及び平均性周期日数には対照群と各被験物質投与群との間に有意差は認められないことから、偶発的変化と判断した。

6.13 交配成績（Table 12、Appendix 11-1~11-4）

全ての組み合わせが交配 6 日までに交尾し、雌全例が受胎した。したがって、交尾までに要した日数、交尾率、授精率及び受胎率は対照群と各被験物質投与群との間に有意差は認められなかった。

6.14 分娩成績（Table 13、Appendix 12-1~12-4）並びに分娩及び哺育状態（Table 1-5 及び 1-6、Appendix 1-17~1-24）

分娩の遅延が 50 mg/kg 投与群の 1 例(動物番号 3103)みられたが、その他の妊娠動物は妊娠 21 から 23 日に全例が正常に分娩し、胎盤及び羊膜の処理は正常に行われた。外表異常児は 50 mg/kg 投与群の死産児 1 例に外脳、脊椎裂及び眼球開裂がみられたのみであった。したがって、出産率、妊娠期間、黄体数、着床痕数、着床率、分娩率、死産児率、出生児数及び外表異常率に被験物質投与の影響は認められなかった。ただし、偶発的変化として、15 mg/kg 投与群で黄体数の有意な低値、50 mg/kg 投与群で出生児数の有意な低値が認められたが、用量との関連はなかった。

哺育状態では、いずれの母動物ともに児集め、営巣及び授乳行動に異常はなかった。

6.15　出生児の生存率（Table 14、Appendix 13-1~13-4）

出生率及び生後 4 日生存率では、対照群と各被験物質投与群との間に有意差は認められなかった。

6.16　出生児の性比（Table 15、Appendix 14-1~14-4）

出産児並びに出生児の生後 0 及び 4 日の性比では、被験物質投与の影響は認められなかった。ただし、偶発的変化として、15 mg/kg 投与群で出産児並びに出生児の生後 0 及び 4 日の性比に有意な低値が認められたが、用量との関連はなかった。

6.17　出生児の体重（Table 16、Appendix 15-1~15-4）

生後 0 及び 4 日の雌雄体重並びに生後 0~4 日の体重増加量では、対照群と各被験物質投与群との間に有意差は認められなかった。

6.18　死亡児の肉眼観察所見（Table 17、Appendix 16-1~16-4）

いずれの死亡児にも肉眼的異常はなかった。

6.19　出生児の生後 4 日肉眼観察所見（Table 18、Appendix 17-1~17-4）

いずれの出生児にも肉眼的異常はなかった。

7. 考察

ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドの 0（対照群：注射用水）、15、50 及び 150 mg/kg を Sprague-Dawley 系 SPF ラットの雄には交配前 14 日間に加え交配期間を通して剖検前日まで（42 日間）、雌には交配前 14 日間に加え交配期間及び妊娠期間を通して授乳 4 日まで（41~47 日間）、非交配群には 42 日間強制経口投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0 及び 150 mg/kg 投与群の一部の動物（各群 4~5 匹）については、42 日間投与した後 14 日間の回復期間を設け、毒性変化の可逆性を検討した。

7.1 反復投与毒性

150 mg/kg 投与群で雄 3 例、交配群の雌 3 例、非交配群の雌 2 例の計 8 例が投与 5 から 39 日の間に死亡又は安楽死させた。これらの動物は、主に死亡/安楽死前にあえぎ呼吸、体重の減少又は増加の抑制、全例に気管の壊死性炎、4/8 例で肺に気管支の壊死性炎及び肺胞の水腫、1/8 例で細気管支-肺胞の炎症が観察されたことから、呼吸器系の障害が死亡あるいは安楽死の原因と考えられた。なお、副腎の皮質細胞の肥大、造血・リンパ系組織の萎縮は一般状態の悪化に伴う二次性変化、骨髄の顆粒球造血の亢進は、気管及び肺の炎症に対する反応性変化と考えられた。

生存動物の一般状態においても、150 mg/kg 投与群の投与期間中に雄 2 例、交配群雌 4 例に流涎、回復期間中に非交配群 1 例にあえぎ呼吸が詳細な一般状態観察時にみられた。150 mg/kg 投与群の生存動物では、細気管支-肺胞の炎症が投与期間終了時及び回復期間終了時の雄各 1 例に観察されたが、他の生存動物の肺及び気管支に組織学的異常はなかった。本被験物質は MSDS によると吸入した場合、粘膜と上気道の組織に非常に有害[7]であり、構造が類似している塩化ジデシルジメチルアンモニウムにおいても、吸入毒性試験において肺への障害性を有することが知られている[8]ことから、肺及び気管支病変及びあえぎ呼吸は、死亡あるいは安楽死動物と同様、本被験物質の誤嚥又は何らかの原因により被験物質が気道に入り、気管及び気管支粘膜が直接障害されて形成された可能性が考えられた。呼吸器系への障害は、偶然に被験物質が気道へ流入することにより発現することから、回復性は明らかにできなかった。これと関連して、150 mg/kg 投与群の雌雄の流涎及び同群の雄で前胃に扁平上皮細胞の過形成がみられた。扁平上皮細胞の過形成は、化学物質などを経口投与した際に様々な刺激に対する反応性変化としてみられることがあり、本被験物質が呼吸器系組織の粘膜に障害性を有する可能性が示唆されていることから、流涎及び扁平上皮細胞の過形成は被験物質の刺激により惹起されたものと考えられた。なお、本変化は回復期間終了時検査では消失し、可逆性の変化であった。

体重では、50 及び 150 mg/kg 投与群の雄で体重増加の抑制が認められた。回復期間中は対照群を僅かに上回る体重増加を示し、回復性の変化であった。

摂餌量では、50 mg/kg 投与群の雄及び 150 mg/kg 投与群の雄と交配群雌で投与 2 日

に低値が認められたが、一時的変化であり、投与初期の体重に影響がないことから毒性学的意義はないと判断した。

尿検査（摂水量測定を含む）では、投与期間終了週検査で 150 mg/kg 投与群の雄及び非交配群に褐色尿がみられ、被験物質投与の影響と考えられたが、溶血及び肝障害を示唆する変化はなく､尿中ビリルビン及びウロビリノーゲンに異常がないことから、毒性学的意義は少ないと判断した。

血液学検査では、150 mg/kg 投与群の雄、交配群雌及び非交配群でフィブリノーゲン量の低値が認められたが、フィブリノーゲンの生産を抑制する肝障害及び消費を亢進する DIC､出血､炎症等の異常がないことから､本変化の作用機序は明らかでない。また、150 mg/kg 投与群の非交配群で赤血球数及びヘマトクリット値の低値（赤血球数は対照群の $863 \times 10^4/\mu L$ に対し $806 \times 10^4/\mu L$、ヘマトクリット値は対照群の 43.4%に対し 41.6%）が認められた。しかし、同変化は雄及び交配群雌にみられず、出血・溶血を示唆する変化はなく、造血系に反応性変化がみられないこと、ヘモグロビン量に有意差はなく、平均赤血球容積、平均赤血球血色素量及び平均赤血球血色素濃度は対照群と大差なく、網赤血球率は低値であり、背景データ内{試験施設の背景データ（添付資料 7）、Mean±2S.D.、n=75、2009/04~2013/03、赤血球数：847.8±64.7、ヘモグロビン量：15.2±1.1、ヘマトクリット値：43.3±3.7、網赤血球率：1.8±0.8}であることを考え合わせると、被験物質投与との関連はないと判断した。これら変化は回復期間終了時検査ではみられなかった。

血液化学検査では、150 mg/kg 投与群の雄、交配群雌及び非交配群で総胆汁酸の低値が認められた。血中コレステロール及びビリルビンに異常はなく、肝及び胆道障害を示唆する変化もないこと、また、小腸及び大腸に組織学的異常がないこと、肉眼的に盲腸の大型化がみられ、被験物質投与による腸内細菌への影響が推測されることを考え合わせると、腸内細菌による二次胆汁酸の変換が対照群と異なり、能動的吸収機構による胆汁酸の吸収が十分でない可能性が考えられた。本変化は回復期間終了時検査では消失した。また､150 mg/kg 投与群の交配群雌でナトリウム及び塩素の低値（ナトリウムは対照群の 141 mmol/L に対し 139 mmol/L、塩素は対照群の 107 mmol/L に対し 104 mmol/L）が認められた。同変化は雄及び非交配群にみられず、腎臓に組織学的異常がないこと、背景データ内（試験施設の背景データ、Mean±2S.D.、n=134、2009/04~2013/03、ナトリウム：141±3、カリウム：4.2±0.8、塩素：107±5）であることから、被験物質との関連がない生理学的変動範囲内の変化と判断した。これら変化は回復期間終了時検査ではみられなかった。

病理学検査では､前述の肺､前胃及び盲腸に被験物質投与の影響がみられた｡他に、150 mg/kg 投与群の非交配群で胸腺の絶対及び相対重量に低値が認められたが、背景データ内（試験施設の背景データ、Mean±2S.D.、n=75、2009/04~2013/03、胸腺の絶対重量：296±137、胸腺の相対重量：107±45）の変化であり、組織学的異常はなく、雄及び交配群雌に同変化がみられないことから、被験物質投与との関連性はないと判断した。本変化は回復期間終了時検査ではみられなかった。

その他の検査では、被験物質投与による影響は認められなかった。

7.2　生殖発生毒性

性周期、交尾までに要した日数、交尾率、授精率及び受胎率では、被験物質投与の影響は認められなかった。また、出産率、妊娠期間、黄体数、着床痕数、着床率、分娩率、死産児率、死産児の外表観察、出生児数、外表異常率及び出生率では、被験物質投与の影響は認められなかった。したがって、150 mg/kg 投与群においても雌雄動物の交尾能、母動物の妊娠維持、分娩に被験物質投与の影響はないと判断した。

出生児では、外表観察、雌雄体重並びに性比、生存率及び肉眼観察所見に被験物質投与による影響は認められないことから、150 mg/kg 投与群においても胎児の子宮内発生、発育及び分化並びに生存性などへの影響はないと判断した。

これらの結果から、本試験条件下でベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドを反復経口投与することにより、50 mg/kg 以上の投与群で体重増加の抑制と投与初期に摂餌量の低値（雄）、150 mg/kg 投与群で安楽死及び死亡動物の発現（雌雄）、投与初期に摂餌量の低値（雌）、流涎（雌雄）がみられ、肺及び前胃（雄）、胸腺（雌）並びに盲腸（雌雄）に被験物質投与による影響が認められた。また、フィブリノーゲン量の低値（雌雄）及び総胆汁酸の低値（雌雄）がみられた。雌雄親動物の生殖能力及び児動物には被験物質投与による影響は認められなかった。したがって、本被験物質の反復投与毒性に対する無影響量及び無毒性量は雄で 15 mg/kg、雌で 50 mg/kg と判断した。また、雌雄親動物の生殖能力に対する無影響量及び無毒性量は雌雄で 150 mg/kg、児動物における無影響量及び無毒性量は 150 mg/kg と判断した。

8. 文献

1) [redacted]ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドの HPLC を用いた被験液中濃度測定法バリデーション及び安定性試験（媒体：注射用水）並びに IR を用いた特性及び安定性試験（株式会社ボゾリサーチセンター御殿場研究所、試験番号：A-2513、2013 年）

2) [redacted]ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドのラットを用いた 14 日間反復経口投与毒性試験（投与量設定試験）（株式会社ボゾリサーチセンター、試験番号：N-R033、2012 年）

3) Snedecor GW, Cochran WG. Statistical methods. 8th ed. Ames: Iowa State University Press; 1989.

4) Dunnett, CW. New tables for multiple comparisons with a control. Biometrics 1964; 20: 482-91.

5) Steel RGD. A multiple comparison rank sum test: Treatments versus control. Biometrics 1959; 15: 560-72.

6) 佐久間昭（1981）：薬効評価－計画と分析–II, pp.23-27, 387-389, 東京大学出版会, 東京.

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8) Ohnuma A, Yoshida T, Tajima H, Fukuyama T, Hayashi K, Yamaguchi S, Ohtsuka R, Sasaki J, Fukumori J, Tomita M, Kojima S, Takahashi N, Takeuchi Y, Kuwahara M, Takeda M, Kosaka T, Nakashima N, Harada T. Didecyldimethylammonium chloride induces pulmonary inflammation and fibrosis in mice. Exp Toxicol Pathol. 2010 Nov;62(6): 643-51.

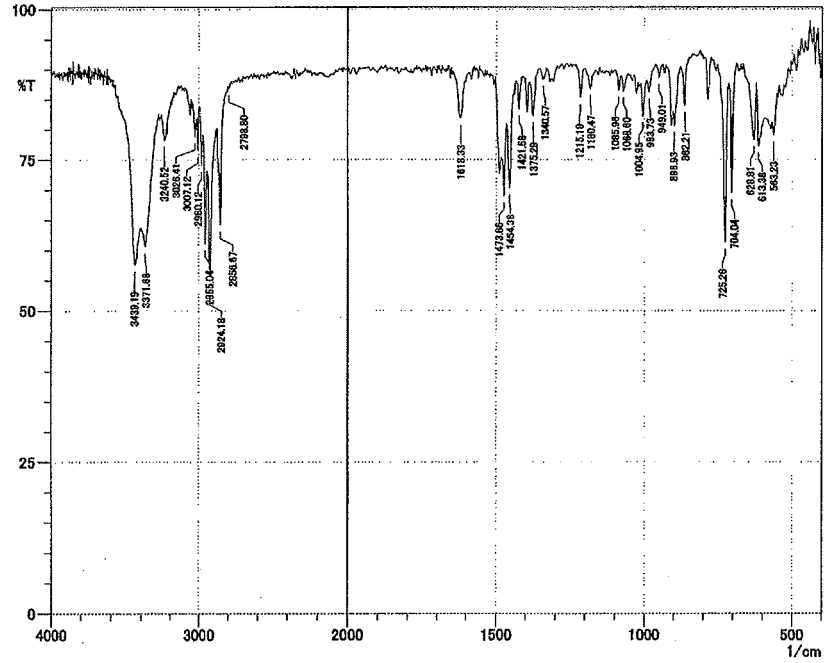
R-1102
添付資料　1

試験番号：A-2513

試験成績書
［ベンジル（ジメチル）（オクタン-1-イル）アンモニウム＝クロリドの特性］

ステージ　：　被験物質の特性
測定日　：　2012年12月7日
被験物質　：　ベンジル（ジメチル）（オクタン-1-イル）アンモニウム＝クロリド（ロット番号：20120927）

試験項目　：　赤外吸収スペクトルの確認（KBr錠剤法）
結果　：　特性のスペクトルを以下に示す。



基準　：　「新規化学物質等に係る試験を実施する試験施設に関する基準」（平成23年3月31日：薬食発0331第8号、平成23･03･29製局第6号、環保企発第110331010号）

[redacted]　2012年12月19日

試験責任者
株式会社ボゾリサーチセンター　御殿場研究所

試験成績書
[ベンジル（ジメチル）（オクタン-1-イル）アンモニウム＝クロリドの安定性]

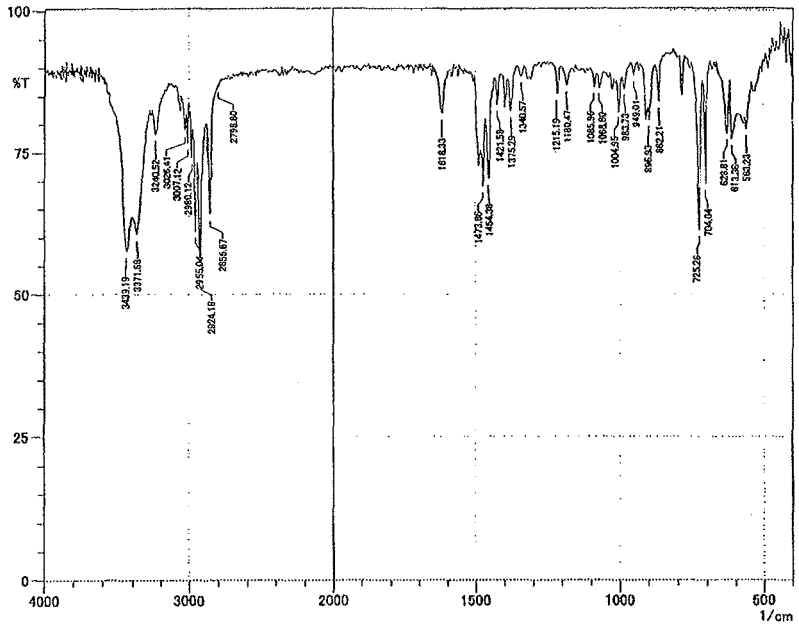
ステージ	：	投与期間終了後
測定日	：	2013 年 4 月 8 日 2012 年 12 月 7 日〔特性のスペクトル（A-2513）〕
被験物質	：	ベンジル（ジメチル）（オクタン-1-イル）アンモニウム＝クロリド （ロット番号：20120927）
試験項目	：	赤外吸収スペクトルの確認（KBr 錠剤法）
評価基準	：	安定性のスペクトルを特性のスペクトル（A-2513）と比較するとき、同様な赤外吸収スペクトルである。
結果	：	安定性のスペクトルを特性のスペクトルと比較したとき、同様な赤外吸収スペクトルが得られた。 なお、赤外吸収スペクトルは次のページに示す。
判定	：	適
基準	：	「新規化学物質等に係る試験を実施する試験施設に関する基準」（平成 23 年 3 月 31 日：薬食発 0331 第 8 号、平成 23･03･29 製局第 6 号、環保企発第 110331010 号）

[redacted]　2013 年 4 月 10 日

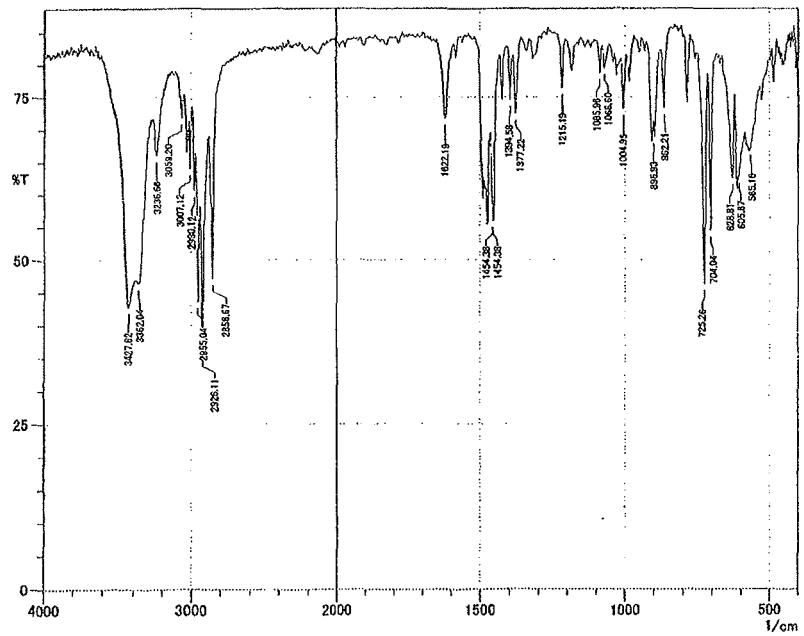
化学分析責任者
株式会社ボゾリサーチセンター　御殿場研究所

結果　　：　赤外吸収スペクトル

（特性のスペクトル：A-2513）



（安定性のスペクトル）



R-1102
添付資料　3

試験番号：A-2513

試験成績書

（被験液中ベンジル（ジメチル）（オクタン-1-イル）アンモニウム＝クロリドの安定性）

被験物質	：	ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリド（ロット番号：20120927）
形態（媒体）	：	溶液（注射用水）
保存条件	：	褐色ガラスビンにて、冷所（冷蔵庫内、許容値：1~10°C）又は室温保存
保存期間	：	冷所 8 日間＋室温 24 時間保存
評価基準		
安定性	：	残存率が 100.0 ±10.0%以内。

結果：

調製濃度（mg/mL）		測定濃度（mg/mL）	
		調製直後	冷所 8 日間+室温 24 時間保存後
1.01		1.04	1.10
		1.06	1.08
		1.05	1.07
	平均値	1.05	1.08
	残存率（%）	–	102.9
200		209	238
		208	216
		213	214
	平均値	210	223
	残存率（%）	–	106.2

判定　：　適

基準　：　「新規化学物質等に係る試験を実施する試験施設に関する基準」（平成 23 年 3 月 31 日：薬食発 0331 第 8 号、平成 23･03･29 製局第 6 号、環保企発第 110331010 号）

[redacted]　2012 年 12 月 27 日

試験責任者
株式会社ボゾリサーチセンター　御殿場研究所

R-1102
添付資料　4

分析結果

試験番号　：　R-1102
項目　：　濃度
ステージ　：　初回投与
分析日　：　2013 年 1 月 30 日

測定試料
　被験物質　：　ベンジル（ジメチル）（オクタン-1-イル）アンモニウム＝クロリド
（ロット番号；20120927）
　形態　：　溶液
　媒体　：　注射用水
　調製日　：　2013 年 1 月 30 日

測定対象物質：　ベンジル（ジメチル）（オクタン-1-イル）アンモニウム＝クロリド

評価基準
　濃度　：　表示値に対する割合が 100.0±10%

結果：

表示値 (mg/mL)	測定濃度 (mg/mL)	表示値に対する割合 (%)
3	2.92	97.3
10	10.0	100.0
30	30.0	100.0

判定　：　適

R-1102
添付資料　5

分析結果

試験番号　：　R-1102
項目　：　濃度
ステージ　：　投与 6 週
分析日　：　2013 年 3 月 13 日

測定試料
　被験物質　：　ベンジル（ジメチル）（オクタン-1-イル）アンモニウム＝クロリド
（ロット番号；20120927）
　形態　：　溶液
　媒体　：　注射用水
　調製日　：　2013 年 3 月 13 日

測定対象物質：　ベンジル（ジメチル）（オクタン-1-イル）アンモニウム＝クロリド

評価基準
　濃度　：　表示値に対する割合が 100.0±10%

結果：

表示値 (mg/mL)	測定濃度 (mg/mL)	表示値に対する割合 (%)
3	3.03	101.0
10	9.97	99.7
30	29.4	98.0

判定　：　適

R-1102
添付資料　6

ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリドのラットを用いた 14 日間反復経口投与毒性試験（投与量設定試験）における所見

試験番号：N-R033

被験物質		媒体 a)	ベンジル（ジメチル）（オクタン-1-イル）アンモニウム=クロリド			
投与量(mg/kg)		0	10	30	100	300
投与容量(mL/kg)		5	5	5	5	5
使用動物数(♂/♀)		5/5	5/5	5/5	5/5	5/5
死亡動物数(♂/♀)		0/0	0/0	0/0	0/0	3/3
死亡発現時期		−	−	−	−	投与 6、8、10 日に各 1 例(♂) 投与 10、11、14 日に各 1 例(♀)
一般状態	生存	−	−	−	−	軟便、粗毛（♂）
	死亡					軟便、糞量の減少、粗毛、自発運動の減少、腹臥・横臥、呼吸数の減少、体温低下（♂） 軟便（♀）
体重	生存	−	−	−	−	体重減少、体重増加の抑制（♂投与 4~14 日）
	死亡					体重減少、体重増加の抑制（♂）
摂餌量	生存	−	−	−	−	摂餌量の低値 (♂投与 4~10 日、 ♀投与 4 日)
	死亡					摂餌量の低値（♂）
血液学検査		−	−	−	−	−
血液化学検査		−	−	−	−	AST：(↑)(♂♀) ALT：(↑)(♂♀)
器官重量	絶対	−	−	−	−	−
	相対	−	−	−	−	−
剖検	生存	−	−	−	腸管の拡張(♂♀)	腸管の拡張(♂♀) 粗毛、胃の拡張(♂)
	死亡					腸管の拡張、胃の拡張(♂♀) 低栄養状態、粗毛、 十二指腸の肥厚、 腺胃の暗赤色巣 腺胃の隆起巣、 胸腺の小型化、 脾臓の小型化、 副腎の大型化(♂) 鼻腔周囲の汚染、 胸腺の水腫(♀)
病理組織学検査		−	−	−	−	

a)　：注射用水
−　：著変なし
/　：データなし又は判別不明あるいは検定不能
↑又は↓；$p<0.05$，↑↑又は↓↓；$p<0.01$，(対照群との間に有意差あり)
(↑)；高値（対照群との間に有意差なし）

R-1102
添付資料　7

背景データ(非交配群の赤血球数、ヘモグロンビン及びヘマトクリット値)

2009 年 4 月~2013 年 3 月

群と検査項目	媒体	試験数	N	媒体毎の Mean±2S.D.	全体の Mean±2S.D.
非交配群♀ RBC (×E4/μL)	注射用水	1	5	847.8 ± 56.8	847.8 ± 64.7
	0.5%MC	4	20	858.3 ± 64.4	
	コーン油	10	50	843.6 ± 64.9	
非交配群♀ Hb (g/dL)	注射用水	1	5	15.1 ± 0.8	15.2 ± 1.1
	0.5%MC	4	20	15.5 ± 1.1	
	コーン油	10	50	15.1 ± 1.1	
非交配群♀ Ht (%)	注射用水	1	5	43.2 ± 2.2	43.3 ± 3.7
	0.5%MC	4	20	44.3 ± 3.2	
	コーン油	10	50	42.9 ± 3.7	
非交配群♀ Retic (%)	注射用水	1	5	1.8 ± 0.8	1.8 ± 0.8
	0.5%MC	4	20	1.9 ± 0.8	
	コーン油	10	50	1.8 ± 0.8	

R-1102

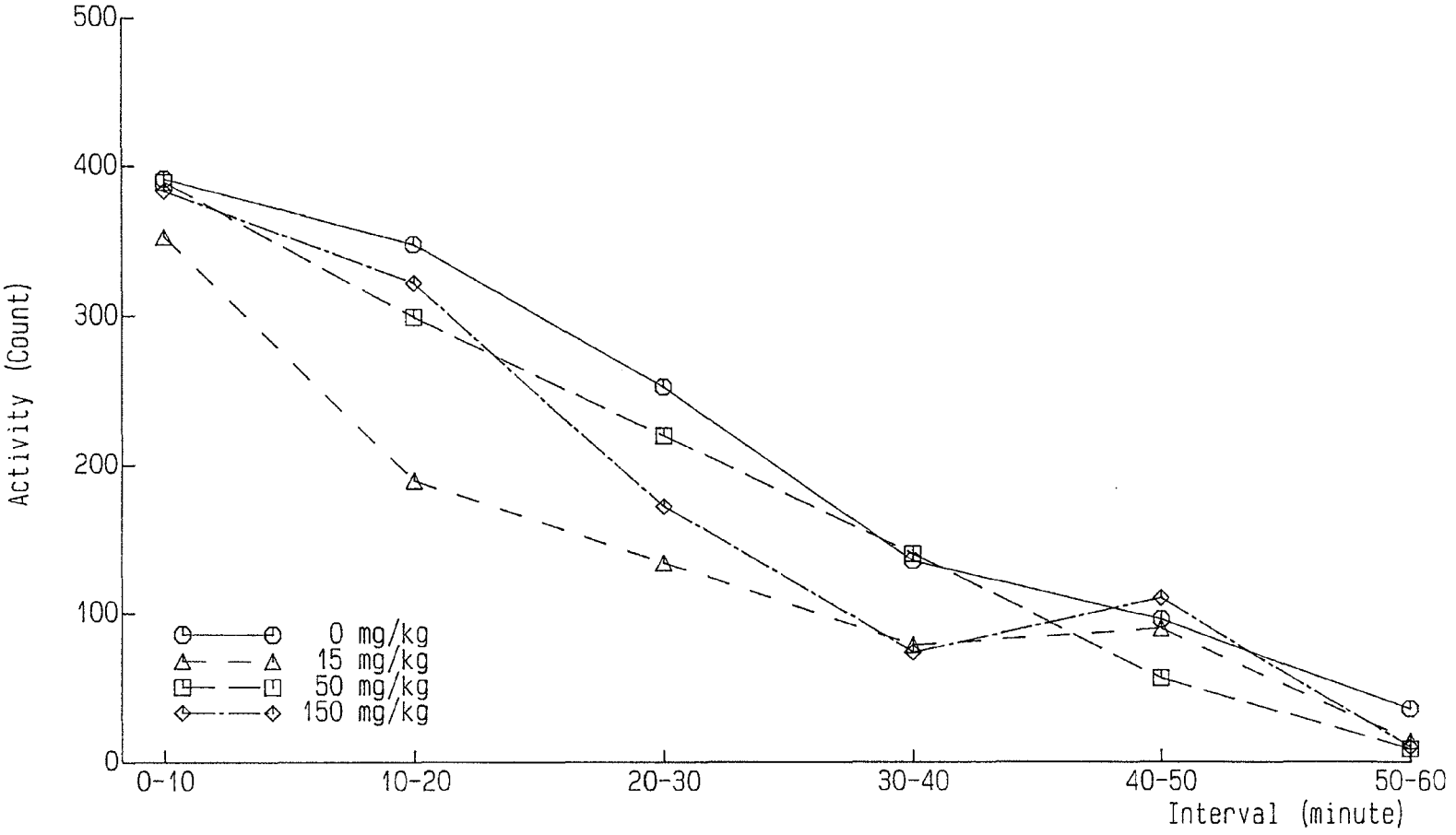


Fig.1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Motor activity of male rats (Week 6 of administration)

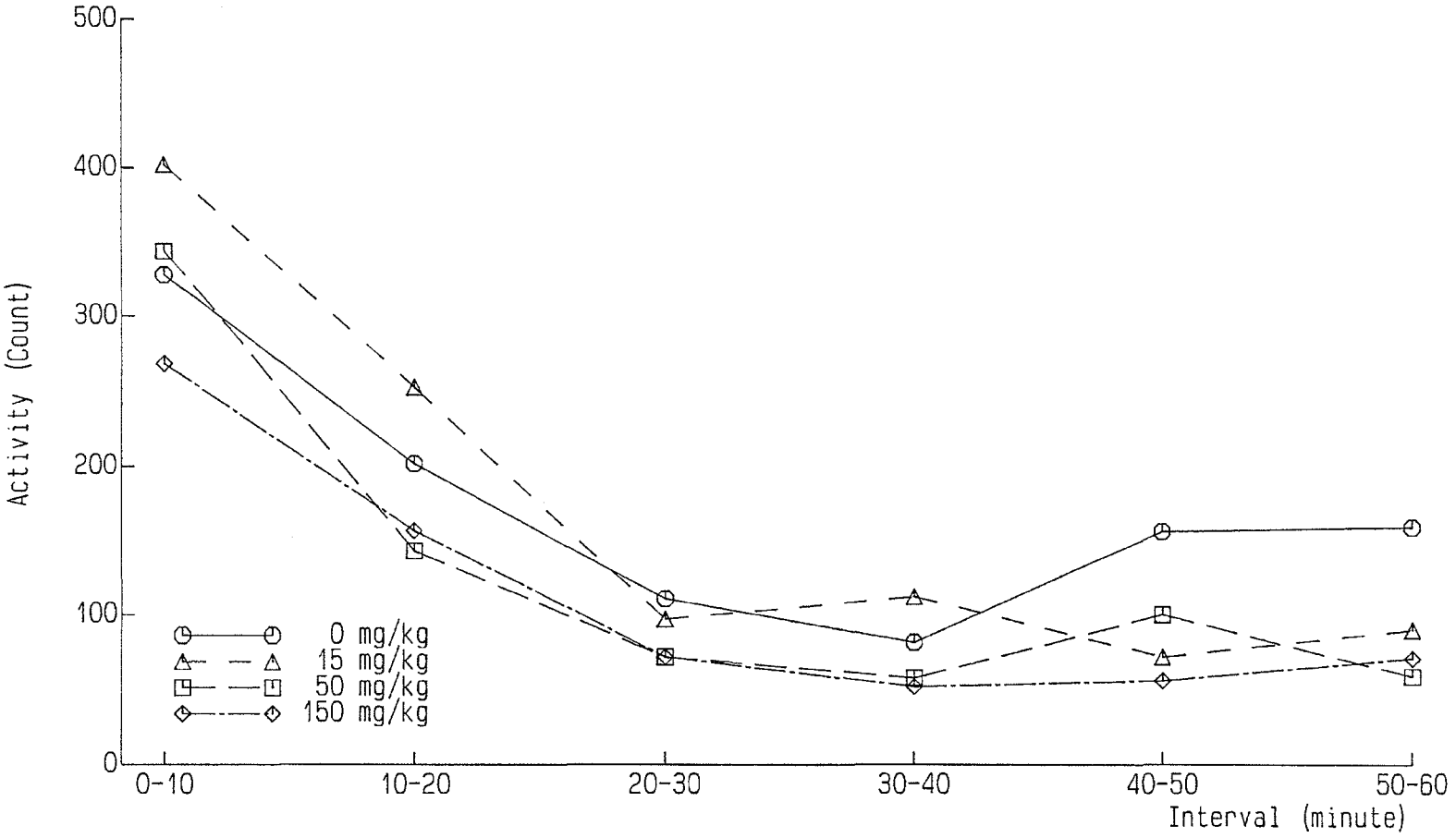


Fig.2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Motor activity of female rats (Main group, Lactation day 4)

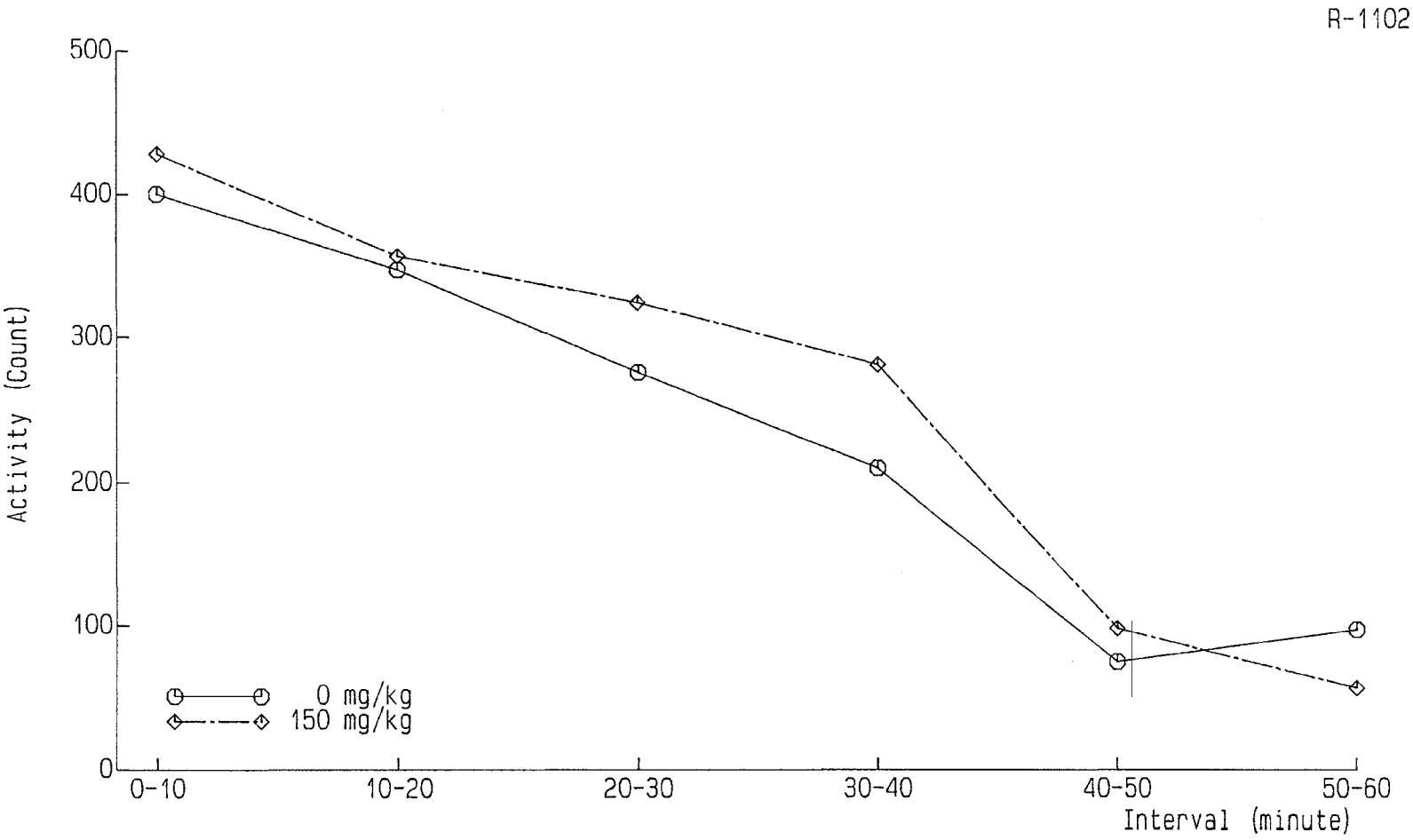


Fig.3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Motor activity of female rats (Satellite group, Week 6 of administration)

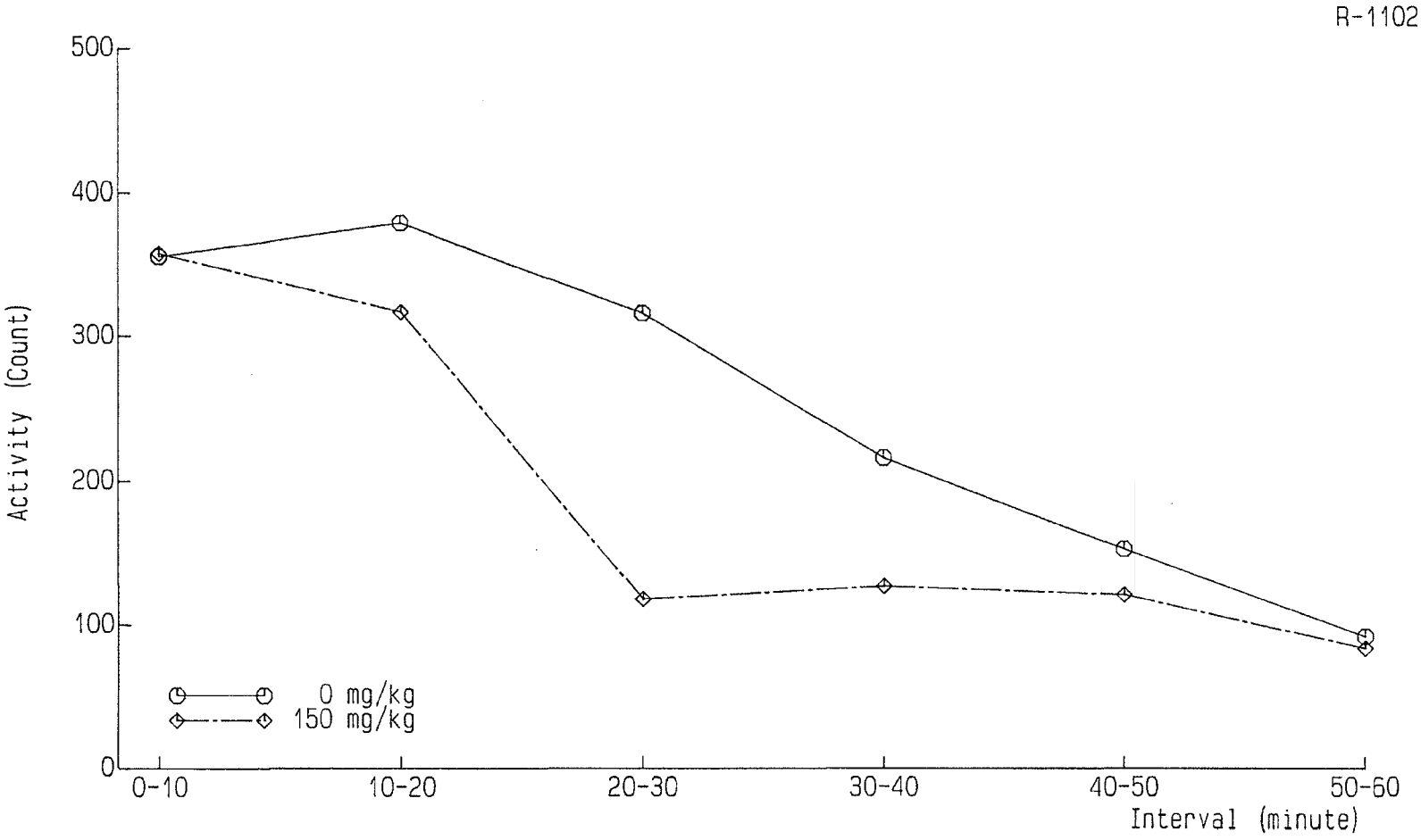


Fig.4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Motor activity of male rats (Week 2 of recovery)

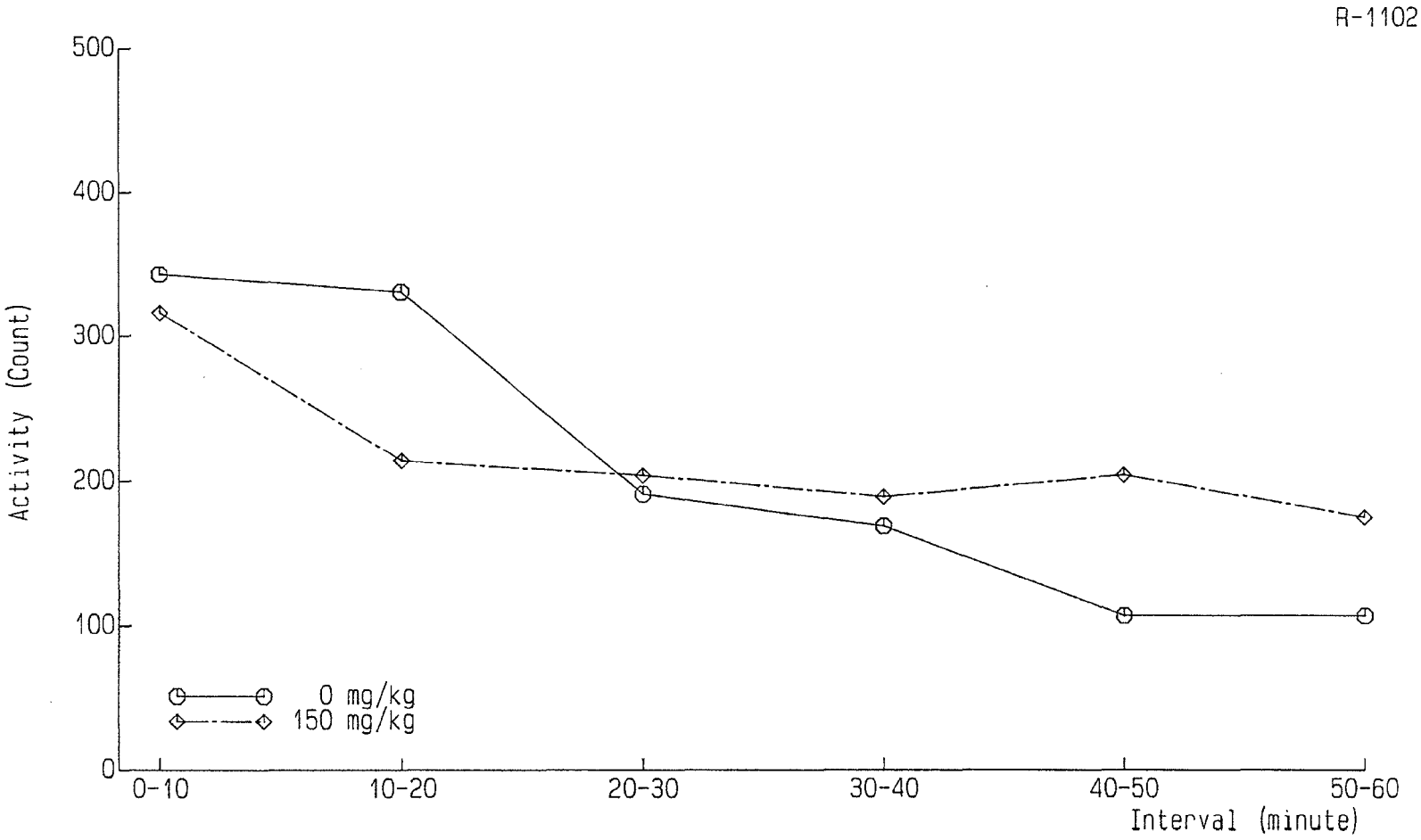


Fig.5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Motor activity of female rats (Week 2 of recovery)

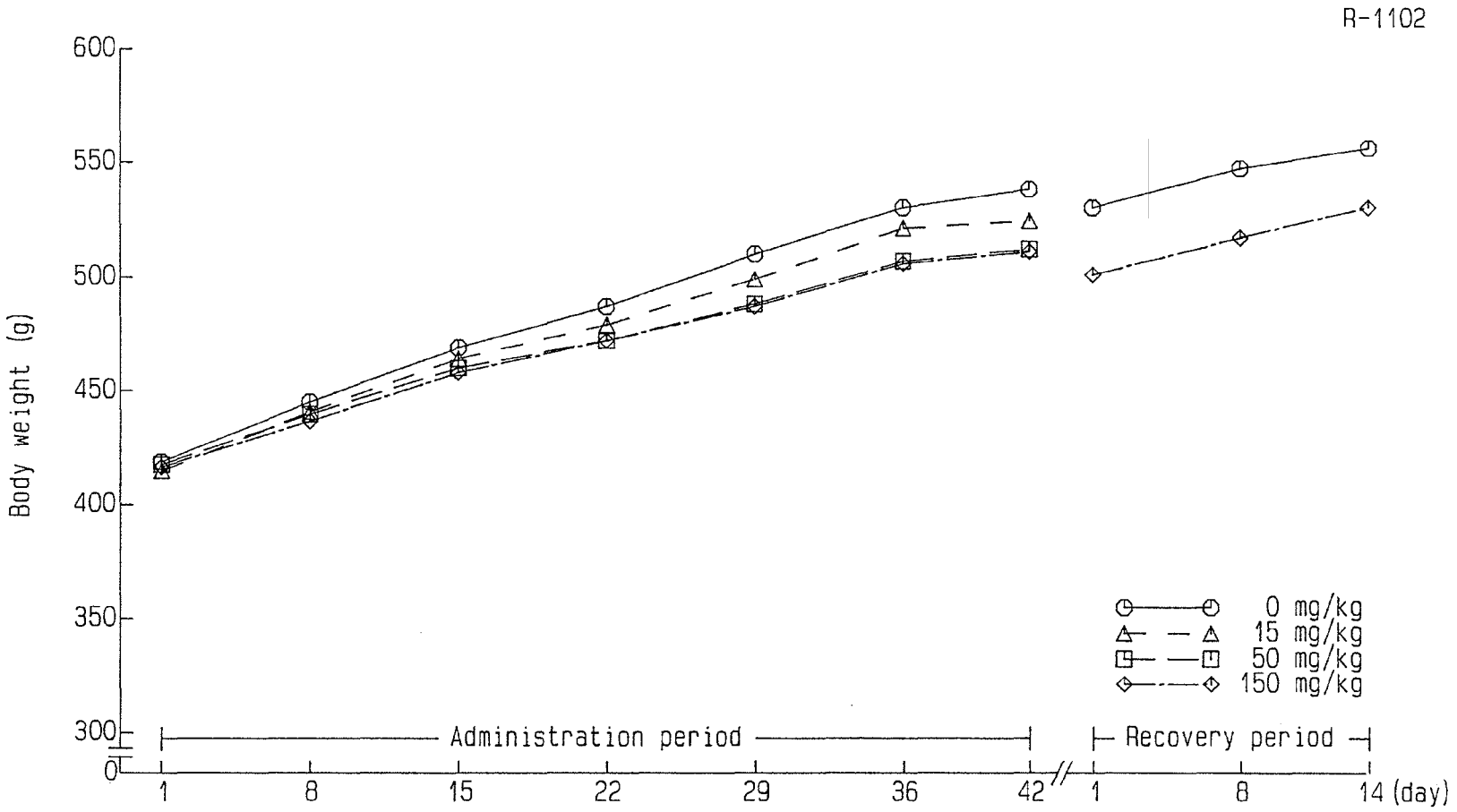


Fig.6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Body weight of male rats

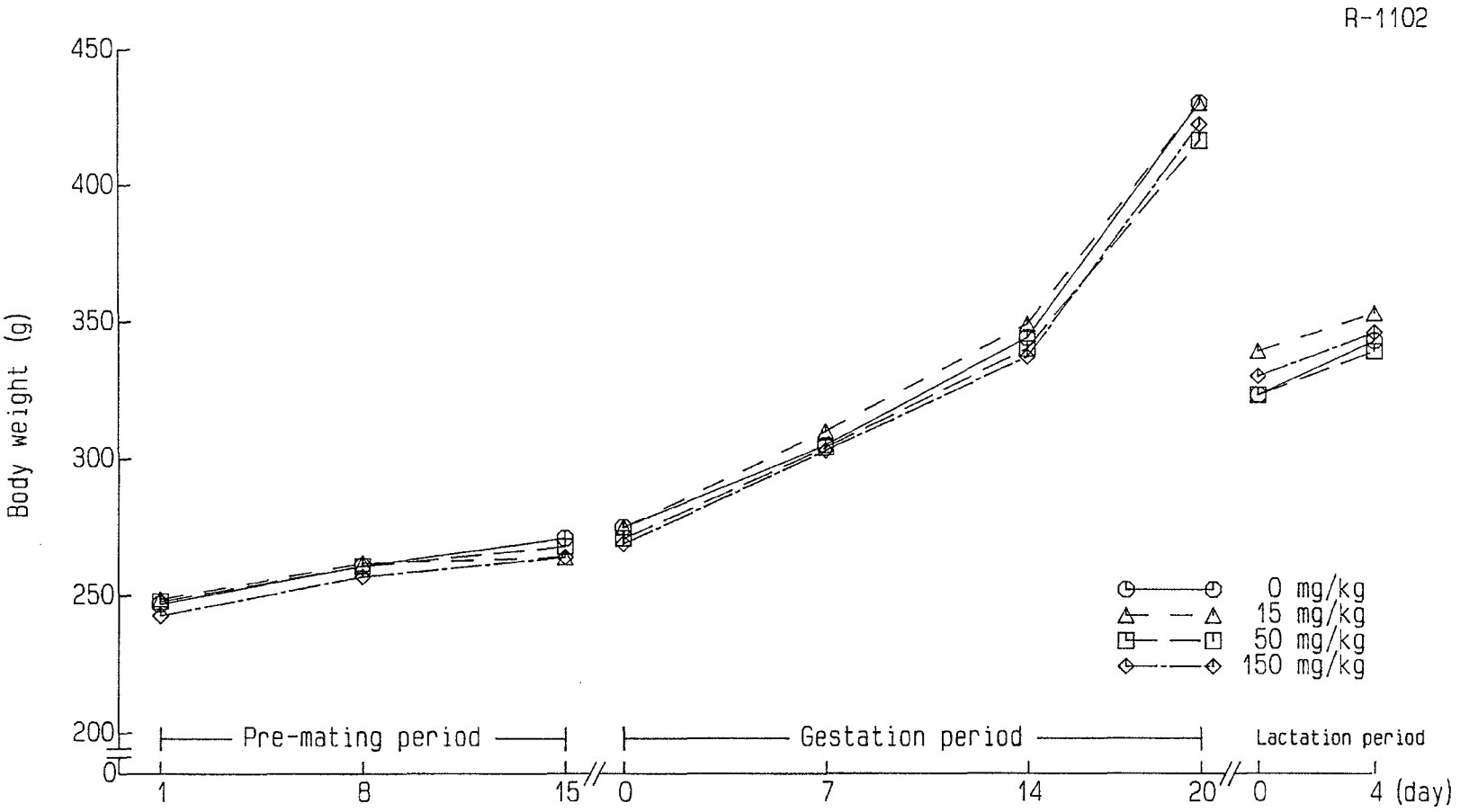


Fig.7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Body weight of female rats (Main group)

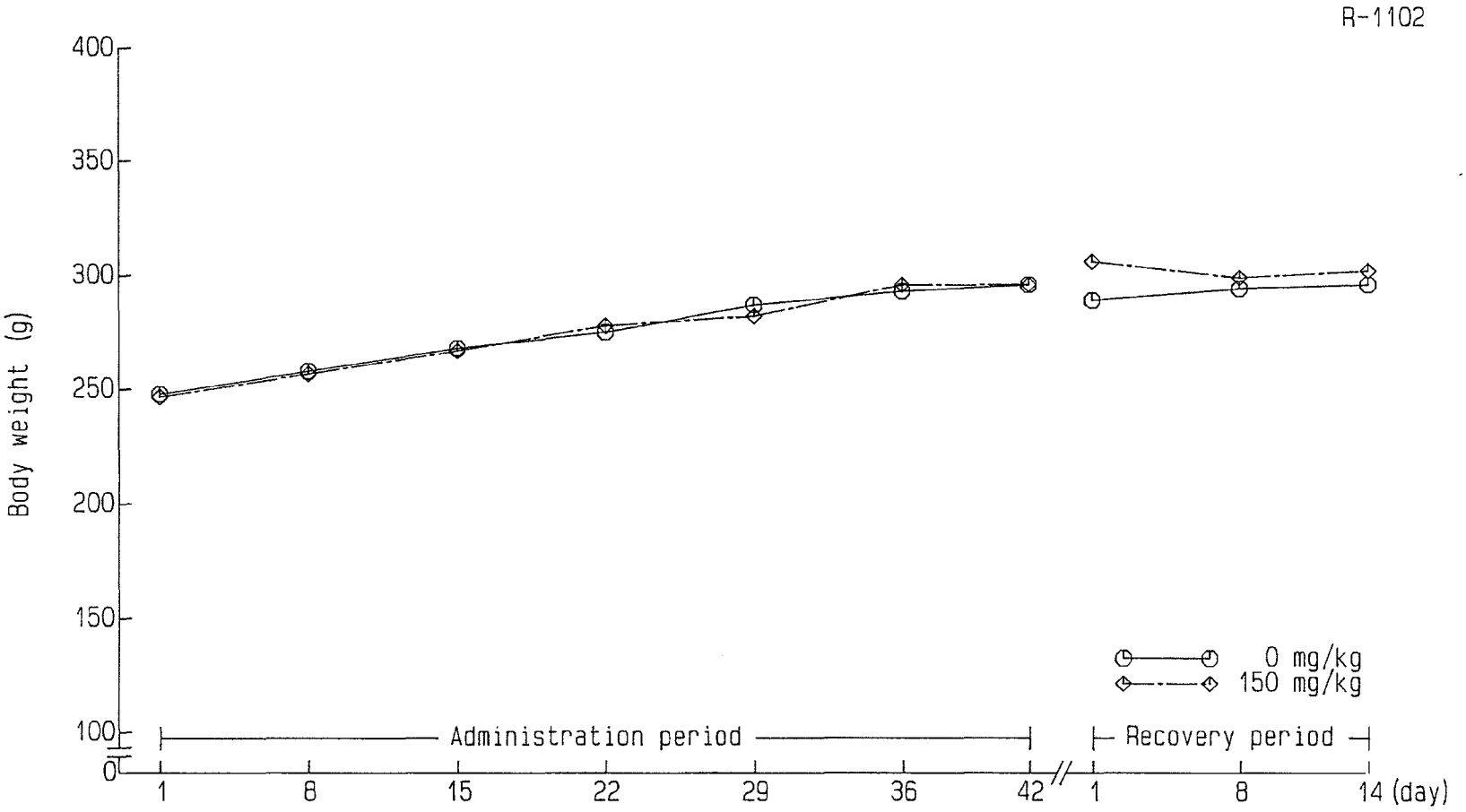


Fig.8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Body weight of female rats (Satellite group)

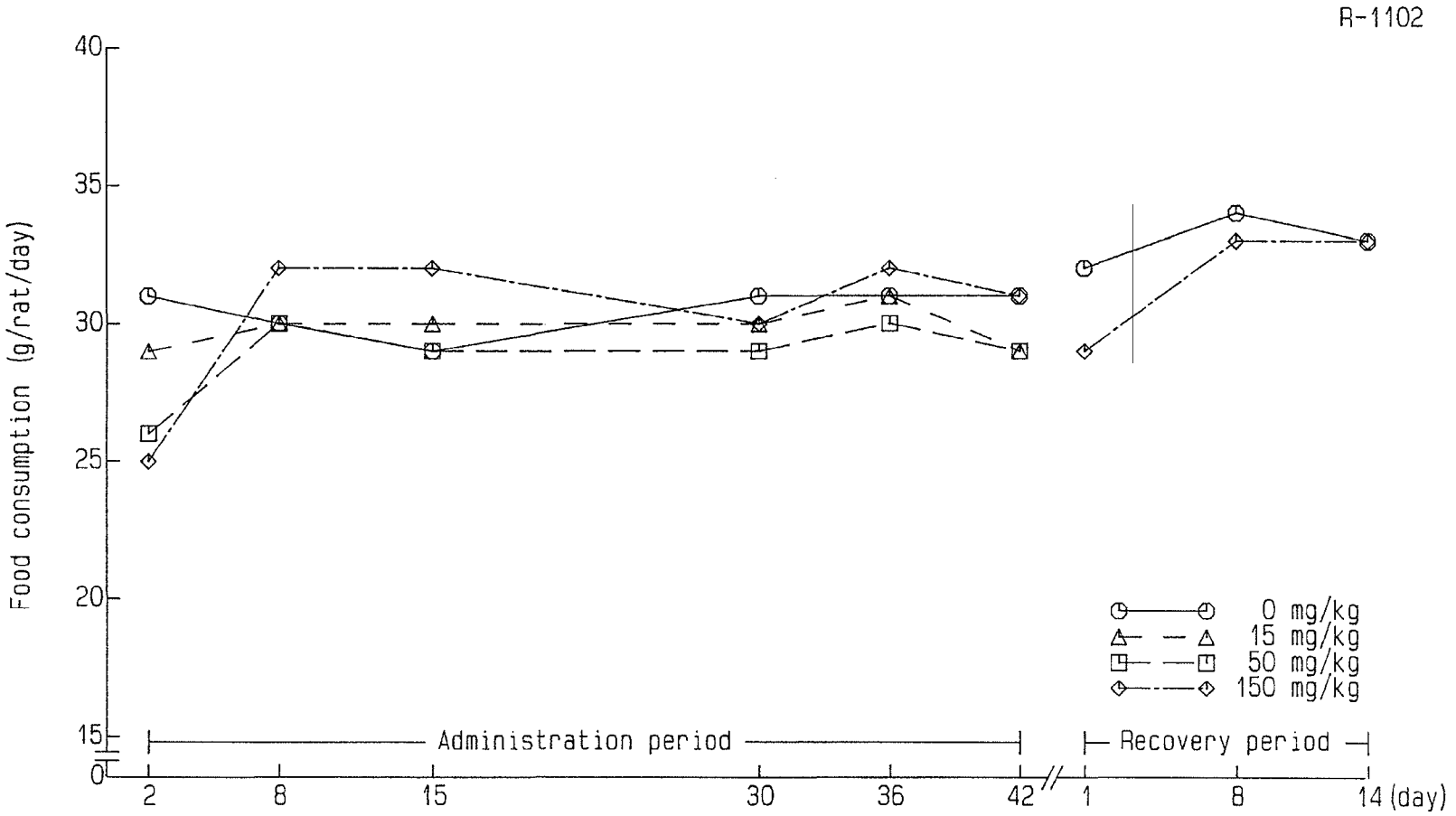


Fig.9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Food consumption of male rats

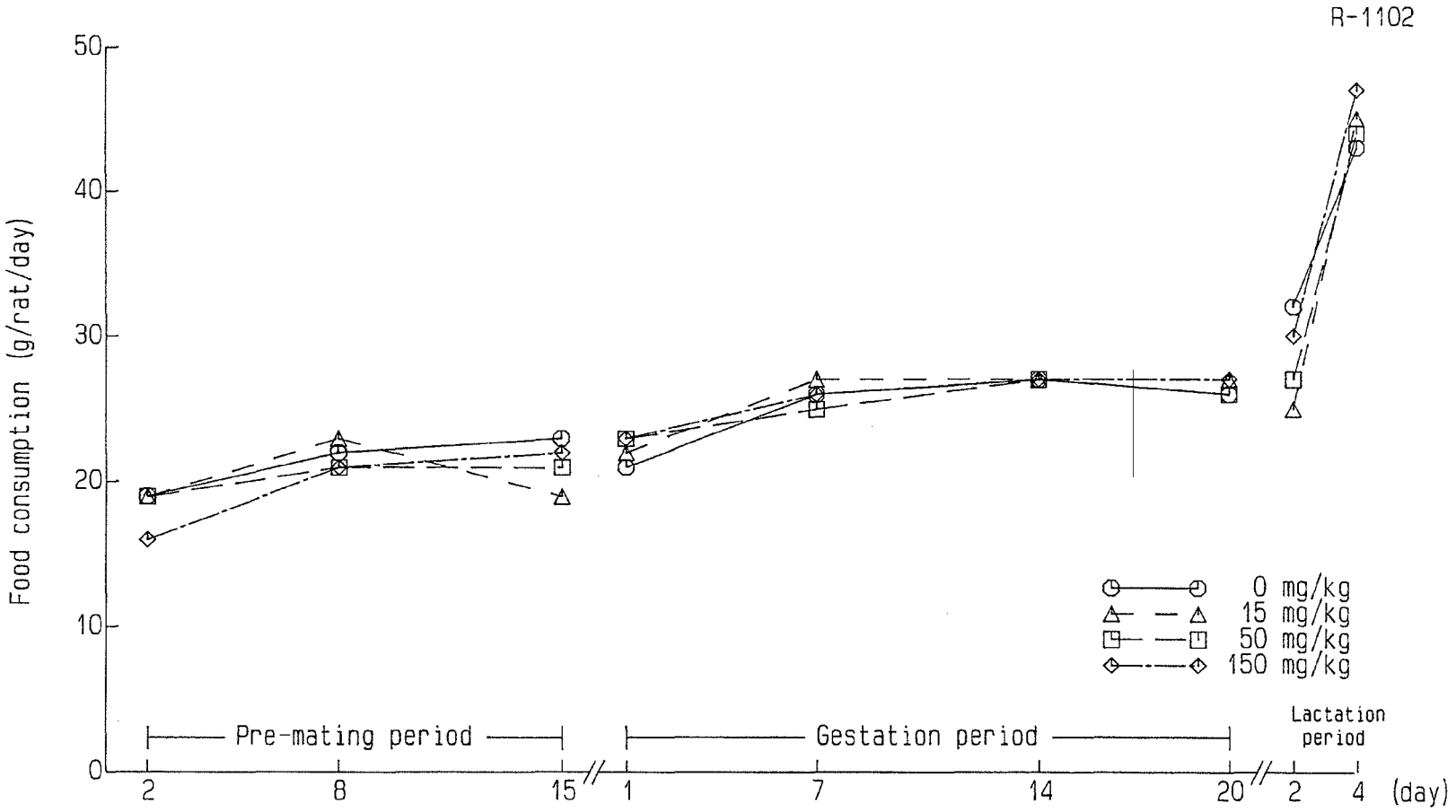


Fig.10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Food consumption of female rats (Main group)

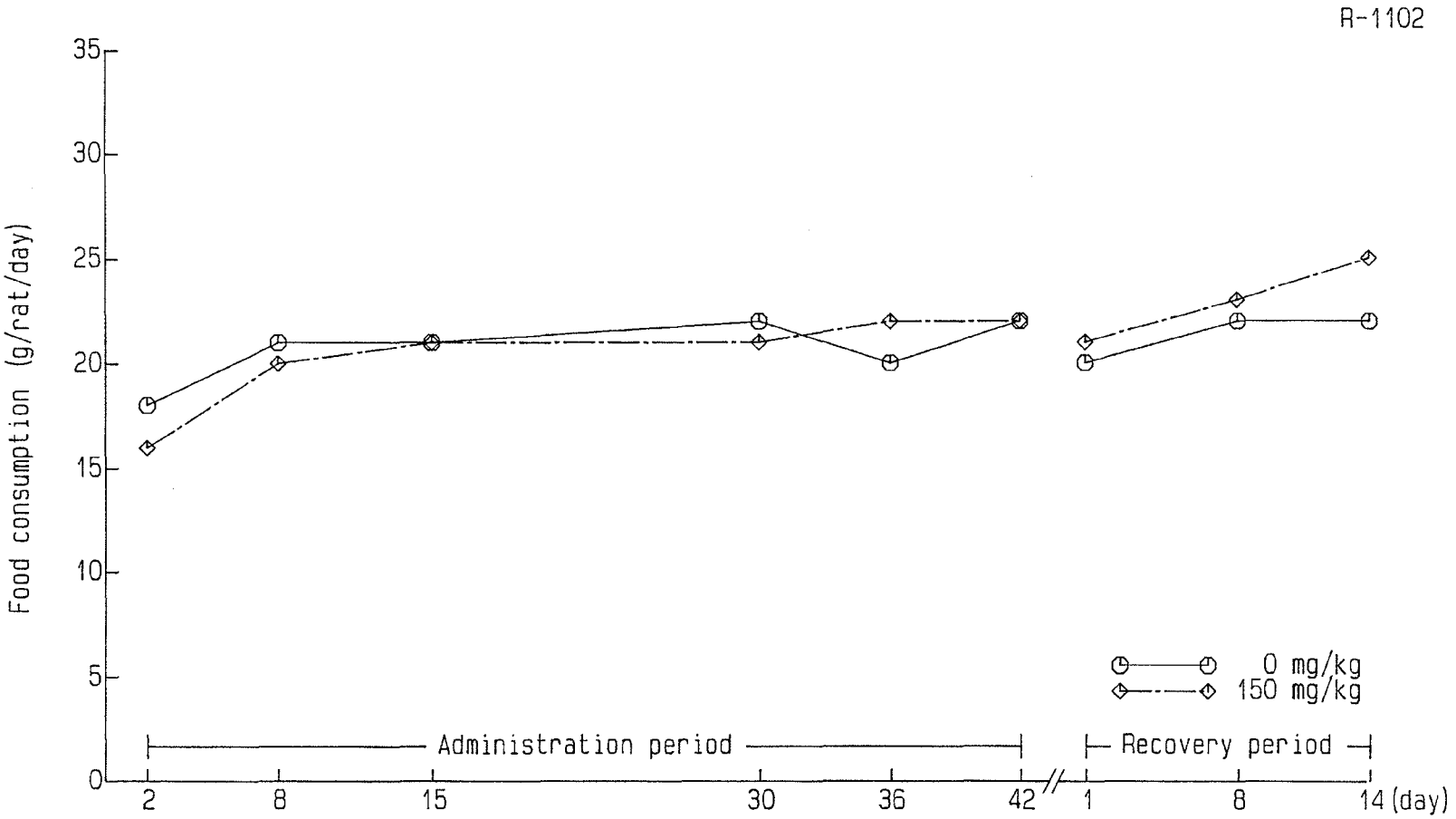


Fig.11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Food consumption of female rats (Satellite group)

Table 1-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in male rats (Administration period)

Dose mg/kg	Signs	Day of administration													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	No. of animals	12	12	12	12	12	10	10	10	10	10	10	10	10	10
	No. of animals with abnormal findings	0	0	0	0	2	1	0	0	0	0	0	0	0	0
	Decrease in spontaneous movement	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	Dyspnea	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	Hypothermia	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	Soft feces	0	0	0	0	0	1	0	0	0	0	0	0	0	0
	Dead	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	Sacrificed moribund	0	0	0	0	1	0	0	0	0	0	0	0	0	0

Table 1-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in male rats (Administration period)

Dose mg/kg	Signs	Day of administration													
		15	16	17	18	19	20	21	22	23	24	25	26	27	28
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in male rats (Administration period)

Dose mg/kg	Signs	Day of administration														
		29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	No. of animals	10	10	10	10	9	9	9	9	9	9	9	9	9	9	5
	No. of animals with abnormal findings	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
	Dyspnea	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	Dead	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0

a): Day of necropsy

Table 1-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in female rats during the pre-mating period (Main group)

Dose mg/kg	Signs	Day of administration														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0
	Decrease in spontaneous movement	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	Dyspnea	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	Swelling of urethral orifice	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0
	Sacrificed moribund	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
15	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	No. of animals	12	12	12	12	12	11	11	11	10	10	10	10	10	10	10
	No. of animals with abnormal findings	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
	Dead	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0

Table 1-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in dams during the gestation period (Main group)

Dose mg/kg	Signs	Administration																						
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
0	No. of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	1	0	
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
15	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	3	0	
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
50	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	0	
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1		
	Continuation of delivery	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1		
150	No. of dams	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9	9	2	0	
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0		
	Dyspnea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0		
	Dead	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0		

a): Gestation day

Table 1-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in dams during the lactation period (Main group)

Dose mg/kg	Signs	Administration 0	1	2	3	4a)	5b)
0	No. of dams	11	11	11	11	11	11
	No. of dams with abnormal findings	0	0	0	0	0	0
15	No. of dams	12	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0	0
50	No. of dams	12	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0	0
150	No. of dams	9	9	9	9	9	9
	No. of dams with abnormal findings	0	0	0	0	0	0

a): Lactation day
b): Day of necropsy

Table 1-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in female rats (Satellite group, Administration period)

Dose mg/kg	Signs	Day of administration													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	9	9
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	1	0	0
	Dead	0	0	0	0	0	0	0	0	0	0	0	1	0	0

Table 1-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in female rats (Satellite group, Administration period)

Dose mg/kg	Signs	Day of administration													
		15	16	17	18	19	20	21	22	23	24	25	26	27	28
0	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	No. of animals	9	9	9	9	9	9	9	9	9	9	9	9	9	9
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in female rats (Satellite group, Administration period)

Dose mg/kg	Signs	Day of administration														
		29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
0	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	No. of animals	9	9	9	9	9	9	9	9	9	9	9	8	8	8	4
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
	Decrease in spontaneous movement	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
	Dyspnea	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
	Hypothermia	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
	Sacrificed moribund	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0

a): Day of necropsy

Table 1-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in male rats (Recovery period)

Dose mg/kg	Signs	Day of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
0	No. of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	No. of animals	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a): Day of necropsy

Table 1-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Clinical signs in female rats (Recovery period)

Dose mg/kg	Signs	Day of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
0	No. of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	No. of animals	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	No. of animals with abnormal findings	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	Dyspnea	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

a): Day of necropsy

Table 2-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 1 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 2 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Posture					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10

Table 2-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 3 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Posture					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10

Table 2-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 4 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Posture					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10

Table 2-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 5 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Posture					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10

Table 2-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 6 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	9
Posture					
Normal		12	12	12	9
Convulsion					
None		12	12	12	9
Abnormal behavior					
None		12	12	12	9

Table 2-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Posture					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10

Table 2-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Gestation day 1)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	10
Posture					
Normal		11	12	12	10
Convulsion					
None		11	12	12	10
Abnormal behavior					
None		11	12	12	10

Table 2-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Gestation day 7)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	10
Posture					
Normal		11	12	12	10
Convulsion					
None		11	12	12	10
Abnormal behavior					
None		11	12	12	10

Table 2-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Gestation day 14)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	10
Posture					
Normal		11	12	12	10
Convulsion					
None		11	12	12	10
Abnormal behavior					
None		11	12	12	10

Table 2-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Gestation day 20)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	9
Posture					
Normal		11	12	12	9
Convulsion					
None		11	12	12	9
Abnormal behavior					
None		11	12	12	9

Table 2-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	9
Posture					
Normal		11	12	12	9
Convulsion					
None		11	12	12	9
Abnormal behavior					
None		11	12	12	9

Table 2-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	10
Posture			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10

Table 2-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	10
Posture			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10

Table 2-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 3 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Posture			
Normal		10	9
Convulsion			
None		10	9
Abnormal behavior			
None		10	9

Table 2-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Posture			
Normal		10	9
Convulsion			
None		10	9
Abnormal behavior			
None		10	9

Table 2-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Posture			
Normal		10	9
Convulsion			
None		10	9
Abnormal behavior			
None		10	9

Table 2-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Posture			
Normal		10	9
Convulsion			
None		10	9
Abnormal behavior			
None		10	9

Table 2-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Posture			
Normal		5	4
Convulsion			
None		5	4
Abnormal behavior			
None		5	4

Table 2-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Posture			
Normal		5	4
Convulsion			
None		5	4
Abnormal behavior			
None		5	4

Table 2-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Posture			
Normal		5	4
Convulsion			
None		5	4
Abnormal behavior			
None		5	4

Table 2-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Posture			
Normal		5	4
Convulsion			
None		5	4
Abnormal behavior			
None		5	4

Table 2-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 1 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		12	12	12	12
Reactivity to handling					
Easy		12	12	12	12

Table 2-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 2 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Ease of removal from cage					
Easy		12	12	12	10
Fur condition					
Normal		12	12	12	10
Skin					
Normal		12	12	12	10
Secretions-Eye, Nose					
Absent		12	12	12	10
Exophthalmos					
Absent		12	12	12	10
Palpebral closure					
Normal		12	12	12	10
Mucosal membranes					
Normal		12	12	12	10
Lacrimation					
Normal		12	12	12	10
Piloerection					
Absent		12	12	12	10
Pupil size					
Normal		12	12	12	10
Salivation					
None		12	12	12	9
Slight		0	0	0	1
Abnormal respiration					
Absent		12	12	12	10
Vocalization					
None		12	11	12	10
Soft		0	1	0	0
Reactivity to handling					
Easy		12	12	12	10

Table 2-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 3 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Ease of removal from cage					
Easy		12	12	12	10
Fur condition					
Normal		12	12	12	10
Skin					
Normal		12	12	12	10
Secretions-Eye, Nose					
Absent		12	12	12	10
Exophthalmos					
Absent		12	12	12	10
Palpebral closure					
Normal		12	12	12	10
Mucosal membranes					
Normal		12	12	12	10
Lacrimation					
Normal		12	12	12	10
Piloerection					
Absent		12	12	12	10
Pupil size					
Normal		12	12	12	10
Salivation					
None		12	12	12	9
Slight		0	0	0	1
Abnormal respiration					
Absent		12	12	12	10
Vocalization					
None		12	12	11	10
Soft		0	0	1	0
Reactivity to handling					
Easy		12	12	12	10

Table 2-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 4 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Ease of removal from cage					
Easy		12	12	12	10
Fur condition					
Normal		12	12	12	10
Skin					
Normal		12	12	12	10
Secretions-Eye, Nose					
Absent		12	12	12	10
Exophthalmos					
Absent		12	12	12	10
Palpebral closure					
Normal		12	12	12	10
Mucosal membranes					
Normal		12	12	12	10
Lacrimation					
Normal		12	12	12	10
Piloerection					
Absent		12	12	12	10
Pupil size					
Normal		12	12	12	10
Salivation					
None		12	12	12	10
Abnormal respiration					
Absent		12	12	12	10
Vocalization					
None		12	12	12	9
Soft		0	0	0	1
Reactivity to handling					
Easy		12	12	12	10

Table 2-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 5 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Ease of removal from cage					
Easy		12	12	12	10
Fur condition					
Normal		12	12	12	10
Skin					
Normal		12	12	12	10
Secretions-Eye, Nose					
Absent		12	12	12	10
Exophthalmos					
Absent		12	12	12	10
Palpebral closure					
Normal		12	12	12	10
Mucosal membranes					
Normal		12	12	12	10
Lacrimation					
Normal		12	12	12	10
Piloerection					
Absent		12	12	12	10
Pupil size					
Normal		12	12	12	10
Salivation					
None		12	12	12	10
Abnormal respiration					
Absent		12	12	12	9
Slight		0	0	0	1a)
Vocalization					
None		12	12	12	10
Reactivity to handling					
Easy		12	12	12	10

a): Dyspnea

Table 2-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 6 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	9
Ease of removal from cage					
Easy		12	12	12	9
Fur condition					
Normal		12	12	12	9
Skin					
Normal		12	12	12	9
Secretions-Eye, Nose					
Absent		12	12	12	9
Exophthalmos					
Absent		12	12	12	9
Palpebral closure					
Normal		12	12	12	9
Mucosal membranes					
Normal		12	12	12	9
Lacrimation					
Normal		12	12	12	9
Piloerection					
Absent		12	12	12	9
Pupil size					
Normal		12	12	12	9
Salivation					
None		12	12	12	9
Abnormal respiration					
Absent		12	12	12	9
Vocalization					
None		12	12	11	9
Soft		0	0	1	0
Reactivity to handling					
Easy		12	12	12	9

Table 2-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		11	11	12	10
Soft		1	1	0	2
Reactivity to handling					
Easy		12	12	12	12

Table 2-31 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Ease of removal from cage					
Easy		12	12	12	10
Fur condition					
Normal		12	12	12	10
Skin					
Normal		12	12	12	10
Secretions-Eye, Nose					
Absent		12	12	12	10
Exophthalmos					
Absent		12	12	12	10
Palpebral closure					
Normal		12	12	12	10
Mucosal membranes					
Normal		12	12	12	10
Lacrimation					
Normal		12	12	12	10
Piloerection					
Absent		12	12	12	10
Pupil size					
Normal		12	12	12	10
Salivation					
None		12	12	12	10
Abnormal respiration					
Absent		12	12	12	10
Vocalization					
None		12	12	12	10
Reactivity to handling					
Easy		12	12	12	10

Table 2-32 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Gestation day 1)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	10
Ease of removal from cage					
Easy		11	12	12	10
Fur condition					
Normal		11	12	12	10
Skin					
Normal		11	12	12	10
Secretions-Eye, Nose					
Absent		11	12	12	10
Exophthalmos					
Absent		11	12	12	10
Palpebral closure					
Normal		11	12	12	10
Mucosal membranes					
Normal		11	12	12	10
Lacrimation					
Normal		11	12	12	10
Piloerection					
Absent		11	12	12	10
Pupil size					
Normal		11	12	12	10
Salivation					
None		11	12	12	10
Abnormal respiration					
Absent		11	12	12	10
Vocalization					
None		11	12	12	10
Reactivity to handling					
Easy		11	12	12	10

Table 2-33 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Gestation day 7)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	10
Ease of removal from cage					
Easy		11	12	12	10
Fur condition					
Normal		11	12	12	10
Skin					
Normal		11	12	12	10
Secretions-Eye, Nose					
Absent		11	12	12	10
Exophthalmos					
Absent		11	12	12	10
Palpebral closure					
Normal		11	12	12	10
Mucosal membranes					
Normal		11	12	12	10
Lacrimation					
Normal		11	12	12	10
Piloerection					
Absent		11	12	12	10
Pupil size					
Normal		11	12	12	10
Salivation					
None		11	12	12	10
Abnormal respiration					
Absent		11	12	12	10
Vocalization					
None		11	12	12	10
Reactivity to handling					
Easy		11	12	12	10

Table 2-34 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Gestation day 14)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	10
Ease of removal from cage					
Easy		11	12	12	10
Fur condition					
Normal		11	12	12	10
Skin					
Normal		11	12	12	10
Secretions-Eye, Nose					
Absent		11	12	12	10
Exophthalmos					
Absent		11	12	12	10
Palpebral closure					
Normal		11	12	12	10
Mucosal membranes					
Normal		11	12	12	10
Lacrimation					
Normal		11	12	12	10
Piloerection					
Absent		11	12	12	10
Pupil size					
Normal		11	12	12	10
Salivation					
None		11	12	12	9
Slight		0	0	0	1
Abnormal respiration					
Absent		11	12	12	9
Moderate		0	0	0	1a)
Vocalization					
None		11	12	12	10
Reactivity to handling					
Easy		11	12	12	10

a): Dyspnea

Table 2-35 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Gestation day 20)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	9
Ease of removal from cage					
Easy		11	12	12	9
Fur condition					
Normal		11	12	12	9
Skin					
Normal		11	12	12	9
Secretions-Eye, Nose					
Absent		11	12	12	9
Exophthalmos					
Absent		11	12	12	9
Palpebral closure					
Normal		11	12	12	9
Mucosal membranes					
Normal		11	12	12	9
Lacrimation					
Normal		11	12	12	9
Piloerection					
Absent		11	12	12	9
Pupil size					
Normal		11	12	12	9
Salivation					
None		11	12	12	6
Slight		0	0	0	3
Abnormal respiration					
Absent		11	12	12	9
Vocalization					
None		11	12	12	9
Reactivity to handling					
Easy		11	12	12	9

Table 2-36 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	9
Ease of removal from cage					
Easy		11	12	12	9
Fur condition					
Normal		11	12	12	9
Skin					
Normal		11	12	12	9
Secretions-Eye, Nose					
Absent		11	12	12	9
Exophthalmos					
Absent		11	12	12	9
Palpebral closure					
Normal		11	12	12	9
Mucosal membranes					
Normal		11	12	12	9
Lacrimation					
Normal		11	12	12	9
Piloerection					
Absent		11	12	12	9
Pupil size					
Normal		11	12	12	9
Salivation					
None		11	12	12	9
Abnormal respiration					
Absent		11	12	12	9
Vocalization					
None		11	12	12	9
Reactivity to handling					
Easy		11	12	12	9

Table 2-37 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	10
Ease of removal from cage			
Easy		10	10
Fur condition			
Normal		10	10
Skin			
Normal		10	10
Secretions-Eye, Nose			
Absent		10	10
Exophthalmos			
Absent		10	10
Palpebral closure			
Normal		10	10
Mucosal membranes			
Normal		10	10
Lacrimation			
Normal		10	10
Piloerection			
Absent		10	10
Pupil size			
Normal		10	10
Salivation			
None		10	10
Abnormal respiration			
Absent		10	10
Vocalization			
None		9	10
Soft		1	0
Reactivity to handling			
Easy		10	10

Table 2-38 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	10
Ease of removal from cage			
Easy		10	10
Fur condition			
Normal		10	10
Skin			
Normal		10	10
Secretions-Eye, Nose			
Absent		10	10
Exophthalmos			
Absent		10	10
Palpebral closure			
Normal		10	10
Mucosal membranes			
Normal		10	10
Lacrimation			
Normal		10	10
Piloerection			
Absent		10	10
Pupil size			
Normal		10	10
Salivation			
None		10	10
Abnormal respiration			
Absent		10	10
Vocalization			
None		10	10
Reactivity to handling			
Easy		10	10

Table 2-39 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 3 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Ease of removal from cage			
Easy		10	9
Fur condition			
Normal		10	9
Skin			
Normal		10	9
Secretions-Eye, Nose			
Absent		10	9
Exophthalmos			
Absent		10	9
Palpebral closure			
Normal		10	9
Mucosal membranes			
Normal		10	9
Lacrimation			
Normal		10	9
Piloerection			
Absent		10	9
Pupil size			
Normal		10	9
Salivation			
None		10	9
Abnormal respiration			
Absent		10	9
Vocalization			
None		10	9
Reactivity to handling			
Easy		10	9

Table 2-40 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Ease of removal from cage			
Easy		10	9
Fur condition			
Normal		10	9
Skin			
Normal		10	9
Secretions-Eye, Nose			
Absent		10	9
Exophthalmos			
Absent		10	9
Palpebral closure			
Normal		10	9
Mucosal membranes			
Normal		10	9
Lacrimation			
Normal		10	9
Piloerection			
Absent		10	9
Pupil size			
Normal		10	9
Salivation			
None		10	9
Abnormal respiration			
Absent		10	9
Vocalization			
None		10	8
Soft		0	1
Reactivity to handling			
Easy		10	8
Slightly awkward		0	1

Table 2-41 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Ease of removal from cage			
Easy		10	9
Fur condition			
Normal		10	9
Skin			
Normal		10	9
Secretions-Eye, Nose			
Absent		10	9
Exophthalmos			
Absent		10	9
Palpebral closure			
Normal		10	9
Mucosal membranes			
Normal		10	9
Lacrimation			
Normal		10	9
Piloerection			
Absent		10	9
Pupil size			
Normal		10	9
Salivation			
None		10	9
Abnormal respiration			
Absent		10	9
Vocalization			
None		10	9
Reactivity to handling			
Easy		10	9

Table 2-42 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Ease of removal from cage			
Easy		10	9
Fur condition			
Normal		10	9
Skin			
Normal		10	9
Secretions-Eye, Nose			
Absent		10	9
Exophthalmos			
Absent		10	9
Palpebral closure			
Normal		10	9
Mucosal membranes			
Normal		10	9
Lacrimation			
Normal		10	9
Piloerection			
Absent		10	9
Pupil size			
Normal		10	9
Salivation			
None		10	9
Abnormal respiration			
Absent		10	8
Moderate		0	1a)
Vocalization			
None		10	9
Reactivity to handling			
Easy		10	9

a): Dyspnea

Table 2-43 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Ease of removal from cage			
Easy		5	4
Fur condition			
Normal		5	4
Skin			
Normal		5	4
Secretions-Eye, Nose			
Absent		5	4
Exophthalmos			
Absent		5	4
Palpebral closure			
Normal		5	4
Mucosal membranes			
Normal		5	4
Lacrimation			
Normal		5	4
Piloerection			
Absent		5	4
Pupil size			
Normal		5	4
Salivation			
None		5	4
Abnormal respiration			
Absent		5	4
Vocalization			
None		5	4
Reactivity to handling			
Easy		5	4

Table 2-44 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Ease of removal from cage			
Easy		5	4
Fur condition			
Normal		5	4
Skin			
Normal		5	4
Secretions-Eye, Nose			
Absent		5	4
Exophthalmos			
Absent		5	4
Palpebral closure			
Normal		5	4
Mucosal membranes			
Normal		5	4
Lacrimation			
Normal		5	4
Piloerection			
Absent		5	4
Pupil size			
Normal		5	4
Salivation			
None		5	4
Abnormal respiration			
Absent		5	4
Vocalization			
None		5	3
Soft		0	1
Reactivity to handling			
Easy		5	3
Slightly awkward		0	1

Table 2-45 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Ease of removal from cage			
Easy		5	4
Fur condition			
Normal		5	4
Skin			
Normal		5	4
Secretions-Eye, Nose			
Absent		5	4
Exophthalmos			
Absent		5	4
Palpebral closure			
Normal		5	4
Mucosal membranes			
Normal		5	4
Lacrimation			
Normal		5	4
Piloerection			
Absent		5	4
Pupil size			
Normal		5	4
Salivation			
None		5	4
Abnormal respiration			
Absent		5	3
Slight		0	1a)
Vocalization			
None		5	4
Reactivity to handling			
Easy		5	4

a): Dyspnea

Table 2-46 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Ease of removal from cage			
Easy		5	4
Fur condition			
Normal		5	4
Skin			
Normal		5	4
Secretions-Eye, Nose			
Absent		5	4
Exophthalmos			
Absent		5	4
Palpebral closure			
Normal		5	4
Mucosal membranes			
Normal		5	4
Lacrimation			
Normal		5	4
Piloerection			
Absent		5	4
Pupil size			
Normal		5	4
Salivation			
None		5	4
Abnormal respiration			
Absent		5	4
Vocalization			
None		5	4
Reactivity to handling			
Easy		5	4

Table 2-47 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 1 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
No/minimal location		0	0	0	1
Normal		12	12	12	11
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		5± 2	4± 1	4± 2	3± 2*D
Defecation count (Mean±S.D.)		0± 1	0± 1	0± 1	0± 1
Urination					
None		10	9	11	11
Small amount		2	3	1	0
Moderate amount		0	0	0	1

*: p<0.05 (Significant difference from control group)
D: Dunnett's test

Table 2-48 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 2 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Arousal					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10
Stereotypy					
None		12	12	12	10
Gait					
Normal		12	12	12	10
Posture					
Normal		12	12	12	10
Grooming					
None		12	12	12	10
Rearing (Mean±S.D.)		4± 2	5± 2	4± 2	3± 2
Defecation count (Mean±S.D.)		1± 1	0± 0	0± 0	0± 0
Urination					
None		10	10	9	10
Small amount		2	2	2	0
Moderate amount		0	0	1	0

No significant difference in any treated groups from control group.

Table 2-49 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 3 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Arousal					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10
Stereotypy					
None		12	12	12	10
Gait					
Normal		12	12	12	10
Posture					
Normal		12	12	12	10
Grooming					
None		12	12	12	10
Rearing (Mean±S.D.)		5± 3	4± 2	3± 2	4± 2
Defecation count (Mean±S.D.)		0± 1	0± 1	0± 0	0± 0
Urination					
None		8	10	11	8
Small amount		4	2	1	2

No significant difference in any treated groups from control group.

Table 2-50 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 4 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Arousal					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10
Stereotypy					
None		12	12	12	10
Gait					
Normal		12	12	12	10
Posture					
Normal		12	12	12	10
Grooming					
None		12	12	12	10
Rearing (Mean±S.D.)		4± 1	4± 1	3± 2	3± 2
Defecation count (Mean±S.D.)		0± 0	0± 1	0± 1	0± 0
Urination					
None		11	10	7	10
Small amount		0	1	5	0
Moderate amount		1	1	0	0

No significant difference in any treated groups from control group.

Table 2-51 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 5 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Arousal					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10
Stereotypy					
None		12	12	12	10
Gait					
Normal		12	12	12	10
Posture					
Normal		12	12	12	10
Grooming					
None		12	12	12	10
Rearing (Mean±S.D.)		4± 2	4± 2	3± 2	3± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		9	8	8	8
Small amount		3	4	4	2

No significant difference in any treated groups from control group.

Table 2-52 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 6 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	9
Arousal					
Normal		12	12	12	9
Convulsion					
None		12	12	12	9
Abnormal behavior					
None		12	12	12	9
Stereotypy					
None		12	12	12	9
Gait					
Normal		12	12	12	9
Posture					
Normal		12	12	12	9
Grooming					
None		12	12	12	9
Rearing (Mean±S.D.)		4± 2	5± 3	3± 2	3± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		9	10	10	9
Small amount		3	2	2	0

No significant difference in any treated groups from control group.

Table 2-53 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	11	12
Occasional bouts (up to four)		0	0	1	0
Rearing (Mean±S.D.)		7± 2	6± 2	6± 3	6± 3
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	12	11	12
Small amount		1	0	1	0

No significant difference in any treated groups from control group.

Table 2-54 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	12	12	12	10
Arousal					
Normal		12	12	12	10
Convulsion					
None		12	12	12	10
Abnormal behavior					
None		12	12	12	10
Stereotypy					
None		12	12	12	10
Gait					
Normal		12	12	12	10
Posture					
Normal		12	12	12	10
Grooming					
None		12	12	12	10
Rearing (Mean±S.D.)		7± 2	7± 2	6± 2	6± 3
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	12	12	10

No significant difference in any treated groups from control group.

Table 2-55 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 1)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	10
Arousal					
Normal		11	12	12	10
Convulsion					
None		11	12	12	10
Abnormal behavior					
None		11	12	12	10
Stereotypy					
None		11	12	12	10
Gait					
Normal		11	12	12	10
Posture					
Normal		11	12	12	10
Grooming					
None		11	12	12	10
Rearing (Mean±S.D.)		7± 3	5± 3	4± 2	5± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	11	12	10
Small amount		0	1	0	0

No significant difference in any treated groups from control group.

Table 2-56 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 7)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	10
Arousal					
Normal		11	12	12	10
Convulsion					
None		11	12	12	10
Abnormal behavior					
None		11	12	12	10
Stereotypy					
None		11	12	12	10
Gait					
Normal		11	12	12	10
Posture					
Normal		11	12	12	10
Grooming					
None		11	12	12	10
Rearing (Mean±S.D.)		6± 2	6± 2	6± 2	6± 1
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	12	12	10

No significant difference in any treated groups from control group.

Table 2-57 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 14)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	10
Arousal					
Normal		11	12	12	10
Convulsion					
None		11	12	12	10
Abnormal behavior					
None		11	12	12	10
Stereotypy					
None		11	12	12	10
Gait					
Normal		11	12	12	10
Posture					
Normal		11	12	12	10
Grooming					
None		11	12	12	10
Rearing (Mean±S.D.)		5± 1	5± 1	6± 2	4± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	12	11	9
Small amount		0	0	1	1

No significant difference in any treated groups from control group.

Table 2-58 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 20)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	9
Arousal					
Normal		11	12	12	9
Convulsion					
None		11	12	12	9
Abnormal behavior					
None		11	12	12	9
Stereotypy					
None		11	12	12	9
Gait					
Normal		11	12	12	9
Posture					
Normal		11	12	12	9
Grooming					
None		11	12	12	9
Rearing (Mean±S.D.)		5± 1	5± 2	5± 2	5± 1
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	12	12	8
Small amount		0	0	0	1

No significant difference in any treated groups from control group.

Table 2-59 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	11	12	12	9
Arousal					
Normal		11	12	12	9
Convulsion					
None		11	12	12	9
Abnormal behavior					
None		11	12	12	9
Stereotypy					
None		11	12	12	9
Gait					
Normal		11	12	12	9
Posture					
Normal		11	12	12	9
Grooming					
None		11	12	12	9
Rearing (Mean±S.D.)		7± 2	7± 2	7± 2	7± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	11	11	8
Small amount		0	1	1	1

No significant difference in any treated groups from control group.

Table 2-60 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	10
Arousal			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10
Stereotypy			
None		10	10
Gait			
Normal		10	10
Posture			
Normal		10	10
Grooming			
None		10	10
Rearing (Mean±S.D.)		7± 1	6± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	10

No significant difference between treated group and control group.

Table 2-61 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	10
Arousal			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10
Stereotypy			
None		10	10
Gait			
Normal		10	10
Posture			
Normal		10	10
Grooming			
None		10	10
Rearing (Mean±S.D.)		7± 2	6± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		9	10
Small amount		1	0

No significant difference between treated group and control group.

Table 2-62 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 3 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Arousal			
Normal		10	9
Convulsion			
None		10	9
Abnormal behavior			
None		10	9
Stereotypy			
None		10	9
Gait			
Normal		10	9
Posture			
Normal		10	9
Grooming			
None		10	9
Rearing (Mean±S.D.)		9± 2	9± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	9

No significant difference between treated group and control group.

Table 2-63 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Arousal			
Normal		10	9
Convulsion			
None		10	9
Abnormal behavior			
None		10	9
Stereotypy			
None		10	9
Gait			
Normal		10	9
Posture			
Normal		10	9
Grooming			
None		10	9
Rearing (Mean±S.D.)		8± 2	8± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	9

No significant difference between treated group and control group.

Table 2-64 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Arousal			
Normal		10	9
Convulsion			
None		10	9
Abnormal behavior			
None		10	9
Stereotypy			
None		10	9
Gait			
Normal		10	9
Posture			
Normal		10	9
Grooming			
None		10	9
Rearing (Mean±S.D.)		8± 2	8± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	9

No significant difference between treated group and control group.

Table 2-65 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	10	9
Arousal			
Normal		10	9
Convulsion			
None		10	9
Abnormal behavior			
None		10	9
Stereotypy			
None		10	9
Gait			
Normal		10	9
Posture			
Normal		10	9
Grooming			
None		10	9
Rearing (Mean±S.D.)		9± 2	7± 3
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	9

No significant difference between treated group and control group.

Table 2-66 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Arousal			
Normal		5	4
Convulsion			
None		5	4
Abnormal behavior			
None		5	4
Stereotypy			
None		5	4
Gait			
Normal		5	4
Posture			
Normal		5	4
Grooming			
None		5	4
Rearing (Mean±S.D.)		5± 2	3± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		3	4
Small amount		2	0

No significant difference between treated group and control group.

Table 2-67 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Arousal			
Normal		5	4
Convulsion			
None		5	4
Abnormal behavior			
None		5	4
Stereotypy			
None		5	4
Gait			
Normal		5	4
Posture			
Normal		5	4
Grooming			
None		5	4
Rearing (Mean±S.D.)		5± 2	4± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		4	3
Small amount		1	1

No significant difference between treated group and control group.

Table 2-68 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Arousal			
Normal		5	4
Convulsion			
None		5	4
Abnormal behavior			
None		5	4
Stereotypy			
None		5	4
Gait			
Normal		5	4
Posture			
Normal		5	4
Grooming			
None		5	4
Rearing (Mean±S.D.)		8± 4	9± 1
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		5	4

No significant difference between treated group and control group.

Table 2-69 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Detailed clinical signs in female rats: open field observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Arousal			
Normal		5	4
Convulsion			
None		5	4
Abnormal behavior			
None		5	4
Stereotypy			
None		5	4
Gait			
Normal		5	4
Posture			
Normal		5	4
Grooming			
None		5	4
Rearing (Mean±S.D.)		10± 2	9± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		5	4

No significant difference between treated group and control group.

Table 2-70 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Manipulative test of male rats (Week 6 of administration)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	5	5	5	4
Auditory response					
Normal		5	5	5	4
Approach response					
Normal		5	5	5	4
Touch response					
Normal		5	5	5	4
Tail pinch response					
Normal		5	5	5	4
Pupillary reflex					
Pass, both		5	5	5	4
Aerial righting reflex					
(Total score: Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		64±27	62±18	68±28	64±15

No significant difference in any treated groups from control group.

Table 2-71 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Manipulative test of female rats (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	15	50	150
	No. of animals	5	5	5	5
Auditory response					
Normal		5	5	5	5
Approach response					
Normal		5	5	5	5
Touch response					
Normal		5	5	5	5
Tail pinch response					
Normal		5	5	5	5
Pupillary reflex					
Pass, both		5	5	5	5
Aerial righting reflex					
(Total score: Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		60±11	56±15	79±26	68±14

No significant difference in any treated groups from control group.

Table 2-72 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Manipulative test of female rats (Satellite group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Auditory response			
Normal		5	4
Approach response			
Normal		5	4
Touch response			
Normal		5	4
Tail pinch response			
Normal		5	4
Pupillary reflex			
Pass, both		5	4
Aerial righting reflex			
(Total score: Mean±S.D.)		0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		54±15	51±19

No significant difference between treated group and control group.

Table 2-73 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Manipulative test of male rats (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Auditory response			
Normal		5	4
Approach response			
Normal		5	4
Touch response			
Normal		5	4
Tail pinch response			
Normal		5	4
Pupillary reflex			
Pass, both		5	4
Aerial righting reflex			
(Total score: Mean±S.D.)		0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		60± 7	66±15

No significant difference between treated group and control group.

Table 2-74 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Manipulative test of female rats (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	150
	No. of animals	5	4
Auditory response			
Normal		5	4
Approach response			
Normal		5	4
Touch response			
Normal		5	4
Tail pinch response			
Normal		5	4
Pupillary reflex			
Pass, both		5	4
Aerial righting reflex			
(Total score: Mean±S.D.)		0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		54±16	49±16

No significant difference between treated group and control group.

Table 2-75 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Grip strength of male rats (Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1193	681
	S.D.	158	111
15	No.	5	5
	Mean	1214	733
	S.D.	383	175
50	No.	5	5
	Mean	1536	752
	S.D.	139	80
150	No.	4	4
	Mean	1488	724
	S.D.	81	136

No.: No. of animals
No significant difference in any treated groups from control group.

Table 2-76 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Grip strength of female rats (Main group, Lactation day 4)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1156	664
	S.D.	79	137
15	No.	5	5
	Mean	1188	661
	S.D.	161	141
50	No.	5	5
	Mean	1319	677
	S.D.	66	122
150	No.	5	5
	Mean	1189	687
	S.D.	112	97

No.: No. of animals
No significant difference in any treated groups from control group.

Table 2-77 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Grip strength of female rats (Satellite group, Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1305	683
	S.D.	154	56
150	No.	4	4
	Mean	1077	613
	S.D.	150	75

No.: No. of animals
No significant difference between treated group and control group.

Table 2-78 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Grip strength of male rats (Week 2 of recovery)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1320	767
	S.D.	107	97
150	No.	4	4
	Mean	1452	827
	S.D.	137	228

No.: No. of animals
No significant difference between treated group and control group.

Table 2-79 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Grip strength of female rats (Week 2 of recovery)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1157	664
	S.D.	91	92
150	No.	4	4
	Mean	1051	725
	S.D.	218	81

No.: No. of animals
No significant difference between treated group and control group.

Table 2-80 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Motor activity of male rats (Week 6 of administration)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	391	348	253	135	96	36	1259
	S.D.	48	95	147	110	100	55	415
15	No.	5	5	5	5	5	5	5
	Mean	353	190	134	79	90	14	861
	S.D.	70	129	98	81	121	4	272
50	No.	5	5	5	5	5	5	5
	Mean	389	299	220	140	57	9	1113
	S.D.	44	141	123	110	60	7	405
150	No.	4	4	4	4	4	4	4
	Mean	383	322	172	74	110	10	1070
	S.D.	53	56	161	107	68	5	247

Unit: Count
No.: No. of animals
No significant difference in any treated groups from control group.

Table 2-81 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Motor activity of female rats (Main group, Lactation day 4)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	328	202	111	82	156	159	1037
	S.D.	56	54	79	65	114	133	339
15	No.	5	5	5	5	5	5	5
	Mean	402	253	97	112	72	90	1027
	S.D.	51	92	93	97	114	101	430
50	No.	5	5	5	5	5	5	5
	Mean	344	143	72	58	100	59	776
	S.D.	112	124	115	96	138	101	540
150	No.	5	5	5	5	5	5	5
	Mean	268	157	72	52	56	71	676
	S.D.	62	124	97	77	55	85	310

Unit: Count
No.: No. of animals
No significant difference in any treated groups from control group.

Table 2-82 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Motor activity of female rats (Satellite group, Week 6 of administration)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	400	347	276	210	75	97	1405
	S.D.	19	33	39	111	82	127	229
150	No.	4	4	4	4	4	4	4
	Mean	428	357	324	281	98	57	1544
	S.D.	54	109	54	127	107	96	413

Unit: Count
No.: No. of animals
No significant difference between treated group and control group.

Table 2-83 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Motor activity of male rats (Week 2 of recovery)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	356	379	316	216	153	92	1513
	S.D.	50	38	39	138	144	83	322
150	No.	4	4	4	4	4	4	4
	Mean	358	317	118*	127	121	84	1125
	S.D.	70	44	110AT	137	118	116	391

Unit: Count
No.: No. of animals
*: p<0.05 (Significant difference from control group)
AT: Aspin-Welch t-test

Table 2-84 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Motor activity of female rats (Week 2 of recovery)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	343	331	191	169	107	107	1248
	S.D.	21	96	106	122	74	153	175
150	No.	4	4	4	4	4	4	4
	Mean	316	214	204	189	204	175	1302
	S.D.	80	161	137	158	175	89	764

Unit: Count
No.: No. of animals
No significant difference between treated group and control group.

Table 3-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Body weight of male rats (Administration period)

Dose mg/kg		Day of administration 1	8	15	22	29	36	42	Gain 1-42
0	No.	12	12	12	12	12	12	12	12
	Mean	419	445	469	487	510	530	538	119
	S.D.	16	16	17	17	18	17	22	13
15	No.	12	12	12	12	12	12	12	12
	Mean	415	441	464	479	499	521	524	109
	S.D.	14	19	21	23	24	25	27	20
50	No.	12	12	12	12	12	12	12	12
	Mean	418	440	460	472	488*	507*	512*	94**
	S.D.	15	15	17	18	17D	18D	20D	18D
150	No.	12	10a)	10	10	10	9b)	9	9
	Mean	417	437	458	472	487*	506*	511*	95**
	S.D.	14	16	14	14	19D	19D	19D	17D

Unit: g
No.: No. of animals
a): One animal died, and another was sacrificed on day 5 of administration.
b): One animal died on day 32 of administration.
*: $p<0.05$; **: $p<0.01$ (Significant difference from control group)
D: Dunnett's test

Table 3-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Body weight of female rats during the pre-mating period (Main group)

Dose mg/kg		Day of administration 1	8	15	Gain 1-15
0	No.	12	12	11a)	11
	Mean	247	261	271	24
	S.D.	13	16	15	7
15	No.	12	12	12	12
	Mean	249	262	264	15*
	S.D.	18	18	16	9D
50	No.	12	12	12	12
	Mean	248	261	268	19
	S.D.	14	14	15	6
150	No.	12	10b)	10	10
	Mean	243	257	264	22
	S.D.	16	15	16	9

Unit: g
No.: No. of animals
a): One animal was sacrificed on day 12 of administration.
b): Two animals died on days 5 and 8 of administration.
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 3-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Body weight of dams during the gestation period (Main group)

Dose mg/kg		Administration 0	7	14	20a)	Gain 0-20
0	No.	11	11	11	11	11
	Mean	275	305	344	430	155
	S.D.	14	18	23	29	22
15	No.	12	12	12	12	12
	Mean	275	310	349	430	154
	S.D.	22	28	33	42	29
50	No.	12	12	12	12	12
	Mean	271	304	340	416	145
	S.D.	13	15	18	25	24
150	No.	10	10	10	9b)	9
	Mean	269	303	337	422	155
	S.D.	15	23	19	29	16

Unit: g
No.: No. of dams
a): Gestation day
b): One dam died on gestation day 15.
No significant difference in any treated groups from control group.

Table 3-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Body weight of dams during the lactation period (Main group)

Dose mg/kg		Administration 0	Administration 4a)	Gain 0-4
0	No.	11	11	11
	Mean	323	343	20
	S.D.	29	27	15
15	No.	12	12	12
	Mean	339	353	14
	S.D.	32	35	12
50	No.	12	12	12
	Mean	323	339	16
	S.D.	20	16	16
150	No.	9	9	9
	Mean	330	346	17
	S.D.	30	24	16

Unit: g
No.: No. of dams
a): Lactation day
No significant difference in any treated groups from control group.

Table 3-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Body weight of female rats (Satellite group, Administration period)

Dose mg/kg		Day of administration 1	8	15	22	29	36	42	Gain 1-42
0	No.	10	10	10	10	10	10	10	10
	Mean	248	258	268	275	287	293	296	48
	S.D.	12	15	15	18	23	21	20	12
150	No.	10	10	9a)	9	9	9	8b)	8
	Mean	247	257	267	278	282	296	296	50
	S.D.	15	14	14	19	18	14	21	14

Unit: g
No.: No. of animals
a): One animal died on day 12 of administration.
b): One animal was sacrificed on day 39 of administration.
No significant difference between treated group and control group.

Table 3-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Body weight of male rats (Recovery period)

Dose mg/kg		Day of recovery 1	8	14	Gain 1-14
0	No.	5	5	5	5
	Mean	530	547	556	25
	S.D.	9	17	21	13
150	No.	4	4	4	4
	Mean	501*	517	530	29
	S.D.	20T	24	20	1

Unit: g
No.: No. of animals
*: p<0.05 (Significant difference from control group)
T: Student's t-test

Table 3-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Body weight of female rats (Recovery period)

Dose mg/kg		Day of recovery 1	8	14	Gain 1-14
0	No.	5	5	5	5
	Mean	289	294	296	7
	S.D.	12	18	12	6
150	No.	4	4	4	4
	Mean	306	299	302	-4
	S.D.	30	29	36	9

Unit: g
No.: No. of animals
No significant difference between treated group and control group.

Table 4-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Food consumption of male rats (Administration period)

Dose mg/kg		Day of administration 2	8	15	30	36	42
0	No.	12	12	12	12	12	12
	Mean	31	30	29	31	31	31
	S.D.	3	3	3	2	2	3
15	No.	12	12	12	12	12	12
	Mean	29	30	30	30	31	29
	S.D.	2	3	2	4	2	3
50	No.	12	12	12	12	12	12
	Mean	26**	30	29	29	30	29
	S.D.	2D	2	3	2	2	2
150	No.	12	10a)	10	10	9b)	9
	Mean	25**	32	32	30	32	31
	S.D.	3D	3	4	2	3	3

Unit: g/rat/day
No.: No. of animals
a): One animal died, and another was sacrificed on day 5 of administration.
b): One animal died on day 32 of administration.
**: $p<0.01$ (Significant difference from control group)
D: Dunnett's test

Table 4-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Food consumption of female rats during the pre-mating period (Main group)

Dose mg/kg		Day of administration 2	8	15
0	No.	12	12	11a)
	Mean	19	22	23
	S.D.	2	2	2
15	No.	12	12	12
	Mean	19	23	19**
	S.D.	2	3	2D
50	No.	12	12	12
	Mean	19	21	21
	S.D.	1	3	2
150	No.	12	10b)	10
	Mean	16**	21	22
	S.D.	3D	2	4

Unit: g/rat/day
No.: No. of animals
a): One animal was sacrificed on day 12 of administration.
b): Two animals died on days 5 and 8 of administration.
**: $p<0.01$ (Significant difference from control group)
D: Dunnett's test

Table 4-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Food consumption of dams during the gestation period (Main group)

Dose mg/kg		Administration 1	7	14	20a)
0	No.	11	11	11	11
	Mean	21	26	27	26
	S.D.	2	3	4	3
15	No.	12	12	12	12
	Mean	22	27	27	27
	S.D.	4	3	4	4
50	No.	12	12	12	12
	Mean	23	25	27	26
	S.D.	4	3	3	3
150	No.	10	10	10	9b)
	Mean	23	26	27	27
	S.D.	5	4	5	5

Unit: g/rat/day
No.: No. of dams
a): Gestation day
b): One dam died on gestation day 15.
No significant difference in any treated groups from control group.

Table 4-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Food consumption of dams during the lactation period (Main group)

Dose mg/kg		Administration 2	Administration 4a)
0	No.	11	11
	Mean	32	43
	S.D.	8	7
15	No.	12	12
	Mean	25	45
	S.D.	7	8
50	No.	12	12
	Mean	27	44
	S.D.	7	4
150	No.	9	9
	Mean	30	47
	S.D.	5	8

Unit: g/rat/day
No.: No. of dams
a): Lactation day
No significant difference in any treated groups from control group.

Table 4-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Food consumption of female rats (Satellite group, Administration period)

Dose mg/kg		Day of administration 2	8	15	30	36	42
0	No.	10	10	10	10	10	10
	Mean	18	21	21	22	20	22
	S.D.	3	3	3	3	4	3
150	No.	10	10	9a)	9	9	8b)
	Mean	16	20	21	21	22	22
	S.D.	4	2	2	5	2	5

Unit: g/rat/day
No.: No. of animals
a): One animal died on day 12 of administration.
b): One animal was sacrificed on day 39 of administration.
No significant difference between treated group and control group.

Table 4-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Food consumption of male rats (Recovery period)

Dose mg/kg		Day of recovery 1	8	14
0	No.	5	5	5
	Mean	32	34	33
	S.D.	2	2	3
150	No.	4	4	4
	Mean	29	33	33
	S.D.	3	6	1

Unit: g/rat/day
No.: No. of animals
No significant difference between treated group and control group.

Table 4-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Food consumption of female rats (Recovery period)

Dose mg/kg		Day of recovery 1	8	14
0	No.	5	5	5
	Mean	20	22	22
	S.D.	3	5	3
150	No.	4	4	4
	Mean	21	23	25
	S.D.	6	3	2

Unit: g/rat/day
No.: No. of animals
No significant difference between treated group and control group.

Table 5-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of male rats (Week 6 of administration)

Dose	No.	pH								Protein 1)					Ketone body 2)					Glucose 3)				
mg/kg		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	-	+-	+	++	+++	-	+-	+	++	+++	-	+	++	+++	++++
0	5	0	0	0	0	0	0	0	4	1	0	3	2	0	0	2	2	0	1	0	5	0	0	0	0
15	5	0	0	0	0	0	0	2	1	2	1	1	3	0	0	2	2	1	0	0	5	0	0	0	0
50	5	0	0	0	0	0	2	1	2	0	0	0	4	1	0	0	0	5	0	0	5	0	0	0	0
150	4	0	0	0	1	0	0	0	1	2	0	0	2	2	0	0	1	2	1	0	4	0	0	0	0

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL

Table 5-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	Occult blood 4)					Bilirubin 5)				Urobilinogen 6)				Color 7)			
		-	+-	+	++	+++	-	+	++	+++	+-	+	++	+++	LY	Y	DY	B
0	5	3	2	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0
15	5	2	3	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0
50	5	5	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0
150	4	2	2	0	0	0	2	2	0	0	4	0	0	0	0	1	0	3

4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Table 5-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	0
15	5	4	1	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	0
50	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	0
150	4	4	0	0	0	0	4	0	0	0	0	0	4	0	0	0	4	0	0	0	0	4	0	0	0	4	0	0	0	0	4	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Water intake and urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
0	5	Mean	48	19.3	1886	1.80	5.42	2.35
		S.D.	14	8.6	544	0.43	0.98	0.44
15	5	Mean	53	20.8	1649	1.65	5.67	2.43
		S.D.	10	6.3	395	0.50	1.77	0.78
50	5	Mean	43	14.7	1992	1.19	4.72	1.99
		S.D.	5	3.6	312	0.43	1.07	0.45
150	4	Mean	42	13.0	2349	1.10	5.18	2.24
		S.D.	4	1.6	264	0.45	1.07	0.47

No significant difference in any treated groups from control group.

Table 5-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of female rats (Satellite group, Week 6 of administration)

Dose	No.	pH									Protein 1)					Ketone body 2)					Glucose 3)				
mg/kg		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	-	+-	+	++	+++	-	+-	+	++	+++	-	+	++	+++	++++
0	5	0	0	0	1	1	0	3	0	0	3	2	0	0	0	3	2	0	0	0	5	0	0	0	0
150	4	0	0	0	1	1	1	0	1	0	0	1	2	1	0	1	3	0	0	0	4	0	0	0	0

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL

Table 5-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of female rats (Satellite group, Week 6 of administration)

Dose mg/kg	No.	Occult blood 4)					Bilirubin 5)				Urobilinogen 6)				Color 7)			
		-	+-	+	++	+++	-	+	++	+++	+-	+	++	+++	LY	Y	DY	B
0	5	5	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0
150	4	3	1	0	0	0	3	1	0	0	4	0	0	0	0	3	0	1

4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Table 5-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of female rats (Satellite group, Week 6 of administration)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	0
150	4	4	0	0	0	0	4	0	0	0	0	0	4	0	0	0	4	0	0	0	0	4	0	0	1	3	0	0	0	4	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Water intake and urinalysis of female rats (Satellite group, Week 6 of administration)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
0	5	Mean	33	11.4	2466	1.12	3.24	1.49
		S.D.	17	9.9	1205	0.51	1.44	0.69
150	4	Mean	31	6.2	2733	0.74	2.64	1.22
		S.D.	5	1.6	540	0.17	0.71	0.27

No significant difference between treated group and control group.

Table 5-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of male rats (Week 2 of recovery)

Dose	No.	pH									Protein 1)					Ketone body 2)					Glucose 3)				
mg/kg		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	-	+-	+	++	+++	-	+-	+	++	+++	-	+	++	+++	++++
0	5	0	0	0	0	0	0	0	3	2	0	1	2	2	0	0	1	3	1	0	5	0	0	0	0
150	4	0	0	0	0	2	1	1	0	0	0	0	1	3	0	0	0	4	0	0	3	1	0	0	0

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL

Table 5-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	Occult blood 4)					Bilirubin 5)				Urobilinogen 6)				Color 7)			
		-	+-	+	++	+++	-	+	++	+++	+-	+	++	+++	LY	Y	DY	B
0	5	3	2	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0
150	4	4	0	0	0	0	3	1	0	0	4	0	0	0	0	4	0	0

4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Table 5-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	5	4	1	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	5	0	0	0	5	0	0	0	0
150	4	4	0	0	0	0	4	0	0	0	0	0	4	0	0	0	4	0	0	0	0	4	0	0	0	4	0	0	0	4	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Water intake and urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
0	5	Mean	49	19.7	1942	1.71	5.67	2.29
		S.D.	17	10.7	596	0.56	1.47	0.60
150	4	Mean	41	13.1	2262	1.31	4.82	1.89
		S.D.	7	3.5	323	0.20	0.70	0.27

No significant difference between treated group and control group.

Table 5-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of female rats (Week 2 of recovery)

Dose mg/kg	No.	pH									Protein 1)					Ketone body 2)					Glucose 3)				
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	-	+-	+	++	+++	-	+-	+	++	+++	-	+	++	+++	++++
0	5	0	0	1	1	2	0	0	1	0	2	2	1	0	0	4	1	0	0	0	5	0	0	0	0
150	4	0	0	2	0	2	0	0	0	0	1	1	2	0	0	1	3	0	0	0	4	0	0	0	0

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL

Table 5-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of female rats (Week 2 of recovery)

Dose mg/kg	No.	Occult blood 4)					Bilirubin 5)				Urobilinogen 6)				Color 7)			
		-	+-	+	++	+++	-	+	++	+++	+-	+	++	+++	LY	Y	DY	B
0	5	5	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0
150	4	4	0	0	0	0	4	0	0	0	4	0	0	0	0	4	0	0

4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Table 5-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Urinalysis of female rats (Week 2 of recovery)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	2	3	0	0	0	5	0	0	0	0
150	4	4	0	0	0	0	4	0	0	0	0	0	4	0	0	0	4	0	0	0	0	4	0	0	2	2	0	0	0	4	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Water intake and urinalysis of female rats (Week 2 of recovery)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
0	5	Mean	32	9.2	2203	1.04	3.15	1.27
		S.D.	6	3.1	406	0.19	0.60	0.21
150	4	Mean	37	13.6	1797	1.22	3.31	1.49
		S.D.	20	8.1	687	0.62	0.97	0.65

No significant difference between treated group and control group.

Table 6-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of male rats (End of administration)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	885	15.0	43.2	48.8	17.0	34.8	2.3	99.9	16.4	20.9	295
		S.D.	31	0.6	1.8	1.7	0.6	0.1	0.8	14.4	0.6	0.8	19
15	5	Mean	871	15.3	43.9	50.5	17.6	34.8	2.2	97.9	14.7*	20.7	268
		S.D.	35	0.3	1.2	1.1	0.6	0.5	0.4	5.7	1.0D	2.5	6
50	5	Mean	898	15.5	44.7	49.7	17.3	34.8	1.9	87.0	18.7**	20.8	269
		S.D.	21	0.6	1.5	1.1	0.4	1.0	0.4	6.3	0.9D	2.7	37
150	3a)	Mean	909	15.8	45.5	50.0	17.4	34.7	1.7	103.1	16.6	19.9	243*
		S.D.	10	0.6	1.3	1.3	0.5	0.5	0.7	6.5	1.2	2.8	28D

a): The examination of two animals was not done due to misunderstanding of protocol which specified the number of animals to be examined.
*: $p<0.05$; **: $p<0.01$ (Significant difference from control group)
D: Dunnett's test

Table 6-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of male rats (End of administration)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	67.0	68.5	26.8	1.6	0.3	2.5	0.4	45.8	18.1	1.0	0.2	1.7	0.3
		S.D.	11.0	4.1	3.5	0.5	0.1	0.8	0.3	7.1	4.6	0.2	0.1	0.7	0.2
15	5	Mean	74.0	73.5	22.3	1.4	0.3	1.9	0.5	54.6	16.4	1.0	0.2	1.4	0.4
		S.D.	24.5	5.6	5.3	0.5	0.1	0.4	0.1	18.9	5.9	0.6	0.2	0.5	0.1
50	5	Mean	83.3	71.9	23.4	1.4	0.3	2.6	0.4	59.7	19.7	1.1	0.2	2.2	0.4
		S.D.	10.1	4.5	4.1	0.4	0.0	0.8	0.2	6.4	5.2	0.4	0.0	0.6	0.2
150	3a)	Mean	64.2	72.6	22.7	1.7	0.3	2.3	0.4	46.7	14.4	1.1	0.2	1.4	0.3
		S.D.	6.0	9.3	9.4	0.4	0.1	0.5	0.1	8.9	5.8	0.3	0.1	0.3	0.1

LUC: Large unstained cells
a): The examination of two animals was not done due to misunderstanding of protocol which specified the number of animals to be examined.
No significant difference in any treated groups from control group.

Table 6-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of female rats (Lactation day 5)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	697	13.3	39.2	56.2	19.2	34.0	8.3	154.5	13.0	18.1	315
		S.D.	27	0.3	1.0	2.2	0.8	0.3	0.9	22.9	0.6	2.9	31
15	5	Mean	705	13.4	40.0	56.8	19.1	33.6	9.0	141.8	13.3	15.4	297
		S.D.	30	0.4	1.6	1.5	0.7	0.6	2.2	14.4	0.7	1.4	42
50	5	Mean	736	13.9	41.0	55.8	18.9	33.9	6.6	135.0	13.7	19.5	269
		S.D.	35	0.5	1.3	1.3	0.4	0.3	1.5	15.5	0.6	3.9	35
150	5	Mean	739	13.6	39.9	54.0	18.4	34.2	6.8	141.7	13.0	18.0	248*
		S.D.	15	0.3	0.6	1.3	0.4	0.6	1.2	7.6	0.7	2.6	13D

*: p<0.05 (Significant difference from control group)
D: Dunnett's test

Table 6-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of female rats (Lactation day 5)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	116.6	51.1	44.5	0.7	0.2	2.9	0.4	61.6	49.9	0.8	0.3	3.5	0.5
		S.D.	16.0	16.0	16.4	0.1	0.1	0.6	0.4	26.6	12.2	0.3	0.2	0.9	0.4
15	5	Mean	130.5	58.8	36.9	0.7	0.3	2.8	0.4	77.3	47.6	0.9	0.3	3.7	0.6
		S.D.	33.9	10.1	10.6	0.4	0.1	0.7	0.2	26.5	15.8	0.2	0.2	1.5	0.3
50	5	Mean	120.7	57.6	38.1	0.8	0.2	3.0	0.3	67.4	48.3	0.9	0.3	3.6	0.4
		S.D.	30.0	13.7	13.9	0.2	0.0	0.6	0.1	15.0	30.1	0.1	0.1	1.0	0.1
150	5	Mean	132.2	57.5	37.9	0.8	0.3	3.2	0.3	76.6	49.7	0.9	0.4	4.2	0.5
		S.D.	38.2	6.0	5.7	0.5	0.1	0.3	0.1	24.0	16.1	0.3	0.3	1.2	0.2

LUC: Large unstained cells
No significant difference in any treated groups from control group.

Table 6-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of female rats (Satellite group, End of administration)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	863	15.3	43.4	50.3	17.7	35.2	2.0	105.7	12.8	17.9	222
		S.D.	28	0.3	1.1	1.4	0.5	0.3	0.3	10.7	0.4	3.3	13
150	4	Mean	806*	14.8	41.6*	51.6	18.4	35.5	1.6*	106.3	12.8	15.3	187**
		S.D.	39T	0.4	0.7T	2.2	0.9	0.4	0.2T	6.2	0.4	2.4	13T

*: p<0.05; **: p<0.01 (Significant difference from control group)
T: Student's t-test

Table 6-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of female rats (Satellite group, End of administration)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	48.1	78.9	16.8	1.7	0.2	2.0	0.4	37.7	8.3	0.8	0.1	1.0	0.2
		S.D.	14.4	4.0	4.2	0.4	0.1	0.2	0.1	10.2	3.9	0.4	0.0	0.3	0.0
150	4	Mean	52.1	71.6	23.4	1.9	0.2	2.5	0.4	37.5	11.9	1.0	0.1	1.4	0.3
		S.D.	12.0	5.4	6.5	0.4	0.1	0.6	0.4	10.6	2.8	0.4	0.0	0.7	0.3

LUC: Large unstained cells
No significant difference between treated group and control group.

Table 6-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of male rats (End of recovery)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	895	15.7	44.4	49.7	17.5	35.2	1.7	104.5	15.5	19.8	271
		S.D.	28	0.4	1.1	0.8	0.2	0.3	0.3	11.5	2.9	1.1	33
150	4	Mean	867	15.7	44.1	50.9*	18.1*	35.5	1.9	115.7	17.8	20.8	268
		S.D.	19	0.5	0.9	0.6T	0.4T	0.6	0.2	12.6	2.6	2.3	23

*: p<0.05 (Significant difference from control group)
T: Student's t-test

Table 6-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of male rats (End of recovery)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	109.5	79.4	16.1	1.2	0.3	2.3	0.7	87.6	17.1	1.3	0.3	2.5	0.7
		S.D.	19.6	4.1	3.4	0.4	0.1	0.9	0.2	19.4	1.7	0.3	0.1	0.8	0.3
150	4	Mean	104.0	76.8	18.5	1.3	0.2	2.6	0.6	79.9	19.2	1.4	0.3	2.7	0.7
		S.D.	14.0	3.5	4.2	0.5	0.1	0.8	0.4	11.4	5.0	0.3	0.1	0.9	0.4

LUC: Large unstained cells
No significant difference between treated group and control group.

Table 6-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of female rats (End of recovery)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	826	15.4	42.8	51.9	18.7	35.9	1.6	113.4	12.8	18.2	190
		S.D.	18	0.4	1.3	0.6	0.3	0.7	0.5	10.4	0.1	2.6	16
150	4	Mean	823	15.2	42.3	51.4	18.5	35.9	1.8	128.9	13.0	16.7	189
		S.D.	10	0.6	1.5	1.4	0.5	0.3	0.5	22.7	0.4	1.7	10

No significant difference between treated group and control group.

Table 6-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Hematology of female rats (End of recovery)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	55.3	77.4	16.8	2.2	0.2	2.8	0.6	42.7	9.1	1.2	0.1	1.8	0.4
		S.D.	19.0	4.8	5.1	0.8	0.1	1.6	0.3	14.6	3.8	0.5	0.1	1.4	0.3
150	4	Mean	62.9	72.3	22.7	1.6	0.3	2.8	0.5	45.3	14.5	1.0	0.2	1.7	0.3
		S.D.	14.4	6.9	7.8	0.5	0.1	0.9	0.2	9.7	7.4	0.3	0.1	0.6	0.1

LUC: Large unstained cells
No significant difference between treated group and control group.

Table 7-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of male rats (End of administration)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	81	37	53	0	389	9.0	54	33	85	0.1	121
		S.D.	14	8	4	1	73	4.5	10	12	12	0.0	13
15	5	Mean	69	31	50	0	431	19.9	49	28	80	0.1	131
		S.D.	2	4	9	1	93	24.9	11	7	15	0.0	20
50	5	Mean	74	37	58	0	476	7.1	40	31	72	0.1	125
		S.D.	2	6	21	1	96	2.1	7	13	9	0.0	14
150	3a)	Mean	67	46	58	1	350	3.3	56	36	86	0.1	129
		S.D.	3	4	15	0	27	0.5	6	16	11	0.1	6

a): The examination of two animals was not done due to misunderstanding of protocol which specified the number of animals to be examined.
No significant difference in any treated groups from control group.

Table 7-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of male rats (End of administration)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	16	0.30	143	4.4	107	9.6	6.0	5.7	3.2	1.28
		S.D.	2	0.02	1	0.1	1	0.3	0.4	0.2	0.1	0.06
15	5	Mean	17	0.29	143	4.4	107	9.6	5.8	5.8	3.3	1.29
		S.D.	2	0.02	1	0.1	1	0.2	0.6	0.2	0.0	0.06
50	5	Mean	15	0.26*	143	4.4	107	9.6	6.5	5.4	3.2	1.40
		S.D.	2	0.04D	1	0.2	2	0.3	0.9	0.1	0.1	0.15
150	3a)	Mean	15	0.29	143	4.6	108	9.5	5.6	5.6	3.2	1.39
		S.D.	2	0.02	1	0.2	2	0.1	0.4	0.3	0.1	0.13

a): The examination of two animals was not done due to misunderstanding of protocol which specified the number of animals to be examined.
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 7-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of female rats (Lactation day 5)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	90	55	52	1	218	55.0	50	37	104	0.1	128
		S.D.	26	16	16	0	45	82.4	11	11	21	0.0	11
15	5	Mean	91	56	57	1	197	12.5	52	74	115	0.1	130
		S.D.	23	17	21	0	14	4.7	13	34	18	0.0	11
50	5	Mean	94	57	50	0	183	13.1	50	51	108	0.1	125
		S.D.	29	27	13	1	18	3.6	4	21	6	0.0	13
150	5	Mean	86	63	55	0	229	7.3*	49	53	100	0.0	126
		S.D.	12	7	10	1	106	2.7ST	5	24	11	0.1	11

*: p<0.05 (Significant difference from control group)
ST: Steel's test

Table 7-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of female rats (Lactation day 5)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	17	0.29	141	4.1	107	10.3	7.0	5.9	3.6	1.56
		S.D.	3	0.03	1	0.5	2	0.1	0.3	0.2	0.1	0.23
15	5	Mean	15	0.28	140*	3.9	104	10.2	6.5	5.9	3.6	1.50
		S.D.	2	0.02	1D	0.7	1	0.2	0.7	0.3	0.2	0.03
50	5	Mean	17	0.28	140	4.3	106	10.2	7.1	5.9	3.5	1.51
		S.D.	2	0.01	1	0.5	2	0.2	0.6	0.2	0.1	0.13
150	5	Mean	15	0.27	139**	4.7	104*	10.2	6.9	5.8	3.5	1.51
		S.D.	2	0.01	1D	0.4	2D	0.3	0.7	0.3	0.2	0.15

*: p<0.05; **: p<0.01 (Significant difference from control group)
D: Dunnett's test

Table 7-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of female rats (Satellite group, End of administration)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	73	38	53	1	281	11.2	55	13	107	0.1	137
		S.D.	11	18	15	0	71	3.3	9	6	18	0.0	15
150	4	Mean	81	44	42	0*	212	6.2*	53	17	98	0.1	127
		S.D.	13	10	6	1T	85	2.1T	15	4	23	0.0	14

*: p<0.05 (Significant difference from control group)
T: Student's t-test

Table 7-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of female rats (Satellite group, End of administration)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	18	0.33	143	4.3	110	9.9	4.9	6.2	3.7	1.51
		S.D.	1	0.01	2	0.3	2	0.4	0.8	0.3	0.2	0.06
150	4	Mean	17	0.35	142	4.3	108	9.7	4.7	5.8	3.5	1.51
		S.D.	2	0.04	1	0.2	1	0.2	0.6	0.4	0.2	0.17

No significant difference between treated group and control group.

Table 7-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of male rats (End of recovery)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	64	31	56	0	347	14.6	49	31	82	0.1	132
		S.D.	4	2	10	1	88	12.7	11	8	8	0.0	12
150	4	Mean	70	31	56	0	363	8.6	36	33	67*	0.1	125
		S.D.	5	6	8	1	39	7.2	7	15	7T	0.0	13

*: p<0.05 (Significant difference from control group)
T: Student's t-test

Table 7-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of male rats (End of recovery)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	16	0.27	142	4.4	104	9.8	6.5	5.9	3.2	1.21
		S.D.	1	0.02	1	0.3	1	0.3	0.3	0.2	0.1	0.09
150	4	Mean	15	0.27	142	4.7	105	9.8	6.5	5.8	3.3	1.29
		S.D.	1	0.01	1	0.2	2	0.1	0.3	0.1	0.1	0.02

No significant difference between treated group and control group.

Table 7-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of female rats (End of recovery)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	69	32	48	1	198	11.0	58	13	109	0.1	121
		S.D.	14	15	6	1	54	3.4	10	6	20	0.0	8
150	4	Mean	72	28	59	1	184	12.1	59	19	115	0.1	131
		S.D.	8	7	11	0	36	2.8	6	14	9	0.0	5

No significant difference between treated group and control group.

Table 7-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Blood chemistry of female rats (End of recovery)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	18	0.34	143	4.3	108	10.3	5.1	6.5	3.8	1.43
		S.D.	1	0.03	1	0.4	1	0.3	1.2	0.3	0.2	0.02
150	4	Mean	18	0.35	141*	4.2	107	9.8	4.6	6.1	3.8	1.63*
		S.D.	4	0.07	1T	0.2	2	0.5	0.6	0.3	0.3	0.11AT

*: p<0.05 (Significant difference from control group)
T: Student's t-test
AT: Aspin-Welch t-test

Table 8-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of male rats (End of administration)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	7	7	7	7	7	7	7
		Mean	513	2.12	13.9	24.1	292	1.39	12.59
		S.D.	19	0.08	1.4	3.0	52	0.12	0.73
	15	No.	12	12	12	12	12	12	12
		Mean	496	2.13	13.9	25.6	289	1.40	12.51
		S.D.	25	0.07	1.6	5.6	34	0.09	0.67
	50	No.	12	12	12	12	12	12	12
		Mean	479**	2.13	13.4	24.9	270	1.44	11.62*
		S.D.	17D	0.10	1.1	6.8	72	0.15	0.82D
	150	No.	5	5	5	5	5	5	5
		Mean	491	2.18	13.4	24.4	320	1.37	11.88
		S.D.	17	0.14	0.9	3.1	41	0.12	0.95
Relative	0	No.		7	7	7	7	7	7
		Mean		0.42	2.7	4.7	57	0.27	2.45
		S.D.		0.02	0.2	0.5	11	0.03	0.09
	15	No.		12	12	12	12	12	12
		Mean		0.43	2.8	5.2	58	0.28	2.52
		S.D.		0.02	0.3	1.1	6	0.01	0.10
	50	No.		12	12	12	12	12	12
		Mean		0.45*	2.8	5.2	56	0.30	2.43
		S.D.		0.03D	0.3	1.4	14	0.03	0.15
	150	No.		5	5	5	5	5	5
		Mean		0.44	2.7	5.0	65	0.28	2.42
		S.D.		0.01	0.2	0.5	6	0.02	0.17

*: $p<0.05$; **: $p<0.01$ (Significant difference from control group)
D: Dunnett's test

Table 8-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of male rats (End of administration)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	0	No.	7	7	7	7	7	7	7
		Mean	0.77	3.43	70	3.17	1419	1.86	1.30
		S.D.	0.13	0.24	7	0.16	153	0.27	0.20
	15	No.	12	12	12	12	12	12	12
		Mean	0.77	3.56	69	3.31	1400	1.83	1.31
		S.D.	0.10	0.27	10	0.29	127	0.22	0.14
	50	No.	12	12	12	12	12	12	12
		Mean	0.76	3.45	71	3.23	1414	1.92	1.39
		S.D.	0.12	0.35	7	0.26	168	0.20	0.13
	150	No.	5	5	5	5	5	5	5
		Mean	0.73	3.31	73	3.41	1363	1.84	1.25
		S.D.	0.08	0.08	13	0.40	144	0.30	0.10
Relative	0	No.	7	7	7	7	7	7	7
		Mean	0.15	0.67	13	0.62	278	0.36	0.25
		S.D.	0.02	0.05	1	0.04	36	0.06	0.04
	15	No.	12	12	12	12	12	12	12
		Mean	0.15	0.72	14	0.67	282	0.37	0.27
		S.D.	0.02	0.05	2	0.05	26	0.05	0.03
	50	No.	12	12	12	12	12	12	12
		Mean	0.16	0.72	15	0.68	296	0.40	0.29*
		S.D.	0.02	0.07	2	0.06	38	0.05	0.04D
	150	No.	5	5	5	5	5	5	5
		Mean	0.15	0.67	15	0.70	278	0.38	0.26
		S.D.	0.02	0.03	2	0.09	34	0.08	0.03

*: p<0.05 (Significant difference from control group)
D: Dunnett's test

Table 8-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of female rats (Main group, End of administration)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	11	11	11	11	11	11	11
		Mean	308	2.00	18.8	15.7	214	1.05	10.37
		S.D.	24	0.05	3.0	2.2	68	0.07	1.28
	15	No.	12	12	12	12	12	12	12
		Mean	321	1.99	17.1	17.7	236	1.05	10.82
		S.D.	34	0.08	2.5	4.7	86	0.08	1.28
	50	No.	12	12	12	12	12	12	12
		Mean	303	1.96	18.3	17.3	209	1.01	10.08
		S.D.	15	0.05	2.1	2.6	45	0.07	0.83
	150	No.	9	9	9	9	9	9	9
		Mean	304	1.97	18.3	16.0	203	0.99	10.22
		S.D.	21	0.08	2.4	2.5	69	0.04	0.84
Relative	0	No.		11	11	11	11	11	11
		Mean		0.65	6.1	5.1	69	0.34	3.36
		S.D.		0.05	0.8	0.9	19	0.02	0.22
	15	No.		12	12	12	12	12	12
		Mean		0.62	5.3	5.5	73	0.33	3.38
		S.D.		0.06	0.8	1.3	22	0.02	0.29
	50	No.		12	12	12	12	12	12
		Mean		0.65	6.1	5.7	69	0.33	3.33
		S.D.		0.03	0.7	0.8	13	0.02	0.27
	150	No.		9	9	9	9	9	9
		Mean		0.65	6.1	5.2	67	0.33	3.37
		S.D.		0.04	1.0	0.6	21	0.02	0.21

No significant difference in any treated groups from control group.

Table 8-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of female rats (Main group, End of administration)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	0	No.	11	11	11	11	11
		Mean	0.66	2.26	85	112.9	678
		S.D.	0.14	0.20	15	17.2	132
	15	No.	12	12	12	12	12
		Mean	0.74	2.28	88	107.5	684
		S.D.	0.12	0.20	12	18.6	125
	50	No.	12	12	12	12	12
		Mean	0.70	2.29	85	105.5	691
		S.D.	0.13	0.22	9	23.4	146
	150	No.	9	9	9	9	9
		Mean	0.67	2.35	90	103.8	678
		S.D.	0.12	0.23	12	16.1	108
Relative	0	No.	11	11	11	11	11
		Mean	0.21	0.73	28	36.6	220
		S.D.	0.03	0.05	4	4.2	40
	15	No.	12	12	12	12	12
		Mean	0.23	0.71	27	33.6	215
		S.D.	0.04	0.06	4	5.9	47
	50	No.	12	12	12	12	12
		Mean	0.23	0.75	28	34.8	228
		S.D.	0.04	0.08	3	7.8	48
	150	No.	9	9	9	9	9
		Mean	0.22	0.78	29	34.2	222
		S.D.	0.05	0.07	3	4.8	27

No significant difference in any treated groups from control group.

Table 8-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of female rats (Satellite group, End of administration)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	5	5	5	5	5	5	5
		Mean	284	1.97	17.2	18.1	283	0.96	7.40
		S.D.	20	0.05	1.7	3.9	36	0.04	0.50
	150	No.	4	4	4	4	4	4	4
		Mean	271	1.97	15.0	16.8	209*	0.82**	6.87
		S.D.	12	0.09	1.5	2.3	31T	0.07T	0.47
Relative	0	No.		5	5	5	5	5	5
		Mean		0.70	6.1	6.3	100	0.34	2.61
		S.D.		0.05	0.9	1.0	12	0.02	0.07
	150	No.		4	4	4	4	4	4
		Mean		0.73	5.6	6.2	77*	0.30	2.53
		S.D.		0.01	0.6	0.7	12T	0.03	0.15

*: $p<0.05$; **: $p<0.01$ (Significant difference from control group)
T: Student's t-test

Table 8-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of female rats (Satellite group, End of administration)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	0	No.	5	5	5	5	5
		Mean	0.52	2.01	82	96.8	767
		S.D.	0.05	0.14	14	20.1	122
	150	No.	4	4	4	4	4
		Mean	0.48	1.88	81	101.7	557*
		S.D.	0.03	0.15	8	19.6	116T
Relative	0	No.	5	5	5	5	5
		Mean	0.18	0.71	29	34.3	273
		S.D.	0.02	0.02	5	7.7	58
	150	No.	4	4	4	4	4
		Mean	0.18	0.69	30	37.5	204
		S.D.	0.01	0.05	3	7.1	35

*: $p<0.05$ (Significant difference from control group)
T: Student's t-test

Table 8-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of male rats (End of recovery)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	5	5	5	5	5	5	5
		Mean	520	2.20	15.0	21.0	305	1.51	13.68
		S.D.	23	0.05	1.8	4.0	119	0.13	1.31
	150	No.	4	4	4	4	4	4	4
		Mean	490	2.14	13.6	20.7	211	1.45	12.10
		S.D.	18	0.01	0.5	2.8	31	0.08	0.50
Relative	0	No.		5	5	5	5	5	5
		Mean		0.42	2.9	4.0	59	0.29	2.63
		S.D.		0.02	0.3	0.6	23	0.03	0.19
	150	No.		4	4	4	4	4	4
		Mean		0.44	2.8	4.2	43	0.30	2.47
		S.D.		0.01	0.0	0.5	6	0.01	0.03

No significant difference between treated group and control group.

Table 8-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of male rats (End of recovery)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	0	No.	5	5	5	5	5	5	5
		Mean	0.75	3.62	71	3.37	1395	2.00	1.39
		S.D.	0.06	0.18	12	0.22	43	0.17	0.07
	150	No.	4	4	4	4	4	4	4
		Mean	0.74	3.44	61	3.32	1272	1.77	1.35
		S.D.	0.10	0.44	4	0.19	143	0.17	0.20
Relative	0	No.	5	5	5	5	5	5	5
		Mean	0.14	0.70	14	0.65	269	0.39	0.27
		S.D.	0.01	0.03	2	0.05	14	0.04	0.00
	150	No.	4	4	4	4	4	4	4
		Mean	0.15	0.70	12	0.68	260	0.36	0.28
		S.D.	0.02	0.10	1	0.06	25	0.03	0.05

No significant difference between treated group and control group.

Table 8-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of female rats (End of recovery)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	5	5	5	5	5	5	5
		Mean	273	1.95	17.5	14.7	260	0.89	6.85
		S.D.	15	0.06	4.4	2.7	33	0.06	0.50
	150	No.	4	4	4	4	4	4	4
		Mean	280	2.00	18.5	16.5	251	0.91	7.13
		S.D.	34	0.07	1.1	2.4	126	0.09	0.84
Relative	0	No.		5	5	5	5	5	5
		Mean		0.72	6.4	5.4	95	0.32	2.51
		S.D.		0.05	1.4	1.2	10	0.02	0.04
	150	No.		4	4	4	4	4	4
		Mean		0.72	6.7	5.9	88	0.33	2.55
		S.D.		0.08	0.6	0.5	42	0.02	0.11

No significant difference between treated group and control group.

Table 8-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Organ weight of female rats (End of recovery)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	0	No.	5	5	5	5	5
		Mean	0.52	1.83	75	88.9	546
		S.D.	0.07	0.04	12	11.8	89
	150	No.	4	4	4	4	4
		Mean	0.54	2.02	73	88.7	669
		S.D.	0.05	0.18	3	18.0	95
Relative	0	No.	5	5	5	5	5
		Mean	0.19	0.67	28	32.4	200
		S.D.	0.03	0.03	5	2.7	35
	150	No.	4	4	4	4	4
		Mean	0.19	0.73	26	31.7	244
		S.D.	0.01	0.06	4	5.4	59

No significant difference between treated group and control group.

Table 9-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Gross pathological findings (End of administration period (D42))

Organs	Sex:	M	M	M	M
	Dose(mg/kg):	0	15	50	150
Findings	Number:	7	12	12	5
Epididymis					
Focus,white		0	1	0	0
Intestine,cecum					
Large		0	0	1	4
Lung(bronchus)					
Focus,dark red		0	0	0	1
Discoloration,white		0	0	1	0
Stomach					
Focus,dark red,glandular stomach		0	1	1	0

M : Male

Table 9-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Gross pathological findings (End of administration period (D42))

Organs	Sex:	F	F
	Dose(mg/kg):	0	150
Findings	Number:	5	4
Intestine,cecum			
Large		0	4
Liver			
Hepatodiaphragmatic nodule		1	0
Stomach			
Focus,dark red,glandular stomach		2	0

F : Female

Table 9-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Gross pathological findings (End of administration period (L4))

Organs	Sex:	F	F	F	F
	Dose(mg/kg):	0	15	50	150
Findings	Number:	11	12	12	9
Intestine,cecum					
Large		0	0	0	4
Liver					
Focus,white		0	0	0	1
Lung(bronchus)					
Focus,dark red		0	1	1	0
Focus,white		0	0	1	0
Stomach					
Focus,dark red,glandular stomach		1	2	3	1

F : Female

R-1102

Table 9-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Gross pathological findings (End of recovery period)

Organs	Sex:	M	M
	Dose(mg/kg):	0	150
Findings	Number:	5	4
All tissues			
Not remarkable		5	4

M : Male

Table 9-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Gross pathological findings (End of recovery period)

Organs	Sex:	F	F
	Dose(mg/kg):	0	150
Findings	Number:	5	4
Stomach			
Focus,dark red,glandular stomach		2	1

F : Female

R-1102

Table 9-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Gross pathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	M	M
	Dose(mg/kg):	150	150
Findings	Number:	2a)	1b)
Intestine,cecum			
Large		1	1
Lung(bronchus)			
Discoloration,dark red		1	0

M : Male
a): Main group
b): Recovery group

Table 9-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Gross pathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	F	F	F
	Dose(mg/kg):	0	150	150
Findings	Number:	1a)	3a)	2b)
Intestine,cecum				
Large		0	3	2
Kidney				
Focus,white		1	0	0
Dilatation,pelvic		1	0	0
Liver				
Focus,dark red		0	0	1
Lung(bronchus)				
Discoloration,dark red		0	1	1
Thymus				
Small		1	0	0
Urinary bladder				
Distention		1	0	0
Ureter				
Dilatation		1	0	0
Urethra				
Dilatation		1	0	0
Urethral orifice				
Swelling		1	0	0

F : Female
a): Main group
b): Satellite group

Table 10-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	M	M	M	M
	Dose(mg/kg):	0	15	50	150
Findings	Number:	7	12	12	5
Adrenal					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Bone+Bone marrow,femoral					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Cerebellum(Pons)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Cerebrum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Epididymis					
Number examined		5	0	0	5
Not remarkable		4	0	0	4
Cell debris,luminal		1	0	0	1
minimal		1	0	0	0
mild		0	0	0	1
Eye					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Heart					
Number examined		5	0	0	5
Not remarkable		5	0	0	4
Cell infiltration		0	0	0	1
minimal		0	0	0	1
Intestine,duodenum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,jejunum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,ileum(Peyer's patch)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,cecum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,colon					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,rectum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Kidney					
Number examined		5	0	0	5
Not remarkable		4	0	0	4
Regeneration,tubular		1	0	0	1
minimal		1	0	0	1

M : Male

Table 10-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	M	M	M	M
	Dose(mg/kg):	0	15	50	150
Findings	Number:	7	12	12	5
Liver					
Number examined		5	0	0	5
Not remarkable		3	0	0	2
Microgranuloma		2	0	0	3
minimal		2	0	0	3
Lung(bronchus)					
Number examined		5	5	5	5
Not remarkable		4	3	3	3
Mineralization,arterial wall		0	1	0	0
minimal		0	1	0	0
Aggregation,alveolar macrophage		1	2	2	1
minimal		1	2	2	1
Inflammation,bronchiolo-alveolar		0	0	0	1
minimal		0	0	0	1
Lymph node,mesenteric					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Lymph node,submandibular					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pancreas					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Parathyroid					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pituitary					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Prostate					
Number examined		5	0	0	5
Not remarkable		3	0	0	4
Cell infiltration		2	0	0	1
minimal		2	0	0	1
Salivary gland,submandibular					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Sciatic nerve					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Seminal vesicle(Coagulating gland)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Skeletal muscle,femoral					
Number examined		5	0	0	5
Not remarkable		5	0	0	5

M : Male

Table 10-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	M	M	M	M
	Dose(mg/kg):	0	15	50	150
Findings	Number:	7	12	12	5
Spinal cord,thoracic					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spleen					
Number examined		5	5	5	5
Not remarkable		1	1	3	2
Hematopoiesis,extramedullary		4	4	2	3
minimal		4	4	2	3
Stomach					
Number examined		5	5	5	5
Not remarkable		5	4	5	3
Erosion,glandular stomach		0	1	0	1
minimal		0	1	0	1
Hyperplasia,squamous,forestomach		0	0	0	2
minimal		0	0	0	1
mild		0	0	0	1
Testis					
Number examined		5	0	0	5
Not remarkable		4	0	0	4
Atrophy,seminiferous tubular		1	0	0	1
minimal		1	0	0	0
mild		0	0	0	1
Thymus					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Thyroid					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Trachea					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Urinary bladder					
Number examined		5	0	0	5
Not remarkable		5	0	0	5

M : Male

Table 10-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	F	F
	Dose(mg/kg):	0	150
Findings	Number:	5	4
Adrenal			
Number examined		5	4
Not remarkable		5	4
Bone+Bone marrow,femoral			
Number examined		5	4
Not remarkable		5	4
Cerebellum(Pons)			
Number examined		5	4
Not remarkable		5	4
Cerebrum			
Number examined		5	4
Not remarkable		5	4
Eye			
Number examined		5	4
Not remarkable		5	4
Heart			
Number examined		5	4
Not remarkable		5	4
Intestine,duodenum			
Number examined		5	4
Not remarkable		5	4
Intestine,jejunum			
Number examined		5	4
Not remarkable		5	4
Intestine,ileum(Peyer's patch)			
Number examined		5	4
Not remarkable		5	4
Intestine,cecum			
Number examined		5	4
Not remarkable		5	4
Intestine,colon			
Number examined		5	4
Not remarkable		5	4
Intestine,rectum			
Number examined		5	4
Not remarkable		5	4
Kidney			
Number examined		5	4
Not remarkable		4	3
Regeneration,tubular		0	1
minimal		0	1
Mineralization		1	0
minimal		1	0
Liver			
Number examined		5	4
Not remarkable		2	2
Hepatodiaphragmatic nodule		1	0
mild		1	0

F : Female

Table 10-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	F	F
	Dose(mg/kg):	0	150
Findings	Number:	5	4
Liver (continued)			
Microgranuloma		3	2
minimal		3	2
Lung(bronchus)			
Number examined		5	4
Not remarkable		5	4
Lymph node,mesenteric			
Number examined		5	4
Not remarkable		5	4
Lymph node,submandibular			
Number examined		5	4
Not remarkable		5	4
Ovary			
Number examined		5	4
Not remarkable		5	4
Pancreas			
Number examined		5	4
Not remarkable		5	4
Parathyroid			
Number examined		5	4
Not remarkable		5	4
Pituitary			
Number examined		5	4
Not remarkable		5	4
Salivary gland,submandibular			
Number examined		5	4
Not remarkable		5	4
Sciatic nerve			
Number examined		5	4
Not remarkable		5	4
Skeletal muscle,femoral			
Number examined		5	4
Not remarkable		5	4
Spinal cord,thoracic			
Number examined		5	4
Not remarkable		5	4
Spleen			
Number examined		5	4
Not remarkable		3	2
Hematopoiesis,extramedullary		2	2
minimal		2	2
Stomach			
Number examined		5	4
Not remarkable		3	4
Erosion,glandular stomach		2	0
minimal		2	0

F : Female

Table 10-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	F	F
	Dose(mg/kg):	0	150
Findings	Number:	5	4
Thymus			
Number examined		5	4
Not remarkable		5	4
Thyroid			
Number examined		5	4
Not remarkable		5	4
Trachea			
Number examined		5	4
Not remarkable		5	4
Urinary bladder			
Number examined		5	4
Not remarkable		5	4
Uterus			
Number examined		5	4
Not remarkable		5	4
Vagina			
Number examined		5	4
Not remarkable		5	4

F : Female

Table 10-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of administration period (L4))

Organs	Sex:	F	F	F	F
	Dose(mg/kg):	0	15	50	150
Findings	Number:	11	12	12	9
Adrenal					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Bone+Bone marrow,femoral					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Cerebellum(Pons)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Cerebrum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Eye					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Heart					
Number examined		5	0	0	5
Not remarkable		5	0	0	4
Cell infiltration		0	0	0	1
minimal		0	0	0	1
Intestine,duodenum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,jejunum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,ileum(Peyer's patch)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,cecum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,colon					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,rectum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Kidney					
Number examined		5	0	0	5
Not remarkable		4	0	0	3
Regeneration,tubular		1	0	0	1
minimal		1	0	0	1
Mineralization		0	0	0	1
minimal		0	0	0	1
Liver					
Number examined		5	0	0	5
Not remarkable		5	0	0	4

F : Female

Table 10-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of administration period (L4))

Organs	Sex:	F	F	F	F
	Dose(mg/kg):	0	15	50	150
Findings	Number:	11	12	12	9
Liver (continued)					
Microgranuloma		0	0	0	1
minimal		0	0	0	1
Lung(bronchus)					
Number examined		5	5	5	5
Not remarkable		4	3	3	4
Mineralization,arterial wall		1	0	0	0
minimal		1	0	0	0
Hemorrhage,focal		0	1	1	0
minimal		0	1	1	0
Aggregation,alveolar macrophage		0	1	2	1
minimal		0	1	2	1
Lymph node,mesenteric					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Lymph node,submandibular					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Ovary					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pancreas					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Parathyroid					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pituitary					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Salivary gland,submandibular					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Sciatic nerve					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Skeletal muscle,femoral					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spinal cord,thoracic					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spleen					
Number examined		5	5	5	5
Hematopoiesis,extramedullary		5	5	5	5
minimal		1	0	0	1
mild		4	5	5	4

F : Female

Table 10-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of administration period (L4))

Organs	Sex:	F	F	F	F
	Dose(mg/kg):	0	15	50	150
Findings	Number:	11	12	12	9
Stomach					
Number examined		5	0	0	5
Not remarkable		4	0	0	4
Erosion,glandular stomach		1	0	0	1
minimal		1	0	0	0
mild		0	0	0	1
Thymus					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Thyroid					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Trachea					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Urinary bladder					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Uterus					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Vagina					
Number examined		5	0	0	5
Not remarkable		5	0	0	5

F : Female

Table 10-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of recovery period)

Organs	Sex:	M	M
	Dose(mg/kg):	0	150
Findings	Number:	5	4
Adrenal			
Number examined		5	4
Not remarkable		5	4
Bone+Bone marrow,femoral			
Number examined		5	4
Not remarkable		5	4
Lung(bronchus)			
Number examined		5	4
Not remarkable		3	1
Aggregation,alveolar macrophage		2	2
minimal		2	2
Inflammation,bronchiolo-alveolar		0	1
minimal		0	1
Spleen			
Number examined		5	4
Not remarkable		1	2
Hematopoiesis,extramedullary		4	2
minimal		4	2
Stomach			
Number examined		5	4
Not remarkable		5	4
Thymus			
Number examined		5	4
Not remarkable		5	4
Trachea			
Number examined		5	4
Not remarkable		5	4

M : Male

Table 10-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (End of recovery period)

Organs	Sex:	F	F
	Dose(mg/kg):	0	150
Findings	Number:	5	4
Adrenal			
Number examined		5	4
Not remarkable		5	4
Lung(bronchus)			
Number examined		5	4
Not remarkable		3	4
Aggregation,alveolar macrophage		2	0
minimal		2	0
Lymph node,mesenteric			
Number examined		5	4
Not remarkable		5	4
Lymph node,submandibular			
Number examined		5	4
Not remarkable		5	4
Spleen			
Number examined		5	4
Not remarkable		3	2
Hematopoiesis,extramedullary		2	2
minimal		2	2
Stomach			
Number examined		2	1
Erosion,glandular stomach		2	1
minimal		1	1
mild		1	0
Thymus			
Number examined		5	4
Not remarkable		5	4
Trachea			
Number examined		5	4
Not remarkable		5	4

F : Female

Table 10-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs / Findings	Sex: / Dose(mg/kg): / Number:	M 150 2a)	M 150 1b)
Adrenal			
Number examined		2	1
Not remarkable		1	0
Hypertrophy,cortical cell		1	1
minimal		1	1
Bone+Bone marrow,femoral			
Number examined		2	1
Not remarkable		1	1
Granulopoiesis,increased		1	0
minimal		1	0
Cerebellum(Pons)			
Number examined		2	1
Not remarkable		2	1
Cerebrum			
Number examined		2	1
Not remarkable		2	1
Epididymis			
Number examined		2	1
Not remarkable		2	0
Granuloma,spermatic		0	1
mild		0	1
Eye			
Number examined		2	1
Not remarkable		2	1
Heart			
Number examined		2	1
Not remarkable		2	1
Intestine,duodenum			
Number examined		2	1
Not remarkable		2	1
Intestine,jejunum			
Number examined		2	1
Not remarkable		2	1
Intestine,ileum(Peyer's patch)			
Number examined		1	1
Not remarkable		1	1
Sample autolysed		1	0
Intestine,cecum			
Number examined		1	1
Not remarkable		1	1
Sample autolysed		1	0
Intestine,colon			
Number examined		2	1
Not remarkable		2	1
Intestine,rectum			
Number examined		2	1
Not remarkable		2	1

M : Male
a): Main group
b): Recovery group

Table 10-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	M	M
	Dose(mg/kg):	150	150
Findings	Number:	2a)	1b)
Kidney			
Number examined		2	1
Not remarkable		1	1
Regeneration,tubular		1	0
minimal		1	0
Liver			
Number examined		2	1
Not remarkable		1	1
Microgranuloma		1	0
minimal		1	0
Lung(bronchus)			
Number examined		2	1
Not remarkable		1	0
Inflammation,necrotizing,bronchial		1	0
mild		1	0
Inflammation,bronchiolo-alveolar		0	1
mild		0	1
Edema,alveolar		1	0
mild		1	0
Lymph node,mesenteric			
Number examined		2	1
Not remarkable		2	1
Lymph node,submandibular			
Number examined		2	1
Not remarkable		2	1
Pancreas			
Number examined		2	1
Not remarkable		2	1
Parathyroid			
Number examined		2	1
Not remarkable		2	1
Pituitary			
Number examined		2	1
Not remarkable		2	1
Prostate			
Number examined		2	1
Not remarkable		1	1
Cell infiltration		1	0
minimal		1	0
Salivary gland,submandibular			
Number examined		2	1
Not remarkable		2	1
Sciatic nerve			
Number examined		2	1
Not remarkable		2	1
Seminal vesicle(Coagulating gland)			
Number examined		2	1
Not remarkable		2	1

M : Male
a): Main group
b): Recovery group

Table 10-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	M	M
	Dose(mg/kg):	150	150
Findings	Number:	2a)	1b)
Skeletal muscle,femoral			
Number examined		2	1
Not remarkable		2	1
Spinal cord,thoracic			
Number examined		2	1
Not remarkable		2	1
Spleen			
Number examined		2	1
Not remarkable		1	1
Atrophy,white pulp		1	0
minimal		1	0
Stomach			
Number examined		2	1
Not remarkable		2	1
Testis			
Number examined		2	1
Not remarkable		2	1
Thymus			
Number examined		2	1
Atrophy		2	1
minimal		2	1
Thyroid			
Number examined		2	1
Not remarkable		2	1
Trachea			
Number examined		2	1
Inflammation,necrotizing		2	1
moderate		1	0
severe		1	1
Urinary bladder			
Number examined		2	1
Not remarkable		2	1

M : Male
a): Main group
b): Recovery group

Table 10-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs / Findings	Sex: / Dose(mg/kg): / Number:	F 0 1a)	F 150 3a)	F 150 2b)
Adrenal				
Number examined		1	3	2
Not remarkable		0	1	2
Hemorrhage,focal		1	0	0
minimal		1	0	0
Hypertrophy,cortical cell		1	2	0
minimal		1	2	0
Bone+Bone marrow,femoral				
Number examined		1	3	2
Not remarkable		0	3	2
Necrosis,focal,bone marrow		1	0	0
mild		1	0	0
Cerebellum(Pons)				
Number examined		1	3	2
Not remarkable		1	3	2
Cerebrum				
Number examined		1	3	2
Not remarkable		1	3	2
Eye				
Number examined		1	3	2
Not remarkable		1	3	2
Heart				
Number examined		1	3	2
Not remarkable		0	3	2
Hemorrhage,focal		1	0	0
mild		1	0	0
Intestine,duodenum				
Number examined		1	3	1
Not remarkable		0	3	1
Sample autolysed		0	0	1
Inflammation		1	0	0
minimal		1	0	0
Intestine,jejunum				
Number examined		1	3	2
Not remarkable		0	3	2
Inflammation		1	0	0
mild		1	0	0
Intestine,ileum(Peyer's patch)				
Number examined		1	3	2
Not remarkable		0	3	2
Inflammation		1	0	0
mild		1	0	0
Necrosis,lymphocytic,Peyer's patch		1	0	0
mild		1	0	0
Intestine,cecum				
Number examined		1	2	1
Not remarkable		0	2	1
Sample autolysed		0	1	1
Inflammation		1	0	0
moderate		1	0	0

F : Female
a): Main group
b): Satellite group

Table 10-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs / Findings	Sex: / Dose(mg/kg): / Number:	F 0 1a)	F 150 3a)	F 150 2b)
Intestine,colon				
Number examined		1	3	1
Not remarkable		0	3	1
Sample autolysed		0	0	1
Inflammation		1	0	0
minimal		1	0	0
Intestine,rectum				
Number examined		1	3	2
Not remarkable		0	3	2
Inflammation		1	0	0
minimal		1	0	0
Kidney				
Number examined		1	3	2
Not remarkable		0	2	2
Dilatation,pelvic		1	0	0
mild		1	0	0
Dilatation,tubular		1	0	0
mild		1	0	0
Necrosis,tubular		1	0	0
mild		1	0	0
Regeneration,tubular		0	1	0
minimal		0	1	0
Pyelonephritis		1	0	0
mild		1	0	0
Liver				
Number examined		1	3	2
Not remarkable		0	3	1
Necrosis,focal		0	0	1
mild		0	0	1
Hyperplasia,Kupffer cell		1	0	0
mild		1	0	0
Lung(bronchus)				
Number examined		1	3	2
Not remarkable		0	1	1
Thrombus		1	0	0
minimal		1	0	0
Inflammation,necrotizing,bronchial		0	2	1
mild		0	1	1
moderate		0	1	0
Edema,alveolar		0	2	1
mild		0	2	1
Lymph node,mesenteric				
Number examined		1	3	2
Not remarkable		0	3	1
Atrophy		0	0	1
minimal		0	0	1
Necrosis,lymphocytic		1	0	0
minimal		1	0	0
Lymph node,submandibular				
Number examined		1	3	2
Not remarkable		0	3	1
Atrophy		0	0	1
minimal		0	0	1
Necrosis,lymphocytic		1	0	0
minimal		1	0	0

F : Female
a): Main group
b): Satellite group

Table 10-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	F	F	F
	Dose(mg/kg):	0	150	150
Findings	Number:	1a)	3a)	2b)
Ovary				
Number examined		1	3	2
Not remarkable		1	3	2
Pancreas				
Number examined		1	3	2
Not remarkable		0	3	2
Edema		1	0	0
mild		1	0	0
Parathyroid				
Number examined		1	3	2
Not remarkable		1	3	2
Pituitary				
Number examined		1	3	2
Not remarkable		1	3	2
Salivary gland,submandibular				
Number examined		1	3	2
Not remarkable		0	3	2
Necrosis,single cell,acinar		1	0	0
mild		1	0	0
Sciatic nerve				
Number examined		1	3	2
Not remarkable		1	3	2
Skeletal muscle,femoral				
Number examined		1	3	2
Not remarkable		1	3	2
Spinal cord,thoracic				
Number examined		1	3	2
Not remarkable		1	3	2
Spleen				
Number examined		1	3	2
Not remarkable		0	1	1
Necrosis,lymphocytic		1	0	0
mild		1	0	0
Hematopoiesis,extramedullary		0	1	0
minimal		0	1	0
Atrophy,white pulp		0	1	1
minimal		0	1	1
Stomach				
Number examined		1	3	2
Not remarkable		0	2	2
Erosion,glandular stomach		1	1	0
minimal		1	1	0
Thymus				
Number examined		1	3	2
Not remarkable		0	0	1
Atrophy		0	3	1
minimal		0	3	1
Necrosis,lymphocytic		1	0	0
moderate		1	0	0

F : Female
a): Main group
b): Satellite group

Table 10-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	F	F	F
	Dose(mg/kg):	0	150	150
Findings	Number:	1a)	3a)	2b)
Thyroid				
Number examined		1	2	1
Not remarkable		1	2	1
Sample autolysed		0	1	1
Trachea				
Number examined		1	3	2
Not remarkable		1	0	0
Inflammation,necrotizing		0	3	2
moderate		0	1	1
severe		0	2	1
Urinary bladder				
Number examined		1	3	2
Not remarkable		0	3	2
Distention		1	0	0
mild		1	0	0
Inflammation		1	0	0
mild		1	0	0
Hyperplasia,trasitional,diffuse		1	0	0
mild		1	0	0
Uterus				
Number examined		1	3	2
Not remarkable		1	3	2
Vagina				
Number examined		1	3	2
Not remarkable		0	3	2
Inflammation		1	0	0
mild		1	0	0
Ureter				
Number examined		1	0	0
Inflammation		1	0	0
mild		1	0	0
Urethra				
Number examined		1	0	0
Inflammation		1	0	0
moderate		1	0	0

F : Female
a): Main group
b): Satellite group

Table 11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Estrous cycle in female rats during the pre-mating period (Main group)

Dose mg/kg	No. of animals	Count of estrus						Mean duration of cycles	Index of animals with abnormal
		0	1	2	3	4	Mean±S.D.	Mean±S.D.	estrous cycle (%)a)
0	11	0	0	0	2	9	3.8±0.4	4.1±0.3	0/11(0.0)
15	12	0	0	0	3	9	3.8±0.5	4.3±0.4	0/12(0.0)
50	12	0	0	0	8	4	3.3±0.5*D	4.2±0.4	1/12(8.3)
150	10	0	0	0	2	8	3.8±0.4	4.2±0.3	0/10(0.0)

a): (No. of animals with abnormal estrous cycle / No. of animals examined)×100
*: p<0.05 (Significant difference from control group)
D: Dunnett's test

Table 12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Mating and fertility of animals

	Male				Female			
Dose mg/kg	No. of males	Days until copulation Mean±S.D.	Copulation index (%) a)	Insemination index (%) b)	No. of females	Days until copulation Mean±S.D.	Copulation index (%) a)	Fertility index (%) c)
0	12	2.5±0.9	12/12(100.0)	12/12(100.0)	11	2.6±0.8	11/11(100.0)	11/11(100.0)
15	12	3.3±1.7	12/12(100.0)	12/12(100.0)	12	3.3±1.7	12/12(100.0)	12/12(100.0)
50	12	2.2±1.3	12/12(100.0)	12/12(100.0)	12	2.2±1.3	12/12(100.0)	12/12(100.0)
150	10	2.5±1.1	10/10(100.0)	10/10(100.0)	10	2.5±1.1	10/10(100.0)	10/10(100.0)

a): (No. of copulated animals / No. of mated animals)×100
b): (No. of males which impregnated females / No. of copulated males)×100
c): (No. of pregnant females / No. of copulated females)×100
No significant difference in any treated groups from control group.

Table 13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Delivery data on dams

Dose mg/kg		No. of pregnant females	No. of females with liveborns	Gestation index % a)	Gestation length in days	No. of corpora lutea	No. of implantation sites	Implantation index % b)	Delivery index % c)	No. of stillborns (%)d)	No. of liveborns	External e) abnormalities(%)f)
	Total	11	11	100.0		188	179			2	165	0
0	Mean				21.7	17.1	16.3	95.5	93.5	(1.1)	15.0	(0.0)
	S.D.				0.5	1.8	1.8	7.5	5.2	(2.6)	1.4	(0.0)
	Total	12	12	100.0		180	176			0	163	0
15	Mean				21.8	15.0*	14.7	97.0	91.1	(0.0)	13.6	(0.0)
	S.D.				0.5	2.8D	3.4	10.5	10.5	(0.0)	4.1	(0.0)
	Total	12	12	100.0		186	186			8	154	1h)
50	Mean				21.8	15.5	15.5	100.0	87.2	(4.6)	12.8**	(0.6)
	S.D.				0.6	1.6	1.6	0.0	8.2	(5.8)	1.5ST	(2.0)
	Total	9g)	9	100.0		137	134			3	123	0
150	Mean				21.9	15.2	14.9	97.7	94.1	(2.7)	13.7	(0.0)
	S.D.				0.6	1.3	1.5	3.4	6.8	(4.0)	2.0	(0.0)

a): (No. of females which delivered liveborns / No. of pregnant females)×100
b): (No. of implantation sites / No. of corpora lutea)×100
c): (No. of delivered pups / No. of implantation sites)×100
d): (No. of stillborns / No. of delivered pups)×100
e): No. of delivered pups with external abnormalities
f): (No. of delivered pups with external abnormalities / No. of delivered pups)×100
g): One out of ten dams was excluded because it died on gestation day 15.
h): Exencephaly, rachischisis and open eye (stillborn)
*: p<0.05; **: p<0.01 (Significant difference from control group)
D: Dunnett's test
ST: Steel's test

Table 14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Viability index of pups

Dose mg/kg		No. of dams	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of dams	No. of live pups		Viability index on postnatal day 4 % b)
							Day 0	Day 4	
0	Total	11	165	167		11	165	160	
	Mean		15.0	15.2	98.9		15.0	14.5	96.9
	S.D.		1.4	1.5	2.6		1.4	1.6	3.6
15	Total	12	163	163		12	163	161	
	Mean		13.6	13.6	100.0		13.6	13.4	98.9
	S.D.		4.1	4.1	0.0		4.1	4.1	3.8
50	Total	12	154	162		12	154	150	
	Mean		12.8	13.5	95.4		12.8	12.5	97.3
	S.D.		1.5	1.7	5.8		1.5	1.6	3.9
150	Total	9	123	126		9	123	122	
	Mean		13.7	14.0	97.3		13.7	13.6	99.1
	S.D.		2.0	1.7	4.0		2.0	2.1	2.6

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100
No significant difference in any treated groups from control group.

Table 15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Sex ratio of pups

Dose mg/kg	No. of dams		Liveborns: No. of males	Liveborns: No. of females	Stillborns: No. of males	Stillborns: No. of females	Sex ratio of delivered pups a)	Sex ratio of liveborns b)	No. of dams	Postnatal day 4: No. of males	Postnatal day 4: No. of females	Sex ratio of live pups on day 4 c)
		Total	99	66	0	2				97	63	
0	11	Mean	9.0	6.0	0.0	0.2	0.59	0.60	11	8.8	5.7	0.61
		S.D.	2.7	2.1	0.0	0.4	0.14	0.14		2.5	2.1	0.14
		Total	71	92	0	0				71	90	
15	12	Mean	5.9	7.7	0.0	0.0	0.41**	0.41**	12	5.9	7.5	0.41**
		S.D.	3.0	2.2	0.0	0.0	0.15D	0.15D		3.0	2.1	0.15D
		Total	87	67	5	3				84	66	
50	12	Mean	7.3	5.6	0.4	0.3	0.57	0.57	12	7.0	5.5	0.57
		S.D.	1.4	1.8	0.7	0.5	0.10	0.11		1.2	1.8	0.11
		Total	66	57	2	1				66	56	
150	9	Mean	7.3	6.3	0.2	0.1	0.55	0.55	9	7.3	6.2	0.55
		S.D.	1.0	2.0	0.4	0.3	0.10	0.10		1.0	2.0	0.10

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4
**: p<0.01 (Significant difference from control group)
D: Dunnett's test

Table 16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Body weight of pups

Dose mg/kg		Male			Female		
		0	4a)	Gain	0	4a)	Gain
0	No.	11	11	11	11	11	11
	Mean	6.3	9.7	3.4	5.9	9.1	3.2
	S.D.	0.4	1.0	0.8	0.4	1.0	0.8
15	No.	12	12	12	12	12	12
	Mean	6.7	10.3	3.6	6.3	9.8	3.4
	S.D.	0.7	1.6	1.1	0.6	1.5	1.0
50	No.	12	12	12	12	12	12
	Mean	6.7	10.4	3.6	6.4	9.9	3.5
	S.D.	0.5	1.1	0.8	0.5	1.3	0.9
150	No.	9	9	9	9	9	9
	Mean	6.7	10.1	3.4	6.3	9.8	3.4
	S.D.	0.5	1.0	0.8	0.5	1.2	0.8

Unit: g
No.: No. of dams
a): Postnatal day
No significant difference in any treated groups from control group.

Table 17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Externally for gross abnormalities in dead pups

Dose (mg/kg)	0	15	50	150
Male				
No. of pups examined	1	0	1	0
No. of pups with abnormal findings	0	0	0	0
Female				
No. of pups examined	2	1	1	0
No. of pups with abnormal findings	0	0	0	0

Table 18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Externally for gross abnormalities in pups on postnatal day 4

Dose (mg/kg)	0	15	50	150
Male				
No. of pups examined	97	71	84	66
No. of pups with abnormal findings	0	0	0	0
Female				
No. of pups examined	63	90	66	56
No. of pups with abnormal findings	0	0	0	0

Appendix 1-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

a): Day of necropsy
-: No abnormal findings

Appendix 1-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 15

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 15

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 15

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 50

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 50

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
3001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 50

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
3001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 150

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4002	-	-	-	-	-	E	-	-	-	-	-	-	-	-
4003	-	-	-	-	+									
4004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4010	-	-	-	-	ABDx									
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
A: Decrease in spontaneous movement
B: Dyspnea
D: Hypothermia
E: Soft feces
+: Dead
x: Sacrificed moribund

Appendix 1-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 150

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
4001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4003														
4004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4010														
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 150

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
4001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4003															
4004	-	-	B	+											
4005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4010															
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

a): Day of necropsy
-: No abnormal findings
B: Dyspnea
+: Dead

Appendix 1-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats during the pre-mating period (Main group)
Dose (mg/kg): 0

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1104	-	-	-	-	-	-	-	-	-	-	F	ABFx			
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
A: Decrease in spontaneous movement
B: Dyspnea
F: Swelling of urethral orifice
x: Sacrificed moribund

Appendix 1-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats during the pre-mating period (Main group)
Dose (mg/kg): 15

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats during the pre-mating period (Main group)
Dose (mg/kg): 50

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
3101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats during the pre-mating period (Main group)
Dose (mg/kg): 150

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
4101	-	-	-	-	-	-	-	+							
4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4107	-	-	-	-	+										
4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
+: Dead

Appendix 1-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in dams during the gestation period (Main group)
Dose (mg/kg): 0

Dam number	Administration																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
1104b)																								
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	

a): Gestation day
b): Sacrificed on day 12 of administration
-: No abnormal findings
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in dams during the gestation period (Main group)
Dose (mg/kg): 15

Dam number	Administration																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	

a): Gestation day
-: No abnormal findings
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in dams during the gestation period (Main group)
Dose (mg/kg): 50

Dam number	Administration																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
3101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
3102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
3103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	cd	d
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
3109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	

a): Gestation day
-: No abnormal findings
cd: Continuation of delivery
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in dams during the gestation period (Main group)
Dose (mg/kg): 150

Dam number	Administration																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23a)
4101b)																								
4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
4107c)																								
4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	B	+								
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	

a): Gestation day
b): Died on day 8 of administration
c): Died on day 5 of administration
-: No abnormal findings
B: Dyspnea
+: Dead
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in dams during the lactation period (Main group)
Dose (mg/kg): 0

Dam number	Administration					
	0	1	2	3	4a)	5b)
1101	-	-	-	-	-	-
1102	-	-	-	-	-	-
1103	-	-	-	-	-	-
1104c)						
1105	-	-	-	-	-	-
1106	-	-	-	-	-	-
1107	-	-	-	-	-	-
1108	-	-	-	-	-	-
1109	-	-	-	-	-	-
1110	-	-	-	-	-	-
1111	-	-	-	-	-	-
1112	-	-	-	-	-	-

a): Lactation day
b): Day of necropsy
c): Sacrificed on day 12 of administration
-: No abnormal findings

Appendix 1-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in dams during the lactation period (Main group)
Dose (mg/kg): 15

Dam number	Administration					
	0	1	2	3	4a)	5b)
2101	-	-	-	-	-	-
2102	-	-	-	-	-	-
2103	-	-	-	-	-	-
2104	-	-	-	-	-	-
2105	-	-	-	-	-	-
2106	-	-	-	-	-	-
2107	-	-	-	-	-	-
2108	-	-	-	-	-	-
2109	-	-	-	-	-	-
2110	-	-	-	-	-	-
2111	-	-	-	-	-	-
2112	-	-	-	-	-	-

a): Lactation day
b): Day of necropsy
-: No abnormal findings

Appendix 1-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in dams during the lactation period (Main group)
Dose (mg/kg): 50

Dam number	Administration					
	0	1	2	3	4a)	5b)
3101	-	-	-	-	-	-
3102	-	-	-	-	-	-
3103	-	-	-	-	-	-
3104	-	-	-	-	-	-
3105	-	-	-	-	-	-
3106	-	-	-	-	-	-
3107	-	-	-	-	-	-
3108	-	-	-	-	-	-
3109	-	-	-	-	-	-
3110	-	-	-	-	-	-
3111	-	-	-	-	-	-
3112	-	-	-	-	-	-

a): Lactation day
b): Day of necropsy
-: No abnormal findings

Appendix 1-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in dams during the lactation period (Main group)
Dose (mg/kg): 150

Dam number	Administration					
	0	1	2	3	4a)	5b)
4101c)						
4102	-	-	-	-	-	-
4103	-	-	-	-	-	-
4104	-	-	-	-	-	-
4105	-	-	-	-	-	-
4106	-	-	-	-	-	-
4107d)						
4108	-	-	-	-	-	-
4109e)						
4110	-	-	-	-	-	-
4111	-	-	-	-	-	-
4112	-	-	-	-	-	-

a): Lactation day
b): Day of necropsy
c): Died on day 8 of administration
d): Died on day 5 of administration
e): Died on gestation day 15
-: No abnormal findings

Appendix 1-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1113	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1114	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1115	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1116	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1117	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1118	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1119	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1120	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1121	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1122	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1113	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1114	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1115	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1116	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1117	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1118	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1119	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1120	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1121	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1122	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
1113	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1114	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1115	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1116	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1117	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1118	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1119	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1121	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1122	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

a): Day of necropsy
-: No abnormal findings

Appendix 1-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 150

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4113	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4114	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4115	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4116	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4117	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4118	-	-	-	-	-	-	-	-	-	-	-	+		
4119	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4120	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4121	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4122	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
+: Dead

Appendix 1-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 150

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
4113	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4114	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4115	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4116	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4117	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4118														
4119	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4120	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4121	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4122	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 150

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
4113	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4114	-	-	-	-	-	-	-	-	-	B	ABDx				
4115	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4116	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4117	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4118															
4119	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4121	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4122	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

a): Day of necropsy
-: No abnormal findings
A: Decrease in spontaneous movement
B: Dyspnea
D: Hypothermia
x: Sacrificed moribund

Appendix 1-31 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-32 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in male rats (Recovery period)
Dose (mg/kg): 150

Animal number	Day of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4010b)															
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
b): Sacrificed on day 5 of administration
-: No abnormal findings

Appendix 1-33 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
1118	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1119	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1121	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1122	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-34 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual clinical signs in female rats (Recovery period)
Dose (mg/kg): 150

Animal number	Day of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
4118b)															
4119	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4120	-	-	B	-	-	-	-	-	-	-	-	-	-	-	-
4121	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4122	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
b): Died on day 12 of administration
-: No abnormal findings
B: Dyspnea

Appendix 2-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
			D							S		
Posture a)	N	N		N	N	N	N	N	N		N	N
Convulsion b)	0	0		0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0		0	0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead
S: Sacrificed moribund

Appendix 2-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 3 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 3 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 3 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
			D							S		
Posture a)	N	N		N	N	N	N	N	N		N	N
Convulsion b)	0	0		0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0		0	0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead
S: Sacrificed moribund

Appendix 2-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 4 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 4 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 4 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
			D							S		
Posture a)	N	N		N	N	N	N	N	N		N	N
Convulsion b)	0	0		0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0		0	0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead
S: Sacrificed moribund

Appendix 2-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 5 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 5 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 5 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
			D							S		
Posture a)	N	N		N	N	N	N	N	N		N	N
Convulsion b)	0	0		0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0		0	0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead
S: Sacrificed moribund

Appendix 2-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 6 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 6 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 6 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3 D	4 D	5	6	7	8	9	10 S	11	12
Posture a)	N	N			N	N	N	N	N		N	N
Convulsion b)	0	0			0	0	0	0	0		0	0
Abnormal behavior c)	0	0			0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead
S: Sacrificed moribund

Appendix 2-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 1 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 1 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 1 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 2 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-31 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 2 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-32 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 2 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Posture a)		N	N	N	N	N		N	N	N	N	N
Convulsion b)		0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)		0	0	0	0	0		0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-33 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 1)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Posture a)	N	N	N		N	N	N	N	N	N	N	N
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
S: Sacrificed moribund

Appendix 2-34 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 1)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-35 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 1)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-36 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual detailed clinical signs in female rats: home cage observation

(Main group, Gestation day 1)

Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Posture a)		N	N	N	N	N		N	N	N	N	N
Convulsion b)		0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)		0	0	0	0	0		0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-37 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 7)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Posture a)	N	N	N		N	N	N	N	N	N	N	N
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
S: Sacrificed moribund

Appendix 2-38 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 7)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-39 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 7)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-40 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 7)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Posture a)		N	N	N	N	N		N	N	N	N	N
Convulsion b)		0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)		0	0	0	0	0		0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-41 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 14)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Posture a)	N	N	N		N	N	N	N	N	N	N	N
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
S: Sacrificed moribund

Appendix 2-42 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 14)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-43 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 14)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-44 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 14)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Posture a)		N	N	N	N	N		N	N	N	N	N
Convulsion b)		0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)		0	0	0	0	0		0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-45 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 20)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Posture a)	N	N	N		N	N	N	N	N	N	N	N
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
S: Sacrificed moribund

Appendix 2-46 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 20)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-47 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 20)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-48 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 20)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D		D			
Posture a)		N	N	N	N	N		N		N	N	N
Convulsion b)		0	0	0	0	0		0		0	0	0
Abnormal behavior c)		0	0	0	0	0		0		0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-49 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Lactation day 4)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Posture a)	N	N	N		N	N	N	N	N	N	N	N
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
S: Sacrificed moribund

Appendix 2-50 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Lactation day 4)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-51 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Lactation day 4)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-52 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Lactation day 4)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D		D			
Posture a)		N	N	N	N	N		N		N	N	N
Convulsion b)		0	0	0	0	0		0		0	0	0
Abnormal behavior c)		0	0	0	0	0		0		0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-53 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-54 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-55 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-56 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-57 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-58 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Posture a)	N	N	N	N	N		N	N	N	N
Convulsion b)	0	0	0	0	0		0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-59 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-60 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Posture a)	N	N	N	N	N		N	N	N	N
Convulsion b)	0	0	0	0	0		0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-61 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-62 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Posture a)	N	N	N	N	N		N	N	N	N
Convulsion b)	0	0	0	0	0		0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-63 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-64 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Posture a)	N	N	N	N	N		N	N	N	N
Convulsion b)	0	0	0	0	0		0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-65 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual detailed clinical signs in male rats: home cage observation

(Week 1 of recovery)

Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-66 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
			S		
Posture a)	N	N		N	N
Convulsion b)	0	0		0	0
Abnormal behavior c)	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
S: Sacrificed moribund

Appendix 2-67 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-68 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
			S		
Posture a)	N	N		N	N
Convulsion b)	0	0		0	0
Abnormal behavior c)	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
S: Sacrificed moribund

Appendix 2-69 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual detailed clinical signs in female rats: home cage observation

(Week 1 of recovery)

Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched

b) 0: None, 1: Minor, 2: Moderate, 3: Severe

c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-70 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual detailed clinical signs in female rats: home cage observation

(Week 1 of recovery)

Dose (mg/kg): 150

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
	D				
Posture a)		N	N	N	N
Convulsion b)		0	0	0	0
Abnormal behavior c)		0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-71 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-72 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Week 2 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
		D			
Posture a)	N	N	N	N	
Convulsion b)	0	0	0	0	
Abnormal behavior c)	0	0	0	0	

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
D: Dead

Appendix 2-73 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-74 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-75 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-76 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-77 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-78 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	1
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-79 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-80 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3 D	4	5	6	7	8	9	10 S	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	1	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead
S: Sacrificed moribund

Appendix 2-81 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-82 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 3 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-83 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 3 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	1	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-84 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 3 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3 D	4	5	6	7	8	9	10 S	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0		0	0
Fur condition b)	0	0	0	0	0	0	0	0	0		0	0
Skin c)	0	0	0	0	0	0	0	0	0		0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0		0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0		0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0		0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0		0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0		0	0
Piloerection i)	0	0	0	0	0	0	0	0	0		0	0
Pupil size j)	0	0	0	0	0	0	0	0	0		0	0
Salivation k)	1	0	0	0	0	0	0	0	0		0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0		0	0
Vocalization m)	0	0	0	0	0	0	0	0	0		0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0		0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead
S: Sacrificed moribund

Appendix 2-85 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual detailed clinical signs in male rats: in-the-hand observation

(Week 4 of administration)

Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-86 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 4 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-87 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 4 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-88 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 4 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3 D	4	5	6	7	8	9	10 S	11	12
Ease of removal from cage a)	0	0		0	0	0	0	0	0		0	0
Fur condition b)	0	0		0	0	0	0	0	0		0	0
Skin c)	0	0		0	0	0	0	0	0		0	0
Secretions-Eye, Nose d)	0	0		0	0	0	0	0	0		0	0
Exophthalmos e)	0	0		0	0	0	0	0	0		0	0
Palpebral closure f)	0	0		0	0	0	0	0	0		0	0
Mucosal membranes g)	0	0		0	0	0	0	0	0		0	0
Lacrimation h)	0	0		0	0	0	0	0	0		0	0
Piloerection i)	0	0		0	0	0	0	0	0		0	0
Pupil size j)	0	0		0	0	0	0	0	0		0	0
Salivation k)	0	0		0	0	0	0	0	0		0	0
Abnormal respiration l)	0	0		0	0	0	0	0	0		0	0
Vocalization m)	0	0		0	0	1	0	0	0		0	0
Reactivity to handling n)	0	0		0	0	0	0	0	0		0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead
S: Sacrificed moribund

Appendix 2-89 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-90 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 5 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-91 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 5 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-92 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 5 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
			D							S		
Ease of removal from cage a)	0	0		0	0	0	0	0	0		0	0
Fur condition b)	0	0		0	0	0	0	0	0		0	0
Skin c)	0	0		0	0	0	0	0	0		0	0
Secretions-Eye, Nose d)	0	0		0	0	0	0	0	0		0	0
Exophthalmos e)	0	0		0	0	0	0	0	0		0	0
Palpebral closure f)	0	0		0	0	0	0	0	0		0	0
Mucosal membranes g)	0	0		0	0	0	0	0	0		0	0
Lacrimation h)	0	0		0	0	0	0	0	0		0	0
Piloerection i)	0	0		0	0	0	0	0	0		0	0
Pupil size j)	0	0		0	0	0	0	0	0		0	0
Salivation k)	0	0		0	0	0	0	0	0		0	0
Abnormal respiration l)	0	0		1o)	0	0	0	0	0		0	0
Vocalization m)	0	0		0	0	0	0	0	0		0	0
Reactivity to handling n)	0	0		0	0	0	0	0	0		0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
o) Dyspnea
D: Dead
S: Sacrificed moribund

Appendix 2-93 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-94 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 6 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-95 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 6 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	1	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-96 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 6 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3 D	4 D	5	6	7	8	9	10 S	11	12
Ease of removal from cage a)	0	0			0	0	0	0	0		0	0
Fur condition b)	0	0			0	0	0	0	0		0	0
Skin c)	0	0			0	0	0	0	0		0	0
Secretions-Eye, Nose d)	0	0			0	0	0	0	0		0	0
Exophthalmos e)	0	0			0	0	0	0	0		0	0
Palpebral closure f)	0	0			0	0	0	0	0		0	0
Mucosal membranes g)	0	0			0	0	0	0	0		0	0
Lacrimation h)	0	0			0	0	0	0	0		0	0
Piloerection i)	0	0			0	0	0	0	0		0	0
Pupil size j)	0	0			0	0	0	0	0		0	0
Salivation k)	0	0			0	0	0	0	0		0	0
Abnormal respiration l)	0	0			0	0	0	0	0		0	0
Vocalization m)	0	0			0	0	0	0	0		0	0
Reactivity to handling n)	0	0			0	0	0	0	0		0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead
S: Sacrificed moribund

Appendix 2-97 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	1	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-98 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 1 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	1	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-99 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 1 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-100 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 1 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	1	1	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-101 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-102 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 2 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-103 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 2 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-104 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 2 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Ease of removal from cage a)		0	0	0	0	0		0	0	0	0	0
Fur condition b)		0	0	0	0	0		0	0	0	0	0
Skin c)		0	0	0	0	0		0	0	0	0	0
Secretions-Eye, Nose d)		0	0	0	0	0		0	0	0	0	0
Exophthalmos e)		0	0	0	0	0		0	0	0	0	0
Palpebral closure f)		0	0	0	0	0		0	0	0	0	0
Mucosal membranes g)		0	0	0	0	0		0	0	0	0	0
Lacrimation h)		0	0	0	0	0		0	0	0	0	0
Piloerection i)		0	0	0	0	0		0	0	0	0	0
Pupil size j)		0	0	0	0	0		0	0	0	0	0
Salivation k)		0	0	0	0	0		0	0	0	0	0
Abnormal respiration l)		0	0	0	0	0		0	0	0	0	0
Vocalization m)		0	0	0	0	0		0	0	0	0	0
Reactivity to handling n)		0	0	0	0	0		0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead

Appendix 2-105 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 1)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0		0	0	0	0	0	0	0	0
Fur condition b)	0	0	0		0	0	0	0	0	0	0	0
Skin c)	0	0	0		0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0		0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0		0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0		0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0		0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0		0	0	0	0	0	0	0	0
Piloerection i)	0	0	0		0	0	0	0	0	0	0	0
Pupil size j)	0	0	0		0	0	0	0	0	0	0	0
Salivation k)	0	0	0		0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0		0	0	0	0	0	0	0	0
Vocalization m)	0	0	0		0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0		0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
S: Sacrificed moribund

Appendix 2-106 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 1)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-107 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 1)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-108 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 1)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Ease of removal from cage a)		0	0	0	0	0		0	0	0	0	0
Fur condition b)		0	0	0	0	0		0	0	0	0	0
Skin c)		0	0	0	0	0		0	0	0	0	0
Secretions-Eye, Nose d)		0	0	0	0	0		0	0	0	0	0
Exophthalmos e)		0	0	0	0	0		0	0	0	0	0
Palpebral closure f)		0	0	0	0	0		0	0	0	0	0
Mucosal membranes g)		0	0	0	0	0		0	0	0	0	0
Lacrimation h)		0	0	0	0	0		0	0	0	0	0
Piloerection i)		0	0	0	0	0		0	0	0	0	0
Pupil size j)		0	0	0	0	0		0	0	0	0	0
Salivation k)		0	0	0	0	0		0	0	0	0	0
Abnormal respiration l)		0	0	0	0	0		0	0	0	0	0
Vocalization m)		0	0	0	0	0		0	0	0	0	0
Reactivity to handling n)		0	0	0	0	0		0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead

Appendix 2-109 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 7)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0		0	0	0	0	0	0	0	0
Fur condition b)	0	0	0		0	0	0	0	0	0	0	0
Skin c)	0	0	0		0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0		0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0		0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0		0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0		0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0		0	0	0	0	0	0	0	0
Piloerection i)	0	0	0		0	0	0	0	0	0	0	0
Pupil size j)	0	0	0		0	0	0	0	0	0	0	0
Salivation k)	0	0	0		0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0		0	0	0	0	0	0	0	0
Vocalization m)	0	0	0		0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0		0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
S: Sacrificed moribund

Appendix 2-110 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 7)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-111 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 7)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-112 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 7)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Ease of removal from cage a)		0	0	0	0	0		0	0	0	0	0
Fur condition b)		0	0	0	0	0		0	0	0	0	0
Skin c)		0	0	0	0	0		0	0	0	0	0
Secretions-Eye, Nose d)		0	0	0	0	0		0	0	0	0	0
Exophthalmos e)		0	0	0	0	0		0	0	0	0	0
Palpebral closure f)		0	0	0	0	0		0	0	0	0	0
Mucosal membranes g)		0	0	0	0	0		0	0	0	0	0
Lacrimation h)		0	0	0	0	0		0	0	0	0	0
Piloerection i)		0	0	0	0	0		0	0	0	0	0
Pupil size j)		0	0	0	0	0		0	0	0	0	0
Salivation k)		0	0	0	0	0		0	0	0	0	0
Abnormal respiration l)		0	0	0	0	0		0	0	0	0	0
Vocalization m)		0	0	0	0	0		0	0	0	0	0
Reactivity to handling n)		0	0	0	0	0		0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead

Appendix 2-113 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 14)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0		0	0	0	0	0	0	0	0
Fur condition b)	0	0	0		0	0	0	0	0	0	0	0
Skin c)	0	0	0		0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0		0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0		0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0		0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0		0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0		0	0	0	0	0	0	0	0
Piloerection i)	0	0	0		0	0	0	0	0	0	0	0
Pupil size j)	0	0	0		0	0	0	0	0	0	0	0
Salivation k)	0	0	0		0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0		0	0	0	0	0	0	0	0
Vocalization m)	0	0	0		0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0		0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
S: Sacrificed moribund

Appendix 2-114 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 14)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-115 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 14)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-116 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 14)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Ease of removal from cage a)		0	0	0	0	0		0	0	0	0	0
Fur condition b)		0	0	0	0	0		0	0	0	0	0
Skin c)		0	0	0	0	0		0	0	0	0	0
Secretions-Eye, Nose d)		0	0	0	0	0		0	0	0	0	0
Exophthalmos e)		0	0	0	0	0		0	0	0	0	0
Palpebral closure f)		0	0	0	0	0		0	0	0	0	0
Mucosal membranes g)		0	0	0	0	0		0	0	0	0	0
Lacrimation h)		0	0	0	0	0		0	0	0	0	0
Piloerection i)		0	0	0	0	0		0	0	0	0	0
Pupil size j)		0	0	0	0	0		0	0	0	0	0
Salivation k)		0	0	0	0	0		0	0	0	1	0
Abnormal respiration l)		0	0	0	0	0		0	2o)	0	0	0
Vocalization m)		0	0	0	0	0		0	0	0	0	0
Reactivity to handling n)		0	0	0	0	0		0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
o) Dyspnea
D: Dead

Appendix 2-117 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 20)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0		0	0	0	0	0	0	0	0
Fur condition b)	0	0	0		0	0	0	0	0	0	0	0
Skin c)	0	0	0		0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0		0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0		0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0		0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0		0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0		0	0	0	0	0	0	0	0
Piloerection i)	0	0	0		0	0	0	0	0	0	0	0
Pupil size j)	0	0	0		0	0	0	0	0	0	0	0
Salivation k)	0	0	0		0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0		0	0	0	0	0	0	0	0
Vocalization m)	0	0	0		0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0		0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
S: Sacrificed moribund

Appendix 2-118 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 20)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-119 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 20)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-120 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 20)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D		D			
Ease of removal from cage a)		0	0	0	0	0		0		0	0	0
Fur condition b)		0	0	0	0	0		0		0	0	0
Skin c)		0	0	0	0	0		0		0	0	0
Secretions-Eye, Nose d)		0	0	0	0	0		0		0	0	0
Exophthalmos e)		0	0	0	0	0		0		0	0	0
Palpebral closure f)		0	0	0	0	0		0		0	0	0
Mucosal membranes g)		0	0	0	0	0		0		0	0	0
Lacrimation h)		0	0	0	0	0		0		0	0	0
Piloerection i)		0	0	0	0	0		0		0	0	0
Pupil size j)		0	0	0	0	0		0		0	0	0
Salivation k)		1	0	1	0	0		0		0	0	1
Abnormal respiration l)		0	0	0	0	0		0		0	0	0
Vocalization m)		0	0	0	0	0		0		0	0	0
Reactivity to handling n)		0	0	0	0	0		0		0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead

Appendix 2-121 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Lactation day 4)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0		0	0	0	0	0	0	0	0
Fur condition b)	0	0	0		0	0	0	0	0	0	0	0
Skin c)	0	0	0		0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0		0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0		0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0		0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0		0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0		0	0	0	0	0	0	0	0
Piloerection i)	0	0	0		0	0	0	0	0	0	0	0
Pupil size j)	0	0	0		0	0	0	0	0	0	0	0
Salivation k)	0	0	0		0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0		0	0	0	0	0	0	0	0
Vocalization m)	0	0	0		0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0		0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
S: Sacrificed moribund

Appendix 2-122 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Lactation day 4)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-123 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Lactation day 4)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-124 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Lactation day 4)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1 D	2	3	4	5	6	7 D	8	9 D	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0		0		0	0	0
Fur condition b)	0	0	0	0	0	0		0		0	0	0
Skin c)	0	0	0	0	0	0		0		0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0		0		0	0	0
Exophthalmos e)	0	0	0	0	0	0		0		0	0	0
Palpebral closure f)	0	0	0	0	0	0		0		0	0	0
Mucosal membranes g)	0	0	0	0	0	0		0		0	0	0
Lacrimation h)	0	0	0	0	0	0		0		0	0	0
Piloerection i)	0	0	0	0	0	0		0		0	0	0
Pupil size j)	0	0	0	0	0	0		0		0	0	0
Salivation k)	0	0	0	0	0	0		0		0	0	0
Abnormal respiration l)	0	0	0	0	0	0		0		0	0	0
Vocalization m)	0	0	0	0	0	0		0		0	0	0
Reactivity to handling n)	0	0	0	0	0	0		0		0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead

Appendix 2-125 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	1
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-126 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-127 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-128 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-129 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-130 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0		0	0	0	0
Fur condition b)	0	0	0	0	0		0	0	0	0
Skin c)	0	0	0	0	0		0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0		0	0	0	0
Exophthalmos e)	0	0	0	0	0		0	0	0	0
Palpebral closure f)	0	0	0	0	0		0	0	0	0
Mucosal membranes g)	0	0	0	0	0		0	0	0	0
Lacrimation h)	0	0	0	0	0		0	0	0	0
Piloerection i)	0	0	0	0	0		0	0	0	0
Pupil size j)	0	0	0	0	0		0	0	0	0
Salivation k)	0	0	0	0	0		0	0	0	0
Abnormal respiration l)	0	0	0	0	0		0	0	0	0
Vocalization m)	0	0	0	0	0		0	0	0	0
Reactivity to handling n)	0	0	0	0	0		0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead

Appendix 2-131 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-132 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0		0	0	0	0
Fur condition b)	0	0	0	0	0		0	0	0	0
Skin c)	0	0	0	0	0		0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0		0	0	0	0
Exophthalmos e)	0	0	0	0	0		0	0	0	0
Palpebral closure f)	0	0	0	0	0		0	0	0	0
Mucosal membranes g)	0	0	0	0	0		0	0	0	0
Lacrimation h)	0	0	0	0	0		0	0	0	0
Piloerection i)	0	0	0	0	0		0	0	0	0
Pupil size j)	0	0	0	0	0		0	0	0	0
Salivation k)	0	0	0	0	0		0	0	0	0
Abnormal respiration l)	0	0	0	0	0		0	0	0	0
Vocalization m)	0	0	0	0	0		0	0	1	0
Reactivity to handling n)	0	0	0	0	0		0	0	1	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead

Appendix 2-133 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-134 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0		0	0	0	0
Fur condition b)	0	0	0	0	0		0	0	0	0
Skin c)	0	0	0	0	0		0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0		0	0	0	0
Exophthalmos e)	0	0	0	0	0		0	0	0	0
Palpebral closure f)	0	0	0	0	0		0	0	0	0
Mucosal membranes g)	0	0	0	0	0		0	0	0	0
Lacrimation h)	0	0	0	0	0		0	0	0	0
Piloerection i)	0	0	0	0	0		0	0	0	0
Pupil size j)	0	0	0	0	0		0	0	0	0
Salivation k)	0	0	0	0	0		0	0	0	0
Abnormal respiration l)	0	0	0	0	0		0	0	0	0
Vocalization m)	0	0	0	0	0		0	0	0	0
Reactivity to handling n)	0	0	0	0	0		0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead

Appendix 2-135 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-136 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0		0	0	0	0
Fur condition b)	0	0	0	0	0		0	0	0	0
Skin c)	0	0	0	0	0		0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0		0	0	0	0
Exophthalmos e)	0	0	0	0	0		0	0	0	0
Palpebral closure f)	0	0	0	0	0		0	0	0	0
Mucosal membranes g)	0	0	0	0	0		0	0	0	0
Lacrimation h)	0	0	0	0	0		0	0	0	0
Piloerection i)	0	0	0	0	0		0	0	0	0
Pupil size j)	0	0	0	0	0		0	0	0	0
Salivation k)	0	0	0	0	0		0	0	0	0
Abnormal respiration l)	0	2o)	0	0	0		0	0	0	0
Vocalization m)	0	0	0	0	0		0	0	0	0
Reactivity to handling n)	0	0	0	0	0		0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
o) Dyspnea
D: Dead

Appendix 2-137 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-138 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4008-4012)				
	8	9	10 S	11	12
Ease of removal from cage a)	0	0	0	0	
Fur condition b)	0	0	0	0	
Skin c)	0	0	0	0	
Secretions-Eye, Nose d)	0	0	0	0	
Exophthalmos e)	0	0	0	0	
Palpebral closure f)	0	0	0	0	
Mucosal membranes g)	0	0	0	0	
Lacrimation h)	0	0	0	0	
Piloerection i)	0	0	0	0	
Pupil size j)	0	0	0	0	
Salivation k)	0	0	0	0	
Abnormal respiration l)	0	0	0	0	
Vocalization m)	0	0	0	0	
Reactivity to handling n)	0	0	0	0	

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
S: Sacrificed moribund

Appendix 2-139 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-140 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4008-4012)				
	8	9	10 S	11	12
Ease of removal from cage a)	0	0	0	0	
Fur condition b)	0	0	0	0	
Skin c)	0	0	0	0	
Secretions-Eye, Nose d)	0	0	0	0	
Exophthalmos e)	0	0	0	0	
Palpebral closure f)	0	0	0	0	
Mucosal membranes g)	0	0	0	0	
Lacrimation h)	0	0	0	0	
Piloerection i)	0	0	0	0	
Pupil size j)	0	0	0	0	
Salivation k)	0	0	0	0	
Abnormal respiration l)	0	0	0	0	
Vocalization m)	0	0	1	0	
Reactivity to handling n)	0	0	1	0	

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
S: Sacrificed moribund

Appendix 2-141 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Week 1 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-142 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Week 1 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4118-4122)				
	18 D	19	20	21	22
Ease of removal from cage a)	0	0	0	0	
Fur condition b)	0	0	0	0	
Skin c)	0	0	0	0	
Secretions-Eye, Nose d)	0	0	0	0	
Exophthalmos e)	0	0	0	0	
Palpebral closure f)	0	0	0	0	
Mucosal membranes g)	0	0	0	0	
Lacrimation h)	0	0	0	0	
Piloerection i)	0	0	0	0	
Pupil size j)	0	0	0	0	
Salivation k)	0	0	0	0	
Abnormal respiration l)	0	1o)	0	0	
Vocalization m)	0	0	0	0	
Reactivity to handling n)	0	0	0	0	

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
o) Dyspnea
D: Dead

Appendix 2-143 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-144 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Week 2 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4118-4122)				
	18 D	19	20	21	22
Ease of removal from cage a)	0	0	0	0	
Fur condition b)	0	0	0	0	
Skin c)	0	0	0	0	
Secretions-Eye, Nose d)	0	0	0	0	
Exophthalmos e)	0	0	0	0	
Palpebral closure f)	0	0	0	0	
Mucosal membranes g)	0	0	0	0	
Lacrimation h)	0	0	0	0	
Piloerection i)	0	0	0	0	
Pupil size j)	0	0	0	0	
Salivation k)	0	0	0	0	
Abnormal respiration l)	0	0	0	0	
Vocalization m)	0	0	0	0	
Reactivity to handling n)	0	0	0	0	

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
D: Dead

Appendix 2-145 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	7	5	6	7	6	6	4	6	7	3	2
Defecation count	3	0	0	0	0	0	0	0	0	0	0	0
Urination h)	1	1	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-146 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	3	6	4	5	6	4	4	4	4	5	5
Defecation count	1	0	0	0	0	0	0	0	0	2	0	0
Urination h)	1	0	1	0	0	0	0	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-147 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	6	5	2	6	2	3	5	5	6	1	6
Defecation count	0	0	0	0	0	0	3	1	0	0	0	1
Urination h)	0	0	0	0	0	0	0	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-148 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	U	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	7	5	4	4	4	4	0	2	4	2	3
Defecation count	0	0	0	0	0	0	0	3	0	1	0	0
Urination h)	0	0	0	0	0	0	0	2	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-149 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	4	7	6	3	3	4	3	7	2	2	4
Defecation count	3	2	0	0	0	0	0	0	0	0	3	0
Urination h)	1	1	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-150 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	4	6	6	6	3	2	10	5	3	4	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	1	0	0	0	0	0	0	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-151 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	4	2	1	3	4	5	4	5	6	1	6
Defecation count	0	0	0	0	1	0	0	1	0	0	0	0
Urination h)	0	0	0	0	0	0	1	2	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-152 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3 D	4	5	6	7	8	9	10 S	11	12
Arousal a)	0	0	0	0	0	0	0	0		0	0	
Convulsion b)	0	0	0	0	0	0	0	0		0	0	
Abnormal behavior c)	0	0	0	0	0	0	0	0		0	0	
Stereotypy d)	0	0	0	0	0	0	0	0		0	0	
Gait e)	0	0	0	0	0	0	0	0		0	0	
Posture f)	N	N	N	N	N	N	N	N		N	N	
Grooming g)	0	0	0	0	0	0	0	0		0	0	
Rearing	0	5	4	2	6	6	3	1		2	1	
Defecation count	0	0	0	0	0	0	0	0		0	0	
Urination h)	0	0	0	0	0	0	0	0		0	0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead
S: Sacrificed moribund

Appendix 2-153 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	6	4	6	9	5	6	4	7	7	0	1
Defecation count	0	2	0	0	0	0	0	0	0	0	1	0
Urination h)	1	0	1	1	0	0	0	0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-154 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 3 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	4	6	5	4	6	4	7	3	2	4	3
Defecation count	0	0	0	0	0	0	0	0	0	2	0	0
Urination h)	1	0	0	0	0	0	0	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-155 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 3 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	1	1	1	4	2	5	5	4	3	5	1	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	1	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-156 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 3 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3 D	4	5	6	7	8	9	10 S	11	12
Arousal a)	0	0	0	0	0	0	0	0	0		0	0
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0		0	0
Gait e)	0	0	0	0	0	0	0	0	0		0	0
Posture f)	N	N	N	N	N	N	N	N	N		N	N
Grooming g)	0	0	0	0	0	0	0	0	0		0	0
Rearing	0	4	2	4	8	5	4	1			2	5
Defecation count	0	0	0	0	0	0	0	0	0		0	0
Urination h)	0	1	0	0	0	0	1	0			0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead
S: Sacrificed moribund

Appendix 2-157 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	1	4	5	4	6	5	4	5	4	3	3	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	2	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-158 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 4 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	4	3	5	3	7	3	5	4	2	4	3
Defecation count	2	0	0	0	0	0	0	0	0	2	0	0
Urination h)	2	0	0	0	0	0	0	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-159 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 4 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	4	0	0	4	4	2	8	1	3	1	3
Defecation count	0	0	0	0	1	0	1	0	0	0	2	0
Urination h)	0	1	0	0	0	0	1	1	0	0	1	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-160 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 4 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
			D							S		
Arousal a)	0	0		0	0	0	0	0	0		0	0
Convulsion b)	0	0		0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0		0	0	0	0	0	0		0	0
Stereotypy d)	0	0		0	0	0	0	0	0		0	0
Gait e)	0	0		0	0	0	0	0	0		0	0
Posture f)	N	N		N	N	N	N	N	N		N	N
Grooming g)	0	0		0	0	0	0	0	0		0	0
Rearing	0	3		2	4	4	5	5	2		3	5
Defecation count	0	0		0	0	0	0	0	0		0	0
Urination h)	0	0		0	0	0	0	0	0		0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead
S: Sacrificed moribund

Appendix 2-161 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	7	5	7	6	5	3	3	5	2	4	1
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	1	0	0	1	0	0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-162 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 5 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	3	6	5	4	5	2	5	2	3	4	1
Defecation count	1	0	0	0	0	0	0	0	0	0	0	0
Urination h)	1	0	0	1	0	1	0	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-163 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 5 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	7	1	0	4	4	5	5	2	4	0	2
Defecation count	0	0	0	0	0	0	0	1	0	0	0	0
Urination h)	0	1	0	0	0	0	1	1	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-164 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 5 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
			D							S		
Arousal a)	0	0		0	0	0	0	0	0		0	0
Convulsion b)	0	0		0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0		0	0	0	0	0	0		0	0
Stereotypy d)	0	0		0	0	0	0	0	0		0	0
Gait e)	0	0		0	0	0	0	0	0		0	0
Posture f)	N	N		N	N	N	N	N	N		N	N
Grooming g)	0	0		0	0	0	0	0	0		0	0
Rearing	1	4		0	7	3	1	6	2		1	4
Defecation count	0	0		0	0	0	0	0	0		0	0
Urination h)	0	0		0	0	0	0	1	0		1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead
S: Sacrificed moribund

Appendix 2-165 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	4	2	4	5	2	4	3	9	4	7	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	1	0	1	0	0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-166 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 6 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	4	3	4	9	3	1	10	5	6	3	4
Defecation count	1	0	0	0	0	0	0	0	0	0	0	0
Urination h)	1	0	0	0	0	0	0	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-167 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 6 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	0	4	3	2	2	6	5	4	2	6	4	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	1	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-168 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 6 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4001-4012)											
	1	2	3 D	4 D	5	6	7	8	9	10 S	11	12
Arousal a)	0	0			0	0	0	0	0		0	0
Convulsion b)	0	0			0	0	0	0	0		0	0
Abnormal behavior c)	0	0			0	0	0	0	0		0	0
Stereotypy d)	0	0			0	0	0	0	0		0	0
Gait e)	0	0			0	0	0	0	0		0	0
Posture f)	N	N			N	N	N	N	N		N	N
Grooming g)	0	0			0	0	0	0	0		0	0
Rearing	1	3			6	2	6	3	0		1	4
Defecation count	0	0			0	0	0	0	0		0	0
Urination h)	0	0			0	0	0	0	0		0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead
S: Sacrificed moribund

Appendix 2-169 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	3	8	7	6	7	6	8	10	7	8	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-170 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 1 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	9	10	9	5	5	6	9	5	4	4	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-171 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 1 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	1	0	0	0
Rearing	9	8	5	5	4	10	6	4	3	2	9	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	1	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-172 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 1 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	8	5	6	1	8	10	8	6	2	5	3	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-173 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	5	8	3	7	10	7	6	7	7	7	8
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-174 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 2 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	11	6	9	5	4	4	9	6	6	4	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-175 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 2 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	9	6	7	7	5	8	9	4	3	1	7	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-176 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 2 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Arousal a)		0	0	0	0	0		0	0	0	0	0
Convulsion b)		0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)		0	0	0	0	0		0	0	0	0	0
Stereotypy d)		0	0	0	0	0		0	0	0	0	0
Gait e)		0	0	0	0	0		0	0	0	0	0
Posture f)		N	N	N	N	N		N	N	N	N	N
Grooming g)		0	0	0	0	0		0	0	0	0	0
Rearing		6	9	2	7	7		5	2	5	3	12
Defecation count		0	0	0	0	0		0	0	0	0	0
Urination h)		0	0	0	0	0		0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-177 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 1)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Arousal a)	0	0	0		0	0	0	0	0	0	0	0
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0		0	0	0	0	0	0	0	0
Gait e)	0	0	0		0	0	0	0	0	0	0	0
Posture f)	N	N	N		N	N	N	N	N	N	N	N
Grooming g)	0	0	0		0	0	0	0	0	0	0	0
Rearing	7	3	6		5	4	6	13	9	4	5	11
Defecation count	0	0	0		0	0	0	0	0	0	0	0
Urination h)	0	0	0		0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
S: Sacrificed moribund

Appendix 2-178 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 1)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	8	3	12	5	4	3	3	6	9	5	0
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-179 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 1)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	4	1	6	5	7	4	6	3	4	4	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-180 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 1)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Arousal a)		0	0	0	0	0		0	0	0	0	0
Convulsion b)		0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)		0	0	0	0	0		0	0	0	0	0
Stereotypy d)		0	0	0	0	0		0	0	0	0	0
Gait e)		0	0	0	0	0		0	0	0	0	0
Posture f)		N	N	N	N	N		N	N	N	N	N
Grooming g)		0	0	0	0	0		0	0	0	0	0
Rearing		5	7	5	7	6		4	2	4	4	5
Defecation count		0	0	0	0	0		0	0	0	0	0
Urination h)		0	0	0	0	0		0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-181 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 7)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Arousal a)	0	0	0		0	0	0	0	0	0	0	0
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0		0	0	0	0	0	0	0	0
Gait e)	0	0	0		0	0	0	0	0	0	0	0
Posture f)	N	N	N		N	N	N	N	N	N	N	N
Grooming g)	0	0	0		0	0	0	0	0	0	0	0
Rearing	6	4	3		6	9	4	4	6	7	6	6
Defecation count	0	0	0		0	0	0	0	0	0	0	0
Urination h)	0	0	0		0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
S: Sacrificed moribund

Appendix 2-182 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 7)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	6	5	11	7	5	2	8	4	7	5	8
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-183 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 7)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	7	4	8	6	8	6	7	2	7	6	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-184 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 7)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Arousal a)		0	0	0	0	0		0	0	0	0	0
Convulsion b)		0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)		0	0	0	0	0		0	0	0	0	0
Stereotypy d)		0	0	0	0	0		0	0	0	0	0
Gait e)		0	0	0	0	0		0	0	0	0	0
Posture f)		N	N	N	N	N		N	N	N	N	N
Grooming g)		0	0	0	0	0		0	0	0	0	0
Rearing		6	7	7	9	6		7	5	5	6	4
Defecation count		0	0	0	0	0		0	0	0	0	0
Urination h)		0	0	0	0	0		0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-185 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 14)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Arousal a)	0	0	0		0	0	0	0	0	0	0	0
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0		0	0	0	0	0	0	0	0
Gait e)	0	0	0		0	0	0	0	0	0	0	0
Posture f)	N	N	N		N	N	N	N	N	N	N	N
Grooming g)	0	0	0		0	0	0	0	0	0	0	0
Rearing	4	4	5		7	7	5	5	6	5	5	7
Defecation count	0	0	0		0	0	0	0	0	0	0	0
Urination h)	0	0	0		0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
S: Sacrificed moribund

Appendix 2-186 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 14)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	6	3	2	4	4	4	6	5	5	6	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-187 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 14)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	6	0	7	8	7	7	7	5	4	6	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-188 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 14)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D					
Arousal a)		0	0	0	0	0		0	0	0	0	0
Convulsion b)		0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)		0	0	0	0	0		0	0	0	0	0
Stereotypy d)		0	0	0	0	0		0	0	0	0	0
Gait e)		0	0	0	0	0		0	0	0	0	0
Posture f)		N	N	N	N	N		N	N	N	N	N
Grooming g)		0	0	0	0	0		0	0	0	0	0
Rearing		4	4	5	5	5		7	1	3	4	5
Defecation count		0	0	0	0	0		0	0	0	0	0
Urination h)		0	0	0	0	0		0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-189 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 20)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Arousal a)	0	0	0		0	0	0	0	0	0	0	0
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0		0	0	0	0	0	0	0	0
Gait e)	0	0	0		0	0	0	0	0	0	0	0
Posture f)	N	N	N		N	N	N	N	N	N	N	N
Grooming g)	0	0	0		0	0	0	0	0	0	0	0
Rearing	6	3	3		4	6	6	7	5	5	4	5
Defecation count	0	0	0		0	0	0	0	0	0	0	0
Urination h)	0	0	0		0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
S: Sacrificed moribund

Appendix 2-190 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 20)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	6	6	6	3	2	6	9	5	3	6	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-191 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 20)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	6	5	6	4	3	5	4	5	1	6	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-192 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 20)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D		D			
Arousal a)		0	0	0	0	0		0		0	0	0
Convulsion b)		0	0	0	0	0		0		0	0	0
Abnormal behavior c)		0	0	0	0	0		0		0	0	0
Stereotypy d)		0	0	0	0	0		0		0	0	0
Gait e)		0	0	0	0	0		0		0	0	0
Posture f)		N	N	N	N	N		N		N	N	N
Grooming g)		0	0	0	0	0		0		0	0	0
Rearing		3	6	4	7	4		5		3	5	6
Defecation count		0	0	0	0	0		0		0	0	0
Urination h)		0	0	1	0	0		0		0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-193 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Lactation day 4)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4 S	5	6	7	8	9	10	11	12
Arousal a)	0	0	0		0	0	0	0	0	0	0	0
Convulsion b)	0	0	0		0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0		0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0		0	0	0	0	0	0	0	0
Gait e)	0	0	0		0	0	0	0	0	0	0	0
Posture f)	N	N	N		N	N	N	N	N	N	N	N
Grooming g)	0	0	0		0	0	0	0	0	0	0	0
Rearing	4	4	7		6	7	7	10	7	6	7	9
Defecation count	0	0	0		0	0	0	0	0	0	0	0
Urination h)	0	0	0		0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
S: Sacrificed moribund

Appendix 2-194 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Lactation day 4)
Dose (mg/kg): 15

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	7	11	7	9	6	6	7	9	7	5	7	8
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	1	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-195 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Lactation day 4)
Dose (mg/kg): 50

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	8	9	4	6	7	7	7	9	6	4	6	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	1	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-196 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Lactation day 4)
Dose (mg/kg): 150

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	D						D		D			
Arousal a)		0	0	0	0	0		0		0	0	0
Convulsion b)		0	0	0	0	0		0		0	0	0
Abnormal behavior c)		0	0	0	0	0		0		0	0	0
Stereotypy d)		0	0	0	0	0		0		0	0	0
Gait e)		0	0	0	0	0		0		0	0	0
Posture f)		N	N	N	N	N		N		N	N	N
Grooming g)		0	0	0	0	0		0		0	0	0
Rearing		11	6	8	5	7		6		6	6	8
Defecation count		0	0	0	0	0		0		0	0	0
Urination h)		0	0	0	0	0		1		0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-197 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	10	7	7	6	7	7	6	8	6	9
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-198 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	6	7	9	7	6	3	5	4	6	6
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-199 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	9	8	9	4	8	10	6	7	6	7
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	1	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-200 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	7	8	6	6	4	2	5	6	9	5
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-201 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	10	8	13	8	9	10	7	10	7	8
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-202 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Arousal a)	0	0	0	0	0		0	0	0	0
Convulsion b)	0	0	0	0	0		0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0
Stereotypy d)	0	0	0	0	0		0	0	0	0
Gait e)	0	0	0	0	0		0	0	0	0
Posture f)	N	N	N	N	N		N	N	N	N
Grooming g)	0	0	0	0	0		0	0	0	0
Rearing	7	10	11	10	6		7	7	8	11
Defecation count	0	0	0	0	0		0	0	0	0
Urination h)	0	0	0	0	0		0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-203 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	10	6	10	7	7	5	6	8	8	11
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-204 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Arousal a)	0	0	0	0	0		0	0	0	0
Convulsion b)	0	0	0	0	0		0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0
Stereotypy d)	0	0	0	0	0		0	0	0	0
Gait e)	0	0	0	0	0		0	0	0	0
Posture f)	N	N	N	N	N		N	N	N	N
Grooming g)	0	0	0	0	0		0	0	0	0
Rearing	7	9	6	9	4		6	7	10	10
Defecation count	0	0	0	0	0		0	0	0	0
Urination h)	0	0	0	0	0		0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-205 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	10	9	9	6	6	10	6	8	9	8
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-206 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Arousal a)	0	0	0	0	0		0	0	0	0
Convulsion b)	0	0	0	0	0		0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0
Stereotypy d)	0	0	0	0	0		0	0	0	0
Gait e)	0	0	0	0	0		0	0	0	0
Posture f)	N	N	N	N	N		N	N	N	N
Grooming g)	0	0	0	0	0		0	0	0	0
Rearing	7	8	12	7	7		10	6	5	8
Defecation count	0	0	0	0	0		0	0	0	0
Urination h)	0	0	0	0	0		0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-207 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	11	9	10	7	10	6	7	10	7	10
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-208 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18 D	19	20	21	22
Arousal a)	0	0	0	0	0		0	0	0	0
Convulsion b)	0	0	0	0	0		0	0	0	0
Abnormal behavior c)	0	0	0	0	0		0	0	0	0
Stereotypy d)	0	0	0	0	0		0	0	0	0
Gait e)	0	0	0	0	0		0	0	0	0
Posture f)	N	N	N	N	N		N	N	N	N
Grooming g)	0	0	0	0	0		0	0	0	0
Rearing	9	0	6	9	7		6	9	6	10
Defecation count	0	0	0	0	0		0	0	0	0
Urination h)	0	0	0	0	0		0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-209 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual detailed clinical signs in male rats: open field observation

(Week 1 of recovery)

Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	8	6	5	3	3
Defecation count	0	0	0	0	0
Urination h)	0	1	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-210 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4008-4012)				
	8	9	10 S	11	12
Arousal a)	0	0	0	0	
Convulsion b)	0	0	0	0	
Abnormal behavior c)	0	0	0	0	
Stereotypy d)	0	0	0	0	
Gait e)	0	0	0	0	
Posture f)	N	N	N	N	
Grooming g)	0	0	0	0	
Rearing	4	2	1	5	
Defecation count	0	0	0	0	
Urination h)	0	0	0	0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
S: Sacrificed moribund

Appendix 2-211 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual detailed clinical signs in male rats: open field observation

(Week 2 of recovery)

Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	4	8	4	5	2
Defecation count	0	0	0	0	0
Urination h)	0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-212 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4008-4012)				
	8	9	10 S	11	12
Arousal a)	0	0	0	0	
Convulsion b)	0	0	0	0	
Abnormal behavior c)	0	0	0	0	
Stereotypy d)	0	0	0	0	
Gait e)	0	0	0	0	
Posture f)	N	N	N	N	
Grooming g)	0	0	0	0	
Rearing	7	2	3	5	
Defecation count	0	0	0	0	
Urination h)	0	0	1	0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
S: Sacrificed moribund

Appendix 2-213 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Week 1 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	9	4	14	8	7
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-214 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Week 1 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4118-4122)				
	18 D	19	20	21	22
Arousal a)	0	0	0	0	
Convulsion b)	0	0	0	0	
Abnormal behavior c)	0	0	0	0	
Stereotypy d)	0	0	0	0	
Gait e)	0	0	0	0	
Posture f)	N	N	N	N	
Grooming g)	0	0	0	0	
Rearing	9	8	8	11	
Defecation count	0	0	0	0	
Urination h)	0	0	0	0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-215 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	13	7	10	11	9
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-216 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Week 2 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4118-4122)				
	18 D	19	20	21	22
Arousal a)	0	0	0	0	
Convulsion b)	0	0	0	0	
Abnormal behavior c)	0	0	0	0	
Stereotypy d)	0	0	0	0	
Gait e)	0	0	0	0	
Posture f)	N	N	N	N	
Grooming g)	0	0	0	0	
Rearing	8	7	10	11	
Defecation count	0	0	0	0	
Urination h)	0	0	0	0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
D: Dead

Appendix 2-217 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of male rats (Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	93	57	40	38	90

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-218 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of male rats (Week 6 of administration)
Dose (mg/kg): 15

Parameter	Animal number (2008-2012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	50	54	43	75	87

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-219 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of male rats (Week 6 of administration)
Dose (mg/kg): 50

Parameter	Animal number (3008-3012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	90	105	42	63	42

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-220 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of male rats (Week 6 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
			S		
Auditory response a)	0	0		0	0
Approach response b)	0	0		0	0
Touch response c)	0	0		0	0
Tail pinch response d)	0	0		0	0
Pupillary reflex e)	P	P		P	P
Aerial righting reflex (Total score)	0	0		0	0
Landing foot splay (mm)	72	44		63	78

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds
S: Sacrificed moribund

Appendix 2-221 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of female rats (Main group, Lactation day 4)
Dose (mg/kg): 0

Parameter	Animal number (1103-1111)				
	3	5	6	10	11
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	50	69	74	50	59

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-222 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of female rats (Main group, Lactation day 4)
Dose (mg/kg): 15

Parameter	Animal number (2104-2112)				
	4	6	7	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	58	71	64	31	54

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-223 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of female rats (Main group, Lactation day 4)
Dose (mg/kg): 50

Parameter	Animal number (3101-3110)				
	1	5	8	9	10
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	39	85	72	98	103

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-224 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of female rats (Main group, Lactation day 4)
Dose (mg/kg): 150

Parameter	Animal number (4103-4108)				
	3	4	5	6	8
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	45	80	64	78	75

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-225 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	58	32	74	48	58

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-226 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 150

Parameter	Animal number (4118-4122)				
	18 D	19	20	21	22
Auditory response a)	0	0	0	0	
Approach response b)	0	0	0	0	
Touch response c)	0	0	0	0	
Tail pinch response d)	0	0	0	0	
Pupillary reflex e)	P	P	P	P	
Aerial righting reflex (Total score)	0	0	0	0	
Landing foot splay (mm)	59	64	22	57	

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds
D: Dead

Appendix 2-227 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	66	57	64	50	63

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-228 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of male rats (Week 2 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4008-4012)				
	8	9	10 S	11	12
Auditory response a)	0	0	0	0	
Approach response b)	0	0	0	0	
Touch response c)	0	0	0	0	
Tail pinch response d)	0	0	0	0	
Pupillary reflex e)	P	P	P	P	
Aerial righting reflex (Total score)	0	0	0	0	
Landing foot splay (mm)	54	66	56	86	

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds
S: Sacrificed moribund

Appendix 2-229 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	38	50	75	64	41

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-230 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual manipulative test of female rats (Week 2 of recovery)
Dose (mg/kg): 150

Parameter	Animal number (4118-4122)				
	18 D	19	20	21	22
Auditory response a)	0	0	0	0	
Approach response b)	0	0	0	0	
Touch response c)	0	0	0	0	
Tail pinch response d)	0	0	0	0	
Pupillary reflex e)	P	P	P	P	
Aerial righting reflex (Total score)	0	0	0	0	
Landing foot splay (mm)	63	61	40	30	

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds
D: Dead

Appendix 2-231 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1008	1090	528
1009	1103	700
1010	1052	658
1011	1410	677
1012	1312	840
Mean	1193	681
S.D.	158	111

Appendix 2-232 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 15

Animal number	Fore limb g	Hind limb g
2008	1091	1026
2009	1791	679
2010	1370	741
2011	1028	657
2012	791	564
Mean	1214	733
S.D.	383	175

Appendix 2-233 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 50

Animal number	Fore limb g	Hind limb g
3008	1759	741
3009	1430	859
3010	1412	647
3011	1562	717
3012	1516	795
Mean	1536	752
S.D.	139	80

Appendix 2-234 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 150

Animal number	Fore limb g	Hind limb g
4008	1441	637
4009	1426	721
4010S		
4011	1478	620
4012	1605	917
Mean	1488	724
S.D.	81	136

S: Sacrificed moribund

Appendix 2-235 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1103	1120	557
1105	1293	861
1106	1149	516
1110	1098	670
1111	1120	717
Mean	1156	664
S.D.	79	137

Appendix 2-236 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 15

Animal number	Fore limb g	Hind limb g
2104	1163	729
2106	1384	554
2107	1308	878
2111	1108	567
2112	979	577
Mean	1188	661
S.D.	161	141

Appendix 2-237 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 50

Animal number	Fore limb g	Hind limb g
3101	1267	610
3105	1412	581
3108	1246	851
3109	1327	584
3110	1344	760
Mean	1319	677
S.D.	66	122

Appendix 2-238 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 150

Animal number	Fore limb g	Hind limb g
4103	1098	744
4104	1359	814
4105	1090	622
4106	1239	568
4108	1158	688
Mean	1189	687
S.D.	112	97

Appendix 2-239 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1118	1387	722
1119	1205	634
1120	1274	730
1121	1134	611
1122	1523	720
Mean	1305	683
S.D.	154	56

Appendix 2-240 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 150

Animal number	Fore limb g	Hind limb g
4118D		
4119	1090	677
4120	1190	647
4121	1166	621
4122	862	505
Mean	1077	613
S.D.	150	75

D: Dead

Appendix 2-241 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1008	1217	627
1009	1228	771
1010	1323	871
1011	1351	724
1012	1480	840
Mean	1320	767
S.D.	107	97

Appendix 2-242 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of male rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	Fore limb g	Hind limb g
4008	1277	885
4009	1596	698
4010S		
4011	1421	604
4012	1512	1121
Mean	1452	827
S.D.	137	228

S: Sacrificed moribund

Appendix 2-243 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1118	1295	662
1119	1080	563
1120	1104	598
1121	1101	697
1122	1204	798
Mean	1157	664
S.D.	91	92

Appendix 2-244 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual grip strength of female rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	Fore limb g	Hind limb g
4118D		
4119	1146	699
4120	879	806
4121	865	771
4122	1315	623
Mean	1051	725
S.D.	218	81

D: Dead

Appendix 2-245 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1008	308	188	32	24	19	3	574
1009	391	334	264	158	22	9	1178
1010	420	421	421	246	101	12	1621
1011	410	397	338	231	76	20	1472
1012	424	399	211	17	264	134	1449
Mean	391	348	253	135	96	36	1259
S.D.	48	95	147	110	100	55	415

Unit: Count

Appendix 2-246 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of male rats (Week 6 of administration)
Dose (mg/kg): 15

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
2008	386	171	275	9	32	11	884
2009	360	212	137	33	14	16	772
2010	263	157	170	181	305	21	1097
2011	311	26	19	20	59	11	446
2012	445	385	70	153	40	12	1105
Mean	353	190	134	79	90	14	861
S.D.	70	129	98	81	121	4	272

Unit: Count

Appendix 2-247 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of male rats (Week 6 of administration)
Dose (mg/kg): 50

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
3008	341	49	18	15	12	8	443
3009	394	357	324	288	162	19	1544
3010	436	377	201	155	27	8	1204
3011	345	334	305	191	44	11	1230
3012	427	380	252	49	38	0	1146
Mean	389	299	220	140	57	9	1113
S.D.	44	141	123	110	60	7	405

Unit: Count

Appendix 2-248 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of male rats (Week 6 of administration)
Dose (mg/kg): 150

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4008	461	255	21	19	72	12	840
4009	364	383	301	234	113	16	1411
4010S							
4011	366	302	320	34	49	4	1075
4012	341	349	44	8	204	7	953
Mean	383	322	172	74	110	10	1070
S.D.	53	56	161	107	68	5	247

Unit: Count
S: Sacrificed moribund

Appendix 2-249 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of female rats (Main group, Lactation day 4)
Dose (mg/kg): 0

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1103	347	240	118	46	12	12	775
1105	390	203	176	159	277	268	1473
1106	300	164	200	145	172	225	1206
1110	246	266	40	33	248	272	1105
1111	359	135	22	25	69	18	628
Mean	328	202	111	82	156	159	1037
S.D.	56	54	79	65	114	133	339

Unit: Count

Appendix 2-250 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of female rats (Main group, Lactation day 4)
Dose (mg/kg): 15

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
2104	333	162	5	79	34	30	643
2106	373	236	92	208	28	11	948
2107	416	171	26	26	5	20	664
2111	422	367	241	223	275	150	1678
2112	468	328	120	25	20	241	1202
Mean	402	253	97	112	72	90	1027
S.D.	51	92	93	97	114	101	430

Unit: Count

Appendix 2-251 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of female rats (Main group, Lactation day 4)
Dose (mg/kg): 50

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
3101	403	215	275	229	323	238	1683
3105	357	256	5	17	17	28	680
3108	167	4	13	15	148	4	351
3109	327	13	14	21	1	6	382
3110	467	229	53	6	12	18	785
Mean	344	143	72	58	100	59	776
S.D.	112	124	115	96	138	101	540

Unit: Count

Appendix 2-252 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of female rats (Main group, Lactation day 4)
Dose (mg/kg): 150

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4103	273	260	64	23	33	95	748
4104	300	52	23	20	145	210	750
4105	269	298	242	189	73	23	1094
4106	332	157	10	8	14	12	533
4108	166	16	21	20	14	16	253
Mean	268	157	72	52	56	71	676
S.D.	62	124	97	77	55	85	310

Unit: Count

Appendix 2-253 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1118	416	367	266	144	204	200	1597
1119	412	375	335	376	107	6	1611
1120	399	345	260	150	48	267	1469
1121	368	356	230	108	6	6	1074
1122	404	292	288	271	12	7	1274
Mean	400	347	276	210	75	97	1405
S.D.	19	33	39	111	82	127	229

Unit: Count

Appendix 2-254 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 150

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4118D							
4119	398	316	282	287	95	200	1578
4120	420	253	287	101	4	2	1067
4121	386	351	328	350	44	3	1462
4122	506	509	398	386	249	21	2069
Mean	428	357	324	281	98	57	1544
S.D.	54	109	54	127	107	96	413

Unit: Count
D: Dead

Appendix 2-255 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1008	290	361	318	374	363	202	1908
1009	335	439	319	277	87	73	1530
1010	396	340	352	246	238	152	1724
1011	342	364	341	182	59	16	1304
1012	416	392	251	3	19	18	1099
Mean	356	379	316	216	153	92	1513
S.D.	50	38	39	138	144	83	322

Unit: Count

Appendix 2-256 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of male rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4008	448	380	53	15	31	0	927
4009	318	291	280	298	258	255	1700
4010S							
4011	289	283	47	176	181	52	1028
4012	377	315	90	18	15	28	843
Mean	358	317	118	127	121	84	1125
S.D.	70	44	110	137	118	116	391

Unit: Count
S: Sacrificed moribund

Appendix 2-257 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1118	356	477	294	311	96	21	1555
1119	362	353	288	172	17	6	1198
1120	333	215	50	0	214	365	1177
1121	353	320	121	253	138	14	1199
1122	311	289	204	109	72	128	1113
Mean	343	331	191	169	107	107	1248
S.D.	21	96	106	122	74	153	175

Unit: Count

Appendix 2-258 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual motor activity of female rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4118D							
4119	257	246	240	131	129	176	1179
4120	241	0	1	0	0	78	320
4121	360	221	285	261	288	151	1566
4122	407	390	288	364	399	293	2141
Mean	316	214	204	189	204	175	1302
S.D.	80	161	137	158	175	89	764

Unit: Count
D: Dead

Appendix 3-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
1001	450	470	497	512	521	538	555	105
1002	429	448	476	497	518	547	556	127
1003	419	441	461	479	507	534	529	110
1004	430	450	473	490	511	529	541	111
1005	422	451	469	493	520	540	558	136
1006	389	420	444	465	485	510	514	125
1007	437	473	500	515	549	565	580	143
1008	413	438	459	470	496	510	530	117
1009	410	443	467	493	510	527	530	120
1010	404	439	470	479	502	525	523	119
1011	415	436	462	492	512	535	538	123
1012	406	425	444	463	484	503	502	96
Mean	419	445	469	487	510	530	538	119
S.D.	16	16	17	17	18	17	22	13

Unit: g

Appendix 3-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of male rats (Administration period)
Dose (mg/kg): 15

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
2001	417	444	465	477	496	518	524	107
2002	391	419	446	457	478	495	507	116
2003	403	427	452	465	490	507	507	104
2004	427	469	493	510	525	537	539	112
2005	438	470	495	519	537	565	566	128
2006	432	459	480	493	513	542	544	112
2007	401	421	439	448	474	494	494	93
2008	424	446	469	477	490	500	491	67
2009	422	452	481	495	527	551	566	144
2010	406	422	433	446	460	485	494	88
2011	405	422	442	473	489	520	513	108
2012	411	440	467	488	511	537	541	130
Mean	415	441	464	479	499	521	524	109
S.D.	14	19	21	23	24	25	27	20

Unit: g

Appendix 3-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of male rats (Administration period)
Dose (mg/kg): 50

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
3001	417	436	471	486	511	525	542	125
3002	404	438	461	464	489	501	499	95
3003	416	431	443	442	465	489	501	85
3004	415	433	459	475	486	515	523	108
3005	410	430	439	458	474	503	516	106
3006	441	471	496	504	507	536	544	103
3007	397	426	441	450	463	481	487	90
3008	418	441	462	475	493	517	510	92
3009	448	464	470	486	508	531	524	76
3010	426	450	471	487	484	485	481	55
3011	420	442	466	479	500	511	520	100
3012	402	422	438	455	473	494	492	90
Mean	418	440	460	472	488	507	512	94
S.D.	15	15	17	18	17	18	20	18

Unit: g

Appendix 3-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of male rats (Administration period)
Dose (mg/kg): 150

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
4001	424	443	467	483	496	510	517	93
4002	411	414	437	458	473	483	500	89
4003a)	401							
4004b)	423	443	461	471	480			
4005	397	425	447	464	478	507	514	117
4006	428	459	479	500	524	532	541	113
4007	439	465	479	488	509	525	527	88
4008	414	431	456	469	477	498	498	84
4009	413	434	459	469	478	498	500	87
4010c)	438							
4011	408	430	445	457	462	477	477	69
4012	404	424	448	464	492	523	521	117
Mean	417	437	458	472	487	506	511	95
S.D.	14	16	14	14	19	19	19	17

Unit: g
a): Died on day 5 of administration
b): Died on day 32 of administration
c): Sacrificed on day 5 of administration

Appendix 3-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of female rats during the pre-mating period (Main group)
Dose (mg/kg): 0

Animal number	Day of administration 1	8	15	Gain 1-15
1101	254	278	279	25
1102	241	264	278	37
1103	249	255	267	18
1104a)	244	248		
1105	225	243	254	29
1106	243	248	260	17
1107	265	282	289	24
1108	263	281	292	29
1109	237	248	251	14
1110	226	241	256	30
1111	259	276	287	28
1112	256	266	271	15
Mean	247	261	271	24
S.D.	13	16	15	7

Unit: g
a): Sacrificed on day 12 of administration

Appendix 3-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of female rats during the pre-mating period (Main group)
Dose (mg/kg): 15

Animal number	Day of administration 1	8	15	Gain 1-15
2101	253	272	269	16
2102	237	260	261	24
2103	251	260	263	12
2104	260	273	272	12
2105	229	232	238	9
2106	234	245	251	17
2107	240	247	261	21
2108	227	248	245	18
2109	289	298	297	8
2110	256	280	283	27
2111	265	265	259	-6
2112	245	259	269	24
Mean	249	262	264	15
S.D.	18	18	16	9

Unit: g

Appendix 3-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of female rats during the pre-mating period (Main group)
Dose (mg/kg): 50

Animal number	Day of administration 1	8	15	Gain 1-15
3101	243	252	255	12
3102	256	258	265	9
3103	226	251	250	24
3104	278	297	298	20
3105	253	265	278	25
3106	237	253	258	21
3107	242	255	251	9
3108	230	242	254	24
3109	257	278	283	26
3110	257	262	274	17
3111	258	266	281	23
3112	242	257	264	22
Mean	248	261	268	19
S.D.	14	14	15	6

Unit: g

Appendix 3-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of female rats during the pre-mating period (Main group)
Dose (mg/kg): 150

Animal number	Day of administration 1	8	15	Gain 1-15
4101a)	258			
4102	232	245	237	5
4103	240	253	263	23
4104	268	273	287	19
4105	247	265	275	28
4106	223	248	262	39
4107b)	240			
4108	237	256	262	25
4109	264	282	285	21
4110	237	249	252	15
4111	217	230	243	26
4112	256	266	270	14
Mean	243	257	264	22
S.D.	16	15	16	9

Unit: g
a): Died on day 8 of administration
b): Died on day 5 of administration

Appendix 3-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of dams during the gestation period (Main group)
Dose (mg/kg): 0

Dam number	Administration 0	7	14	20a)	Gain 0-20
1101	280	310	342	426	146
1102	281	310	352	440	159
1103	264	302	341	438	174
1104b)					
1105	265	303	353	439	174
1106	260	280	317	399	139
1107	294	325	365	437	143
1108	295	342	389	499	204
1109	258	276	302	389	131
1110	262	300	338	416	154
1111	287	311	349	431	144
1112	281	298	340	415	134
Mean	275	305	344	430	155
S.D.	14	18	23	29	22

Unit: g
a): Gestation day
b): Sacrificed on day 12 of administration

Appendix 3-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of dams during the gestation period (Main group)
Dose (mg/kg): 15

Dam number	Administration 0	7	14	20a)	Gain 0-20
2101	294	337	376	440	146
2102	277	304	337	373	96
2103	279	323	369	459	180
2104	281	319	362	466	185
2105	254	288	325	394	140
2106	250	286	332	424	174
2107	262	270	297	377	115
2108	258	288	315	395	137
2109	329	363	403	505	176
2110	294	342	389	480	186
2111	260	286	319	407	147
2112	267	318	368	436	169
Mean	275	310	349	430	154
S.D.	22	28	33	42	29

Unit: g
a): Gestation day

Appendix 3-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of dams during the gestation period (Main group)
Dose (mg/kg): 50

Dam number	Administration 0	7	14	20a)	Gain 0-20
3101	254	296	337	422	168
3102	274	311	346	427	153
3103	265	301	340	423	158
3104	303	338	378	451	148
3105	264	306	336	414	150
3106	265	302	349	431	166
3107	271	287	312	362	91
3108	255	284	315	392	137
3109	277	319	363	446	169
3110	270	306	336	417	147
3111	284	306	339	392	108
3112	266	286	325	409	143
Mean	271	304	340	416	145
S.D.	13	15	18	25	24

Unit: g
a): Gestation day

Appendix 3-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of dams during the gestation period (Main group)
Dose (mg/kg): 150

Dam number	Administration 0	7	14	20a)	Gain 0-20
4101b)					
4102	259	280	320	397	138
4103	263	288	329	409	146
4104	283	310	346	426	143
4105	281	320	350	439	158
4106	260	299	344	427	167
4107c)					
4108	263	298	338	423	160
4109d)	283	328	337		
4110	259	293	329	413	154
4111	244	269	305	383	139
4112	294	343	376	484	190
Mean	269	303	337	422	155
S.D.	15	23	19	29	16

Unit: g
a): Gestation day
b): Died on day 8 of administration
c): Died on day 5 of administration
d): Died on gestation day 15

Appendix 3-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of dams during the lactation period (Main group)
Dose (mg/kg): 0

Dam number	Administration 0	Administration 4a)	Gain 0-4
1101	307	338	31
1102	355	356	1
1103	332	329	-3
1104b)			
1105	327	362	35
1106	270	307	37
1107	346	364	18
1108	369	399	30
1109	288	315	27
1110	312	312	0
1111	332	341	9
1112	320	351	31
Mean	323	343	20
S.D.	29	27	15

Unit: g
a): Lactation day
b): Sacrificed on day 12 of administration

Appendix 3-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of dams during the lactation period (Main group)
Dose (mg/kg): 15

Dam number	Administration 0	Administration 4a)	Gain 0-4
2101	356	377	21
2102	344	341	-3
2103	343	376	33
2104	326	354	28
2105	324	322	-2
2106	324	325	1
2107	292	308	16
2108	293	310	17
2109	385	393	8
2110	364	387	23
2111	320	328	8
2112	394	410	16
Mean	339	353	14
S.D.	32	35	12

Unit: g
a): Lactation day

Appendix 3-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of dams during the lactation period (Main group)
Dose (mg/kg): 50

Dam number	Administration 0	Administration 4a)	Gain 0-4
3101	334	336	2
3102	327	340	13
3103	305	338	33
3104	350	374	24
3105	311	336	25
3106	321	359	38
3107	314	313	-1
3108	314	322	8
3109	370	352	-18
3110	317	337	20
3111	303	330	27
3112	312	332	20
Mean	323	339	16
S.D.	20	16	16

Unit: g
a): Lactation day

Appendix 3-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of dams during the lactation period (Main group)
Dose (mg/kg): 150

Dam number	Administration 0	Administration 4a)	Gain 0-4
4101b)			
4102	286	334	48
4103	322	341	19
4104	331	357	26
4105	370	366	-4
4106	339	338	-1
4107c)			
4108	332	337	5
4109d)			
4110	312	333	21
4111	299	315	16
4112	377	397	20
Mean	330	346	17
S.D.	30	24	16

Unit: g
a): Lactation day
b): Died on day 8 of administration
c): Died on day 5 of administration
d): Died on gestation day 15

Appendix 3-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
1113	245	253	271	277	284	287	304	59
1114	232	242	257	267	274	270	285	53
1115	251	245	260	269	274	284	296	45
1116	265	284	301	309	326	331	324	59
1117	257	271	280	295	317	320	328	71
1118	266	275	273	293	309	311	312	46
1119	234	241	250	252	268	270	274	40
1120	251	258	261	260	265	284	279	28
1121	244	257	270	268	293	294	286	42
1122	235	250	257	264	264	281	274	39
Mean	248	258	268	275	287	293	296	48
S.D.	12	15	15	18	23	21	20	12

Unit: g

Appendix 3-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of female rats (Satellite group, Administration period)
Dose (mg/kg): 150

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
4113	222	235	247	252	257	273	278	56
4114a)	262	271	283	290	290	302		
4115	237	245	258	272	278	291	280	43
4116	256	261	271	289	279	295	306	50
4117	245	254	260	279	279	293	291	46
4118b)	234	247						
4119	240	251	265	277	269	297	296	56
4120	240	257	254	260	275	287	277	37
4121	266	266	274	267	286	295	298	32
4122	266	281	290	317	321	327	342	76
Mean	247	257	267	278	282	296	296	50
S.D.	15	14	14	19	18	14	21	14

Unit: g
a): Sacrificed on day 39 of administration
b): Died on day 12 of administration

Appendix 3-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of male rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery 1	8	14	Gain 1-14
1008	534	554	565	31
1009	536	556	560	24
1010	530	537	547	17
1011	537	565	581	44
1012	514	522	525	11
Mean	530	547	556	25
S.D.	9	17	21	13

Unit: g

Appendix 3-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of male rats (Recovery period)
Dose (mg/kg): 150

Animal number	Day of recovery 1	8	14	Gain 1-14
4008	498	518	529	31
4009	506	523	534	28
4010a)				
4011	476	485	504	28
4012	523	543	552	29
Mean	501	517	530	29
S.D.	20	24	20	1

Unit: g
a): Sacrificed on day 5 of administration

Appendix 3-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of female rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery 1	8	14	Gain 1-14
1118	307	318	316	9
1119	278	275	294	16
1120	287	281	292	5
1121	295	308	295	0
1122	280	287	284	4
Mean	289	294	296	7
S.D.	12	18	12	6

Unit: g

Appendix 3-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of female rats (Recovery period)
Dose (mg/kg): 150

Animal number	Day of recovery 1	8	14	Gain 1-14
4118a)				
4119	287	294	289	2
4120	279	267	262	-17
4121	311	298	310	-1
4122	346	337	348	2
Mean	306	299	302	-4
S.D.	30	29	36	9

Unit: g
a): Died on day 12 of administration

Appendix 4-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration					
	2	8	15	30	36	42
1001	29	27	31	28	28	33
1002	30	26	28	30	33	29
1003	28	29	27	34	31	30
1004	27	27	28	31	30	31
1005	27	28	27	27	30	31
1006	29	28	27	30	30	27
1007	38	36	34	30	32	33
1008	34	33	30	33	35	35
1009	30	33	25	32	28	28
1010	31	32	34	30	30	30
1011	33	31	32	34	35	37
1012	33	33	30	29	34	26
Mean	31	30	29	31	31	31
S.D.	3	3	3	2	2	3

Unit: g/rat/day

Appendix 4-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of male rats (Administration period)
Dose (mg/kg): 15

Animal number	Day of administration 2	8	15	30	36	42
2001	30	30	30	28	28	27
2002	26	27	28	27	29	27
2003	25	26	27	22	30	30
2004	30	35	30	30	30	28
2005	32	36	33	37	33	32
2006	31	31	29	34	33	30
2007	29	27	29	26	30	27
2008	31	32	33	30	30	25
2009	30	32	30	33	31	33
2010	27	28	30	29	32	32
2011	28	29	29	29	31	29
2012	29	31	31	33	33	32
Mean	29	30	30	30	31	29
S.D.	2	3	2	4	2	3

Unit: g/rat/day

Appendix 4-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of male rats (Administration period)
Dose (mg/kg): 50

Animal number	Day of administration					
	2	8	15	30	36	42
3001	26	30	32	28	30	30
3002	26	32	33	32	31	28
3003	23	26	24	27	26	26
3004	25	28	30	29	30	31
3005	27	28	29	30	29	30
3006	27	31	31	31	34	33
3007	26	32	30	24	29	29
3008	27	32	31	30	32	27
3009	30	30	25	28	30	26
3010	26	32	30	30	27	30
3011	24	30	31	30	29	28
3012	25	30	27	31	30	28
Mean	26	30	29	29	30	29
S.D.	2	2	3	2	2	2

Unit: g/rat/day

Appendix 4-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of male rats (Administration period)
Dose (mg/kg): 150

Animal number	Day of administration					
	2	8	15	30	36	42
4001	29	34	30	31	33	30
4002	19	31	30	28	31	29
4003a)	25					
4004b)	29	36	39	30		
4005	22	30	28	29	31	29
4006	24	31	28	31	34	31
4007	27	32	32	27	28	29
4008	26	35	32	31	35	36
4009	30	34	37	34	34	37
4010c)	22					
4011	25	29	28	28	30	28
4012	24	29	33	34	36	28
Mean	25	32	32	30	32	31
S.D.	3	3	4	2	3	3

Unit: g/rat/day
a): Died on day 5 of administration
b): Died on day 32 of administration
c): Sacrificed on day 5 of administration

Appendix 4-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 0

Animal number	Day of administration 2	8	15
1101	19	25	21
1102	21	24	24
1103	22	19	22
1104a)	17	18	
1105	19	21	24
1106	21	20	25
1107	19	23	24
1108	16	24	29
1109	18	20	21
1110	17	21	22
1111	22	21	24
1112	17	23	21
Mean	19	22	23
S.D.	2	2	2

Unit: g/rat/day
a): Sacrificed on day 12 of administration

Appendix 4-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 15

Animal number	Day of administration 2	8	15
2101	17	23	18
2102	20	27	19
2103	21	22	19
2104	17	26	21
2105	17	19	15
2106	19	19	21
2107	17	19	23
2108	20	25	16
2109	20	23	16
2110	18	24	19
2111	22	22	19
2112	19	22	22
Mean	19	23	19
S.D.	2	3	2

Unit: g/rat/day

Appendix 4-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 50

Animal number	Day of administration 2	8	15
3101	19	18	21
3102	19	19	24
3103	15	22	19
3104	19	25	23
3105	20	19	22
3106	19	22	18
3107	18	23	16
3108	20	17	22
3109	19	23	24
3110	18	16	21
3111	18	22	23
3112	20	22	21
Mean	19	21	21
S.D.	1	3	2

Unit: g/rat/day

Appendix 4-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 150

Animal number	Day of administration 2	8	15
4101a)	18		
4102	15	21	15
4103	12	19	24
4104	18	19	21
4105	19	25	23
4106	17	23	25
4107b)	16		
4108	16	21	21
4109	21	23	30
4110	15	22	22
4111	13	19	21
4112	15	21	19
Mean	16	21	22
S.D.	3	2	4

Unit: g/rat/day
a): Died on day 8 of administration
b): Died on day 5 of administration

Appendix 4-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of dams during the gestation period (Main group)
Dose (mg/kg): 0

Dam number	Administration 1	7	14	20a)
1101	16	27	28	26
1102	19	27	26	27
1103	20	28	23	23
1104b)				
1105	25	28	29	30
1106	20	24	22	22
1107	23	26	30	26
1108	22	31	34	29
1109	21	21	22	22
1110	22	26	29	27
1111	22	24	29	26
1112	24	24	25	26
Mean	21	26	27	26
S.D.	2	3	4	3

Unit: g/rat/day
a): Gestation day
b): Sacrificed on day 12 of administration

Appendix 4-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of dams during the gestation period (Main group)
Dose (mg/kg): 15

Dam number	Administration 1	7	14	20a)
2101	25	27	29	25
2102	19	27	24	25
2103	26	28	31	31
2104	24	27	29	26
2105	15	27	28	27
2106	21	24	26	27
2107	22	20	24	19
2108	16	29	25	24
2109	28	30	27	30
2110	23	28	31	27
2111	21	23	19	23
2112	23	28	33	35
Mean	22	27	27	27
S.D.	4	3	4	4

Unit: g/rat/day
a): Gestation day

Appendix 4-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of dams during the gestation period (Main group)
Dose (mg/kg): 50

Dam number	Administration 1	7	14	20a)
3101	26	24	30	25
3102	24	32	28	28
3103	21	25	26	23
3104	26	26	32	24
3105	21	24	26	26
3106	21	24	30	27
3107	22	22	26	25
3108	23	22	22	33
3109	24	28	30	27
3110	27	27	25	22
3111	26	25	27	21
3112	13	25	27	27
Mean	23	25	27	26
S.D.	4	3	3	3

Unit: g/rat/day
a): Gestation day

Appendix 4-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of dams during the gestation period (Main group)
Dose (mg/kg): 150

Dam number	Administration 1	7	14	20a)
4101b)				
4102	22	23	28	25
4103	18	25	28	29
4104	22	23	29	27
4105	30	29	26	28
4106	25	28	31	28
4107c)				
4108	24	24	26	21
4109d)	30	28	16	
4110	19	25	28	23
4111	15	24	22	23
4112	29	35	32	37
Mean	23	26	27	27
S.D.	5	4	5	5

Unit: g/rat/day
a): Gestation day
b): Died on day 8 of administration
c): Died on day 5 of administration
d): Died on gestation day 15

Appendix 4-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of dams during the lactation period (Main group)
Dose (mg/kg): 0

Dam number	Administration	
	2	4a)
1101	31	40
1102	26	43
1103	24	36
1104b)		
1105	42	44
1106	32	57
1107	36	47
1108	46	50
1109	29	45
1110	23	31
1111	23	38
1112	37	46
Mean	32	43
S.D.	8	7

Unit: g/rat/day
a): Lactation day
b): Sacrificed on day 12 of administration

Appendix 4-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of dams during the lactation period (Main group)
Dose (mg/kg): 15

Dam number	Administration	
	2	4a)
2101	28	40
2102	18	28
2103	35	54
2104	32	45
2105	24	37
2106	19	47
2107	18	41
2108	16	46
2109	33	51
2110	32	55
2111	23	52
2112	25	43
Mean	25	45
S.D.	7	8

Unit: g/rat/day
a): Lactation day

Appendix 4-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of dams during the lactation period (Main group)
Dose (mg/kg): 50

Dam number	Administration	
	2	4a)
3101	14	47
3102	26	47
3103	37	47
3104	33	45
3105	32	40
3106	33	51
3107	24	39
3108	30	45
3109	27	43
3110	28	43
3111	15	47
3112	30	38
Mean	27	44
S.D.	7	4

Unit: g/rat/day
a): Lactation day

Appendix 4-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of dams during the lactation period (Main group)
Dose (mg/kg): 150

Dam number	Administration 2	4a)
4101b)		
4102	36	57
4103	30	36
4104	38	50
4105	24	52
4106	26	42
4107c)		
4108	22	45
4109d)		
4110	33	45
4111	31	36
4112	30	58
Mean	30	47
S.D.	5	8

Unit: g/rat/day
a): Lactation day
b): Died on day 8 of administration
c): Died on day 5 of administration
d): Died on gestation day 15

Appendix 4-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration 2	8	15	30	36	42
1113	19	19	23	25	20	22
1114	15	21	22	21	14	22
1115	20	18	20	25	17	25
1116	20	25	26	19	25	23
1117	20	22	19	25	20	25
1118	22	27	16	24	26	24
1119	20	19	22	21	17	23
1120	16	19	22	15	23	19
1121	14	20	21	23	21	14
1122	18	21	21	18	21	19
Mean	18	21	21	22	20	22
S.D.	3	3	3	3	4	3

Unit: g/rat/day

Appendix 4-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of female rats (Satellite group, Administration period)
Dose (mg/kg): 150

Animal number	Day of administration					
	2	8	15	30	36	42
4113	16	19	20	20	20	17
4114a)	21	24	22	23	23	
4115	21	20	23	26	21	29
4116	19	18	24	25	21	26
4117	18	18	22	22	23	21
4118b)	14	17				
4119	13	22	21	19	25	25
4120	10	20	20	17	24	20
4121	14	21	21	11	24	16
4122	17	21	17	29	20	25
Mean	16	20	21	21	22	22
S.D.	4	2	2	5	2	5

Unit: g/rat/day
a): Sacrificed on day 39 of administration
b): Died on day 12 of administration

Appendix 4-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of male rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery 1	8	14
1008	32	34	35
1009	29	34	29
1010	32	33	31
1011	32	37	36
1012	33	32	32
Mean	32	34	33
S.D.	2	2	3

Unit: g/rat/day

Appendix 4-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of male rats (Recovery period)
Dose (mg/kg): 150

Animal number	Day of recovery 1	8	14
4008	31	34	32
4009	32	40	34
4010a)			
4011	25	25	32
4012	29	34	32
Mean	29	33	33
S.D.	3	6	1

Unit: g/rat/day
a): Sacrificed on day 5 of administration

Appendix 4-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of female rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery 1	8	14
1118	16	25	24
1119	24	18	25
1120	21	15	24
1121	19	26	17
1122	19	24	20
Mean	20	22	22
S.D.	3	5	3

Unit: g/rat/day

Appendix 4-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual food consumption of female rats (Recovery period)
Dose (mg/kg): 150

Animal number	Day of recovery 1	8	14
4118a)			
4119	17	24	23
4120	14	27	24
4121	27	20	26
4122	26	21	27
Mean	21	23	25
S.D.	6	3	2

Unit: g/rat/day
a): Died on day 12 of administration

Appendix 5-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
1008	8.5	+-	-	-	-	-	+-	Y
1009	>=9.0	+	++	-	-	-	+-	Y
1010	8.5	+-	+-	-	-	-	+-	Y
1011	8.5	+	+-	-	+-	-	+-	Y
1012	8.5	+-	-	-	+-	-	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Appendix 5-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
1008	-	-	+-	-	-	+-	-
1009	-	-	+-	-	-	+-	-
1010	-	-	+-	-	-	+-	-
1011	-	-	+-	-	-	+-	-
1012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
1008	45	16.5	1912	1.78	5.17	2.44
1009	31	8.4	2598	1.11	3.84	1.66
1010	47	21.3	1744	2.09	6.21	2.85
1011	47	18.0	2078	2.23	6.21	2.56
1012	71	32.2	1098	1.80	5.67	2.25
Mean	48	19.3	1886	1.80	5.42	2.35
S.D.	14	8.6	544	0.43	0.98	0.44

Appendix 5-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 15

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
2008	>=9.0	+	-	-	+-	-	+-	Y
2009	>=9.0	-	-	-	+-	-	+-	Y
2010	8.0	+-	+-	-	+-	-	+-	Y
2011	8.0	+	+	-	-	-	+-	Y
2012	8.5	+	+-	-	-	-	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Appendix 5-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 15

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
2008	-	-	+-	-	-	+-	-
2009	-	-	+-	-	-	+-	-
2010	+-	-	+-	-	-	+-	-
2011	-	-	+-	-	-	+-	-
2012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 15

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
2008	56	15.3	1344	0.89	3.46	1.41
2009	55	30.3	1640	2.18	8.27	3.51
2010	68	24.0	1190	1.44	4.80	2.06
2011	46	18.1	1936	1.95	6.10	2.72
2012	41	16.2	2136	1.78	5.72	2.43
Mean	53	20.8	1649	1.65	5.67	2.43
S.D.	10	6.3	395	0.50	1.77	0.78

Appendix 5-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 50

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
3008	7.5	+	+	-	-	-	+-	Y
3009	8.5	+	+	-	-	-	+-	Y
3010	8.0	+	+	-	-	-	+-	Y
3011	8.5	++	+	-	-	-	+-	Y
3012	7.5	+	+	-	-	-	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Appendix 5-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 50

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
3008	-	-	+-	-	-	+-	-
3009	-	-	+-	-	-	+-	-
3010	-	-	+-	-	-	+-	-
3011	-	-	+-	-	-	+-	-
3012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 50

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
3008	37	18.0	1970	1.76	6.06	2.48
3009	44	16.7	1778	1.34	5.10	1.97
3010	45	16.5	1606	1.19	4.27	1.98
3011	49	8.9	2324	0.57	3.19	1.28
3012	38	13.6	2282	1.09	4.99	2.26
Mean	43	14.7	1992	1.19	4.72	1.99
S.D.	5	3.6	312	0.43	1.07	0.45

Appendix 5-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 150

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
4008	>=9.0	++	++	-	-	+	+-	B
4009	>=9.0	++	+	-	+-	-	+-	B
4010S								
4011	6.5	+	+-	-	-	-	+-	Y
4012	8.5	+	+	-	+-	+	+-	B

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown
S: Sacrificed moribund

Appendix 5-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 150

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4008	-	-	+-	-	-	+-	-
4009	-	-	+-	-	-	+-	-
4010S							
4011	-	-	+-	-	-	+-	-
4012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

S: Sacrificed moribund

Appendix 5-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 150

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
4008	39	14.2	2726	1.68	6.58	2.93
4009	44	14.4	2124	0.58	5.17	2.02
4010S						
4011	37	11.1	2224	1.02	3.99	1.93
4012	46	12.3	2320	1.13	4.96	2.07
Mean	42	13.0	2349	1.10	5.18	2.24
S.D.	4	1.6	264	0.45	1.07	0.47

S: Sacrificed moribund

Appendix 5-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
1118	8.0	-	-	-	-	-	+-	Y
1119	7.0	+-	+-	-	-	-	+-	Y
1120	8.0	-	-	-	-	-	+-	Y
1121	6.5	+-	+-	-	-	-	+-	Y
1122	8.0	-	-	-	-	-	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Appendix 5-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

	URINE SEDIMENT						
						CRYSTALLIZATION	
Animal number	RBC	WBC	SEC	SREC	Cast	PS	CO
1118	-	-	+-	-	-	+-	-
1119	-	-	+-	-	-	+-	-
1120	-	-	+-	-	-	+-	-
1121	-	-	+-	-	-	+-	-
1122	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
1118	60	27.1	1030	1.84	4.54	2.28
1119	27	5.9	2906	0.96	2.79	1.38
1120	36	15.0	1776	1.41	4.92	2.10
1121	17	2.6	4218	0.58	1.56	0.72
1122	24	6.6	2402	0.79	2.40	0.95
Mean	33	11.4	2466	1.12	3.24	1.49
S.D.	17	9.9	1205	0.51	1.44	0.69

Appendix 5-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 150

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
4118D								
4119	6.5	++	-	-	-	-	+-	Y
4120	7.5	+	+-	-	-	-	+-	Y
4121	8.5	+	+-	-	+-	+	+-	B
4122	7.0	+-	+-	-	-	-	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown
D: Dead

Appendix 5-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 150

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4118D							
4119	-	-	+-	-	-	+-	-
4120	-	-	+-	-	-	+-	-
4121	-	-	+-	-	-	+-	-
4122	-	-	+-	-	-	-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

D: Dead

Appendix 5-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 150

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
4118D						
4119	32	4.6	2914	0.65	1.92	0.87
4120	24	6.9	3122	0.99	3.56	1.52
4121	33	8.1	1934	0.71	2.80	1.30
4122	35	5.0	2962	0.61	2.28	1.19
Mean	31	6.2	2733	0.74	2.64	1.22
S.D.	5	1.6	540	0.17	0.71	0.27

D: Dead

Appendix 5-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
1008	>=9.0	+	+	-	-	-	+-	Y
1009	8.5	++	++	-	-	-	+-	Y
1010	>=9.0	++	+	-	+-	-	+-	Y
1011	8.5	+	+	-	-	-	+-	Y
1012	8.5	+-	+-	-	+-	-	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Appendix 5-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
1008	-	-	+-	-	-	+-	-
1009	-	-	+-	-	-	+-	-
1010	-	-	+-	-	-	+-	-
1011	-	-	+-	-	-	+-	-
1012	+-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
1008	40	15.2	2036	1.49	5.41	2.16
1009	34	7.6	2640	1.02	3.56	1.38
1010	41	15.3	2214	1.47	5.76	2.26
1011	52	25.1	1788	2.16	7.69	2.91
1012	78	35.4	1032	2.41	5.93	2.76
Mean	49	19.7	1942	1.71	5.67	2.29
S.D.	17	10.7	596	0.56	1.47	0.60

Appendix 5-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
4008	7.0	++	+	+	-	+	+-	Y
4009	7.5	++	+	-	-	-	+-	Y
4010S								
4011	7.0	++	+	-	-	-	+-	Y
4012	8.0	+	+	-	-	-	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown
S: Sacrificed moribund

Appendix 5-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4008	-	-	+-	-	-	+-	-
4009	-	-	+-	-	-	+-	-
4010S							
4011	-	-	+-	-	-	+-	-
4012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

S: Sacrificed moribund

Appendix 5-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
4008	37	9.1	2710	1.11	4.12	1.51
4009	42	14.2	2102	1.33	5.10	2.02
4010S						
4011	33	11.7	2268	1.57	4.40	1.90
4012	50	17.4	1966	1.22	5.67	2.12
Mean	41	13.1	2262	1.31	4.82	1.89
S.D.	7	3.5	323	0.20	0.70	0.27

S: Sacrificed moribund

Appendix 5-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
1118	7.0	-	-	-	-	-	+-	Y
1119	6.5	+-	-	-	-	-	+-	Y
1120	6.0	-	-	-	-	-	+-	Y
1121	7.0	+-	-	-	-	-	+-	Y
1122	8.5	+	+-	-	-	-	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown

Appendix 5-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
1118	-	-	+-	-	-	-	-
1119	-	-	+-	-	-	+-	-
1120	-	-	+-	-	-	-	-
1121	-	-	+-	-	-	+-	-
1122	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
1118	39	13.9	1552	1.20	3.23	1.17
1119	29	5.9	2380	0.71	2.24	0.99
1120	37	9.8	2268	1.10	3.93	1.47
1121	24	7.2	2648	1.08	3.21	1.21
1122	33	9.0	2168	1.13	3.12	1.49
Mean	32	9.2	2203	1.04	3.15	1.27
S.D.	6	3.1	406	0.19	0.60	0.21

Appendix 5-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	6) Urobi-linogen	7) Color
4118D								
4119	6.0	+	+-	-	-	-	+-	Y
4120	7.0	+-	+-	-	-	-	+-	Y
4121	6.0	+	+-	-	-	-	+-	Y
4122	7.0	-	-	-	-	-	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow B : Brown
D: Dead

Appendix 5-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4118D							
4119	-	-	+-	-	-	-	-
4120	-	-	+-	-	-	+-	-
4121	-	-	+-	-	-	-	-
4122	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

D: Dead

Appendix 5-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual water intake and urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 150

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
4118D						
4119	29	8.4	2210	1.11	2.89	0.99
4120	19	18.2	1298	2.11	3.94	2.29
4121	32	5.3	2544	0.71	2.15	0.93
4122	66	22.4	1134	0.94	4.26	1.75
Mean	37	13.6	1797	1.22	3.31	1.49
S.D.	20	8.1	687	0.62	0.97	0.65

D: Dead

Appendix 6-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1001	889	14.8	42.4	47.7	16.7	34.9	2.2	95.1	17.2	20.4	284
1002	914	16.0	46.0	50.3	17.5	34.7	2.6	99.7	16.8	20.8	284
1003	915	14.8	42.5	46.5	16.1	34.7	1.5	101.7	16.0	20.5	276
1004	866	15.2	43.7	50.5	17.6	34.7	1.7	81.4	16.1	22.2	316
1005	842	14.4	41.4	49.2	17.1	34.8	3.6	121.4	15.8	20.4	315
Mean	885	15.0	43.2	48.8	17.0	34.8	2.3	99.9	16.4	20.9	295
S.D.	31	0.6	1.8	1.7	0.6	0.1	0.8	14.4	0.6	0.8	19

Appendix 6-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1001	64.8	65.5	28.8	1.8	0.5	2.9	0.5	42.5	18.6	1.2	0.3	1.9	0.3
1002	77.9	63.1	31.8	1.1	0.3	3.6	0.1	49.2	24.8	0.9	0.2	2.8	0.1
1003	49.3	70.8	24.3	2.3	0.2	2.2	0.2	34.9	12.0	1.1	0.1	1.1	0.1
1004	69.9	73.3	23.3	1.0	0.2	1.9	0.2	51.3	16.3	0.7	0.2	1.3	0.2
1005	73.1	69.9	25.7	1.6	0.2	1.7	0.9	51.1	18.8	1.1	0.2	1.2	0.6
Mean	67.0	68.5	26.8	1.6	0.3	2.5	0.4	45.8	18.1	1.0	0.2	1.7	0.3
S.D.	11.0	4.1	3.5	0.5	0.1	0.8	0.3	7.1	4.6	0.2	0.1	0.7	0.2

LUC: Large unstained cells

Appendix 6-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 15

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
2001	848	15.5	44.1	52.0	18.3	35.2	2.8	99.3	13.4	17.3	269
2002	883	15.5	44.7	50.6	17.6	34.8	2.3	90.5	14.0	18.9	259
2003	922	15.3	45.2	49.0	16.6	33.9	2.2	94.1	14.5	22.1	273
2004	872	15.3	43.7	50.1	17.6	35.1	1.7	100.0	15.8	23.1	264
2005	829	14.7	42.0	50.7	17.8	35.1	1.8	105.4	15.6	22.0	274
Mean	871	15.3	43.9	50.5	17.6	34.8	2.2	97.9	14.7	20.7	268
S.D.	35	0.3	1.2	1.1	0.6	0.5	0.4	5.7	1.0	2.5	6

Appendix 6-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 15

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
2001	112.3	75.3	20.8	1.0	0.4	2.0	0.5	84.6	23.4	1.1	0.5	2.3	0.6
2002	84.2	70.1	25.0	2.3	0.2	1.7	0.6	59.0	21.1	2.0	0.1	1.5	0.5
2003	59.7	72.7	23.8	1.2	0.2	1.6	0.5	43.4	14.2	0.7	0.1	1.0	0.3
2004	52.8	67.5	27.9	1.1	0.3	2.5	0.6	35.7	14.7	0.6	0.2	1.3	0.3
2005	61.1	82.1	14.0	1.4	0.3	1.8	0.5	50.2	8.6	0.8	0.2	1.1	0.3
Mean	74.0	73.5	22.3	1.4	0.3	1.9	0.5	54.6	16.4	1.0	0.2	1.4	0.4
S.D.	24.5	5.6	5.3	0.5	0.1	0.4	0.1	18.9	5.9	0.6	0.2	0.5	0.1

LUC: Large unstained cells

Appendix 6-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 50

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
3001	930	16.6	46.6	50.1	17.9	35.7	1.7	85.5	18.0	23.2	265
3002	881	15.1	42.4	48.1	17.2	35.7	2.1	84.9	19.3	18.1	256
3003	879	15.0	44.8	51.0	17.0	33.4	1.3	96.8	19.9	20.2	219
3004	907	15.5	45.2	49.9	17.1	34.4	2.3	79.6	18.6	23.9	317
3005	893	15.4	44.3	49.6	17.2	34.8	2.1	88.0	17.8	18.5	288
Mean	898	15.5	44.7	49.7	17.3	34.8	1.9	87.0	18.7	20.8	269
S.D.	21	0.6	1.5	1.1	0.4	1.0	0.4	6.3	0.9	2.7	37

Appendix 6-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 50

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
3001	100.4	68.4	27.2	1.5	0.3	2.3	0.3	68.7	27.3	1.5	0.3	2.3	0.3
3002	75.3	75.9	19.4	2.1	0.3	2.1	0.3	57.1	14.6	1.6	0.2	1.6	0.2
3003	81.0	77.4	18.6	1.2	0.3	2.1	0.5	62.7	15.1	0.9	0.2	1.7	0.4
3004	76.5	67.4	26.5	1.0	0.3	4.0	0.8	51.6	20.3	0.7	0.2	3.1	0.6
3005	83.2	70.2	25.3	1.2	0.3	2.6	0.3	58.4	21.0	1.0	0.2	2.2	0.3
Mean	83.3	71.9	23.4	1.4	0.3	2.6	0.4	59.7	19.7	1.1	0.2	2.2	0.4
S.D.	10.1	4.5	4.1	0.4	0.0	0.8	0.2	6.4	5.2	0.4	0.0	0.6	0.2

LUC: Large unstained cells

Appendix 6-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 150

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4001	920	16.2	45.9	49.8	17.6	35.3	1.5	102.6	17.0	22.9	257
4002	906	16.0	46.5	51.4	17.7	34.4	2.4	96.8	17.6	19.5	211
4003D											
4004D											
4005	901	15.1	44.0	48.8	16.8	34.4	1.1	109.8	15.2	17.3	261
4006a)											
4007a)											
Mean	909	15.8	45.5	50.0	17.4	34.7	1.7	103.1	16.6	19.9	243
S.D.	10	0.6	1.3	1.3	0.5	0.5	0.7	6.5	1.2	2.8	28

D: Dead
a): Examination was not done due to misunderstanding of protocol which specified the number of animals (five animals) to be examined.

Appendix 6-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 150

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4001	70.4	80.5	14.8	1.7	0.4	2.3	0.4	56.7	10.4	1.2	0.3	1.6	0.3
4002	63.7	62.4	33.1	2.1	0.3	1.8	0.3	39.7	21.1	1.3	0.2	1.1	0.2
4003D													
4004D													
4005	58.5	74.9	20.2	1.3	0.3	2.8	0.5	43.8	11.8	0.8	0.2	1.6	0.3
4006a)													
4007a)													
Mean	64.2	72.6	22.7	1.7	0.3	2.3	0.4	46.7	14.4	1.1	0.2	1.4	0.3
S.D.	6.0	9.3	9.4	0.4	0.1	0.5	0.1	8.9	5.8	0.3	0.1	0.3	0.1

LUC: Large unstained cells
D: Dead
a): Examination was not done due to misunderstanding of protocol which specified the number of animals (five animals) to be examined.

Appendix 6-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1103	689	13.4	39.1	56.8	19.4	34.2	7.5	140.9	12.8	16.9	290
1104S	1150Z	20.9Z	59.1Z	51.4Z	18.2Z	35.3Z	3.4Z	5.7Z	-	-	-
1105	664	13.5	39.5	59.4	20.4	34.2	8.1	140.6	12.7	18.3	301
1106	693	13.2	39.2	56.5	19.1	33.7	9.8	133.0	12.4	17.2	366
1110	704	12.9	37.7	53.6	18.4	34.3	8.4	173.5	13.7	15.2	325
1111	737	13.7	40.5	54.9	18.6	33.8	7.9	184.3	13.5	22.8	294
Mean	697	13.3	39.2	56.2	19.2	34.0	8.3	154.5	13.0	18.1	315
S.D.	27	0.3	1.0	2.2	0.8	0.3	0.9	22.9	0.6	2.9	31

-: Not done. A sufficient amount of blood sample was not obtained due to severe moribundity.
S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 6-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1103	121.9	61.8	33.3	0.8	0.3	3.6	0.2	75.3	40.6	0.9	0.4	4.4	0.3
1104S	166.7Z	26.0Z	64.2Z	0.0Z	0.7Z	7.4Z	1.6Z	43.4Z	107.0Z	0.1Z	1.1Z	12.3Z	2.7Z
1105	94.5	31.6	65.5	0.5	0.1	2.1	0.1	29.9	61.9	0.5	0.1	2.0	0.1
1106	109.2	38.9	55.7	0.7	0.2	3.3	1.1	42.5	60.8	0.8	0.2	3.6	1.2
1110	119.9	52.7	43.1	0.7	0.1	3.0	0.4	63.2	51.7	0.8	0.1	3.6	0.5
1111	137.6	70.7	24.9	0.9	0.4	2.7	0.4	97.2	34.3	1.2	0.5	3.7	0.6
Mean	116.6	51.1	44.5	0.7	0.2	2.9	0.4	61.6	49.9	0.8	0.3	3.5	0.5
S.D.	16.0	16.0	16.4	0.1	0.1	0.6	0.4	26.6	12.2	0.3	0.2	0.9	0.4

LUC: Large unstained cells
S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 6-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 15

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
2104	694	13.3	39.6	57.0	19.2	33.7	10.6	125.5	13.3	13.5	313
2106	714	13.6	41.2	57.7	19.0	33.0	10.1	136.2	13.4	15.1	256
2107	750	13.9	42.1	56.1	18.6	33.1	7.2	148.4	14.5	17.4	290
2111	697	12.9	38.0	54.5	18.4	33.8	11.0	163.1	13.0	15.4	361
2112	668	13.5	39.1	58.5	20.1	34.4	6.0	136.0	12.5	15.7	267
Mean	705	13.4	40.0	56.8	19.1	33.6	9.0	141.8	13.3	15.4	297
S.D.	30	0.4	1.6	1.5	0.7	0.6	2.2	14.4	0.7	1.4	42

Appendix 6-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 15

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
2104	153.5	60.1	35.0	0.6	0.3	3.4	0.5	92.2	53.8	1.0	0.5	5.2	0.8
2106	156.6	60.6	34.7	0.6	0.2	3.3	0.5	95.0	54.4	1.0	0.3	5.2	0.7
2107	146.3	69.9	26.4	0.5	0.4	2.3	0.6	102.2	38.6	0.7	0.5	3.3	0.9
2111	120.4	42.3	54.8	0.6	0.2	1.8	0.3	51.0	66.0	0.7	0.2	2.1	0.4
2112	75.5	61.3	33.5	1.4	0.2	3.4	0.2	46.3	25.3	1.0	0.2	2.6	0.2
Mean	130.5	58.8	36.9	0.7	0.3	2.8	0.4	77.3	47.6	0.9	0.3	3.7	0.6
S.D.	33.9	10.1	10.6	0.4	0.1	0.7	0.2	26.5	15.8	0.2	0.2	1.5	0.3

LUC: Large unstained cells

Appendix 6-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 50

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
3101	739	14.2	41.6	56.2	19.2	34.1	7.4	144.2	14.0	21.2	318
3105	795	14.6	42.7	53.7	18.4	34.2	4.1	107.8	13.0	20.6	220
3108	710	13.2	39.4	55.5	18.6	33.6	6.5	145.2	14.4	15.9	269
3109	724	13.8	41.2	56.9	19.0	33.4	6.8	138.2	13.2	15.2	274
3110	710	13.7	40.2	56.6	19.2	34.0	8.0	139.4	13.9	24.4	262
Mean	736	13.9	41.0	55.8	18.9	33.9	6.6	135.0	13.7	19.5	269
S.D.	35	0.5	1.3	1.3	0.4	0.3	1.5	15.5	0.6	3.9	35

Appendix 6-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 50

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
3101	166.1	35.1	60.8	0.5	0.2	3.1	0.2	58.3	101.0	0.8	0.4	5.2	0.3
3105	86.7	63.2	31.4	1.1	0.2	3.8	0.3	54.8	27.2	1.0	0.1	3.3	0.3
3108	129.1	65.7	30.5	0.7	0.2	2.5	0.3	84.8	39.4	0.9	0.3	3.2	0.4
3109	102.8	54.7	41.6	0.8	0.2	2.4	0.3	56.3	42.8	0.8	0.2	2.5	0.3
3110	119.0	69.4	26.0	0.8	0.3	3.0	0.5	82.6	30.9	0.9	0.3	3.6	0.6
Mean	120.7	57.6	38.1	0.8	0.2	3.0	0.3	67.4	48.3	0.9	0.3	3.6	0.4
S.D.	30.0	13.7	13.9	0.2	0.0	0.6	0.1	15.0	30.1	0.1	0.1	1.0	0.1

LUC: Large unstained cells

Appendix 6-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 150

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4103	749	13.3	39.6	52.9	17.8	33.6	7.6	135.3	12.8	17.2	246
4104	714	13.5	39.2	54.9	18.8	34.3	6.1	140.4	12.7	15.3	244
4105	747	14.0	39.9	53.4	18.7	35.0	6.1	134.4	12.1	20.6	270
4106	749	13.6	39.7	53.0	18.2	34.3	5.6	152.3	13.6	16.0	241
4108	734	13.7	40.9	55.7	18.7	33.6	8.4	146.2	13.7	20.9	237
Mean	739	13.6	39.9	54.0	18.4	34.2	6.8	141.7	13.0	18.0	248
S.D.	15	0.3	0.6	1.3	0.4	0.6	1.2	7.6	0.7	2.6	13

Appendix 6-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 150

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4103	113.1	62.1	32.9	0.9	0.2	3.4	0.4	70.3	37.2	1.0	0.3	3.9	0.5
4104	174.2	52.2	43.2	0.6	0.2	3.3	0.4	91.0	75.2	1.1	0.4	5.8	0.7
4105	135.3	59.1	36.5	0.6	0.3	3.3	0.3	79.9	49.3	0.9	0.3	4.5	0.4
4106	78.2	50.4	44.6	1.5	0.2	3.1	0.2	39.4	34.8	1.2	0.1	2.4	0.1
4108	160.1	63.8	32.3	0.3	0.5	2.7	0.4	102.2	51.8	0.5	0.8	4.2	0.6
Mean	132.2	57.5	37.9	0.8	0.3	3.2	0.3	76.6	49.7	0.9	0.4	4.2	0.5
S.D.	38.2	6.0	5.7	0.5	0.1	0.3	0.1	24.0	16.1	0.3	0.3	1.2	0.2

LUC: Large unstained cells

Appendix 6-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1113	819	15.0	42.7	52.1	18.3	35.1	2.5	109.9	12.6	15.5	216
1114	861	14.9	41.9	48.7	17.3	35.6	2.0	121.6	12.8	23.3	223
1115	886	15.2	43.6	49.2	17.2	35.0	2.0	105.3	13.5	19.0	242
1116	861	15.6	44.1	51.2	18.1	35.3	1.6	96.8	12.8	16.1	205
1117	887	15.6	44.5	50.1	17.5	35.0	2.1	95.1	12.5	15.6	222
Mean	863	15.3	43.4	50.3	17.7	35.2	2.0	105.7	12.8	17.9	222
S.D.	28	0.3	1.1	1.4	0.5	0.3	0.3	10.7	0.4	3.3	13

Appendix 6-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1113	53.7	76.8	19.0	1.4	0.4	2.1	0.3	41.2	10.2	0.7	0.2	1.2	0.2
1114	36.8	81.3	14.2	1.5	0.2	2.3	0.5	30.0	5.2	0.5	0.1	0.8	0.2
1115	37.1	75.8	20.4	1.4	0.2	1.7	0.4	28.1	7.6	0.5	0.1	0.6	0.2
1116	42.1	84.8	10.7	2.1	0.2	1.8	0.4	35.7	4.5	0.9	0.1	0.8	0.2
1117	70.7	75.6	19.9	2.1	0.2	2.0	0.3	53.4	14.1	1.5	0.1	1.4	0.2
Mean	48.1	78.9	16.8	1.7	0.2	2.0	0.4	37.7	8.3	0.8	0.1	1.0	0.2
S.D.	14.4	4.0	4.2	0.4	0.1	0.2	0.1	10.2	3.9	0.4	0.0	0.3	0.0

LUC: Large unstained cells

Appendix 6-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Satellite group, End of administration)
Dose (mg/kg): 150

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4113	773	14.2	40.5	52.3	18.4	35.1	1.5	114.5	12.9	16.5	187
4114S	878Z	17.0Z	46.8Z	53.2Z	19.4Z	36.4Z	2.7Z	116.2Z	14.3Z	14.6Z	262Z
4115	782	15.0	41.8	53.5	19.2	35.9	1.8	107.5	12.5	14.9	203
4116	810	15.1	42.2	52.1	18.7	35.9	1.7	102.5	12.4	12.1	188
4117	859	14.7	41.7	48.5	17.1	35.2	1.3	100.6	13.3	17.6	171
Mean	806	14.8	41.6	51.6	18.4	35.5	1.6	106.3	12.8	15.3	187
S.D.	39	0.4	0.7	2.2	0.9	0.4	0.2	6.2	0.4	2.4	13

S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 6-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (Satellite group, End of administration)
Dose (mg/kg): 150

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4113	69.2	76.5	16.5	2.3	0.2	3.4	1.0	52.9	11.4	1.6	0.1	2.3	0.7
4114S	210.3Z	13.1Z	81.3Z	0.2Z	0.2Z	4.4Z	0.8Z	27.5Z	171.0Z	0.4Z	0.5Z	9.2Z	1.6Z
4115	41.7	70.1	25.7	1.8	0.2	2.0	0.2	29.2	10.7	0.8	0.1	0.8	0.1
4116	50.5	64.5	31.4	1.4	0.3	2.3	0.2	32.6	15.9	0.7	0.1	1.2	0.1
4117	46.8	75.1	20.1	2.0	0.2	2.3	0.3	35.1	9.4	0.9	0.1	1.1	0.1
Mean	52.1	71.6	23.4	1.9	0.2	2.5	0.4	37.5	11.9	1.0	0.1	1.4	0.3
S.D.	12.0	5.4	6.5	0.4	0.1	0.6	0.4	10.6	2.8	0.4	0.0	0.7	0.3

LUC: Large unstained cells
S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 6-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of recovery)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1008	903	15.8	44.7	49.6	17.5	35.2	1.8	109.3	13.3	20.8	223
1009	910	15.7	44.1	48.5	17.2	35.6	2.0	104.7	13.6	19.2	258
1010	913	15.9	45.7	50.1	17.4	34.7	1.7	84.7	18.3	18.1	310
1011	846	15.0	42.8	50.6	17.7	35.1	1.8	110.0	13.3	20.7	288
1012	902	15.9	44.8	49.7	17.6	35.4	1.2	113.7	18.9	20.2	278
Mean	895	15.7	44.4	49.7	17.5	35.2	1.7	104.5	15.5	19.8	271
S.D.	28	0.4	1.1	0.8	0.2	0.3	0.3	11.5	2.9	1.1	33

Appendix 6-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of recovery)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1008	131.4	81.3	14.4	0.9	0.3	2.4	0.7	106.9	18.9	1.1	0.4	3.2	0.9
1009	90.5	77.0	18.3	1.9	0.3	1.9	0.7	69.7	16.5	1.7	0.2	1.7	0.6
1010	87.1	73.5	20.7	1.2	0.2	3.8	0.4	64.0	18.0	1.1	0.2	3.4	0.4
1011	117.7	81.5	15.0	0.8	0.5	1.8	0.5	95.9	17.7	1.0	0.5	2.1	0.5
1012	121.0	83.7	12.1	1.2	0.3	1.7	1.0	101.4	14.6	1.4	0.3	2.1	1.2
Mean	109.5	79.4	16.1	1.2	0.3	2.3	0.7	87.6	17.1	1.3	0.3	2.5	0.7
S.D.	19.6	4.1	3.4	0.4	0.1	0.9	0.2	19.4	1.7	0.3	0.1	0.8	0.3

LUC: Large unstained cells

Appendix 6-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of recovery)
Dose (mg/kg): 150

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4008	882	15.9	45.2	51.3	18.1	35.2	1.6	98.6	20.8	24.2	283
4009	885	16.0	44.5	50.4	18.1	35.9	2.0	123.6	15.7	19.2	243
4010S	1004Z	20.0Z	60.1Z	59.9Z	19.9Z	33.3Z	1.9Z	66.8Z	-	-	-
4011	848	15.8	43.7	51.5	18.6	36.1	2.1	126.7	15.5	19.8	254
4012	854	15.0	43.1	50.4	17.6	34.9	1.8	114.0	19.0	20.0	291
Mean	867	15.7	44.1	50.9	18.1	35.5	1.9	115.7	17.8	20.8	268
S.D.	19	0.5	0.9	0.6	0.4	0.6	0.2	12.6	2.6	2.3	23

-: Not done. A sufficient amount of blood sample was not obtained due to severe moribundity.
S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 6-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of male rats (End of recovery)
Dose (mg/kg): 150

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4008	98.8	75.5	20.4	1.2	0.2	2.1	0.6	74.6	20.1	1.2	0.2	2.0	0.6
4009	90.1	74.3	21.3	2.0	0.2	2.0	0.2	67.0	19.2	1.8	0.2	1.8	0.2
4010S	50.7Z	37.1Z	59.3Z	0.2Z	0.5Z	2.8Z	0.1Z	18.8Z	30.1Z	0.1Z	0.3Z	1.4Z	0.1Z
4011	123.1	75.4	20.1	1.1	0.3	2.4	0.6	92.8	24.8	1.3	0.4	3.0	0.8
4012	103.8	81.9	12.2	1.0	0.2	3.7	1.1	85.0	12.6	1.1	0.2	3.8	1.1
Mean	104.0	76.8	18.5	1.3	0.2	2.6	0.6	79.9	19.2	1.4	0.3	2.7	0.7
S.D.	14.0	3.5	4.2	0.5	0.1	0.8	0.4	11.4	5.0	0.3	0.1	0.9	0.4

LUC: Large unstained cells
S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 6-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (End of recovery)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1118	844	15.7	44.5	52.7	18.6	35.2	1.0	131.5	12.9	18.2	173
1119	836	15.9	43.6	52.1	19.1	36.6	2.2	104.4	12.7	18.6	206
1120	815	15.3	41.6	51.1	18.8	36.7	1.9	110.5	12.9	13.9	181
1121	799	14.9	41.6	52.0	18.6	35.8	1.4	111.0	12.9	21.1	208
1122	834	15.2	42.9	51.5	18.2	35.4	1.3	109.8	12.6	19.1	182
Mean	826	15.4	42.8	51.9	18.7	35.9	1.6	113.4	12.8	18.2	190
S.D.	18	0.4	1.3	0.6	0.3	0.7	0.5	10.4	0.1	2.6	16

Appendix 6-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (End of recovery)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1118	51.9	71.1	23.8	2.0	0.1	2.5	0.4	36.9	12.3	1.1	0.1	1.3	0.2
1119	75.9	73.8	17.8	1.8	0.3	5.3	1.0	56.0	13.5	1.4	0.2	4.0	0.8
1120	71.6	81.3	12.4	2.1	0.3	3.2	0.8	58.2	8.8	1.5	0.2	2.3	0.6
1121	47.7	82.4	11.3	3.6	0.3	1.9	0.5	39.3	5.4	1.7	0.1	0.9	0.3
1122	29.2	78.5	18.6	1.4	0.1	1.2	0.2	22.9	5.4	0.4	0.0	0.4	0.1
Mean	55.3	77.4	16.8	2.2	0.2	2.8	0.6	42.7	9.1	1.2	0.1	1.8	0.4
S.D.	19.0	4.8	5.1	0.8	0.1	1.6	0.3	14.6	3.8	0.5	0.1	1.4	0.3

LUC: Large unstained cells

Appendix 6-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (End of recovery)
Dose (mg/kg): 150

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4118D											
4119	834	15.6	43.1	51.7	18.7	36.2	2.0	153.4	12.6	18.1	175
4120	809	14.5	40.5	50.1	17.9	35.7	1.2	104.8	12.8	14.3	192
4121	824	15.0	41.7	50.6	18.2	36.0	2.3	142.2	13.6	16.6	192
4122	824	15.7	44.0	53.3	19.0	35.6	1.6	115.1	13.0	17.9	198
Mean	823	15.2	42.3	51.4	18.5	35.9	1.8	128.9	13.0	16.7	189
S.D.	10	0.6	1.5	1.4	0.5	0.3	0.5	22.7	0.4	1.7	10

D: Dead

Appendix 6-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual hematology of female rats (End of recovery)
Dose (mg/kg): 150

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4118D													
4119	52.6	71.7	24.2	1.7	0.2	1.6	0.6	37.8	12.8	0.9	0.1	0.8	0.3
4120	51.6	69.8	24.3	1.8	0.1	3.4	0.5	36.0	12.6	0.9	0.1	1.8	0.3
4121	82.6	65.6	30.3	0.9	0.4	2.5	0.3	54.2	25.1	0.7	0.3	2.1	0.2
4122	64.7	81.9	11.8	1.9	0.3	3.5	0.7	53.0	7.6	1.3	0.2	2.2	0.4
Mean	62.9	72.3	22.7	1.6	0.3	2.8	0.5	45.3	14.5	1.0	0.2	1.7	0.3
S.D.	14.4	6.9	7.8	0.5	0.1	0.9	0.2	9.7	7.4	0.3	0.1	0.6	0.1

LUC: Large unstained cells
D: Dead

Appendix 7-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1001	72	33	54	1	379	4.9	58	42	95	0.0	118
1002	82	40	58	0	370	7.1	41	50	75	0.1	131
1003	85	33	53	0	449	16.6	58	27	94	0.1	106
1004	64	31	46	0	282	7.4	46	20	70	0.1	139
1005	101	50	54	1	465	8.9	67	28	90	0.1	113
Mean	81	37	53	0	389	9.0	54	33	85	0.1	121
S.D.	14	8	4	1	73	4.5	10	12	12	0.0	13

Appendix 7-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1001	12	0.27	144	4.5	107	9.3	5.4	5.7	3.2	1.28
1002	15	0.32	144	4.5	108	9.8	6.0	5.7	3.2	1.28
1003	17	0.32	143	4.4	105	10.0	6.1	6.0	3.4	1.31
1004	17	0.30	143	4.3	106	9.8	6.4	5.9	3.2	1.19
1005	17	0.31	143	4.3	108	9.3	6.2	5.4	3.1	1.35
Mean	16	0.30	143	4.4	107	9.6	6.0	5.7	3.2	1.28
S.D.	2	0.02	1	0.1	1	0.3	0.4	0.2	0.1	0.06

Appendix 7-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 15

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
2001	72	38	59	1	546	12.7	53	32	87	0.1	116
2002	69	27	51	1	370	64.1	36	16	61	0.1	107
2003	70	32	41	0	519	7.1	57	33	92	0.1	156
2004	69	32	40	0	355	6.3	39	32	67	0.1	134
2005	66	28	57	0	365	9.1	61	26	95	0.1	142
Mean	69	31	50	0	431	19.9	49	28	80	0.1	131
S.D.	2	4	9	1	93	24.9	11	7	15	0.0	20

Appendix 7-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 15

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
2001	16	0.27	142	4.4	106	9.9	6.7	6.0	3.3	1.22
2002	16	0.31	144	4.3	105	9.7	6.0	5.9	3.3	1.27
2003	15	0.29	143	4.5	108	9.5	5.2	5.9	3.3	1.27
2004	19	0.31	143	4.2	108	9.5	5.7	5.6	3.2	1.33
2005	20	0.27	142	4.4	107	9.6	5.5	5.7	3.3	1.38
Mean	17	0.29	143	4.4	107	9.6	5.8	5.8	3.3	1.29
S.D.	2	0.02	1	0.1	1	0.2	0.6	0.2	0.0	0.06

Appendix 7-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 50

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
3001	77	32	59	1	566	10.1	47	24	82	0.1	137
3002	73	36	81	0	460	4.9	47	24	73	0.1	139
3003	76	35	40	0	369	5.7	33	19	58	0.1	107
3004	74	47	34	0	401	6.9	42	48	78	0.1	113
3005	71	33	75	1	584	8.1	33	41	69	0.1	130
Mean	74	37	58	0	476	7.1	40	31	72	0.1	125
S.D.	2	6	21	1	96	2.1	7	13	9	0.0	14

Appendix 7-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 50

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
3001	13	0.26	143	4.4	104	9.7	5.7	5.6	3.2	1.33
3002	16	0.31	141	4.5	108	9.4	6.0	5.4	3.2	1.45
3003	12	0.27	145	4.2	108	9.2	6.4	5.3	3.0	1.30
3004	17	0.26	143	4.5	107	9.7	6.5	5.5	3.1	1.29
3005	17	0.21	144	4.6	107	10.0	8.1	5.3	3.3	1.65
Mean	15	0.26	143	4.4	107	9.6	6.5	5.4	3.2	1.40
S.D.	2	0.04	1	0.2	2	0.3	0.9	0.1	0.1	0.15

Appendix 7-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 150

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4001	68	50	41	1	323	3.7	62	51	97	0.1	133
4002	69	44	68	1	350	2.7	57	20	85	0.0	122
4003D											
4004D											
4005	63	43	64	1	376	3.4	50	36	76	0.1	133
4006a)											
4007a)											
Mean	67	46	58	1	350	3.3	56	36	86	0.1	129
S.D.	3	4	15	0	27	0.5	6	16	11	0.1	6

D: Dead
a): Examination was not done due to misunderstanding of protocol which specified the number of animals (five animals) to be examined.

Appendix 7-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 150

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4001	17	0.29	142	4.6	106	9.5	5.1	5.9	3.3	1.27
4002	14	0.30	143	4.7	109	9.4	5.8	5.5	3.2	1.39
4003D										
4004D										
4005	15	0.27	143	4.4	108	9.6	5.8	5.3	3.2	1.52
4006a)										
4007a)										
Mean	15	0.29	143	4.6	108	9.5	5.6	5.6	3.2	1.39
S.D.	2	0.02	1	0.2	2	0.1	0.4	0.3	0.1	0.13

D: Dead
a): Examination was not done due to misunderstanding of protocol which specified the number of animals (five animals) to be examined.

Appendix 7-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1103	81	51	69	1	202	201.3	39	34	79	0.1	129
1104S	217Z	53Z	1053Z	6Z	1187Z	4.3Z	93Z	143Z	147Z	0.1Z	294Z
1105	136	80	63	1	170	11.3	47	19	104	0.1	133
1106	81	58	38	1	191	11.4	60	42	118	0.1	112
1110	76	40	32	1	284	16.0	63	49	131	0.1	125
1111	75	45	56	1	242	35.2	40	41	87	0.1	143
Mean	90	55	52	1	218	55.0	50	37	104	0.1	128
S.D.	26	16	16	0	45	82.4	11	11	21	0.0	11

S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 7-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1103	21	0.31	140	4.3	104	10.3	7.4	5.9	3.4	1.36
1104S	351Z	5.27Z	142Z	9.1Z	93Z	10.4Z	28.5*Z	5.2Z	2.3Z	0.79Z
1105	14	0.31	141	3.8	107	10.2	6.9	6.2	3.7	1.48
1106	19	0.32	141	3.5	107	10.3	7.1	5.8	3.7	1.76
1110	14	0.28	141	4.4	109	10.4	6.7	5.7	3.7	1.85
1111	17	0.24	142	4.6	107	10.1	6.8	6.1	3.5	1.35
Mean	17	0.29	141	4.1	107	10.3	7.0	5.9	3.6	1.56
S.D.	3	0.03	1	0.5	2	0.1	0.3	0.2	0.1	0.23

*: Re-analyzed value
S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 7-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 15

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
2104	82	56	50	1	207	13.2	46	94	113	0.1	121
2106	89	62	61	1	213	10.4	53	123	114	0.1	130
2107	75	44	45	1	181	7.0	34	61	87	0.1	141
2111	132	81	91	0	184	19.7	64	52	137	0.1	140
2112	78	37	37	1	198	12.4	64	40	123	0.0	116
Mean	91	56	57	1	197	12.5	52	74	115	0.1	130
S.D.	23	17	21	0	14	4.7	13	34	18	0.0	11

Appendix 7-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 15

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
2104	14	0.28	139	4.2	103	10.4	7.0	6.1	3.7	1.54
2106	15	0.29	140	3.8	105	10.3	6.8	5.9	3.5	1.46
2107	13	0.25	139	4.0	105	10.1	5.6	6.0	3.6	1.50
2111	14	0.28	140	2.8	103	9.9	5.9	6.2	3.7	1.48
2112	18	0.31	140	4.6	106	10.3	7.2	5.5	3.3	1.50
Mean	15	0.28	140	3.9	104	10.2	6.5	5.9	3.6	1.50
S.D.	2	0.02	1	0.7	1	0.2	0.7	0.3	0.2	0.03

Appendix 7-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 50

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
3101	145	104	66	1	201	15.6	49	39	108	0.1	139
3105	87	55	49	0	197	11.4	56	74	117	0.1	130
3108	86	51	42	0	162	7.5	51	32	104	0.1	134
3109	80	34	35	0	166	15.1	48	35	102	0.1	108
3110	74	43	59	1	190	15.8	46	73	108	0.1	114
Mean	94	57	50	0	183	13.1	50	51	108	0.1	125
S.D.	29	27	13	1	18	3.6	4	21	6	0.0	13

Appendix 7-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 50

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
3101	14	0.28	140	3.4	103	10.3	6.5	6.1	3.6	1.44
3105	16	0.27	139	4.5	106	10.0	6.4	5.9	3.4	1.36
3108	15	0.27	139	4.5	106	10.3	7.6	5.7	3.4	1.48
3109	18	0.28	140	4.7	106	10.2	7.2	5.7	3.5	1.59
3110	20	0.29	141	4.2	107	10.4	7.7	5.9	3.7	1.68
Mean	17	0.28	140	4.3	106	10.2	7.1	5.9	3.5	1.51
S.D.	2	0.01	1	0.5	2	0.2	0.6	0.2	0.1	0.13

Appendix 7-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 150

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4103	78	66	62	1	199	4.8	54	93	114	0.0	142
4104	87	61	38	0	157	10.5	51	46	107	0.1	115
4105	97	68	55	0	134	7.9	47	30	95	0.0	118
4106	69	51	59	1	254	4.2	42	44	85	0.0	128
4108	97	67	60	0	399	9.2	50	54	99	0.1	127
Mean	86	63	55	0	229	7.3	49	53	100	0.0	126
S.D.	12	7	10	1	106	2.7	5	24	11	0.1	11

Appendix 7-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 150

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4103	14	0.25	138	4.4	103	10.2	6.1	5.5	3.3	1.50
4104	14	0.27	137	4.4	104	9.7	6.2	5.6	3.5	1.67
4105	13	0.27	139	4.3	104	10.4	7.5	6.3	3.9	1.63
4106	19	0.29	139	5.3	107	10.3	7.2	5.6	3.3	1.43
4108	15	0.28	140	4.9	103	10.4	7.6	6.0	3.4	1.31
Mean	15	0.27	139	4.7	104	10.2	6.9	5.8	3.5	1.51
S.D.	2	0.01	1	0.4	2	0.3	0.7	0.3	0.2	0.15

Appendix 7-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1113	82	34	54	1	239	9.3	46	8	98	0.1	147
1114	67	32	43	1	300	11.4	48	9	95	0.1	152
1115	66	29	79	1	395	14.5	59	13	110	0.1	113
1116	62	26	47	1	258	14.1	56	13	97	0.1	133
1117	86	70	44	2	215	6.8	67	24	137	0.1	139
Mean	73	38	53	1	281	11.2	55	13	107	0.1	137
S.D.	11	18	15	0	71	3.3	9	6	18	0.0	15

Appendix 7-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1113	19	0.34	143	4.4	111	10.1	4.9	6.6	4.0	1.54
1114	19	0.34	144	4.5	111	9.4	3.8	6.2	3.7	1.48
1115	18	0.35	144	4.4	111	10.0	4.5	6.3	3.7	1.42
1116	17	0.32	141	3.8	108	9.7	5.3	5.8	3.5	1.52
1117	17	0.32	141	4.5	107	10.3	5.8	6.2	3.8	1.58
Mean	18	0.33	143	4.3	110	9.9	4.9	6.2	3.7	1.51
S.D.	1	0.01	2	0.3	2	0.4	0.8	0.3	0.2	0.06

Appendix 7-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Satellite group, End of administration)
Dose (mg/kg): 150

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4113	84	54	35	0	201	5.5	63	21	115	0.1	141
4114S	466Z	309Z	608Z	1Z	564Z	9.6Z	68Z	20Z	122Z	0.1Z	138Z
4115	77	42	40	0	120	6.2	58	19	107	0.1	131
4116	66	31	41	1	202	4.0	58	15	105	0.1	128
4117	96	47	50	0	326	8.9	31	12	64	0.1	107
Mean	81	44	42	0	212	6.2	53	17	98	0.1	127
S.D.	13	10	6	1	85	2.1	15	4	23	0.0	14

S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 7-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (Satellite group, End of administration)
Dose (mg/kg): 150

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4113	18	0.37	140	4.4	107	9.6	4.5	5.7	3.3	1.38
4114S	27Z	0.27Z	136Z	4.8Z	99Z	9.3Z	6.9Z	5.3Z	3.5Z	1.94Z
4115	14	0.31	143	4.4	106	9.9	4.3	6.1	3.8	1.65
4116	17	0.33	142	4.0	109	9.5	4.2	6.1	3.5	1.35
4117	18	0.40	143	4.3	108	9.7	5.6	5.3	3.3	1.65
Mean	17	0.35	142	4.3	108	9.7	4.7	5.8	3.5	1.51
S.D.	2	0.04	1	0.2	1	0.2	0.6	0.4	0.2	0.17

S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 7-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of recovery)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1008	66	29	40	1	284	4.7	43	35	80	0.1	146
1009	58	31	59	0	303	13.6	56	28	88	0.1	123
1010	65	31	64	1	405	9.8	43	41	79	0.1	144
1011	68	31	63	0	269	8.4	66	31	92	0.1	120
1012	65	34	54	0	472	36.6	39	20	73	0.1	125
Mean	64	31	56	0	347	14.6	49	31	82	0.1	132
S.D.	4	2	10	1	88	12.7	11	8	8	0.0	12

Appendix 7-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of recovery)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1008	15	0.24	140	4.1	102	9.9	6.4	5.9	3.2	1.19
1009	16	0.29	141	4.5	104	9.6	6.3	5.9	3.1	1.11
1010	17	0.26	141	4.8	105	9.5	6.8	5.7	3.2	1.28
1011	16	0.28	143	4.3	104	10.3	6.8	6.3	3.4	1.17
1012	16	0.29	143	4.5	105	9.7	6.3	5.8	3.3	1.32
Mean	16	0.27	142	4.4	104	9.8	6.5	5.9	3.2	1.21
S.D.	1	0.02	1	0.3	1	0.3	0.3	0.2	0.1	0.09

Appendix 7-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of recovery)
Dose (mg/kg): 150

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4008	76	36	51	0	394	6.8	28	12	59	0.1	123
4009	67	27	55	0	385	4.1	34	43	66	0.1	142
4010S	347Z	196Z	1565Z	2Z	966Z	25.3Z	101Z	22Z	132Z	0.1Z	243Z
4011	69	37	49	0	365	19.2	45	43	77	0.1	112
4012	66	25	67	1	308	4.4	38	35	67	0.1	121
Mean	70	31	56	0	363	8.6	36	33	67	0.1	125
S.D.	5	6	8	1	39	7.2	7	15	7	0.0	13

S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 7-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of male rats (End of recovery)
Dose (mg/kg): 150

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4008	13	0.26	141	4.6	103	9.6	6.6	5.9	3.3	1.27
4009	16	0.27	141	4.9	105	9.7	6.8	5.8	3.3	1.32
4010S	23Z	0.34Z	141Z	7.3Z	89Z	11.8Z	19.1Z	6.1Z	3.1Z	1.03Z
4011	14	0.27	142	4.6	105	9.8	6.1	5.7	3.2	1.28
4012	15	0.29	143	4.5	107	9.9	6.6	5.9	3.3	1.27
Mean	15	0.27	142	4.7	105	9.8	6.5	5.8	3.3	1.29
S.D.	1	0.01	1	0.2	2	0.1	0.3	0.1	0.1	0.02

S: Sacrificed moribund
Z: Data was excluded from statistical analysis.

Appendix 7-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (End of recovery)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1118	89	58	56	1	148	16.4	71	22	139	0.1	121
1119	58	22	42	2	185	11.0	55	10	101	0.1	108
1120	77	35	53	1	157	11.1	49	9	88	0.1	125
1121	56	24	45	1	282	7.5	50	9	100	0.1	127
1122	66	23	46	2	216	8.9	66	13	119	0.1	124
Mean	69	32	48	1	198	11.0	58	13	109	0.1	121
S.D.	14	15	6	1	54	3.4	10	6	20	0.0	8

Appendix 7-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (End of recovery)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1118	18	0.37	142	3.9	106	10.6	3.7	6.9	4.1	1.46
1119	20	0.32	142	3.9	107	10.1	5.6	6.5	3.8	1.41
1120	18	0.32	143	4.4	107	10.1	4.5	6.1	3.6	1.44
1121	17	0.34	143	4.6	109	10.0	4.7	6.5	3.8	1.41
1122	16	0.37	144	4.7	109	10.5	6.8	6.3	3.7	1.42
Mean	18	0.34	143	4.3	108	10.3	5.1	6.5	3.8	1.43
S.D.	1	0.03	1	0.4	1	0.3	1.2	0.3	0.2	0.02

Appendix 7-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (End of recovery)
Dose (mg/kg): 150

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4118D											
4119	73	23	50	1	189	10.1	62	7	119	0.1	132
4120	82	39	51	1	232	11.9	67	39	126	0.1	132
4121	63	24	64	1	154	16.1	53	13	105	0.1	124
4122	70	27	72	1	160	10.4	55	17	110	0.1	136
Mean	72	28	59	1	184	12.1	59	19	115	0.1	131
S.D.	8	7	11	0	36	2.8	6	14	9	0.0	5

D: Dead

Appendix 7-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual blood chemistry of female rats (End of recovery)
Dose (mg/kg): 150

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4118D										
4119	19	0.31	142	4.1	110	9.9	4.4	6.3	3.9	1.63
4120	22	0.45	140	4.0	106	9.4	3.9	5.7	3.4	1.48
4121	12	0.28	140	4.5	105	9.5	4.6	6.0	3.8	1.73
4122	17	0.34	141	4.0	106	10.4	5.3	6.4	4.0	1.67
Mean	18	0.35	141	4.2	107	9.8	4.6	6.1	3.8	1.63
S.D.	4	0.07	1	0.2	2	0.5	0.6	0.3	0.3	0.11

D: Dead

Appendix 8-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1001	514	2.17	11.9	11.8	12.5	24.3	203
	1002	522	2.12	14.6	17.5	11.8	29.3	267
	1003	501	2.23	14.0	10.3	10.5	20.8	365
	1004	504	2.08	13.0	12.9	10.5	23.4	330
	1005	523	2.18	14.1	12.9	10.1	23.0	277
	1006	483	2.06	13.5	9.1	12.2	21.3	312
	1007	544	2.01	16.4	13.5	13.4	26.9	287
	Mean	513	2.12	13.9	12.6	11.6	24.1	292
	S.D.	19	0.08	1.4	2.7	1.2	3.0	52
Relative	1001		0.42	2.3	2.3	2.4	4.7	39
	1002		0.41	2.8	3.4	2.3	5.6	51
	1003		0.45	2.8	2.1	2.1	4.2	73
	1004		0.41	2.6	2.6	2.1	4.6	65
	1005		0.42	2.7	2.5	1.9	4.4	53
	1006		0.43	2.8	1.9	2.5	4.4	65
	1007		0.37	3.0	2.5	2.5	4.9	53
	Mean		0.42	2.7	2.5	2.3	4.7	57
	S.D.		0.02	0.2	0.5	0.2	0.5	11

Appendix 8-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1001	1.29	12.49	0.75	1.67	1.67	3.34
	1002	1.31	12.33	0.69	1.52	1.63	3.15
	1003	1.59	12.03	0.80	1.70	1.83	3.53
	1004	1.25	12.19	0.69	1.58	1.66	3.24
	1005	1.39	12.52	1.04	1.89	1.98	3.87
	1006	1.39	12.37	0.65	1.71	1.67	3.38
	1007	1.51	14.19	0.79	1.75	1.78	3.53
	Mean	1.39	12.59	0.77	1.69	1.75	3.43
	S.D.	0.12	0.73	0.13	0.12	0.13	0.24
Relative	1001	0.25	2.43	0.15	0.32	0.32	0.65
	1002	0.25	2.36	0.13	0.29	0.31	0.60
	1003	0.32	2.40	0.16	0.34	0.37	0.70
	1004	0.25	2.42	0.14	0.31	0.33	0.64
	1005	0.27	2.39	0.20	0.36	0.38	0.74
	1006	0.29	2.56	0.13	0.35	0.35	0.70
	1007	0.28	2.61	0.15	0.32	0.33	0.65
	Mean	0.27	2.45	0.15	0.33	0.34	0.67
	S.D.	0.03	0.09	0.02	0.02	0.03	0.05

Appendix 8-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	1001	36	40	76	1.57	1.57	3.14
	1002	39	39	78	1.44	1.54	2.98
	1003	35	36	71	1.66	1.65	3.31
	1004	31	34	65	1.68	1.73	3.41
	1005	31	34	65	1.48	1.49	2.97
	1006	30	30	60	1.58	1.58	3.16
	1007	33	40	73	1.66	1.59	3.25
	Mean	34	36	70	1.58	1.59	3.17
	S.D.	3	4	7	0.09	0.08	0.16
Relative	1001	7	8	15	0.31	0.31	0.61
	1002	7	7	15	0.28	0.30	0.57
	1003	7	7	14	0.33	0.33	0.66
	1004	6	7	13	0.33	0.34	0.68
	1005	6	7	12	0.28	0.28	0.57
	1006	6	6	12	0.33	0.33	0.65
	1007	6	7	13	0.31	0.29	0.60
	Mean	6	7	13	0.31	0.31	0.62
	S.D.	1	1	1	0.02	0.02	0.04

Appendix 8-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 0

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	1001	800	673	1473	1.94	1.49
	1002	630	662	1292	1.62	1.06
	1003	867	840	1707	2.30	1.28
	1004	665	652	1317	1.76	1.08
	1005	648	610	1258	1.47	1.23
	1006	718	748	1466	1.93	1.36
	1007	704	717	1421	2.00	1.60
	Mean	719	700	1419	1.86	1.30
	S.D.	86	76	153	0.27	0.20
Relative	1001	156	131	287	0.38	0.29
	1002	121	127	248	0.31	0.20
	1003	173	168	341	0.46	0.26
	1004	132	129	261	0.35	0.21
	1005	124	117	241	0.28	0.24
	1006	149	155	304	0.40	0.28
	1007	129	132	261	0.37	0.29
	Mean	141	137	278	0.36	0.25
	S.D.	19	18	36	0.06	0.04

Appendix 8-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 15

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	2001	502	2.23	15.0	16.9	17.6	34.5	347
	2002	479	2.03	11.8	11.7	11.3	23.0	271
	2003	482	2.10	14.3	6.7	9.8	16.5	257
	2004	515	2.21	14.3	15.5	9.9	25.4	342
	2005	540	2.13	13.4	15.8	16.4	32.2	316
	2006	516	2.10	14.9	12.4	13.2	25.6	282
	2007	466	2.11	14.4	15.2	16.0	31.2	270
	2008	477	2.02	11.4	14.3	16.4	30.7	225
	2009	525	2.22	16.8	13.2	11.6	24.8	296
	2010	467	2.11	14.4	11.7	10.0	21.7	299
	2011	477	2.16	14.3	12.9	9.8	22.7	276
	2012	508	2.09	11.9	10.2	8.5	18.7	285
	Mean	496	2.13	13.9	13.0	12.5	25.6	289
	S.D.	25	0.07	1.6	2.8	3.2	5.6	34
Relative	2001		0.44	3.0	3.4	3.5	6.9	69
	2002		0.42	2.5	2.4	2.4	4.8	57
	2003		0.44	3.0	1.4	2.0	3.4	53
	2004		0.43	2.8	3.0	1.9	4.9	66
	2005		0.39	2.5	2.9	3.0	6.0	59
	2006		0.41	2.9	2.4	2.6	5.0	55
	2007		0.45	3.1	3.3	3.4	6.7	58
	2008		0.42	2.4	3.0	3.4	6.4	47
	2009		0.42	3.2	2.5	2.2	4.7	56
	2010		0.45	3.1	2.5	2.1	4.6	64
	2011		0.45	3.0	2.7	2.1	4.8	58
	2012		0.41	2.3	2.0	1.7	3.7	56
	Mean		0.43	2.8	2.6	2.5	5.2	58
	S.D.		0.02	0.3	0.6	0.6	1.1	6

Appendix 8-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 15

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	2001	1.36	12.07	0.71	1.79	1.93	3.72
	2002	1.38	11.65	0.77	1.66	1.72	3.38
	2003	1.46	12.89	0.72	1.57	1.57	3.14
	2004	1.37	12.43	0.70	1.63	1.75	3.38
	2005	1.59	13.97	0.83	1.79	1.92	3.71
	2006	1.39	13.00	0.94	2.06	2.13	4.19
	2007	1.30	11.75	0.67	1.76	1.76	3.52
	2008	1.29	12.28	0.93	1.64	1.73	3.37
	2009	1.43	13.11	0.73	1.77	1.75	3.52
	2010	1.28	12.67	0.60	1.74	1.79	3.53
	2011	1.45	11.86	0.82	1.84	1.96	3.80
	2012	1.46	12.44	0.77	1.72	1.76	3.48
	Mean	1.40	12.51	0.77	1.75	1.81	3.56
	S.D.	0.09	0.67	0.10	0.13	0.15	0.27
Relative	2001	0.27	2.40	0.14	0.36	0.38	0.74
	2002	0.29	2.43	0.16	0.35	0.36	0.71
	2003	0.30	2.67	0.15	0.33	0.33	0.65
	2004	0.27	2.41	0.14	0.32	0.34	0.66
	2005	0.29	2.59	0.15	0.33	0.36	0.69
	2006	0.27	2.52	0.18	0.40	0.41	0.81
	2007	0.28	2.52	0.14	0.38	0.38	0.76
	2008	0.27	2.57	0.19	0.34	0.36	0.71
	2009	0.27	2.50	0.14	0.34	0.33	0.67
	2010	0.27	2.71	0.13	0.37	0.38	0.76
	2011	0.30	2.49	0.17	0.39	0.41	0.80
	2012	0.29	2.45	0.15	0.34	0.35	0.69
	Mean	0.28	2.52	0.15	0.35	0.37	0.72
	S.D.	0.01	0.10	0.02	0.03	0.03	0.05

Appendix 8-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 15

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	2001	28	33	61	1.62	1.58	3.20
	2002	33	31	64	1.55	1.57	3.12
	2003	37	40	77	1.59	1.50	3.09
	2004	31	34	65	1.62	1.60	3.22
	2005	31	35	66	1.70	1.70	3.40
	2006	30	32	62	2.06	2.01	4.07
	2007	33	37	70	1.54	1.49	3.03
	2008	33	34	67	1.70	1.70	3.40
	2009	46	48	94	1.77	1.74	3.51
	2010	35	40	75	1.70	1.73	3.43
	2011	37	39	76	1.51	1.56	3.07
	2012	27	29	56	1.59	1.59	3.18
	Mean	33	36	69	1.66	1.65	3.31
	S.D.	5	5	10	0.15	0.14	0.29
Relative	2001	6	7	12	0.32	0.31	0.64
	2002	7	6	13	0.32	0.33	0.65
	2003	8	8	16	0.33	0.31	0.64
	2004	6	7	13	0.31	0.31	0.63
	2005	6	6	12	0.31	0.31	0.63
	2006	6	6	12	0.40	0.39	0.79
	2007	7	8	15	0.33	0.32	0.65
	2008	7	7	14	0.36	0.36	0.71
	2009	9	9	18	0.34	0.33	0.67
	2010	7	9	16	0.36	0.37	0.73
	2011	8	8	16	0.32	0.33	0.64
	2012	5	6	11	0.31	0.31	0.63
	Mean	7	7	14	0.33	0.33	0.67
	S.D.	1	1	2	0.03	0.03	0.05

Appendix 8-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 15

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	2001	783	750	1533	1.54	1.36
	2002	601	582	1183	1.81	1.34
	2003	601	547	1148	2.03	1.49
	2004	734	691	1425	1.78	1.22
	2005	734	716	1450	1.78	1.52
	2006	779	755	1534	2.03	1.27
	2007	703	700	1403	1.69	1.54
	2008	799	738	1537	1.96	1.24
	2009	699	666	1365	1.55	1.20
	2010	724	740	1464	1.64	1.22
	2011	668	676	1344	1.88	1.11
	2012	709	705	1414	2.30	1.25
	Mean	711	689	1400	1.83	1.31
	S.D.	64	65	127	0.22	0.14
Relative	2001	156	149	305	0.31	0.27
	2002	125	122	247	0.38	0.28
	2003	125	113	238	0.42	0.31
	2004	143	134	277	0.35	0.24
	2005	136	133	269	0.33	0.28
	2006	151	146	297	0.39	0.25
	2007	151	150	301	0.36	0.33
	2008	168	155	322	0.41	0.26
	2009	133	127	260	0.30	0.23
	2010	155	158	313	0.35	0.26
	2011	140	142	282	0.39	0.23
	2012	140	139	278	0.45	0.25
	Mean	144	139	282	0.37	0.27
	S.D.	13	14	26	0.05	0.03

Appendix 8-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 50

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	3001	504	2.00	14.2	9.8	11.6	21.4	357
	3002	470	2.21	14.9	18.0	15.0	33.0	188
	3003	469	1.97	14.9	12.2	11.7	23.9	253
	3004	491	2.16	11.9	10.3	11.6	21.9	273
	3005	482	2.11	13.8	19.9	17.7	37.6	352
	3006	501	2.11	13.2	13.9	14.7	28.6	203
	3007	455	2.06	13.7	10.0	9.6	19.6	220
	3008	478	2.33	12.4	9.3	7.6	16.9	249
	3009	490	2.22	13.7	15.8	17.3	33.1	419
	3010	453	2.18	13.5	13.7	11.8	25.5	194
	3011	491	2.03	12.2	11.3	9.4	20.7	269
	3012	462	2.16	11.9	6.6	9.8	16.4	261
	Mean	479	2.13	13.4	12.6	12.3	24.9	270
	S.D.	17	0.10	1.1	3.9	3.2	6.8	72
Relative	3001		0.40	2.8	1.9	2.3	4.2	71
	3002		0.47	3.2	3.8	3.2	7.0	40
	3003		0.42	3.2	2.6	2.5	5.1	54
	3004		0.44	2.4	2.1	2.4	4.5	56
	3005		0.44	2.9	4.1	3.7	7.8	73
	3006		0.42	2.6	2.8	2.9	5.7	41
	3007		0.45	3.0	2.2	2.1	4.3	48
	3008		0.49	2.6	1.9	1.6	3.5	52
	3009		0.45	2.8	3.2	3.5	6.8	86
	3010		0.48	3.0	3.0	2.6	5.6	43
	3011		0.41	2.5	2.3	1.9	4.2	55
	3012		0.47	2.6	1.4	2.1	3.5	56
	Mean		0.45	2.8	2.6	2.6	5.2	56
	S.D.		0.03	0.3	0.8	0.6	1.4	14

Appendix 8-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 50

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	3001	1.66	12.07	0.84	1.91	2.11	4.02
	3002	1.63	11.94	1.01	1.80	1.77	3.57
	3003	1.33	10.50	0.72	1.82	1.77	3.59
	3004	1.38	11.68	0.71	1.69	1.73	3.42
	3005	1.39	12.78	0.92	1.92	2.02	3.94
	3006	1.41	12.56	0.63	1.85	1.94	3.79
	3007	1.25	11.51	0.69	1.55	1.64	3.19
	3008	1.50	10.84	0.64	1.50	1.50	3.00
	3009	1.66	12.78	0.82	1.68	1.77	3.45
	3010	1.26	11.19	0.67	1.50	1.55	3.05
	3011	1.49	10.63	0.70	1.49	1.48	2.97
	3012	1.26	11.00	0.74	1.66	1.77	3.43
	Mean	1.44	11.62	0.76	1.70	1.75	3.45
	S.D.	0.15	0.82	0.12	0.16	0.20	0.35
Relative	3001	0.33	2.39	0.17	0.38	0.42	0.80
	3002	0.35	2.54	0.21	0.38	0.38	0.76
	3003	0.28	2.24	0.15	0.39	0.38	0.77
	3004	0.28	2.38	0.14	0.34	0.35	0.70
	3005	0.29	2.65	0.19	0.40	0.42	0.82
	3006	0.28	2.51	0.13	0.37	0.39	0.76
	3007	0.27	2.53	0.15	0.34	0.36	0.70
	3008	0.31	2.27	0.13	0.31	0.31	0.63
	3009	0.34	2.61	0.17	0.34	0.36	0.70
	3010	0.28	2.47	0.15	0.33	0.34	0.67
	3011	0.30	2.16	0.14	0.30	0.30	0.60
	3012	0.27	2.38	0.16	0.36	0.38	0.74
	Mean	0.30	2.43	0.16	0.35	0.37	0.72
	S.D.	0.03	0.15	0.02	0.03	0.04	0.07

Appendix 8-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 50

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	3001	33	34	67	1.58	1.56	3.14
	3002	32	34	66	1.67	1.63	3.30
	3003	36	36	72	1.76	1.75	3.51
	3004	38	35	73	1.59	1.55	3.14
	3005	33	37	70	1.53	1.59	3.12
	3006	31	33	64	1.53	1.56	3.09
	3007	34	37	71	1.69	1.69	3.38
	3008	36	38	74	1.77	1.72	3.49
	3009	41	47	88	1.82	1.83	3.65
	3010	36	40	76	1.34	1.32	2.66
	3011	29	32	61	1.56	1.54	3.10
	3012	35	40	75	1.61	1.57	3.18
	Mean	35	37	71	1.62	1.61	3.23
	S.D.	3	4	7	0.13	0.13	0.26
Relative	3001	7	7	13	0.31	0.31	0.62
	3002	7	7	14	0.36	0.35	0.70
	3003	8	8	15	0.38	0.37	0.75
	3004	8	7	15	0.32	0.32	0.64
	3005	7	8	15	0.32	0.33	0.65
	3006	6	7	13	0.31	0.31	0.62
	3007	7	8	16	0.37	0.37	0.74
	3008	8	8	15	0.37	0.36	0.73
	3009	8	10	18	0.37	0.37	0.74
	3010	8	9	17	0.30	0.29	0.59
	3011	6	7	12	0.32	0.31	0.63
	3012	8	9	16	0.35	0.34	0.69
	Mean	7	8	15	0.34	0.34	0.68
	S.D.	1	1	2	0.03	0.03	0.06

Appendix 8-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 50

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	3001	701	680	1381	1.61	1.27
	3002	688	727	1415	1.98	1.35
	3003	730	714	1444	1.97	1.41
	3004	670	773	1443	2.14	1.18
	3005	762	767	1529	2.28	1.46
	3006	663	702	1365	1.74	1.29
	3007	815	844	1659	1.90	1.41
	3008	548	574	1122	2.15	1.35
	3009	835	839	1674	1.79	1.41
	3010	601	592	1193	1.82	1.61
	3011	609	648	1257	1.67	1.37
	3012	718	764	1482	1.98	1.62
	Mean	695	719	1414	1.92	1.39
	S.D.	85	86	168	0.20	0.13
Relative	3001	139	135	274	0.32	0.25
	3002	146	155	301	0.42	0.29
	3003	156	152	308	0.42	0.30
	3004	136	157	294	0.44	0.24
	3005	158	159	317	0.47	0.30
	3006	132	140	272	0.35	0.26
	3007	179	185	365	0.42	0.31
	3008	115	120	235	0.45	0.28
	3009	170	171	342	0.37	0.29
	3010	133	131	263	0.40	0.36
	3011	124	132	256	0.34	0.28
	3012	155	165	321	0.43	0.35
	Mean	145	150	296	0.40	0.29
	S.D.	19	19	38	0.05	0.04

Appendix 8-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 150

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4001	482	2.06	13.1	10.6	10.2	20.8	284
	4002	466	2.02	13.3	11.6	9.7	21.3	268
	4003a)	364Z	2.40Z	12.3Z	21.3Z	14.1Z	35.4Z	378Z
	4004b)	466Z	2.34Z	14.6Z	11.8Z	12.7Z	24.5Z	352Z
	4005	498	2.17	12.7	14.2	13.2	27.4	357
	4006	507	2.29	12.8	13.1	13.2	26.3	347
	4007	504	2.34	15.0	12.6	13.6	26.2	342
	Mean	491	2.18	13.4	12.4	12.0	24.4	320
	S.D.	17	0.14	0.9	1.4	1.9	3.1	41
Relative	4001		0.43	2.7	2.2	2.1	4.3	59
	4002		0.43	2.9	2.5	2.1	4.6	58
	4003a)		0.66Z	3.4Z	5.9Z	3.9Z	9.7Z	104Z
	4004b)		0.50Z	3.1Z	2.5Z	2.7Z	5.3Z	76Z
	4005		0.44	2.6	2.9	2.7	5.5	72
	4006		0.45	2.5	2.6	2.6	5.2	68
	4007		0.46	3.0	2.5	2.7	5.2	68
	Mean		0.44	2.7	2.5	2.4	5.0	65
	S.D.		0.01	0.2	0.3	0.3	0.5	6

a): Died on day 5 of administration
b): Died on day 32 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 150

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4001	1.22	12.75	0.70	1.64	1.66	3.30
	4002	1.33	10.49	0.74	1.63	1.66	3.29
	4003a)	1.58Z	14.16Z	0.49Z	1.84Z	1.88Z	3.72Z
	4004b)	1.88Z	24.66Z	0.71Z	2.40Z	2.40Z	4.80Z
	4005	1.51	11.86	0.61	1.67	1.75	3.42
	4006	1.46	12.76	0.79	1.61	1.59	3.20
	4007	1.31	11.55	0.82	1.63	1.72	3.35
	Mean	1.37	11.88	0.73	1.64	1.68	3.31
	S.D.	0.12	0.95	0.08	0.02	0.06	0.08
Relative	4001	0.25	2.65	0.15	0.34	0.34	0.68
	4002	0.29	2.25	0.16	0.35	0.36	0.71
	4003a)	0.43Z	3.89Z	0.13Z	0.51Z	0.52Z	1.02Z
	4004b)	0.40Z	5.29Z	0.15Z	0.52Z	0.52Z	1.03Z
	4005	0.30	2.38	0.12	0.34	0.35	0.69
	4006	0.29	2.52	0.16	0.32	0.31	0.63
	4007	0.26	2.29	0.16	0.32	0.34	0.66
	Mean	0.28	2.42	0.15	0.33	0.34	0.67
	S.D.	0.02	0.17	0.02	0.01	0.02	0.03

a): Died on day 5 of administration
b): Died on day 32 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 150

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	4001	32	31	63	1.59	1.45	3.04
	4002	32	34	66	1.89	1.88	3.77
	4003a)	52Z	48Z	100Z	1.32Z	1.38Z	2.70Z
	4004b)	36Z	37Z	73Z	1.51Z	1.52Z	3.03Z
	4005	28	33	61	1.83	1.87	3.70
	4006	39	44	83	1.81	1.82	3.63
	4007	42	49	91	1.60	1.32	2.92
	Mean	35	38	73	1.74	1.67	3.41
	S.D.	6	8	13	0.14	0.26	0.40
Relative	4001	7	6	13	0.33	0.30	0.63
	4002	7	7	14	0.41	0.40	0.81
	4003a)	14Z	13Z	27Z	0.36Z	0.38Z	0.74Z
	4004b)	8Z	8Z	16Z	0.32Z	0.33Z	0.65Z
	4005	6	7	12	0.37	0.38	0.74
	4006	8	9	16	0.36	0.36	0.72
	4007	8	10	18	0.32	0.26	0.58
	Mean	7	8	15	0.36	0.34	0.70
	S.D.	1	2	2	0.04	0.06	0.09

a): Died on day 5 of administration
b): Died on day 32 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 150

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	4001	630	610	1240	1.79	1.16
	4002	773	750	1523	2.37	1.38
	4003a)	545Z	528Z	1073Z	1.15Z	0.99Z
	4004b)	657Z	694Z	1351Z	1.80Z	1.02Z
	4005	638	667	1305	1.67	1.21
	4006	724	789	1513	1.73	1.35
	4007	592	643	1235	1.64	1.17
	Mean	671	692	1363	1.84	1.25
	S.D.	75	75	144	0.30	0.10
Relative	4001	131	127	257	0.37	0.24
	4002	166	161	327	0.51	0.30
	4003a)	150Z	145Z	295Z	0.32Z	0.27Z
	4004b)	141Z	149Z	290Z	0.39Z	0.22Z
	4005	128	134	262	0.34	0.24
	4006	143	156	298	0.34	0.27
	4007	117	128	245	0.33	0.23
	Mean	137	141	278	0.38	0.26
	S.D.	19	16	34	0.08	0.03

a): Died on day 5 of administration
b): Died on day 32 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1101	303	2.00	12.7	9.6	8.7	18.3	134
	1102	327	1.96	22.8	8.7	7.9	16.6	250
	1103	299	1.96	19.9	8.5	7.5	16.0	196
	1104a)	235Z	1.93Z	16.4Z	5.2Z	5.6Z	10.8Z	78Z
	1105	316	2.05	18.9	8.0	8.6	16.6	205
	1106	273	2.05	19.2	8.2	8.8	17.0	113
	1107	330	1.99	19.3	8.5	6.4	14.9	221
	1108	361	2.03	22.7	5.6	6.8	12.4	312
	1109	288	2.03	17.3	3.8	7.9	11.7	218
	1110	292	1.92	14.9	8.0	7.2	15.2	131
	1111	294	1.96	19.5	9.4	9.5	18.9	254
	1112	309	2.06	20.0	6.8	8.1	14.9	315
	Mean	308	2.00	18.8	7.7	7.9	15.7	214
	S.D.	24	0.05	3.0	1.7	0.9	2.2	68
Relative	1101		0.66	4.2	3.2	2.9	6.0	44
	1102		0.60	7.0	2.7	2.4	5.1	76
	1103		0.66	6.7	2.8	2.5	5.4	66
	1104a)		0.82Z	7.0Z	2.2Z	2.4Z	4.6Z	33Z
	1105		0.65	6.0	2.5	2.7	5.3	65
	1106		0.75	7.0	3.0	3.2	6.2	41
	1107		0.60	5.8	2.6	1.9	4.5	67
	1108		0.56	6.3	1.6	1.9	3.4	86
	1109		0.70	6.0	1.3	2.7	4.1	76
	1110		0.66	5.1	2.7	2.5	5.2	45
	1111		0.67	6.6	3.2	3.2	6.4	86
	1112		0.67	6.5	2.2	2.6	4.8	102
	Mean		0.65	6.1	2.5	2.6	5.1	69
	S.D.		0.05	0.8	0.6	0.4	0.9	19

a): Sacrificed on day 12 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1101	1.04	9.18	0.54	1.07	1.09	2.16
	1102	1.03	10.78	0.71	1.13	1.16	2.29
	1103	1.06	9.83	0.64	1.04	1.08	2.12
	1104a)	1.13Z	8.92Z	0.55Z	1.64Z	1.53Z	3.17Z
	1105	1.03	10.79	0.69	1.15	1.12	2.27
	1106	0.98	9.60	0.50	1.14	1.07	2.21
	1107	1.00	10.99	0.59	1.23	1.27	2.50
	1108	1.26	13.47	0.96	1.33	1.33	2.66
	1109	1.07	9.16	0.60	1.03	1.08	2.11
	1110	1.01	8.96	0.51	1.03	1.00	2.03
	1111	1.03	10.49	0.70	1.21	1.24	2.45
	1112	1.02	10.82	0.79	1.04	1.04	2.08
	Mean	1.05	10.37	0.66	1.13	1.13	2.26
	S.D.	0.07	1.28	0.14	0.10	0.10	0.20
Relative	1101	0.34	3.03	0.18	0.35	0.36	0.71
	1102	0.31	3.30	0.22	0.35	0.35	0.70
	1103	0.35	3.29	0.21	0.35	0.36	0.71
	1104a)	0.48Z	3.80Z	0.23Z	0.70Z	0.65Z	1.35Z
	1105	0.33	3.41	0.22	0.36	0.35	0.72
	1106	0.36	3.52	0.18	0.42	0.39	0.81
	1107	0.30	3.33	0.18	0.37	0.38	0.76
	1108	0.35	3.73	0.27	0.37	0.37	0.74
	1109	0.37	3.18	0.21	0.36	0.38	0.73
	1110	0.35	3.07	0.17	0.35	0.34	0.70
	1111	0.35	3.57	0.24	0.41	0.42	0.83
	1112	0.33	3.50	0.26	0.34	0.34	0.67
	Mean	0.34	3.36	0.21	0.37	0.37	0.73
	S.D.	0.02	0.22	0.03	0.03	0.02	0.05

a): Sacrificed on day 12 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	1101	37	43	80	47.4	42.4	89.8	592
	1102	40	43	83	73.7	63.0	136.7	747
	1103	46	47	93	65.7	61.8	127.5	687
	1104a)	47Z	54Z	101Z	38.6Z	46.2Z	84.8Z	394Z
	1105	50	62	112	68.6	44.6	113.2	500
	1106	40	39	79	48.5	45.1	93.6	662
	1107	41	45	86	57.7	49.6	107.3	686
	1108	48	55	103	75.5	68.2	143.7	899
	1109	27	30	57	63.3	40.7	104.0	567
	1110	34	38	72	62.3	48.9	111.2	915
	1111	43	47	90	59.1	57.0	116.1	617
	1112	37	42	79	43.3	55.6	98.9	588
	Mean	40	45	85	60.5	52.4	112.9	678
	S.D.	7	9	15	10.6	9.2	17.2	132
Relative	1101	12	14	26	15.6	14.0	29.6	195
	1102	12	13	25	22.5	19.3	41.8	228
	1103	15	16	31	22.0	20.7	42.6	230
	1104a)	20Z	23Z	43Z	16.4Z	19.7Z	36.1Z	168Z
	1105	16	20	35	21.7	14.1	35.8	158
	1106	15	14	29	17.8	16.5	34.3	242
	1107	12	14	26	17.5	15.0	32.5	208
	1108	13	15	29	20.9	18.9	39.8	249
	1109	9	10	20	22.0	14.1	36.1	197
	1110	12	13	25	21.3	16.7	38.1	313
	1111	15	16	31	20.1	19.4	39.5	210
	1112	12	14	26	14.0	18.0	32.0	190
	Mean	13	14	28	19.6	17.0	36.6	220
	S.D.	2	2	4	2.9	2.4	4.2	40

a): Sacrificed on day 12 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 15

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	2101	342	1.95	17.1	6.4	8.4	14.8	288
	2102	309	1.97	13.7	6.5	7.9	14.4	189
	2103	341	2.11	20.5	9.4	9.0	18.4	206
	2104	321	1.97	16.8	12.9	14.4	27.3	243
	2105	304	1.91	15.3	6.0	6.8	12.8	177
	2106	295	1.87	15.0	6.9	7.0	13.9	248
	2107	265	1.97	16.1	8.5	6.2	14.7	220
	2108	290	2.07	17.1	7.0	6.0	13.0	156
	2109	378	2.12	19.0	10.8	7.5	18.3	187
	2110	354	2.02	21.7	13.7	10.5	24.2	252
	2111	296	1.87	18.8	9.7	8.7	18.4	187
	2112	360	2.03	14.1	11.5	10.9	22.4	480
	Mean	321	1.99	17.1	9.1	8.6	17.7	236
	S.D.	34	0.08	2.5	2.7	2.4	4.7	86
Relative	2101		0.57	5.0	1.9	2.5	4.3	84
	2102		0.64	4.4	2.1	2.6	4.7	61
	2103		0.62	6.0	2.8	2.6	5.4	60
	2104		0.61	5.2	4.0	4.5	8.5	76
	2105		0.63	5.0	2.0	2.2	4.2	58
	2106		0.63	5.1	2.3	2.4	4.7	84
	2107		0.74	6.1	3.2	2.3	5.5	83
	2108		0.71	5.9	2.4	2.1	4.5	54
	2109		0.56	5.0	2.9	2.0	4.8	49
	2110		0.57	6.1	3.9	3.0	6.8	71
	2111		0.63	6.4	3.3	2.9	6.2	63
	2112		0.56	3.9	3.2	3.0	6.2	133
	Mean		0.62	5.3	2.8	2.7	5.5	73
	S.D.		0.06	0.8	0.7	0.7	1.3	22

Appendix 8-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 15

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	2101	1.05	10.20	0.59	1.11	1.04	2.15
	2102	1.08	9.38	0.71	1.17	1.09	2.26
	2103	1.14	12.68	0.88	1.30	1.39	2.69
	2104	1.07	11.13	0.86	1.12	1.19	2.31
	2105	0.96	9.46	0.52	1.07	1.10	2.17
	2106	0.98	9.90	0.82	1.08	1.05	2.13
	2107	0.97	9.39	0.66	1.06	1.03	2.09
	2108	0.94	10.69	0.65	1.09	1.06	2.15
	2109	1.05	12.91	0.78	1.29	1.37	2.66
	2110	1.21	12.52	0.79	1.10	1.08	2.18
	2111	1.04	11.02	0.73	1.13	1.14	2.27
	2112	1.15	10.60	0.88	1.20	1.15	2.35
	Mean	1.05	10.82	0.74	1.14	1.14	2.28
	S.D.	0.08	1.28	0.12	0.08	0.12	0.20
Relative	2101	0.31	2.98	0.17	0.32	0.30	0.63
	2102	0.35	3.04	0.23	0.38	0.35	0.73
	2103	0.33	3.72	0.26	0.38	0.41	0.79
	2104	0.33	3.47	0.27	0.35	0.37	0.72
	2105	0.32	3.11	0.17	0.35	0.36	0.71
	2106	0.33	3.36	0.28	0.37	0.36	0.72
	2107	0.37	3.54	0.25	0.40	0.39	0.79
	2108	0.32	3.69	0.22	0.38	0.37	0.74
	2109	0.28	3.42	0.21	0.34	0.36	0.70
	2110	0.34	3.54	0.22	0.31	0.31	0.62
	2111	0.35	3.72	0.25	0.38	0.39	0.77
	2112	0.32	2.94	0.24	0.33	0.32	0.65
	Mean	0.33	3.38	0.23	0.36	0.36	0.71
	S.D.	0.02	0.29	0.04	0.03	0.03	0.06

Appendix 8-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 15

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	2101	39	43	82	46.6	39.7	86.3	613
	2102	37	39	76	90.6	54.9	145.5	649
	2103	47	52	99	54.7	61.3	116.0	574
	2104	47	53	100	67.4	48.1	115.5	659
	2105	40	45	85	58.5	30.8	89.3	500
	2106	32	41	73	53.7	41.1	94.8	885
	2107	46	49	95	46.6	45.7	92.3	675
	2108	33	33	66	37.9	55.5	93.4	770
	2109	43	48	91	51.3	55.4	106.7	746
	2110	46	47	93	70.1	65.5	135.6	524
	2111	40	46	86	61.7	51.2	112.9	730
	2112	52	52	104	48.2	53.8	102.0	881
	Mean	42	46	88	57.3	50.3	107.5	684
	S.D.	6	6	12	13.9	9.7	18.6	125
Relative	2101	11	13	24	13.6	11.6	25.2	179
	2102	12	13	25	29.3	17.8	47.1	210
	2103	14	15	29	16.0	18.0	34.0	168
	2104	15	17	31	21.0	15.0	36.0	205
	2105	13	15	28	19.2	10.1	29.4	164
	2106	11	14	25	18.2	13.9	32.1	300
	2107	17	18	36	17.6	17.2	34.8	255
	2108	11	11	23	13.1	19.1	32.2	266
	2109	11	13	24	13.6	14.7	28.2	197
	2110	13	13	26	19.8	18.5	38.3	148
	2111	14	16	29	20.8	17.3	38.1	247
	2112	14	14	29	13.4	14.9	28.3	245
	Mean	13	14	27	18.0	15.7	33.6	215
	S.D.	2	2	4	4.6	2.8	5.9	47

Appendix 8-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 50

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	3101	300	1.87	18.1	7.4	7.4	14.8	180
	3102	298	1.92	18.6	9.6	9.0	18.6	157
	3103	301	2.01	19.9	9.1	8.1	17.2	193
	3104	338	1.96	16.4	9.0	8.7	17.7	246
	3105	311	2.03	17.7	6.2	10.4	16.6	279
	3106	309	2.04	20.2	11.6	11.9	23.5	229
	3107	285	1.94	18.5	6.2	6.8	13.0	210
	3108	281	1.89	17.3	8.6	9.7	18.3	223
	3109	319	1.92	20.8	9.7	9.2	18.9	285
	3110	303	1.96	15.4	9.3	7.4	16.7	150
	3111	295	1.97	15.4	9.5	8.2	17.7	167
	3112	300	1.98	21.8	9.4	5.2	14.6	183
	Mean	303	1.96	18.3	8.8	8.5	17.3	209
	S.D.	15	0.05	2.1	1.5	1.8	2.6	45
Relative	3101		0.62	6.0	2.5	2.5	4.9	60
	3102		0.64	6.2	3.2	3.0	6.2	53
	3103		0.67	6.6	3.0	2.7	5.7	64
	3104		0.58	4.9	2.7	2.6	5.2	73
	3105		0.65	5.7	2.0	3.3	5.3	90
	3106		0.66	6.5	3.8	3.9	7.6	74
	3107		0.68	6.5	2.2	2.4	4.6	74
	3108		0.67	6.2	3.1	3.5	6.5	79
	3109		0.60	6.5	3.0	2.9	5.9	89
	3110		0.65	5.1	3.1	2.4	5.5	50
	3111		0.67	5.2	3.2	2.8	6.0	57
	3112		0.66	7.3	3.1	1.7	4.9	61
	Mean		0.65	6.1	2.9	2.8	5.7	69
	S.D.		0.03	0.7	0.5	0.6	0.8	13

Appendix 8-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 50

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	3101	1.00	9.90	0.60	1.12	1.17	2.29
	3102	0.97	10.13	0.76	1.22	1.19	2.41
	3103	1.13	12.26	0.96	1.42	1.37	2.79
	3104	1.08	10.41	0.73	1.18	1.13	2.31
	3105	0.99	9.36	0.67	1.09	1.07	2.16
	3106	1.04	10.48	0.69	1.12	1.10	2.22
	3107	0.91	9.20	0.60	0.99	0.99	1.98
	3108	0.89	9.26	0.54	1.15	1.15	2.30
	3109	1.06	10.25	0.93	1.25	1.29	2.54
	3110	1.00	9.44	0.70	1.07	0.97	2.04
	3111	1.07	9.99	0.58	1.13	1.12	2.25
	3112	0.98	10.23	0.60	1.10	1.06	2.16
	Mean	1.01	10.08	0.70	1.15	1.13	2.29
	S.D.	0.07	0.83	0.13	0.11	0.11	0.22
Relative	3101	0.33	3.30	0.20	0.37	0.39	0.76
	3102	0.33	3.40	0.26	0.41	0.40	0.81
	3103	0.38	4.07	0.32	0.47	0.46	0.93
	3104	0.32	3.08	0.22	0.35	0.33	0.68
	3105	0.32	3.01	0.22	0.35	0.34	0.69
	3106	0.34	3.39	0.22	0.36	0.36	0.72
	3107	0.32	3.23	0.21	0.35	0.35	0.69
	3108	0.32	3.30	0.19	0.41	0.41	0.82
	3109	0.33	3.21	0.29	0.39	0.40	0.80
	3110	0.33	3.12	0.23	0.35	0.32	0.67
	3111	0.36	3.39	0.20	0.38	0.38	0.76
	3112	0.33	3.41	0.20	0.37	0.35	0.72
	Mean	0.33	3.33	0.23	0.38	0.37	0.75
	S.D.	0.02	0.27	0.04	0.04	0.04	0.08

Appendix 8-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 50

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	3101	45	45	90	48.1	58.9	107.0	667
	3102	46	49	95	39.7	47.2	86.9	771
	3103	42	50	92	84.6	87.3	171.9	621
	3104	44	46	90	56.1	46.9	103.0	590
	3105	34	40	74	50.8	47.4	98.2	548
	3106	44	46	90	50.5	59.3	109.8	552
	3107	42	46	88	46.3	60.7	107.0	550
	3108	40	38	78	47.6	53.7	101.3	667
	3109	44	49	93	56.0	57.2	113.2	1034
	3110	37	41	78	52.4	46.7	99.1	662
	3111	38	42	80	44.3	49.3	93.6	856
	3112	31	36	67	37.4	38.0	75.4	777
	Mean	41	44	85	51.2	54.4	105.5	691
	S.D.	5	5	9	12.0	12.4	23.4	146
Relative	3101	15	15	30	16.0	19.6	35.7	222
	3102	15	16	32	13.3	15.8	29.2	259
	3103	14	17	31	28.1	29.0	57.1	206
	3104	13	14	27	16.6	13.9	30.5	175
	3105	11	13	24	16.3	15.2	31.6	176
	3106	14	15	29	16.3	19.2	35.5	179
	3107	15	16	31	16.2	21.3	37.5	193
	3108	14	14	28	16.9	19.1	36.0	237
	3109	14	15	29	17.6	17.9	35.5	324
	3110	12	14	26	17.3	15.4	32.7	218
	3111	13	14	27	15.0	16.7	31.7	290
	3112	10	12	22	12.5	12.7	25.1	259
	Mean	13	15	28	16.8	18.0	34.8	228
	S.D.	2	1	3	3.9	4.3	7.8	48

Appendix 8-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 150

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4101a)	254Z	1.99Z	16.4Z	11.5Z	13.9Z	25.4Z	314Z
	4102	278	1.89	21.5	8.4	6.6	15.0	193
	4103	306	1.99	17.4	7.1	7.1	14.2	186
	4104	318	1.94	15.4	9.0	8.5	17.5	310
	4105	315	2.06	20.1	11.5	8.7	20.2	325
	4106	303	1.99	16.5	9.6	7.7	17.3	139
	4107b)	231Z	2.17Z	13.3Z	9.2Z	11.3Z	20.5Z	131Z
	4108	292	1.96	21.6	6.9	5.8	12.7	192
	4109c)	321Z	2.10Z	16.2Z	14.9Z	11.1Z	26.0Z	293Z
	4110	302	1.83	15.5	8.6	6.3	14.9	194
	4111	277	2.01	17.7	8.9	4.8	13.7	131
	4112	344	2.09	19.2	9.3	9.0	18.3	157
	Mean	304	1.97	18.3	8.8	7.2	16.0	203
	S.D.	21	0.08	2.4	1.4	1.4	2.5	69
Relative	4101a)		0.78Z	6.5Z	4.5Z	5.5Z	10.0Z	124Z
	4102		0.68	7.7	3.0	2.4	5.4	69
	4103		0.65	5.7	2.3	2.3	4.6	61
	4104		0.61	4.8	2.8	2.7	5.5	97
	4105		0.65	6.4	3.7	2.8	6.4	103
	4106		0.66	5.4	3.2	2.5	5.7	46
	4107b)		0.94Z	5.8Z	4.0Z	4.9Z	8.9Z	57Z
	4108		0.67	7.4	2.4	2.0	4.3	66
	4109c)		0.65Z	5.0Z	4.6Z	3.5Z	8.1Z	91Z
	4110		0.61	5.1	2.8	2.1	4.9	64
	4111		0.73	6.4	3.2	1.7	4.9	47
	4112		0.61	5.6	2.7	2.6	5.3	46
	Mean		0.65	6.1	2.9	2.3	5.2	67
	S.D.		0.04	1.0	0.4	0.4	0.6	21

a): Died on day 8 of administration
b): Died on day 5 of administration
c): Died on gestation day 15
Z: Data was excluded from statistical analysis.

Appendix 8-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 150

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4101a)	1.18Z	8.51Z	0.38Z	1.06Z	1.04Z	2.10Z
	4102	0.98	9.79	0.79	1.25	1.21	2.46
	4103	1.00	10.71	0.51	1.13	1.18	2.31
	4104	1.00	9.60	0.72	1.28	1.25	2.53
	4105	1.04	11.44	0.82	1.25	1.34	2.59
	4106	1.02	9.30	0.61	0.98	1.00	1.98
	4107b)	1.37Z	9.58Z	0.49Z	1.33Z	1.33Z	2.66Z
	4108	0.94	9.98	0.69	1.16	1.17	2.33
	4109c)	1.24Z	13.23Z	0.63Z	1.45Z	1.29Z	2.74Z
	4110	0.94	9.93	0.47	1.08	0.99	2.07
	4111	0.94	9.61	0.79	1.10	1.14	2.24
	4112	1.02	11.63	0.65	1.33	1.34	2.67
	Mean	0.99	10.22	0.67	1.17	1.18	2.35
	S.D.	0.04	0.84	0.12	0.11	0.13	0.23
Relative	4101a)	0.46Z	3.35Z	0.15Z	0.42Z	0.41Z	0.83Z
	4102	0.35	3.52	0.28	0.45	0.44	0.88
	4103	0.33	3.50	0.17	0.37	0.39	0.75
	4104	0.31	3.02	0.23	0.40	0.39	0.80
	4105	0.33	3.63	0.26	0.40	0.43	0.82
	4106	0.34	3.07	0.20	0.32	0.33	0.65
	4107b)	0.59Z	4.15Z	0.21Z	0.58Z	0.58Z	1.15Z
	4108	0.32	3.42	0.24	0.40	0.40	0.80
	4109c)	0.39Z	4.12Z	0.20Z	0.45Z	0.40Z	0.85Z
	4110	0.31	3.29	0.16	0.36	0.33	0.69
	4111	0.34	3.47	0.29	0.40	0.41	0.81
	4112	0.30	3.38	0.19	0.39	0.39	0.78
	Mean	0.33	3.37	0.22	0.39	0.39	0.78
	S.D.	0.02	0.21	0.05	0.04	0.04	0.07

a): Died on day 8 of administration
b): Died on day 5 of administration
c): Died on gestation day 15
Z: Data was excluded from statistical analysis.

Appendix 8-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 150

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	4101a)	44Z	49Z	93Z	43.2Z	47.0Z	90.2Z	423Z
	4102	46	47	93	57.1	48.0	105.1	585
	4103	36	42	78	47.5	52.5	100.0	697
	4104	41	48	89	50.5	40.5	91.0	823
	4105	52	55	107	54.1	57.3	111.4	831
	4106	41	44	85	63.5	58.1	121.6	669
	4107b)	48Z	49Z	97Z	52.1Z	53.6Z	105.7Z	437Z
	4108	40	42	82	41.0	64.1	105.1	669
	4109c)	69Z	76Z	145Z	75.3Z	74.9Z	150.2Z	14200Zd)
	4110	36	40	76	37.2	38.3	75.5	562
	4111	41	49	90	51.8	43.6	95.4	526
	4112	46	63	109	58.9	70.2	129.1	736
	Mean	42	48	90	51.3	52.5	103.8	678
	S.D.	5	7	12	8.4	10.9	16.1	108
Relative	4101a)	17Z	19Z	37Z	17.0Z	18.5Z	35.5Z	167Z
	4102	17	17	33	20.5	17.3	37.8	210
	4103	12	14	25	15.5	17.2	32.7	228
	4104	13	15	28	15.9	12.7	28.6	259
	4105	17	17	34	17.2	18.2	35.4	264
	4106	14	15	28	21.0	19.2	40.1	221
	4107b)	21Z	21Z	42Z	22.6Z	23.2Z	45.8Z	189Z
	4108	14	14	28	14.0	22.0	36.0	229
	4109c)	21Z	24Z	45Z	23.5Z	23.3Z	46.8Z	4424Z
	4110	12	13	25	12.3	12.7	25.0	186
	4111	15	18	32	18.7	15.7	34.4	190
	4112	13	18	32	17.1	20.4	37.5	214
	Mean	14	16	29	16.9	17.3	34.2	222
	S.D.	2	2	3	2.9	3.2	4.8	27

a): Died on day 8 of administration
b): Died on day 5 of administration
c): Died on gestation day 15
d): Including conceptus
Z: Data was excluded from statistical analysis.

Appendix 8-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1113	280	2.04	16.7	8.6	9.2	17.8	223
	1114	259	1.93	18.7	6.5	6.1	12.6	275
	1115	273	1.98	16.8	7.3	9.1	16.4	297
	1116	299	1.92	19.1	12.3	9.4	21.7	311
	1117	309	1.99	14.9	13.4	8.4	21.8	308
	Mean	284	1.97	17.2	9.6	8.4	18.1	283
	S.D.	20	0.05	1.7	3.1	1.4	3.9	36
Relative	1113		0.73	6.0	3.1	3.3	6.4	80
	1114		0.75	7.2	2.5	2.4	4.9	106
	1115		0.73	6.2	2.7	3.3	6.0	109
	1116		0.64	6.4	4.1	3.1	7.3	104
	1117		0.64	4.8	4.3	2.7	7.1	100
	Mean		0.70	6.1	3.3	3.0	6.3	100
	S.D.		0.05	0.9	0.8	0.4	1.0	12

Appendix 8-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1113	0.93	7.37	0.46	0.93	1.01	1.94
	1114	0.90	6.99	0.50	0.98	0.92	1.90
	1115	1.00	6.90	0.51	0.97	0.91	1.88
	1116	0.99	7.62	0.59	1.11	1.03	2.14
	1117	0.96	8.12	0.55	1.10	1.07	2.17
	Mean	0.96	7.40	0.52	1.02	0.99	2.01
	S.D.	0.04	0.50	0.05	0.08	0.07	0.14
Relative	1113	0.33	2.63	0.16	0.33	0.36	0.69
	1114	0.35	2.70	0.19	0.38	0.36	0.73
	1115	0.37	2.53	0.19	0.36	0.33	0.69
	1116	0.33	2.55	0.20	0.37	0.34	0.72
	1117	0.31	2.63	0.18	0.36	0.35	0.70
	Mean	0.34	2.61	0.18	0.36	0.35	0.71
	S.D.	0.02	0.07	0.02	0.02	0.01	0.02

Appendix 8-31 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	1113	35	43	78	59.9	61.5	121.4	897
	1114	41	41	82	54.6	36.1	90.7	879
	1115	35	39	74	43.1	52.2	95.3	743
	1116	53	52	105	54.9	53.9	108.8	607
	1117	32	37	69	40.3	27.6	67.9	707
	Mean	39	42	82	50.6	46.3	96.8	767
	S.D.	8	6	14	8.4	13.9	20.1	122
Relative	1113	13	15	28	21.4	22.0	43.4	320
	1114	16	16	32	21.1	13.9	35.0	339
	1115	13	14	27	15.8	19.1	34.9	272
	1116	18	17	35	18.4	18.0	36.4	203
	1117	10	12	22	13.0	8.9	22.0	229
	Mean	14	15	29	17.9	16.4	34.3	273
	S.D.	3	2	5	3.6	5.1	7.7	58

Appendix 8-32 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 150

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4113	270	1.91	13.0	5.7	8.1	13.8	253
	4114a)	281Z	1.95Z	17.6Z	6.5Z	8.4Z	14.9Z	341Z
	4115	256	1.86	15.6	8.3	8.2	16.5	189
	4116	285	2.05	16.4	8.6	10.5	19.1	185
	4117	274	2.04	15.1	8.9	9.0	17.9	209
	Mean	271	1.97	15.0	7.9	9.0	16.8	209
	S.D.	12	0.09	1.5	1.5	1.1	2.3	31
Relative	4113		0.71	4.8	2.1	3.0	5.1	94
	4114a)		0.69Z	6.3Z	2.3Z	3.0Z	5.3Z	121Z
	4115		0.73	6.1	3.2	3.2	6.4	74
	4116		0.72	5.8	3.0	3.7	6.7	65
	4117		0.74	5.5	3.2	3.3	6.5	76
	Mean		0.73	5.6	2.9	3.3	6.2	77
	S.D.		0.01	0.6	0.5	0.3	0.7	12

a): Sacrificed on day 39 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-33 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 150

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4113	0.88	6.69	0.49	0.88	0.85	1.73
	4114a)	0.93Z	7.52Z	0.32Z	0.85Z	0.81Z	1.66Z
	4115	0.82	6.84	0.49	0.88	0.91	1.79
	4116	0.85	7.52	0.51	0.98	0.95	1.93
	4117	0.72	6.41	0.44	1.04	1.02	2.06
	Mean	0.82	6.87	0.48	0.95	0.93	1.88
	S.D.	0.07	0.47	0.03	0.08	0.07	0.15
Relative	4113	0.33	2.48	0.18	0.33	0.31	0.64
	4114a)	0.33Z	2.68Z	0.11Z	0.30Z	0.29Z	0.59Z
	4115	0.32	2.67	0.19	0.34	0.36	0.70
	4116	0.30	2.64	0.18	0.34	0.33	0.68
	4117	0.26	2.34	0.16	0.38	0.37	0.75
	Mean	0.30	2.53	0.18	0.35	0.34	0.69
	S.D.	0.03	0.15	0.01	0.02	0.03	0.05

a): Sacrificed on day 39 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-34 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 150

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	4113	34	39	73	51.0	51.2	102.2	574
	4114a)	43Z	48Z	91Z	40.5Z	33.6Z	74.1Z	413Z
	4115	40	42	82	41.3	48.0	89.3	389
	4116	38	41	79	35.1	50.9	86.0	645
	4117	45	46	91	69.5	59.6	129.1	619
	Mean	39	42	81	49.2	52.4	101.7	557
	S.D.	5	3	8	15.0	5.0	19.6	116
Relative	4113	13	14	27	18.9	19.0	37.9	213
	4114a)	15Z	17Z	32Z	14.4Z	12.0Z	26.4Z	147Z
	4115	16	16	32	16.1	18.8	34.9	152
	4116	13	14	28	12.3	17.9	30.2	226
	4117	16	17	33	25.4	21.8	47.1	226
	Mean	15	15	30	18.2	19.4	37.5	204
	S.D.	2	2	3	5.5	1.7	7.1	35

a): Sacrificed on day 39 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-35 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1008	525	2.24	14.7	9.6	9.3	18.9	495
	1009	538	2.24	13.2	14.2	11.6	25.8	256
	1010	513	2.21	16.0	10.9	10.9	21.8	177
	1011	539	2.11	17.6	12.4	10.6	23.0	267
	1012	484	2.20	13.7	9.6	5.8	15.4	329
	Mean	520	2.20	15.0	11.3	9.6	21.0	305
	S.D.	23	0.05	1.8	2.0	2.3	4.0	119
Relative	1008		0.43	2.8	1.8	1.8	3.6	94
	1009		0.42	2.5	2.6	2.2	4.8	48
	1010		0.43	3.1	2.1	2.1	4.2	35
	1011		0.39	3.3	2.3	2.0	4.3	50
	1012		0.45	2.8	2.0	1.2	3.2	68
	Mean		0.42	2.9	2.2	1.9	4.0	59
	S.D.		0.02	0.3	0.3	0.4	0.6	23

Appendix 8-36 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1008	1.65	14.06	0.84	1.65	1.82	3.47
	1009	1.48	12.96	0.70	1.81	1.80	3.61
	1010	1.63	14.35	0.79	1.81	1.99	3.80
	1011	1.35	15.20	0.69	1.91	1.89	3.80
	1012	1.43	11.82	0.74	1.67	1.73	3.40
	Mean	1.51	13.68	0.75	1.77	1.85	3.62
	S.D.	0.13	1.31	0.06	0.11	0.10	0.18
Relative	1008	0.31	2.68	0.16	0.31	0.35	0.66
	1009	0.28	2.41	0.13	0.34	0.33	0.67
	1010	0.32	2.80	0.15	0.35	0.39	0.74
	1011	0.25	2.82	0.13	0.35	0.35	0.71
	1012	0.30	2.44	0.15	0.35	0.36	0.70
	Mean	0.29	2.63	0.14	0.34	0.36	0.70
	S.D.	0.03	0.19	0.01	0.02	0.02	0.03

Appendix 8-37 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	1008	45	46	91	1.80	1.68	3.48
	1009	29	29	58	1.53	1.54	3.07
	1010	34	33	67	1.75	1.69	3.44
	1011	33	36	69	1.82	1.82	3.64
	1012	33	36	69	1.62	1.62	3.24
	Mean	35	36	71	1.70	1.67	3.37
	S.D.	6	6	12	0.12	0.10	0.22
Relative	1008	9	9	17	0.34	0.32	0.66
	1009	5	5	11	0.28	0.29	0.57
	1010	7	6	13	0.34	0.33	0.67
	1011	6	7	13	0.34	0.34	0.68
	1012	7	7	14	0.33	0.33	0.67
	Mean	7	7	14	0.33	0.32	0.65
	S.D.	1	1	2	0.03	0.02	0.05

Appendix 8-38 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	1008	735	691	1426	1.71	1.42
	1009	661	666	1327	2.04	1.41
	1010	733	680	1413	2.12	1.36
	1011	715	715	1430	2.05	1.46
	1012	684	696	1380	2.10	1.29
	Mean	706	690	1395	2.00	1.39
	S.D.	32	18	43	0.17	0.07
Relative	1008	140	132	272	0.33	0.27
	1009	123	124	247	0.38	0.26
	1010	143	133	275	0.41	0.27
	1011	133	133	265	0.38	0.27
	1012	141	144	285	0.43	0.27
	Mean	136	133	269	0.39	0.27
	S.D.	8	7	14	0.04	0.00

Appendix 8-39 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 150

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4008	487	2.15	13.4	11.1	10.8	21.9	187
	4009	499	2.14	14.0	8.8	8.6	17.4	187
	4010a)	426Z	2.58Z	15.9Z	12.5Z	12.3Z	24.8Z	417Z
	4011	466	2.12	12.9	10.3	9.5	19.8	220
	4012	507	2.15	14.0	11.5	12.3	23.8	251
	Mean	490	2.14	13.6	10.4	10.3	20.7	211
	S.D.	18	0.01	0.5	1.2	1.6	2.8	31
Relative	4008		0.44	2.8	2.3	2.2	4.5	38
	4009		0.43	2.8	1.8	1.7	3.5	37
	4010a)		0.61Z	3.7Z	2.9Z	2.9Z	5.8Z	98Z
	4011		0.45	2.8	2.2	2.0	4.2	47
	4012		0.42	2.8	2.3	2.4	4.7	50
	Mean		0.44	2.8	2.2	2.1	4.2	43
	S.D.		0.01	0.0	0.2	0.3	0.5	6

a): Sacrificed on day 5 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-40 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 150

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4008	1.52	12.24	0.62	2.02	2.07	4.09
	4009	1.48	12.25	0.71	1.62	1.52	3.14
	4010a)	1.38Z	13.75Z	0.65Z	1.82Z	1.87Z	3.69Z
	4011	1.34	11.37	0.84	1.63	1.60	3.23
	4012	1.44	12.52	0.79	1.67	1.61	3.28
	Mean	1.45	12.10	0.74	1.74	1.70	3.44
	S.D.	0.08	0.50	0.10	0.19	0.25	0.44
Relative	4008	0.31	2.51	0.13	0.41	0.43	0.84
	4009	0.30	2.45	0.14	0.32	0.30	0.63
	4010a)	0.32Z	3.23Z	0.15Z	0.43Z	0.44Z	0.87Z
	4011	0.29	2.44	0.18	0.35	0.34	0.69
	4012	0.28	2.47	0.16	0.33	0.32	0.65
	Mean	0.30	2.47	0.15	0.35	0.35	0.70
	S.D.	0.01	0.03	0.02	0.04	0.06	0.10

a): Sacrificed on day 5 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-41 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 150

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	4008	28	31	59	1.60	1.54	3.14
	4009	29	30	59	1.59	1.59	3.18
	4010a)	34Z	35Z	69Z	1.61Z	1.58Z	3.19Z
	4011	33	34	67	1.76	1.79	3.55
	4012	29	29	58	1.68	1.71	3.39
	Mean	30	31	61	1.66	1.66	3.32
	S.D.	2	2	4	0.08	0.11	0.19
Relative	4008	6	6	12	0.33	0.32	0.64
	4009	6	6	12	0.32	0.32	0.64
	4010a)	8Z	8Z	16Z	0.38Z	0.37Z	0.75Z
	4011	7	7	14	0.38	0.38	0.76
	4012	6	6	11	0.33	0.34	0.67
	Mean	6	6	12	0.34	0.34	0.68
	S.D.	1	1	1	0.03	0.03	0.06

a): Sacrificed on day 5 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-42 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 150

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	4008	601	498	1099	1.76	1.40
	4009	637	653	1290	1.61	1.06
	4010a)	526Z	609Z	1135Z	1.27Z	1.00Z
	4011	633	618	1251	1.68	1.54
	4012	702	746	1448	2.01	1.39
	Mean	643	629	1272	1.77	1.35
	S.D.	42	103	143	0.17	0.20
Relative	4008	123	102	226	0.36	0.29
	4009	128	131	259	0.32	0.21
	4010a)	123Z	143Z	266Z	0.30Z	0.23Z
	4011	136	133	268	0.36	0.33
	4012	138	147	286	0.40	0.27
	Mean	131	128	260	0.36	0.28
	S.D.	7	19	25	0.03	0.05

a): Sacrificed on day 5 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-43 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1118	297	1.87	18.5	4.1	6.4	10.5	301
	1119	266	1.92	14.7	9.5	6.8	16.3	211
	1120	264	1.99	16.1	9.2	5.6	14.8	275
	1121	279	1.98	24.6	8.0	6.4	14.4	258
	1122	260	2.01	13.6	8.1	9.4	17.5	254
	Mean	273	1.95	17.5	7.8	6.9	14.7	260
	S.D.	15	0.06	4.4	2.2	1.5	2.7	33
Relative	1118		0.63	6.2	1.4	2.2	3.5	101
	1119		0.72	5.5	3.6	2.6	6.1	79
	1120		0.75	6.1	3.5	2.1	5.6	104
	1121		0.71	8.8	2.9	2.3	5.2	92
	1122		0.77	5.2	3.1	3.6	6.7	98
	Mean		0.72	6.4	2.9	2.6	5.4	95
	S.D.		0.05	1.4	0.9	0.6	1.2	10

Appendix 8-44 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1118	0.95	7.65	0.50	0.94	0.91	1.85
	1119	0.80	6.62	0.55	0.91	0.93	1.84
	1120	0.85	6.59	0.61	0.94	0.90	1.84
	1121	0.91	7.00	0.53	0.94	0.93	1.87
	1122	0.92	6.39	0.42	0.89	0.88	1.77
	Mean	0.89	6.85	0.52	0.92	0.91	1.83
	S.D.	0.06	0.50	0.07	0.02	0.02	0.04
Relative	1118	0.32	2.58	0.17	0.32	0.31	0.62
	1119	0.30	2.49	0.21	0.34	0.35	0.69
	1120	0.32	2.50	0.23	0.36	0.34	0.70
	1121	0.33	2.51	0.19	0.34	0.33	0.67
	1122	0.35	2.46	0.16	0.34	0.34	0.68
	Mean	0.32	2.51	0.19	0.34	0.33	0.67
	S.D.	0.02	0.04	0.03	0.01	0.02	0.03

Appendix 8-45 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	1118	36	44	80	54.9	50.3	105.2	536
	1119	31	30	61	43.2	44.9	88.1	395
	1120	31	36	67	44.4	39.5	83.9	581
	1121	38	37	75	46.0	48.1	94.1	615
	1122	45	48	93	32.8	40.6	73.4	602
	Mean	36	39	75	44.3	44.7	88.9	546
	S.D.	6	7	12	7.9	4.7	11.8	89
Relative	1118	12	15	27	18.5	16.9	35.4	180
	1119	12	11	23	16.2	16.9	33.1	148
	1120	12	14	25	16.8	15.0	31.8	220
	1121	14	13	27	16.5	17.2	33.7	220
	1122	17	18	36	12.6	15.6	28.2	232
	Mean	13	14	28	16.1	16.3	32.4	200
	S.D.	2	3	5	2.2	1.0	2.7	35

Appendix 8-46 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 150

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4118a)	244Z	1.98Z	14.2Z	10.0Z	11.9Z	21.9Z	473Z
	4119	268	1.97	19.4	5.6	9.7	15.3	242
	4120	242	1.94	17.4	5.7	8.1	13.8	99
	4121	286	2.10	17.8	10.9	7.9	18.8	407
	4122	322	1.97	19.4	9.3	8.9	18.2	257
	Mean	280	2.00	18.5	7.9	8.7	16.5	251
	S.D.	34	0.07	1.1	2.7	0.8	2.4	126
Relative	4118a)		0.81Z	5.8Z	4.1Z	4.9Z	9.0Z	194Z
	4119		0.74	7.2	2.1	3.6	5.7	90
	4120		0.80	7.2	2.4	3.3	5.7	41
	4121		0.73	6.2	3.8	2.8	6.6	142
	4122		0.61	6.0	2.9	2.8	5.7	80
	Mean		0.72	6.7	2.8	3.1	5.9	88
	S.D.		0.08	0.6	0.7	0.4	0.5	42

a): Died on day 12 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-47 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 150

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4118a)	1.06Z	8.93Z	0.42Z	1.05Z	0.99Z	2.04Z
	4119	0.93	7.01	0.53	1.02	1.04	2.06
	4120	0.79	6.35	0.48	0.92	0.84	1.76
	4121	0.91	6.83	0.55	1.13	1.06	2.19
	4122	1.00	8.32	0.59	1.03	1.05	2.08
	Mean	0.91	7.13	0.54	1.03	1.00	2.02
	S.D.	0.09	0.84	0.05	0.09	0.11	0.18
Relative	4118a)	0.43Z	3.66Z	0.17Z	0.43Z	0.41Z	0.84Z
	4119	0.35	2.62	0.20	0.38	0.39	0.77
	4120	0.33	2.62	0.20	0.38	0.35	0.73
	4121	0.32	2.39	0.19	0.40	0.37	0.77
	4122	0.31	2.58	0.18	0.32	0.33	0.65
	Mean	0.33	2.55	0.19	0.37	0.36	0.73
	S.D.	0.02	0.11	0.01	0.03	0.03	0.06

a): Died on day 12 of administration
Z: Data was excluded from statistical analysis.

Appendix 8-48 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 150

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	4118a)	34Z	32Z	66Z	40.3Z	31.4Z	71.7Z	764Z
	4119	33	40	73	54.5	42.1	96.6	631
	4120	36	40	76	32.9	30.2	63.1	764
	4121	35	39	74	53.6	51.0	104.6	726
	4122	34	34	68	45.6	44.7	90.3	553
	Mean	35	38	73	46.7	42.0	88.7	669
	S.D.	1	3	3	10.0	8.7	18.0	95
Relative	4118a)	14Z	13Z	27Z	16.5Z	12.9Z	29.4Z	313Z
	4119	12	15	27	20.3	15.7	36.0	235
	4120	15	17	31	13.6	12.5	26.1	316
	4121	12	14	26	18.7	17.8	36.6	254
	4122	11	11	21	14.2	13.9	28.0	172
	Mean	13	14	26	16.7	15.0	31.7	244
	S.D.	2	3	4	3.3	2.3	5.4	59

a): Died on day 12 of administration
Z: Data was excluded from statistical analysis.

Appendix 9-1(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1001 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal
Prostate	Cell infiltration: minimal, mononuclear ventral
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Parathyroid
Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-2(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1002 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Kidney	Regeneration,tubular: minimal
Liver	Microgranuloma: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Lung(bronchus), Parathyroid, Pancreas, Pituitary
Prostate, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-3(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1003 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration: minimal, mononuclear ventral
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-4(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1004 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Parathyroid, Pancreas
Pituitary, Prostate, Salivary gland,submandibular, Sciatic nerve, Spleen
Stomach, Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-5(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1005 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Epididymis	Cell debris,luminal: minimal, bilateral
Spleen	Hematopoiesis,extramedullary: minimal
Testis	Atrophy,seminiferous tubular: minimal, bilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pancreas, Pituitary, Prostate, Salivary gland,submandibular
Sciatic nerve, Stomach, Skeletal muscle,femoral
Seminal vesicle(Coagulating gland), Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder

Appendix 9-6(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1006 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-7(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1007 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-8(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1008 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Stomach, Thymus, Trachea

Appendix 9-9(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1009 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Stomach, Thymus, Trachea

Appendix 9-10(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1010 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Stomach, Thymus, Trachea

Appendix 9-11(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1011 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Stomach, Thymus, Trachea

Appendix 9-12(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1012 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Spleen, Stomach, Thymus
Trachea

Appendix 9-13(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2001 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Stomach, Thymus, Trachea

Appendix 9-14(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2002 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Mineralization,arterial wall: minimal Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Stomach, Thymus, Trachea

Appendix 9-15(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2003 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 1x2mm
Other tissues	Not remarkable

Histopathology:

Stomach	Erosion,glandular stomach: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Spleen, Thymus, Trachea

Appendix 9-16(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2004 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Stomach, Thymus, Trachea

Appendix 9-17(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2005 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Stomach, Thymus, Trachea

Appendix 9-18(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2006 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-19(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2007 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-20(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2008 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-21(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2009 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Epididymis	Focus,white: 1 present, left cauda,4x3mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-22(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2010 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-23(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2011 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-24(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2012 Male 15 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-25(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3001 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Spleen, Stomach, Thymus
Trachea

Appendix 9-26(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3002 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Spleen, Stomach, Thymus
Trachea

Appendix 9-27(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3003 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Spleen, Stomach, Thymus
Trachea

Appendix 9-28(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3004 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Stomach, Thymus, Trachea

Appendix 9-29(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3005 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Stomach, Thymus, Trachea

Appendix 9-30(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3006 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Intestine,cecum	Large: moderate
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-31(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3007 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-32(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3008 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-33(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3009 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Lung(bronchus)	Discoloration,white: partial
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-34(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3010 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-35(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3011 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-36(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3012 Male 50 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-37(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4001 Male 150 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Lung(bronchus)	Focus,dark red: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

Kidney	Regeneration,tubular: minimal
Lung(bronchus)	Inflammation,bronchiolo-alveolar: minimal subacute
Stomach	Hyperplasia,squamous,forestomach: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Parathyroid, Pancreas, Pituitary, Prostate
Salivary gland,submandibular, Sciatic nerve, Spleen, Skeletal muscle,femoral
Seminal vesicle(Coagulating gland), Spinal cord,thoracic, Testis, Thymus
Trachea, Thyroid, Urinary bladder

Appendix 9-38(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4002 Male 150 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Intestine,cecum	Large: moderate
Other tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Parathyroid
Pancreas, Pituitary, Prostate, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-39(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4003 Male 150 mg/kg Day 5 Found dead

Gross pathology:

All tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy,cortical cell: minimal
Bone+Bone marrow,femoral	Granulopoiesis,increased: minimal
Kidney	Regeneration,tubular: minimal
Spleen	Atrophy,white pulp: minimal
Thymus	Atrophy: minimal
Trachea	Inflammation,necrotizing: severe fibrinoid
Cause of demise	Respiratory lesion

Following tissues : Not remarkable

Cerebellum(Pons), Cerebrum, Epididymis, Eye, Heart, Intestine,duodenum
Intestine,jejunum, Intestine,ileum(Peyer's patch), Intestine,cecum
Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Parathyroid, Pancreas
Pituitary, Prostate, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thyroid, Urinary bladder

Appendix 9-40(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4004 Male 150 mg/kg Day 32 Found dead

Gross pathology:

Intestine,cecum	Large: moderate
Lung(bronchus)	Discoloration,dark red
Other tissues	Not remarkable

Histopathology:

Intestine,ileum(Peyer's patch)	Sample autolysed
Intestine,cecum	Sample autolysed
Liver	Microgranuloma: minimal
Lung(bronchus)	Inflammation,necrotizing,bronchial: mild fibrinoid Edema,alveolar: mild
Prostate	Cell infiltration: minimal, mononuclear ventral
Thymus	Atrophy: minimal
Trachea	Inflammation,necrotizing: moderate fibrinoid
Cause of demise	Respiratory lesion

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,colon, Intestine,rectum
Kidney, Lymph node,mesenteric, Lymph node,submandibular, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thyroid, Urinary bladder

Appendix 9-41(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4005 Male 150 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Intestine,cecum	Large: moderate
Other tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal
Prostate	Cell infiltration: minimal, inflammatory ventral and dorsolateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Parathyroid
Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve, Spleen
Stomach, Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-42(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4006 Male 150 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Intestine,cecum	Large: moderate
Other tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal
Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal
Stomach	Erosion,glandular stomach: minimal Hyperplasia,squamous,forestomach: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Parathyroid, Pancreas
Pituitary, Prostate, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-43(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4007 Male 150 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Intestine,cecum	Large: moderate
Other tissues	Not remarkable

Histopathology:

Epididymis	Cell debris,luminal: mild, bilateral
Heart	Cell infiltration: minimal, focal, mononuclear
Spleen	Hematopoiesis,extramedullary: minimal
Testis	Atrophy,seminiferous tubular: mild, bilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pancreas, Pituitary, Prostate, Salivary gland,submandibular
Sciatic nerve, Stomach, Skeletal muscle,femoral
Seminal vesicle(Coagulating gland), Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder

Appendix 9-44(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4008 Male 150 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Inflammation,bronchiolo-alveolar: minimal subacute

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Spleen, Stomach, Thymus, Trachea

Appendix 9-45(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4009 Male 150 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Stomach, Thymus, Trachea

Appendix 9-46(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4010 Male 150 mg/kg Day 5 Moribund sacrifice

Gross pathology:

Intestine,cecum	Large: mild
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy,cortical cell: minimal
Epididymis	Granuloma,spermatic: mild, unilateral
Lung(bronchus)	Inflammation,bronchiolo-alveolar: mild acute
Thymus	Atrophy: minimal
Trachea	Inflammation,necrotizing: severe fibrinoid
Cause of demise	Respiratory lesion

Following tissues : Not remarkable

Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Parathyroid, Pancreas
Pituitary, Prostate, Salivary gland,submandibular, Sciatic nerve, Spleen
Stomach, Skeletal muscle,femoral, Seminal vesicle(Coagulating gland)
Spinal cord,thoracic, Testis, Thyroid, Urinary bladder

Appendix 9-47(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4011 Male 150 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Lung(bronchus), Stomach, Thymus, Trachea

Appendix 9-48(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4012 Male 150 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Spleen, Stomach, Thymus, Trachea

Appendix 9-49(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1101 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-50(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1102 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-51(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1103 Female 0 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Kidney	Regeneration,tubular: minimal
Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-52(1/2) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1104 Female 0 mg/kg Day 12 Moribund sacrifice

Gross pathology:

Kidney	Focus,white: many, left 1x1-3x3mm Dilatation,pelvic: mild, bilateral
Thymus	Small: mild
Urinary bladder	Distention: moderate, uroschesis
Ureter	Dilatation: mild, bilateral
Urethral orifice	Swelling
Urethra	Dilatation: mild
Other tissues	Not remarkable

Histopathology:

Adrenal	Hemorrhage,focal: minimal, cortical Hypertrophy,cortical cell: minimal
Bone+Bone marrow,femoral	Necrosis,focal,bone marrow: mild
Heart	Hemorrhage,focal: mild
Intestine,duodenum	Inflammation: minimal
Intestine,jejunum	Inflammation: mild
Intestine,ileum(Peyer's patch)	Inflammation: mild Necrosis,lymphocytic,Peyer's patch: mild
Intestine,cecum	Inflammation: moderate hemorrhagic,with thrombus
Intestine,colon	Inflammation: minimal with submucosal edema
Intestine,rectum	Inflammation: minimal
Kidney	Dilatation,pelvic: mild, bilateral Dilatation,tubular: mild, bilateral Necrosis,tubular: mild, bilateral, multifocal Pyelonephritis: mild, bilateral with bacteriosis and trasitional cell hyperplasia
Lymph node,mesenteric	Necrosis,lymphocytic: minimal
Lymph node,submandibular	Necrosis,lymphocytic: minimal
Liver	Hyperplasia,Kupffer cell: mild
Lung(bronchus)	Thrombus: minimal
Pancreas	Edema: mild

Appendix 9-52(2/2) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1104 Female 0 mg/kg Day 12 Moribund sacrifice

Histopathology: (continued)

Salivary gland,submandibular	Necrosis,single cell,acinar: mild
Spleen	Necrosis,lymphocytic: mild
Stomach	Erosion,glandular stomach: minimal
Thymus	Necrosis,lymphocytic: moderate
Urinary bladder	Distention: mild Inflammation: mild Hyperplasia,trasitional,diffuse: mild
Ureter	Inflammation: mild, bilateral with dilatation
Urethra	Inflammation: moderate with dilatation
Vagina	Inflammation: mild
Cause of demise	Urogenital tract lesion

Following tissues : Not remarkable

Cerebellum(Pons), Cerebrum, Eye, Ovary, Parathyroid, Pituitary, Sciatic nerve
Skeletal muscle,femoral, Spinal cord,thoracic, Trachea, Thyroid, Uterus

Appendix 9-53(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1105 Female 0 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Mineralization,arterial wall: minimal
Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Ovary, Parathyroid
Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-54(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1106 Female 0 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-55(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1107 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-56(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1108 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-57(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1109 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-58(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1110 Female 0 mg/kg Day 44 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 2x1mm
Other tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild
Stomach	Erosion,glandular stomach: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-59(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1111 Female 0 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-60(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1112 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-61(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1113 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 2 present 1x2mm,1x2mm
Other tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal
Spleen	Hematopoiesis,extramedullary: minimal
Stomach	Erosion,glandular stomach: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-62(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1114 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-63(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1115 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-64(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1116 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

Kidney	Mineralization: minimal, medullary
Stomach	Erosion,glandular stomach: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Spleen
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-65(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1117 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Liver	Hepatodiaphragmatic nodule: 1 present 3x2x2mm
Other tissues	Not remarkable

Histopathology:

Liver	Hepatodiaphragmatic nodule: mild Microgranuloma: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-66(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1118 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Thymus, Trachea

Appendix 9-67(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1119 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Thymus
Trachea

Appendix 9-68(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1120 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Spleen
Thymus, Trachea

Appendix 9-69(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1121 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

Stomach	Erosion,glandular stomach: minimal

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Spleen
Thymus, Trachea

Appendix 9-70(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 1122 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 2 present 1x3mm,1x3mm
Other tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Stomach	Erosion,glandular stomach: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Spleen, Thymus
Trachea

Appendix 9-71(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2101 Female 15 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-72(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2102 Female 15 mg/kg Day 48 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-73(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2103 Female 15 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-74(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2104 Female 15 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Thymus
Trachea

Appendix 9-75(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2105 Female 15 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-76(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2106 Female 15 mg/kg Day 43 End of administration period (L4)

Gross pathology:

Lung(bronchus)	Focus,dark red: 1 present 1.5x1.5mm
Other tissues	Not remarkable

Histopathology:

Lung(bronchus)	Hemorrhage,focal: minimal
Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Thymus, Trachea

Appendix 9-77(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2107 Female 15 mg/kg Day 42 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Thymus
Trachea

Appendix 9-78(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2108 Female 15 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-79(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2109 Female 15 mg/kg Day 46 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 2x1mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-80(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2110 Female 15 mg/kg Day 47 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-81(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2111 Female 15 mg/kg Day 42 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Thymus, Trachea

Appendix 9-82(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 2112 Female 15 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Thymus
Trachea

Appendix 9-83(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3101 Female 50 mg/kg Day 42 End of administration period (L4)

Gross pathology:

Lung(bronchus)	Focus,dark red: 2 present 1x1mm,1x1mm
Stomach	Focus,dark red,glandular stomach: 1 present 3x1mm
Other tissues	Not remarkable

Histopathology:

Lung(bronchus)	Hemorrhage,focal: minimal Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Thymus, Trachea

Appendix 9-84(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3102 Female 50 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-85(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3103 Female 50 mg/kg Day 47 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-86(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3104 Female 50 mg/kg Day 45 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 3x1mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-87(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3105 Female 50 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Thymus
Trachea

Appendix 9-88(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3106 Female 50 mg/kg Day 46 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 3x1mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-89(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3107 Female 50 mg/kg Day 46 End of administration period (L4)

Gross pathology:

Lung(bronchus)	Focus,white: many less than 1x1mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-90(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3108 Female 50 mg/kg Day 42 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Thymus
Trachea

Appendix 9-91(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3109 Female 50 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Thymus, Trachea

Appendix 9-92(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3110 Female 50 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Thymus
Trachea

Appendix 9-93(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3111 Female 50 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-94(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 3112 Female 50 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-95(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4101 Female 150 mg/kg Day 8 Found dead

Gross pathology:

Intestine,cecum	Large: mild
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy,cortical cell: minimal
Intestine,cecum	Sample autolysed
Spleen	Atrophy,white pulp: minimal
Thymus	Atrophy: minimal
Trachea	Inflammation,necrotizing: severe fibrinoid
Cause of demise	Respiratory lesion

Following tissues : Not remarkable

Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thyroid, Urinary bladder, Uterus
Vagina

Appendix 9-96(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4102 Female 150 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-97(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4103 Female 150 mg/kg Day 44 End of administration period (L4)

Gross pathology:

Intestine,cecum	Large: mild
Other tissues	Not remarkable

Histopathology:

Kidney	Mineralization: minimal, medullary
Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-98(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4104 Female 150 mg/kg Day 43 End of administration period (L4)

Gross pathology:

Intestine,cecum	Large: mild
Other tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal
Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-99(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4105 Female 150 mg/kg Day 43 End of administration period (L4)

Gross pathology:

Intestine,cecum	Large: moderate
Other tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-100(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4106 Female 150 mg/kg Day 43 End of administration period (L4)

Gross pathology:

Intestine,cecum	Large: mild
Other tissues	Not remarkable

Histopathology:

Kidney	Regeneration,tubular: minimal
Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Stomach, Skeletal muscle,femoral
Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-101(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4107 Female 150 mg/kg Day 5 Found dead

Gross pathology:

Intestine,cecum	Large: mild
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy,cortical cell: minimal
Lung(bronchus)	Inflammation,necrotizing,bronchial: moderate fibrinoid Edema,alveolar: mild
Stomach	Erosion,glandular stomach: minimal
Thymus	Atrophy: minimal
Trachea	Inflammation,necrotizing: severe fibrinoid
Cause of demise	Respiratory lesion

Following tissues : Not remarkable

Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Ovary, Parathyroid
Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve, Spleen
Skeletal muscle,femoral, Spinal cord,thoracic, Thyroid, Urinary bladder, Uterus
Vagina

Appendix 9-102(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4108 Female 150 mg/kg Day 45 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 2x1mm
Other tissues	Not remarkable

Histopathology:

Heart	Cell infiltration: minimal, focal, mononuclear
Spleen	Hematopoiesis,extramedullary: mild
Stomach	Erosion,glandular stomach: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-103(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4109 Female 150 mg/kg Day 32(Gestation day 15) Found dead

Gross pathology:

Intestine,cecum	Large: mild
Lung(bronchus)	Discoloration,dark red
Other tissues	Not remarkable

Histopathology:

Kidney	Regeneration,tubular: minimal
Lung(bronchus)	Inflammation,necrotizing,bronchial: mild fibrinoid Edema,alveolar: mild
Spleen	Hematopoiesis,extramedullary: minimal
Thymus	Atrophy: minimal
Trachea	Inflammation,necrotizing: moderate fibrinoid
Thyroid	Sample autolysed
Cause of demise	Respiratory lesion

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Stomach, Skeletal muscle,femoral
Spinal cord,thoracic, Urinary bladder, Uterus, Vagina

Appendix 9-104(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4110 Female 150 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-105(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4111 Female 150 mg/kg Day 45 End of administration period (L4)

Gross pathology:

Liver	Focus,white: 1 present 5x5mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-106(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4112 Female 150 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-107(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4113 Female 150 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Intestine,cecum	Large: moderate
Other tissues	Not remarkable

Histopathology:

Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-108(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4114 Female 150 mg/kg Day 39 Moribund sacrifice

Gross pathology:

Intestine,cecum	Large: mild
Liver	Focus,dark red: 2 present 6x5mm,4x3mm
Lung(bronchus)	Discoloration,dark red: partial
Other tissues	Not remarkable

Histopathology:

Lymph node,mesenteric	Atrophy: minimal
Lymph node,submandibular	Atrophy: minimal
Liver	Necrosis,focal: mild
Lung(bronchus)	Inflammation,necrotizing,bronchial: mild fibrinoid Edema,alveolar: mild
Spleen	Atrophy,white pulp: minimal
Thymus	Atrophy: minimal
Trachea	Inflammation,necrotizing: severe fibrinoid
Cause of demise	Respiratory lesion

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Ovary, Parathyroid
Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thyroid, Urinary bladder, Uterus
Vagina

Appendix 9-109(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4115 Female 150 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Intestine,cecum	Large: mild
Other tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-110(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4116 Female 150 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Intestine,cecum	Large: mild
Other tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-111(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4117 Female 150 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Intestine,cecum	Large: moderate
Other tissues	Not remarkable

Histopathology:

Kidney	Regeneration,tubular: minimal
Liver	Microgranuloma: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-112(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4118 Female 150 mg/kg Day 12 Found dead

Gross pathology:

Intestine,cecum	Large: mild
Other tissues	Not remarkable

Histopathology:

Intestine,duodenum	Sample autolysed
Intestine,cecum	Sample autolysed
Intestine,colon	Sample autolysed
Trachea	Inflammation,necrotizing: moderate fibrinoid
Thyroid	Sample autolysed
Cause of demise	Respiratory lesion

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,jejunum, Intestine,ileum(Peyer's patch), Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus
Urinary bladder, Uterus, Vagina

Appendix 9-113(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4119 Female 150 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Spleen
Thymus, Trachea

Appendix 9-114(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4120 Female 150 mg/kg Day 57 End of recovery period

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

Stomach	Erosion,glandular stomach: minimal

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Spleen
Thymus, Trachea

Appendix 9-115(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4121 Female 150 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Thymus
Trachea

Appendix 9-116(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats

Individual gross and histopathological findings

Animal No. 4122 Female 150 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Thymus
Trachea

Appendix 10-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual estrous cycle in female rats during the pre-mating period (Main group)
Dose (mg/kg): 0

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles	Index of animals with abnormal estrous cycle (%)
1101	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
1102	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
1103	D	P	E	E	M	D	P	E	E	M	D	P	E	M	D	3	5.0	
1104c)	D	P	E	E	M	D	P	E	E	M	D	D						
1105	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
1106	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
1107	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
1108	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
1109	E	M	D	P	E	E	M	D	P	E	M	D	P	E	M	4	4.3	
1110	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
1111	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
1112	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
Total(%)b)																		0/11(0.0)
Mean																3.8	4.1	
S.D.																0.4	0.3	

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling
b): (No. of animals with abnormal estrous cycle / No. of animals examined)×100
c): Sacrificed on day 12 of administration

Appendix 10-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual estrous cycle in female rats during the pre-mating period (Main group)
Dose (mg/kg): 15

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles	Index of animals with abnormal estrous cycle (%)
2101	E	E	M	D	P	E	M	D	P	E	M	D	D	P	E	4	4.7	
2102	M	D	D	P	E	M	D	D	P	E	M	D	D	P	E	3	5.0	
2103	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
2104	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
2105	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
2106	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
2107	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
2108	E	M	D	P	E	E	M	D	P	E	M	D	D	P	E	4	4.7	
2109	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
2110	M	D	D	P	E	M	D	D	P	E	M	D	P	E	E	3	4.5	
2111	P	E	M	D	P	E	M	D	P	E	E	M	D	P	E	4	4.3	
2112	E	M	D	P	E	M	D	P	E	M	D	D	P	E	M	4	4.3	
Total(%)b)																		0/12(0.0)
Mean																3.8	4.3	
S.D.																0.5	0.4	

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling
b): (No. of animals with abnormal estrous cycle / No. of animals examined)×100

Appendix 10-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual estrous cycle in female rats during the pre-mating period (Main group)
Dose (mg/kg): 50

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles	Index of animals with abnormal estrous cycle (%)
3101	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
3102	D	D	P	E	M	D	P	E	M	D	D	P	E	M	D	3	4.5	
3103	E	M	D	D	P	E	M	D	P	E	E	M	D	P	E	4	4.7	
3104	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
3105	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
3106	D	D	P	E	M	D	D	P	E	M	D	P	E	E	M	3	4.5	
3107c)	M	D	D	P	E	M	D	P	E	E	M	D	D	P	E	3	5.0	
3108	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
3109	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
3110	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
3111	D	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
3112	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
Total(%)b)																		1/12(8.3)
Mean																3.3	4.2	
S.D.																0.5	0.4	

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling
b): (No. of animals with abnormal estrous cycle / No. of animals examined)×100
c): Abnormal estrous cycle

Appendix 10-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual estrous cycle in female rats during the pre-mating period (Main group)
Dose (mg/kg): 150

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles	Index of animals with abnormal estrous cycle (%)
4101c)	E	M	D	P	E	M	D											
4102	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
4103	E	E	M	D	P	E	E	M	D	P	E	E	M	D	P	3	5.0	
4104	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
4105	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
4106	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
4107d)	D	D	P	E														
4108	E	M	D	P	E	E	M	D	P	E	M	D	P	E	M	4	4.3	
4109	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
4110	E	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.3	
4111	E	M	D	P	E	M	D	P	E	M	D	D	P	E	M	4	4.3	
4112	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
Total(%)b)																		0/10(0.0)
Mean																3.8	4.2	
S.D.																0.4	0.3	

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling
b): (No. of animals with abnormal estrous cycle / No. of animals examined)×100
c): Died on day 8 of administration
d): Died on day 5 of administration

Appendix 11-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 0

Pairing number		Copulated or	Days until	Pregnant or
Male	Female	not copulated	copulation	non-pregnant
1001	1101	C	3	P
1002	1102	C	4	P
1003	1103	C	3	P
1004	NT501	C	1	P
1005	1105	C	2	P
1006	1106	C	1	P
1007	1107	C	3	P
1008	1108	C	3	P
1009	1109	C	3	P
1010	1110	C	2	P
1011	1111	C	2	P
1012	1112	C	3	P

C: Copulated P: Pregnant
NT501: Non-treatment animal, Tag No.501

Appendix 11-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 15

Pairing number		Copulated or	Days until	Pregnant or
Male	Female	not copulated	copulation	non-pregnant
2001	2101	C	4	P
2002	2102	C	6	P
2003	2103	C	4	P
2004	2104	C	3	P
2005	2105	C	4	P
2006	2106	C	2	P
2007	2107	C	1	P
2008	2108	C	4	P
2009	2109	C	4	P
2010	2110	C	5	P
2011	2111	C	1	P
2012	2112	C	1	P

C: Copulated P: Pregnant

Appendix 11-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 50

Pairing number		Copulated or	Days until	Pregnant or
Male	Female	not copulated	copulation	non-pregnant
3001	3101	C	1	P
3002	3102	C	2	P
3003	3103	C	4	P
3004	3104	C	3	P
3005	3105	C	1	P
3006	3106	C	4	P
3007	3107	C	4	P
3008	3108	C	1	P
3009	3109	C	2	P
3010	3110	C	1	P
3011	3111	C	1	P
3012	3112	C	2	P

C: Copulated P: Pregnant

Appendix 11-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 150

Pairing number		Copulated or	Days until	Pregnant or
Male	Female	not copulated	copulation	non-pregnant
4001	4103	C	1	P
4002	4102	C	4	P
4004	4104	C	1	P
4005	4105	C	2	P
4006	4106	C	2	P
4007	4110	C	3	P
4008	4108	C	3	P
4009	4109	C	2	P
4011	4111	C	3	P
4012	4112	C	4	P

C: Copulated P: Pregnant

Appendix 12-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Delivery data on dams
Dose (mg/kg): 0

Dam number	Gestation length in days	No. of corpora lutea	No. of implantation sites	Implantation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnormalities(%)e)
1101	22	15	15	100.0	93.3	0(0.0)	14	0(0.0)
1102	21	18	18	100.0	88.9	0(0.0)	16	0(0.0)
1103	21	17	17	100.0	100.0	1(5.9)	16	0(0.0)
1104f)								
1105	22	20	16	80.0	93.8	0(0.0)	15	0(0.0)
1106	22	18	18	100.0	94.4	0(0.0)	17	0(0.0)
1107	22	16	15	93.8	100.0	0(0.0)	15	0(0.0)
1108	22	20	20	100.0	85.0	0(0.0)	17	0(0.0)
1109	22	17	14	82.4	92.9	0(0.0)	13	0(0.0)
1110	22	15	15	100.0	100.0	0(0.0)	15	0(0.0)
1111	21	17	16	94.1	93.8	1(6.7)	14	0(0.0)
1112	22	15	15	100.0	86.7	0(0.0)	13	0(0.0)
Total		188	179			2	165	0
Mean	21.7	17.1	16.3	95.5	93.5	(1.1)	15.0	(0.0)
S.D.	0.5	1.8	1.8	7.5	5.2	(2.6)	1.4	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100
f): Sacrificed on day 12 of administration

Appendix 12-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Delivery data on dams
Dose (mg/kg): 15

Dam number	Gestation length in days	No. of corpora lutea	No. of implantation sites	Implantation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnormalities(%)e)
2101	22	14	14	100.0	78.6	0(0.0)	11	0(0.0)
2102	22	9	9	100.0	66.7	0(0.0)	6	0(0.0)
2103	22	15	15	100.0	100.0	0(0.0)	15	0(0.0)
2104	22	18	18	100.0	100.0	0(0.0)	18	0(0.0)
2105	22	14	14	100.0	92.9	0(0.0)	13	0(0.0)
2106	21	17	17	100.0	100.0	0(0.0)	17	0(0.0)
2107	21	15	15	100.0	100.0	0(0.0)	15	0(0.0)
2108	22	17	17	100.0	88.2	0(0.0)	15	0(0.0)
2109	22	17	17	100.0	100.0	0(0.0)	17	0(0.0)
2110	22	18	18	100.0	94.4	0(0.0)	17	0(0.0)
2111	21	15	15	100.0	86.7	0(0.0)	13	0(0.0)
2112	22	11	7	63.6	85.7	0(0.0)	6	0(0.0)
Total		180	176			0	163	0
Mean	21.8	15.0	14.7	97.0	91.1	(0.0)	13.6	(0.0)
S.D.	0.5	2.8	3.4	10.5	10.5	(0.0)	4.1	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100

Appendix 12-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Delivery data on dams
Dose (mg/kg): 50

Dam number	Gestation length in days	No. of corpora lutea	No. of implantation sites	Implantation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnormalities(%)e)
3101	21	17	17	100.0	88.2	0(0.0)	15	0(0.0)
3102	22	16	16	100.0	87.5	1(7.1)	13	0(0.0)
3103	23	18	18	100.0	88.9	3(18.8)	13	0(0.0)
3104	22	17	17	100.0	76.5	1(7.7)	12	0(0.0)
3105	22	14	14	100.0	92.9	1(7.7)	12	0(0.0)
3106	22	17	17	100.0	82.4	1(7.1)	13	0(0.0)
3107	22	13	13	100.0	69.2	0(0.0)	9	0(0.0)
3108	21	16	16	100.0	87.5	1(7.1)	13	1(7.1)f)
3109	21	15	15	100.0	93.3	0(0.0)	14	0(0.0)
3110	22	14	14	100.0	92.9	0(0.0)	13	0(0.0)
3111	22	15	15	100.0	86.7	0(0.0)	13	0(0.0)
3112	22	14	14	100.0	100.0	0(0.0)	14	0(0.0)
Total		186	186			8	154	1
Mean	21.8	15.5	15.5	100.0	87.2	(4.6)	12.8	(0.6)
S.D.	0.6	1.6	1.6	0.0	8.2	(5.8)	1.5	(2.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100
f): Exencephaly, rachischisis and open eye (stillborn)

Appendix 12-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Delivery data on dams
Dose (mg/kg): 150

Dam number	Gestation length in days	No. of corpora lutea	No. of implantation sites	Implantation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnormalities(%)e)
4101f)								
4102	22	16	16	100.0	93.8	0(0.0)	15	0(0.0)
4103	23	14	13	92.9	84.6	1(9.1)	10	0(0.0)
4104	22	14	14	100.0	92.9	1(7.7)	12	0(0.0)
4105	21	17	17	100.0	82.4	0(0.0)	14	0(0.0)
4106	21	14	14	100.0	100.0	0(0.0)	14	0(0.0)
4107g)								
4108	22	16	15	93.8	100.0	0(0.0)	15	0(0.0)
4109h)								
4110	22	15	15	100.0	93.3	1(7.1)	13	0(0.0)
4111	22	14	13	92.9	100.0	0(0.0)	13	0(0.0)
4112	22	17	17	100.0	100.0	0(0.0)	17	0(0.0)
Total		137	134			3	123	0
Mean	21.9	15.2	14.9	97.7	94.1	(2.7)	13.7	(0.0)
S.D.	0.6	1.3	1.5	3.4	6.8	(4.0)	2.0	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100
f): Died on day 8 of administration
g): Died on day 5 of administration
h): Died on gestation day 15

Appendix 13-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual viability index of pups
Dose (mg/kg): 0

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups		Viability index on postnatal day 4 % b)
				Day 0	Day 4	
1101	14	14	100.0	14	13	92.9
1102	16	16	100.0	16	16	100.0
1103	16	17	94.1	16	16	100.0
1104c)						
1105	15	15	100.0	15	15	100.0
1106	17	17	100.0	17	16	94.1
1107	15	15	100.0	15	14	93.3
1108	17	17	100.0	17	17	100.0
1109	13	13	100.0	13	13	100.0
1110	15	15	100.0	15	15	100.0
1111	14	15	93.3	14	13	92.9
1112	13	13	100.0	13	12	92.3
Total	165	167		165	160	
Mean	15.0	15.2	98.9	15.0	14.5	96.9
S.D.	1.4	1.5	2.6	1.4	1.6	3.6

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100
c): Sacrificed on day 12 of administration

Appendix 13-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual viability index of pups
Dose (mg/kg): 15

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups		Viability index on postnatal day 4 % b)
				Day 0	Day 4	
2101	11	11	100.0	11	11	100.0
2102	6	6	100.0	6	6	100.0
2103	15	15	100.0	15	15	100.0
2104	18	18	100.0	18	18	100.0
2105	13	13	100.0	13	13	100.0
2106	17	17	100.0	17	17	100.0
2107	15	15	100.0	15	13	86.7
2108	15	15	100.0	15	15	100.0
2109	17	17	100.0	17	17	100.0
2110	17	17	100.0	17	17	100.0
2111	13	13	100.0	13	13	100.0
2112	6	6	100.0	6	6	100.0
Total	163	163		163	161	
Mean	13.6	13.6	100.0	13.6	13.4	98.9
S.D.	4.1	4.1	0.0	4.1	4.1	3.8

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 13-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual viability index of pups
Dose (mg/kg): 50

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups		Viability index on postnatal day 4 % b)
				Day 0	Day 4	
3101	15	15	100.0	15	15	100.0
3102	13	14	92.9	13	12	92.3
3103	13	16	81.3	13	13	100.0
3104	12	13	92.3	12	11	91.7
3105	12	13	92.3	12	11	91.7
3106	13	14	92.9	13	13	100.0
3107	9	9	100.0	9	9	100.0
3108	13	14	92.9	13	13	100.0
3109	14	14	100.0	14	14	100.0
3110	13	13	100.0	13	12	92.3
3111	13	13	100.0	13	13	100.0
3112	14	14	100.0	14	14	100.0
Total	154	162		154	150	
Mean	12.8	13.5	95.4	12.8	12.5	97.3
S.D.	1.5	1.7	5.8	1.5	1.6	3.9

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 13-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual viability index of pups
Dose (mg/kg): 150

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups		Viability index on postnatal day 4 % b)
				Day 0	Day 4	
4101c)						
4102	15	15	100.0	15	15	100.0
4103	10	11	90.9	10	10	100.0
4104	12	13	92.3	12	12	100.0
4105	14	14	100.0	14	14	100.0
4106	14	14	100.0	14	14	100.0
4107d)						
4108	15	15	100.0	15	15	100.0
4109e)						
4110	13	14	92.9	13	12	92.3
4111	13	13	100.0	13	13	100.0
4112	17	17	100.0	17	17	100.0
Total	123	126		123	122	
Mean	13.7	14.0	97.3	13.7	13.6	99.1
S.D.	2.0	1.7	4.0	2.0	2.1	2.6

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100
c): Died on day 8 of administration
d): Died on day 5 of administration
e): Died on gestation day 15

Appendix 14-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual sex ratio of pups
Dose (mg/kg): 0

Dam number	Liveborns		Stillborns		Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4		Sex ratio of live pups on day 4 c)
	No. of males	No. of females	No. of males	No. of females			No. of males	No. of females	
1101	8	6	0	0	0.57	0.57	8	5	0.62
1102	8	8	0	0	0.50	0.50	8	8	0.50
1103	10	6	0	1	0.59	0.63	10	6	0.63
1104d)									
1105	9	6	0	0	0.60	0.60	9	6	0.60
1106	15	2	0	0	0.88	0.88	14	2	0.88
1107	6	9	0	0	0.40	0.40	6	8	0.43
1108	12	5	0	0	0.71	0.71	12	5	0.71
1109	7	6	0	0	0.54	0.54	7	6	0.54
1110	6	9	0	0	0.40	0.40	6	9	0.40
1111	10	4	0	1	0.67	0.71	10	3	0.77
1112	8	5	0	0	0.62	0.62	7	5	0.58
Total	99	66	0	2			97	63	
Mean	9.0	6.0	0.0	0.2	0.59	0.60	8.8	5.7	0.61
S.D.	2.7	2.1	0.0	0.4	0.14	0.14	2.5	2.1	0.14

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4
d): Sacrificed on day 12 of administration

Appendix 14-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual sex ratio of pups
Dose (mg/kg): 15

Dam number	Liveborns		Stillborns		Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4		Sex ratio of live pups on day 4 c)
	No. of males	No. of females	No. of males	No. of females			No. of males	No. of females	
2101	5	6	0	0	0.45	0.45	5	6	0.45
2102	1	5	0	0	0.17	0.17	1	5	0.17
2103	6	9	0	0	0.40	0.40	6	9	0.40
2104	8	10	0	0	0.44	0.44	8	10	0.44
2105	7	6	0	0	0.54	0.54	7	6	0.54
2106	7	10	0	0	0.41	0.41	7	10	0.41
2107	5	10	0	0	0.33	0.33	5	8	0.38
2108	4	11	0	0	0.27	0.27	4	11	0.27
2109	11	6	0	0	0.65	0.65	11	6	0.65
2110	9	8	0	0	0.53	0.53	9	8	0.53
2111	7	6	0	0	0.54	0.54	7	6	0.54
2112	1	5	0	0	0.17	0.17	1	5	0.17
Total	71	92	0	0			71	90	
Mean	5.9	7.7	0.0	0.0	0.41	0.41	5.9	7.5	0.41
S.D.	3.0	2.2	0.0	0.0	0.15	0.15	3.0	2.1	0.15

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 14-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual sex ratio of pups
Dose (mg/kg): 50

Dam number	Liveborns		Stillborns		Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4		Sex ratio of live pups on day 4 c)
	No. of males	No. of females	No. of males	No. of females			No. of males	No. of females	
3101	7	8	0	0	0.47	0.47	7	8	0.47
3102	10	3	0	1	0.71	0.77	9	3	0.75
3103	8	5	2	1	0.63	0.62	8	5	0.62
3104	7	5	0	1	0.54	0.58	6	5	0.55
3105	6	6	1	0	0.54	0.50	6	5	0.55
3106	8	5	1	0	0.64	0.62	8	5	0.62
3107	6	3	0	0	0.67	0.67	6	3	0.67
3108	5	8	1	0	0.43	0.38	5	8	0.38
3109	8	6	0	0	0.57	0.57	8	6	0.57
3110	9	4	0	0	0.69	0.69	8	4	0.67
3111	7	6	0	0	0.54	0.54	7	6	0.54
3112	6	8	0	0	0.43	0.43	6	8	0.43
Total	87	67	5	3			84	66	
Mean	7.3	5.6	0.4	0.3	0.57	0.57	7.0	5.5	0.57
S.D.	1.4	1.8	0.7	0.5	0.10	0.11	1.2	1.8	0.11

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 14-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual sex ratio of pups
Dose (mg/kg): 150

Dam number	Liveborns		Stillborns		Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4		Sex ratio of live pups on day 4 c)
	No. of males	No. of females	No. of males	No. of females			No. of males	No. of females	
4101d)									
4102	6	9	0	0	0.40	0.40	6	9	0.40
4103	7	3	1	0	0.73	0.70	7	3	0.70
4104	7	5	0	1	0.54	0.58	7	5	0.58
4105	8	6	0	0	0.57	0.57	8	6	0.57
4106	6	8	0	0	0.43	0.43	6	8	0.43
4107e)									
4108	9	6	0	0	0.60	0.60	9	6	0.60
4109f)									
4110	7	6	1	0	0.57	0.54	7	5	0.58
4111	8	5	0	0	0.62	0.62	8	5	0.62
4112	8	9	0	0	0.47	0.47	8	9	0.47
Total	66	57	2	1			66	56	
Mean	7.3	6.3	0.2	0.1	0.55	0.55	7.3	6.2	0.55
S.D.	1.0	2.0	0.4	0.3	0.10	0.10	1.0	2.0	0.10

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4
d): Died on day 8 of administration
e): Died on day 5 of administration
f): Died on gestation day 15

Appendix 15-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of pups
Dose (mg/kg): 0

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
1101	6.7	10.3	3.6	6.3	9.7	3.4
1102	5.9	7.7	1.8	5.5	7.3	1.8
1103	6.1	9.2	3.1	5.7	8.8	3.1
1104b)						
1105	6.0	9.9	3.9	5.8	9.4	3.6
1106	5.7	8.6	2.9	5.3	7.8	2.5
1107	6.5	10.4	3.9	6.1	10.0	3.9
1108	6.3	9.8	3.5	5.7	8.9	3.2
1109	7.1	10.9	3.8	6.6	10.0	3.4
1110	6.7	9.5	2.8	6.4	8.4	2.0
1111	6.2	9.4	3.2	5.7	9.0	3.3
1112	6.2	10.9	4.7	6.1	10.7	4.6
Mean	6.3	9.7	3.4	5.9	9.1	3.2
S.D.	0.4	1.0	0.8	0.4	1.0	0.8

Unit: g
a): Postnatal day
b): Sacrificed on day 12 of administration

Appendix 15-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of pups
Dose (mg/kg): 15

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
2101	7.0	11.4	4.4	6.4	10.8	4.4
2102	6.1	11.4	5.3	6.5	11.5	5.0
2103	7.3	11.4	4.1	6.8	10.5	3.7
2104	6.0	9.1	3.1	5.6	8.3	2.7
2105	6.2	10.5	4.3	6.0	10.0	4.0
2106	5.9	8.7	2.8	5.8	8.1	2.3
2107	5.8	8.2	2.4	5.3	7.9	2.6
2108	6.8	9.8	3.0	6.4	9.1	2.7
2109	7.6	11.2	3.6	7.1	10.0	2.9
2110	6.4	9.1	2.7	6.2	9.0	2.8
2111	6.8	9.2	2.4	6.4	9.2	2.8
2112	8.1	13.6	5.5	7.6	12.8	5.2
Mean	6.7	10.3	3.6	6.3	9.8	3.4
S.D.	0.7	1.6	1.1	0.6	1.5	1.0

Unit: g
a): Postnatal day

Appendix 15-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of pups
Dose (mg/kg): 50

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
3101	6.1	8.6	2.5	5.8	8.2	2.4
3102	7.2	10.8	3.6	6.6	9.7	3.1
3103	7.1	11.8	4.7	6.9	11.3	4.4
3104	6.8	11.4	4.6	6.7	11.0	4.3
3105	6.3	10.4	4.1	6.1	10.1	4.0
3106	6.9	10.7	3.8	6.3	10.2	3.9
3107	7.4	12.0	4.6	7.2	11.9	4.7
3108	6.1	9.2	3.1	5.7	8.4	2.7
3109	6.3	8.7	2.4	6.1	8.5	2.4
3110	7.2	10.8	3.6	6.6	11.3	4.7
3111	7.0	10.2	3.2	7.0	9.5	2.5
3112	6.4	9.6	3.2	6.2	9.0	2.8
Mean	6.7	10.4	3.6	6.4	9.9	3.5
S.D.	0.5	1.1	0.8	0.5	1.3	0.9

Unit: g
a): Postnatal day

Appendix 15-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual body weight of pups
Dose (mg/kg): 150

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
4101b)						
4102	6.5	9.4	2.9	5.9	9.1	3.2
4103	7.2	12.2	5.0	7.3	12.5	5.2
4104	7.5	11.5	4.0	6.8	10.6	3.8
4105	6.5	9.3	2.8	6.4	9.6	3.2
4106	5.9	9.3	3.4	5.7	8.7	3.0
4107c)						
4108	7.0	9.7	2.7	6.1	8.7	2.6
4109d)						
4110	5.9	9.7	3.8	5.8	9.5	3.7
4111	6.5	10.1	3.6	6.4	10.1	3.7
4112	6.9	9.7	2.8	6.6	9.0	2.4
Mean	6.7	10.1	3.4	6.3	9.8	3.4
S.D.	0.5	1.0	0.8	0.5	1.2	0.8

Unit: g
a): Postnatal day
b): Died on day 8 of administration
c): Died on day 5 of administration
d): Died on gestation day 15

Appendix 16-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 0

Dam number	No. of pups examined Total (Male + Female)	Findings
1101	1 (0 + 1)	NAF
1102	0	
1103	0	
1104a)		
1105	0	
1106	1 (1 + 0)	NAF
1107	1 (0 + 1)	NAF
1108	0	
1109	0	
1110	0	
1111	0	
1112	0	

NAF: No abnormal findings
a): Sacrificed on day 12 of administration

Appendix 16-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 15

Dam number	No. of pups examined Total (Male + Female)	Findings
2101	0	
2102	0	
2103	0	
2104	0	
2105	0	
2106	0	
2107	1 (0 + 1)	NAF
2108	0	
2109	0	
2110	0	
2111	0	
2112	0	

NAF: No abnormal findings

Appendix 16-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 50

Dam number	No. of pups examined Total (Male + Female)	Findings
3101	0	
3102	0	
3103	0	
3104	1 (1 + 0)	NAF
3105	1 (0 + 1)	NAF
3106	0	
3107	0	
3108	0	
3109	0	
3110	0	
3111	0	
3112	0	

NAF: No abnormal findings

Appendix 16-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 150

Dam number	No. of pups examined Total (Male + Female)	Findings
4101a)		
4102	0	
4103	0	
4104	0	
4105	0	
4106	0	
4107b)		
4108	0	
4109c)		
4110	0	
4111	0	
4112	0	

NAF: No abnormal findings
a): Died on day 8 of administration
b): Died on day 5 of administration
c): Died on gestation day 15

Appendix 17-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 0

Dam number	No. of pups examined Total (Male + Female)	Findings
1101	13 (8 + 5)	NAF
1102	16 (8 + 8)	NAF
1103	16 (10 + 6)	NAF
1104a)		
1105	15 (9 + 6)	NAF
1106	16 (14 + 2)	NAF
1107	14 (6 + 8)	NAF
1108	17 (12 + 5)	NAF
1109	13 (7 + 6)	NAF
1110	15 (6 + 9)	NAF
1111	13 (10 + 3)	NAF
1112	12 (7 + 5)	NAF

NAF: No abnormal findings
a): Sacrificed on day 12 of administration

Appendix 17-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 15

Dam number	No. of pups examined Total	(Male	+ Female)	Findings
2101	11	5	6	NAF
2102	6	1	5	NAF
2103	15	6	9	NAF
2104	18	8	10	NAF
2105	13	7	6	NAF
2106	17	7	10	NAF
2107	13	5	8	NAF
2108	15	4	11	NAF
2109	17	11	6	NAF
2110	17	9	8	NAF
2111	13	7	6	NAF
2112	6	1	5	NAF

NAF: No abnormal findings

Appendix 17-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 50

Dam number	No. of pups examined Total (Male + Female)	Findings
3101	15 (7 + 8)	NAF
3102	12 (9 + 3)	NAF
3103	13 (8 + 5)	NAF
3104	11 (6 + 5)	NAF
3105	11 (6 + 5)	NAF
3106	13 (8 + 5)	NAF
3107	9 (6 + 3)	NAF
3108	13 (5 + 8)	NAF
3109	14 (8 + 6)	NAF
3110	12 (8 + 4)	NAF
3111	13 (7 + 6)	NAF
3112	14 (6 + 8)	NAF

NAF: No abnormal findings

Appendix 17-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of Benzyl(dimethyl)(octan-1-yl)ammonium chloride by oral administration in rats
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 150

Dam number	No. of pups examined Total (Male + Female)	Findings
4101a)		
4102	15 (6 + 9)	NAF
4103	10 (7 + 3)	NAF
4104	12 (7 + 5)	NAF
4105	14 (8 + 6)	NAF
4106	14 (6 + 8)	NAF
4107b)		
4108	15 (9 + 6)	NAF
4109c)		
4110	12 (7 + 5)	NAF
4111	13 (8 + 5)	NAF
4112	17 (8 + 9)	NAF

NAF: No abnormal findings
a): Died on day 8 of administration
b): Died on day 5 of administration
c): Died on gestation day 15