



最 終 報 告 書

ジデカー1-イル（メチル）アミンのラットを用いた
経口投与による反復投与毒性・生殖発生毒性併合試験

試験番号：R-1103

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試験施設

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1. GLP 陳述書

試験番号 : R-1103

試験表題 : ジデカー1-イル (メチル) アミンのラットを用いた
経口投与による反復投与毒性・生殖発生毒性併合試験

本試験は以下に示す基準を遵守して実施したものであります。

- 「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」
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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

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3. 試験実施概要

3.1 試験番号

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3.2 試験表題

ジデカ-1-イル（メチル）アミン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 didec-1-yl(methyl)amine by oral administration in rats)

3.3 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。

3.4 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

3.5 試験受託者

株式会社ボゾリサーチセンター
〒151-0065 東京都渋谷区大山町 36-7

3.6 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
〒412-0039 静岡県御殿場市かまど 1284

3.7 被験物質

製造者	:	████████████████████
名称	:	ジデカ-1-イル（メチル）アミン
別名	:	Didecylmethylamine
CAS 番号	:	7396-58-9
官報公示整理番号	:	2-176
入手日	:	2012年6月28日

3.8 試験日程

試験開始日	:	2012年9月10日
被験物質出庫日	:	2012年9月26日

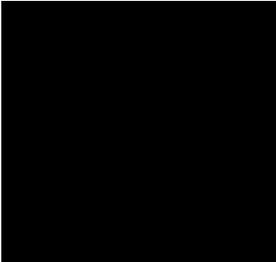
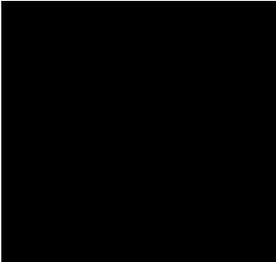
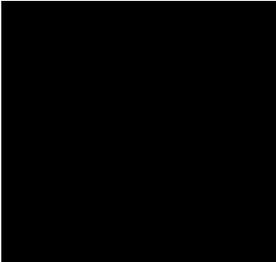
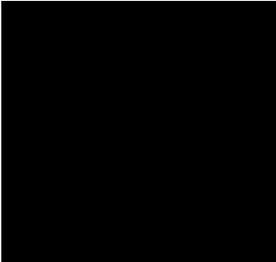
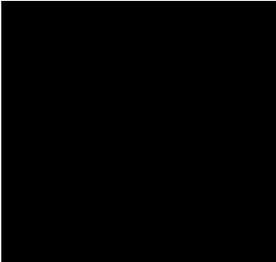
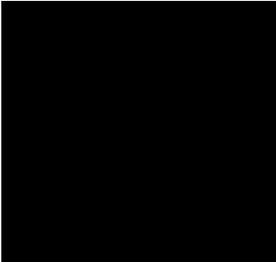
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動物入荷日 : 2012年 9月 12日
実験開始日 (投与開始日)
: 2012年 10月 1日
投与終了剖検日 : 2012年 10月 16日 (非交配群)
交配開始日 : 2012年 10月 15日
分娩開始日 : 2012年 11月 7日
母動物剖検開始日 : 2012年 11月 12日
投与終了剖検日 : 2012年 11月 12日 (雄)
回復開始日 : 2012年 11月 12日
回復終了剖検日 : 2012年 11月 26日
動物試験終了日 : 2012年 11月 26日
実験終了日 (病理組織学検査終了日)
: 2013年 2月 7日
試験終了日 : 2013年 3月 28日

3.9 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

3.10 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 : 

3.11 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。

3.12 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) 動物番号 2107 及び 4003 の上皮小体が標本上欠落していた。しかし、検索動物では動物番号 4003 の 1 例のみであり、動物番号 2107 は検索対象外の動物であることから、上皮小体の病理組織学評価は可能と判断されたため、試験成績へ及ぼす影響はなかった。
- 2) 投与終了時のあるいは瀕死期剖検動物の血液学及び血液化学検査において、下記の特記事項がみられたが、データ採用の判断は標準操作手順書に従ったものであ

り、対処法及びその記録は適切であることから、試験結果への影響は無いと判断した。

動物番号	項目	内 容
3005	FIB	初回測定値が機器の測定上限を超えたため、2倍希釈試料を用いた再測定を実施し、得られた再測定値を採用した。
4009,4112	ADVIA 項目	初回測定時において、赤血球数またはヘモグロビン量がオーバーレンジしたため、2倍希釈試料を用いて再測定を実施した結果、血小板数が初回値に比べ高値を示した。血液塗抹標本による確認から再測定値に問題はないと判断し、再測定値を採用した。
4007	ADVIA 項目	機器より白血球系の測定不良である可能性を示す旨の表示がなされたため、再測定を実施した結果、再現性が認められたことから初回値を採用した。
瀕死期剖検 動物全例	採血量 (血漿 EDTA)	動物の衰弱により、規定の採血が困難と予想されたため、採血瓶をSB-41(採血量約1mL)からマイクロティナ(採血量約0.5mL)に変更して採血を実施、測定可能であったため問題はみられなかった。
4002,4006 4007,4008 4009,4111 4118,4122	採血量 (血漿へ パリン)	動物の衰弱により、規定の採血が困難と予想されたため、採血量を約2mLから約1mLに変更して採血を実施、測定可能であったため問題はみられなかった。
瀕死期剖検 動物全例 (4106 除く)	採血量 (血清)	動物の衰弱により、規定の採血が困難と予想されたため、採血量を約6mLから約1~3mLに変更して採血を実施、測定可能であったため問題はみられなかった。
4106	血液化学 検査 (血清)	動物の衰弱により、血清の採取は不可能であったため、血液化学検査(血清項目)は測定出来なかった。
4006,4007 4009,4106 4112,4120	血液凝固 検査	動物の衰弱により、クエン酸血漿の採取は不可能であったため、血液凝固検査項目は測定出来なかった。
4112	血液化学 検査 (血清)	採取できた血清が約100 μ L未満(採血量は約0.5mL)と、測定可能量に満たなかったため血液化学検査は測定出来なかった。なお、採取した血清は凍結保存した。

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

3.13 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(試験計画書変更書を含む)原本、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)及び腔垢標本については、試験終了までに廃棄した。また、死産児、死亡児及び生後4日生存児については、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。

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3.14 試験責任者の記名・なつ印



2013年3月28日



4. 要約

ジデカー1-イル(メチル)アミンの0(対照群:コーン油)、10、30及び100 mg/kgをSprague-Dawley系SPFラット(交配群として雌雄各12匹/群、雌には非交配群として対照群及び100 mg/kg群に各10匹を追加)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(42~50日間)、非交配群雌には6~15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30 mg/kg群の一部の動物(交配群雄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。

4.1 反復投与毒性

100 mg/kg群の雄、交配群雌及び非交配群雌で自発運動の減少、よろめき歩行、腹臥/横臥、流涎、削瘦、過敏、痙攣、はいずり姿勢がみられ、顕著な摂餌量の低値を伴った体重減少と全身状態の悪化に伴い投与6~12日の間に全例が瀕死期剖検あるいは死亡した。心臓に限局性心筋炎増強、前胃の扁平上皮過形成及びびらん/潰瘍、胃底腺単細胞壊死、腺頸部延長、十二指腸、空腸及び回腸に粘膜変性/壊死、膀胱に粘膜好塩基性化、被蓋上皮細胞空胞化、内腔拡張、粘膜/粘膜下細胞浸潤、びらん/潰瘍、粘膜下出血、副腎限局性出血、大腿骨(骨髄)骨髄細胞減少、脾臓髓外造血減少、直腸粘膜細胞浸潤、腔粘膜/粘膜下細胞浸潤、腸間膜リンパ節洞内組織球活性化、前立腺に出血及び細胞浸潤(中等度例)、一般状態悪化及びストレスに伴う変化として脾臓、顎下リンパ節、腸間膜リンパ節、胸腺、回腸パイエル板、前立腺、子宮及び膣の粘膜の萎縮、腺胃幽門部粘液減少、盲腸、結腸及び直腸の杯細胞減少、副腎皮質細胞肥大、脾臓チモゲン顆粒減少がみられた。

30 mg/kg群では、雄及び母動物で投与3週間から流涎がみられ、雄で投与期間中、交配群雌で交配前投与期間中に体重増加抑制が認められた。雄でヘモグロビン量、ヘマトクリット値、平均赤血球容積及び平均赤血球血色素量の低値が認められた。

一般状態、体重及び血液学検査でみられた変化は投与終了とともに消失し、いずれも回復性がみられた。

10 mg/kg群では、被験物質の毒性影響はみられなかった。

4.2 生殖発生毒性

10及び30 mg/kg群の親動物及び児動物のいずれの検査においても、被験物質投与による影響は認められなかった。

これらの結果から、本試験条件下において、本被験物質の反復投与毒性に対する無毒性量は10 mg/kgと判断した。また、雌雄親動物と児動物における生殖発生毒性に対する無毒性量はいずれも30 mg/kgと判断した。

5. 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、ジデカー1-イル（メチル）アミン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、本試験は試験実施施設の動物実験委員会の承認を受けて実施した。

5.1 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・3・29 製局第 6 号、
環境企発第 110331010 号）

5.2 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、
環境企発第 110331009 号）

5.3 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、最終改正：平成 23 年 8 月 30 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）

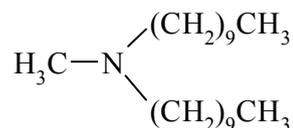
6. 試験材料及び方法

6.1 被験物質及び媒体

6.1.1 被験物質

ジデカ-1-イル（メチル）アミンは [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-2514、添付資料1）。

製造者	:	[REDACTED]
名称	:	ジデカ-1-イル（メチル）アミン
別名	:	Didecylmethyamine
CAS 番号	:	7396-58-9
官報公示整理番号	:	2-176
構造式又は示性式	:	



分子式	:	C ₂₁ H ₄₅ N
分子量	:	311.60
常温における性状	:	無色~わずかにうすい黄色透明液体
融点	:	-7°C*
沸点	:	145°C/0.3kPa*
ロット番号	:	Z2J4C
純度	:	96.2%
不純物	:	不明
比重（20/20）	:	0.8088
屈折率（n _{20/D} ）	:	1.4481
保存条件	:	密栓、冷暗所
保存方法	:	気密容器に入れ冷蔵庫内（許容値：1~10°C、実測値：2~8°C）に保存した。
保存場所	:	御殿場研究所被験物質保存室、第2研究棟4階被験物質調製室及び生化学部標準物質保存場所
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）。

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- 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。
- 残量の処理 : 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。

* : 製造元製品安全データシートに基づく

6.1.2 媒体

- 名称 : コーン油
- 規格 : 生化学用
- 製造者 : 和光純薬工業株式会社
- ロット番号 : WEN1861
- 有効期限 : 2017年7月12日、2017年8月29日、
2017年9月30日
- 保存方法 : 室温
- 保存場所 : 御殿場研究所第2研究棟4階被験物質調製室

なお、媒体については、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安定性試験（試験番号：A-2514）[1]において、コーン油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、コーン油を選択した。

6.2 投与液の調製

6.2.1 対照群投与液の採取

被験液調製当日の被験物質を取り扱う前に、対照群投与液として、必要量の媒体を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。

6.2.2 被験液の調製

濃度ごとに必要量の被験物質をガラスシリンジで採り、ビーカーに正確に秤取した。秤取した被験物質をメスシリンダーに移すとともに、ビーカーを少量の媒体で数回洗い、その液もメスシリンダーに加えた。手で振り攪拌して混合し、完全に溶解したことを目視により確認した。更に媒体をメスシリンダーに加え規定量にメスアップし、2、6及び20 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。

6.2.3 投与液の保存

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：3.6~9°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。

6.2.4 被験液の安定性

本被験物質の 1.01 及び 200 mg/mL 濃度の被験液（媒体：コーン油）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-2514、添付資料 3） [1]。

6.2.5 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 GC 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 96.0~98.0% であり、いずれも許容範囲内（濃度：表示値に対する割合； $100.0 \pm 10.0\%$ ）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、GC を用いた被験液中濃度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-2514） [1] で実施された。分析法の概略を以下に示した。

[標準物質]

被験物質から一部分配したものを用いた。

名称	:	ジデカー1-イル（メチル）アミン
ロット番号	:	Z2J4C
保存条件	:	密栓、冷暗所
保存方法	:	気密容器に入れ冷蔵庫内（許容値：1~10°C、実測値：2~8°C）に保存した。
保存場所	:	御殿場研究所 被験物質保存室、第 2 研究棟 4 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]

各測定試料を任意の場所から n=1 で採取し、以下の表に従い、アセトンで溶解・希釈した測定実測試料を用時調製した。

濃度 (mg/mL)	溶解		希釈		希釈率
	採取量 (mL)	定容量 (mL)	溶解溶液 採取量 (mL)	定容量 (mL)	
2	1	20	10	20	40
6	1	30	5	20	120
20	1	20	1	20	400

溶媒：アセトン

[GC システム]

機器名及び型式		メーカー
GC	HP6890N	Agilent Technologies, Inc.
インジェクタ	G2613A	
オートサンプラトレイ	G2614A	
データ処理ソフト	GC ChemStation G2070AJ	

[GC 測定条件]

カラム	:	DB-1 (0.32 mm I.D.×30 m、膜厚 0.25 μm、 Agilent Technologies Inc.)
キャリアガス	:	He
流量モード	:	コンスタントフローモード
流量	:	3.0 mL/min
注入口	:	スプリット注入口
スプリット比	:	5:1
注入口温度	:	250°C
検出器	:	Flame ionization detector (FID)
検出器温度	:	250°C
H ₂ 流量	:	45 mL/min
Air 流量	:	450 mL/min
メイクアップガス (N ₂) 流量	:	40 mL/min
オープン温度	:	120°C (Hold 0 分) →280°C (20°C/min、Hold 2 分)
注入量	:	1 μL

6.3 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。

6.4 試験動物

Sprague-Dawley 系 SPF ラット [CrI: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 19 日間の馴化飼育を行った。その間、一般状態の観察 (1 回/日)、体重測定 (馴化 1、3、8、15 及び 19 日の 5 回)、詳細な一般状態の観察 (群分け 3 日前の馴化 16 日に 1 回) を実施した。更に、雄について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実施し、雌については腔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 14 日間) を調べた。そ

の結果、性周期の異常が3例（耳標番号：96、102及び122）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、精巢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62匹中48匹及び雌80匹中68匹を選択し、10週齢で投与に使用した。投与開始時（10週齢）の体重の変動範囲は雄で365~418g（平均体重：389g）、雌は216~271g（平均体重：242g）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、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た。その他の雌雄残余動物は群分け当日に試験から除外した。なお、試験から除外された動物は、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。

6.5 飼育条件

動物は、温度 $23\pm 3^{\circ}\text{C}$ （実測値：21~23 $^{\circ}\text{C}$ ）、相対湿度 $50\pm 20\%$ （実測値：46~57%）、換気回数10~15回/h、照明12時間/日（07:00~19:00）の動物飼育室（飼育室番号：906号室）でブラケット式金属製網ケージ（W254×D350×H170mm：リードエンジニアリング株式会社）に交配中を除いて個別に収容した。なお、妊娠17日から授乳4日までは、床敷（ホワイトフレック：日本チャールス・リバー株式会社、ロット番号：2012-2）を入れたプラスチック製エコンケージ（W340×D400×H185mm：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：120413、120815、120919）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。

6.6 動物の識別

動物は番号（雄：1~62、雌：63~145）が刻印された耳標を入荷時に装着し、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（雄及び非交配群の雌）、交尾成立日（交配群の雌雄）及び分娩日（交配群の雌）を明記した。

6.7 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、投与日数として、交配群雌雄ともに交配前14日、更に、雄については交配開始後28日（計42日）、雌については交配期間及び妊娠期間を通して授乳4日まで（計42~50日）とした。非交配群の雌については15日とした。また、交尾不成立であった動物（動物番号：2101）については53日とした。回復動物については、42日の投与期間が終了した後、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。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。

6.8 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08:51~11:47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、14:18~16:40の間に投与した。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。

6.9 投与量及び群構成

投与量は10、30及び100 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、対照群及び中用量群における雄の群内番号8番以降の各5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	10	2	5	12	2001~2012
中用量群	30	6	5	12	3001~3012 ^{注1}
高用量群	100	20	5	12	4001~4012

注1： 群内番号 8 番以降の 5 匹は、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
低用量群	10	2	5	12	2101~2112	—	—
中用量群	30	6	5	12	3101~3112	—	—
高用量群	100	20	5	12	4101~4112	10	4113~4122

6.10 投与量の設定根拠

本試験の投与量は、先に実施した「ジデカー1-イル（メチル）アミンのラットを用いた 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-R034、投与量：10、50、250、500 及び 1000 mg/kg/day」[2]の結果（添付資料 6）を参考に設定した。投与量設定試験では、250 mg/kg 以上の投与群で投与開始翌日から軟便、はいずり姿勢、腹臥/横臥、自発運動の減少、糞量の減少、よろめき歩行、下痢、被毛の汚れ（口腔周囲又は下腹部）、痙攣、呼吸数の減少、体温低下、過敏及び削瘦がみられ、継続的な摂餌量の低値と体重減少を示し、投与 10 日までに全例の瀕死/死亡が認められた。剖検では、低栄養状態、被毛の汚れ（口腔周囲又は下腹部）、胸水貯留、胸腺又は脾臓の小型化、肺の暗赤色巣、肝臓の白色巣、副腎の大型化、胃の拡張、前胃又は腺胃の暗赤色巣、前胃の白色巣、隆起巣又は壁肥厚、盲腸の拡張、十二指腸から回腸の壁肥厚がみられた。50 mg/kg 投与群では、雌雄で投与 7 日まで摂餌量の低値を伴った体重増加抑制が認められたが、以降の体重増加量に対照群と明らかな差はみられなかった。50 mg/kg 投与群の雌雄の摂餌量は投与期間を通じ低値傾向を示した。50 mg/kg 投与群の雄でグルコース(GLU)の低値傾向、胸腺重量の低値傾向及び脾臓重量の高値傾向が、雌で平均赤血球血色素濃度(MCHC)の低値傾向、AST の低値傾向及び総コレステロール(T-CHO)の高値傾向がみられた。10 mg/kg 投与群では、雌雄ともいずれの検査にも異常はみられなかった。したがって、反復投与毒性・生殖発生毒性併合試験の投与期間は投与量設定試験の 3 倍以上になること、当該試験が生殖発生毒性試験との併合試験であることを考慮し、本試験では全体の毒性プロファイルを把握するため、また NOAEL を抑えるため、明らかな毒性徴候の発現が予測される 100 mg/kg を高用量とし、以下公比約 3 で除して 30 及び 10 mg/kg をそれぞれ中及び低用量に設定した。

6.11 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。なお、高用量群において雌雄全例が死亡又は瀕死期剖検されたことから、被験物質投与群の非交配群雌がいなくなり、その比較対照である対照群の非交配群雌が不要となったため、対照群の非交配群雌については、投与 15 日で投与を中断するとともに交配開始日に相当する日から一夜（16~21 時間）絶食し、血液及び血液化学検査並びに血中ホルモン測定用試料として採血した後、剖検及び器官重量測定を行い、病理組織学検査を実施した。

6.11.1 一般状態の観察

全個体について、検疫・馴化期間中は毎日 1 回、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。

6.11.2 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行った。投与開始前（馴化期間中）に 1 回、また、雄は投与期間中及び回復期間中毎週 1 回、非交配群は投与期間中毎週 1 回、交配群雌は交配前投与期間中毎週 1 回、交配期間中、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、未交尾動物は交配開始後 6 及び 13 日、分娩動物は授乳 4 日）にそれぞれ行った。

機能検査、握力測定及び自発運動量測定は、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^註）について行った。投与期間中は交配群の雌で授乳 4 日（投与 42~44 日）に、雄で投与期間終了週（投与 6 週、投与 39 日）に、回復期間中は対照群及び中用量群の雄で回復期間終了週（回復 2 週、回復 11 日）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、自発運動量測定に関しては、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。

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注：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	1101、1105、1106、1107、1112
低用量群	2102、2103、2105、2111、2112
中用量群	3101、3102、3104、3107、3111

1) 詳細な一般状態の観察

ケージ内観察として姿勢、痙攣、異常行動、手に持つての観察として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、オープンフィールド内観察として覚醒状態、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）について観察した。

2) 機能検査

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、着地開脚幅について検査した。

3) 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。

4) 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。

6.11.3 体重測定

全個体について、馴化 1、3、8、15 及び 19 日に体重を測定した。交配群の雄は投与 1、8、15、22、29、36、42 日及び剖検日に、非交配群の雌は投与 1、8、15 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、交配群の雌は投与 1、8、15 日（未交尾動物は交配期間中の投与 22 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分娩の終了が確認された個体の授乳 0 日の体重測定（14:02~17:10 の間）を除き、体重測定は測定日の 08:20~10:39 の間（投与期間中は投与前）に行った。剖検日には、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 07:38~09:10 の間に測定した。また、死亡/瀕死期剖検動物及び交尾不成立雌動物については、搬出前に体重を測定した。

6.11.4 摂餌量測定

全個体について、雄は投与 2、8、15、30、36 及び 42 日に、非交配群の雌は投与 2、8、15 日に、回復動物は更に回復 1、8 及び 14 日に、交配群の雌は投与 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 08:20~11:05 の間（投与期間中は投与前）に行った。

6.11.5 膣垢検査

馴化期間中は雌全個体について検疫期間終了後から群分け日まで毎日膣垢を採取し、性周期異常の有無について調べた。

投与期間中は交配群の雌の全個体について、投与開始日から交尾成立まで毎日膣垢を採取し、交配前期間中の標本について多数の角化上皮細胞から成る膣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。交配期間中は膣垢内の精子の有無を調べるのに加え膣垢像を発情前期(P)、発情期(E)、発情後期(M)及び発情休止期(D)に分類した。

未交尾雌は、剖検 6 日前から剖検日まで毎日（午前）膣垢を採取し、鏡検した。鏡検結果については、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。

6.11.6 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 14 日間であった。交尾が確認されなかった 10 mg/kg 投与群の 1 例（動物番号：2101）は交配期間終了日を妊娠 0 日と仮定して一般状態の観察、体重・摂餌量測定及び投与を継続し、25 日後にイソフルラン麻酔下で採血後、腹大動脈切断により放血致死させ、病理学検査に供した。妊娠の有無を確認した結果、着床は認められなかったため、交尾不成立とみなした。

6.11.7 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 日まで 1 日 2 回（午前・午後）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、児集め、営巣及び授乳を指標として哺育状態を観察し、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。出産児の外表面

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異常^{注)}の有無を観察して性別を確認した。外表異常の認められた出産児は、イソフルラン深麻酔下でリン酸緩衝 10 vol%ホルマリン液に浸漬し、固定して保存した。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。死産児はブアン液で固定して保存した。

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。

6.11.8 尿検査（摂水量測定を含む）

投与期間終了週（投与6週、投与37~38日）及び回復期間終了週（回復2週、回復9~10日）に検査を実施した。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）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。

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	マルティステックス試験紙 [シーメンスヘルスケア・タ [®] イアグ [®] ノスティクス株式会社] a)
たん白質	マルティステックス試験紙 [シーメンスヘルスケア・タ [®] イアグ [®] ノスティクス株式会社] a)
ケトン体	マルティステックス試験紙 [シーメンスヘルスケア・タ [®] イアグ [®] ノスティクス株式会社] a)
グルコース	マルティステックス試験紙 [シーメンスヘルスケア・タ [®] イアグ [®] ノスティクス株式会社] a)
潜血	マルティステックス試験紙 [シーメンスヘルスケア・タ [®] イアグ [®] ノスティクス株式会社] a)
ビリルビン	マルティステックス試験紙 [シーメンスヘルスケア・タ [®] イアグ [®] ノスティクス株式会社] a)
ウロビリノーゲン	マルティステックス試験紙 [シーメンスヘルスケア・タ [®] イアグ [®] 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., Illinois, USA)	
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)	

6.11.9 血液学検査

全例について剖検前日（最終投与日あるいは回復 14 日）から一夜（16~21 時間）絶食させた。各群雌雄各 5 匹（動物番号が若い順、ただし、交配群雌は分娩順の 5 匹^注）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（3,000 rpm、1,600×g、10 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。瀕死期剖検動物及び交尾不成立雌動物についても採血し同様に検査した。

注：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	1101、1105、1106、1107、1112
低用量群	2102、2103、2105、2111、2112
中用量群	3101、3102、3104、3107、3111

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 /μL
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 /μL
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 /μL
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 /μL
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)		

6.11.10 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（3,000 rpm、1,670×g、10 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（3,000 rpm、1,600×g、10 分間）して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。瀕死期剖検動物及び交尾不成立雌動物についても同様に検査した。血清の一部は血中ホルモン測定に備え、約 0.5 mL×3 本をサンプルチューブに分注し、-80°C の冷凍庫（許容範囲：-70°C 以下）に保存した。

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)	3 α -ヒドロキシステロイドデヒドロゲナーゼ ^{a)}	μ mol/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）		

6.11.11 血中ホルモン測定

他の観察及び検査結果から下垂体-甲状腺系への影響が認められなかったため 6.11.10 で得られた血清について血中ホルモン（T₃、T₄及び TSH）測定は実施しなかった。

6.11.12 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全ての生存動物について、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。なお、母動物については剖検時に黄体数及び着床痕数を数えた。次いで、全例について、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。瀕死期剖検動物及び交尾不成立雌動物については採血して放血致死させた後、また、死亡動物は発見後速やかに、同様に剖検を行い器官の重量を測定したが、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*、精巣上部*、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。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。ただし、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、精巣及び精巣上部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）染色標本作製した。鏡検は、まず投与終了時剖検群における対照群及び中用量群の採血を行った動物並びに死亡/瀕死期剖検動物、交尾不成立雌及びその交配相手雄の全検査対象器官/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、精巣上部及び精嚢（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、高用量群の雌雄で副腎、大腿骨（骨髄）、心臓、胃、空腸、回腸（パイエル板）、盲腸、結腸、直腸、顎下リンパ節、腸間膜リンパ節、脾臓、胸腺、膀胱に、雄で前立腺、雌で十二指腸、膵臓、子宮、腔に被験物質投与による影響が疑われたため、低用量群の採血を行った動物並びに回復動物（雄のみ）の当該器官・組織について鏡検した。非交配対照群の雌は、交配開始以前に死亡/瀕死期殺された雌の100 mg/kg投与群と週齢が近いこと、これらの動物に対する対照群として評価した。また、30 mg/kg投与群の雄は、被験物質投与の影響がみられなかったため、変化の回復性については評価しなかった。

大脳、小脳（橋を含む）、坐骨神経、脊髓（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、膣、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）

6.12 統計解析

6.12.1 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、受胎率及び出産率を群ごとに、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日の性比を母動物（腹）ごとに算出した。なお、出生児の体重については母動物ごと雌雄別に平均値を求めた。

$$\text{性周期異常率(\%)} = (\text{性周期異常を示した個体数} / \text{観察雌個体数}) \times 100$$

$$\text{交尾率(\%)} = (\text{交尾動物数} / \text{同居動物数}) \times 100$$

$$\text{授精率(\%)} = (\text{雌を妊娠させた雄の数} / \text{交尾した雄の数}) \times 100$$

$$\text{受胎率(\%)} = (\text{妊娠した雌の数} / \text{交尾した雌の数}) \times 100$$

$$\text{出産率(\%)} = (\text{出生児出産雌数} / \text{妊娠雌数}) \times 100$$

$$\text{妊娠期間(日)} = \text{妊娠0日から分娩した日までの日数}$$

$$\text{着床率(\%)} = (\text{着床痕数} / \text{黄体数}) \times 100$$

$$\text{分娩率(\%)} = (\text{出産児数} / \text{着床痕数}) \times 100$$

$$\text{死産児率(\%)} = (\text{死産児数} / \text{出産児数}) \times 100$$

$$\text{外表異常率(\%)} = (\text{外表異常児数} / \text{出産児数}) \times 100$$

$$\text{出生率(\%)} = (\text{出生児数} / \text{出産児数}) \times 100$$

$$\text{生後4日生存率(\%)} = (\text{生後4日の生存児数} / \text{出生児数}) \times 100$$

$$\text{生後0日（死産児含む）の性比} = \text{雄出産児数} / \text{出産児数}$$

$$\text{生後0日（出生児）の性比} = \text{雄出生児数} / \text{出生児数}$$

$$\text{生後4日の性比} = \text{生後4日の雄生存児数} / \text{生後4日の生存児数}$$

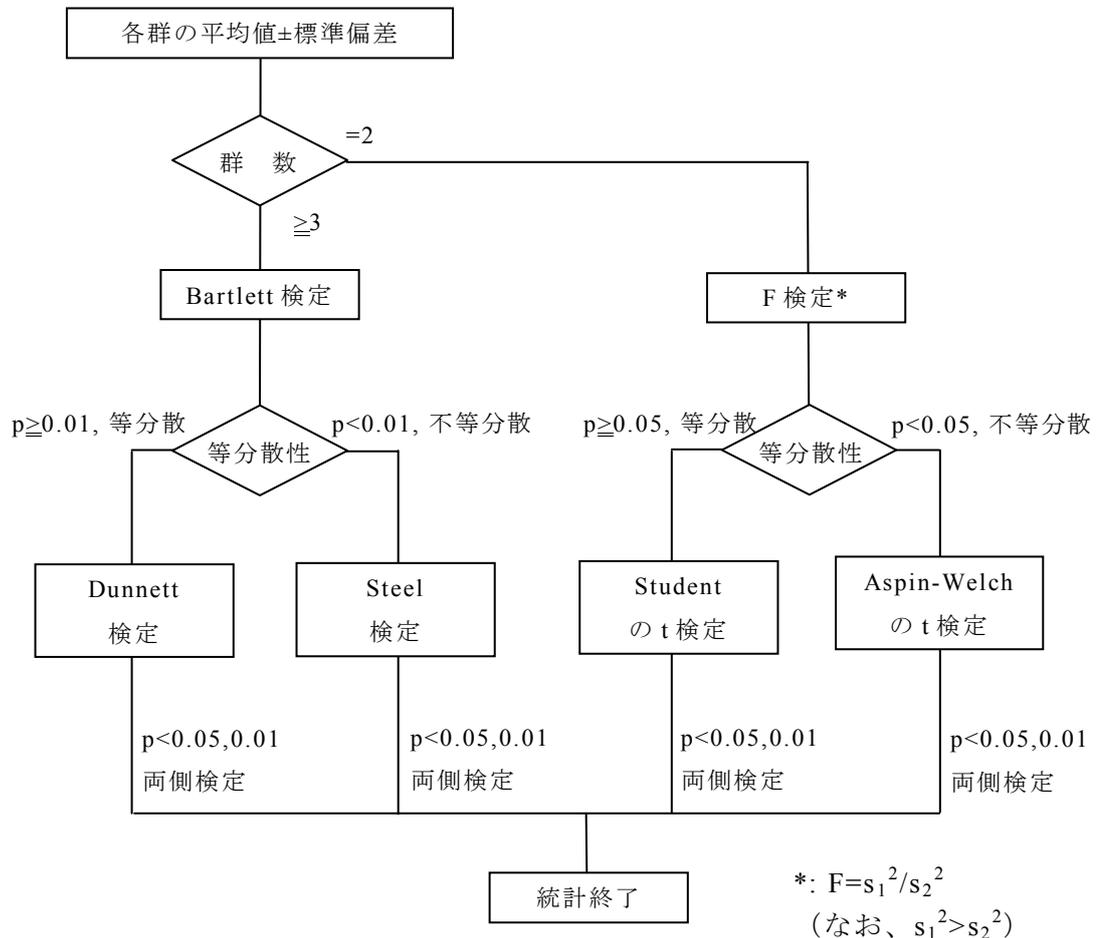
6.12.2 検定

対照群と各用量群との差について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（雄及び非交配群雌：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（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]。

なお、交尾不成立雌の交配開始後の交配成績を除くデータは統計解析より除外した。



着床率、分娩率、出生率、死産児率、外表異常率及び生後4日生存率については、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]。

7. 試験結果

7.1 一般状態 (Table 1-1~1-8、Appendix 1-1~1-28)

1) 投与期間

100 mg/kg 投与群では投与 5 日以降、雌雄で自発運動の減少、よろめき歩行、腹臥/横臥、流涎、削瘦、過敏、痙攣、被毛の汚れ（下腹部及び口腔周囲）、体温低下、軟便、糞量の減少、はいずり姿勢が、雄で赤色尿、前肢腫脹が順次みられ、投与 6~12 日の間に雌雄全例が瀕死期剖検あるいは死亡した。

雄では 30 mg/kg 投与群で投与 19 日以降、流涎が 1~6 例にみられたが、対照群及び 10 mg/kg 投与群ではいずれの動物にも異常はみられなかった。

交配群雌では 30 mg/kg 投与群で妊娠 0~17 日の間に流涎が 0~2 例にみられたが、対照群及び 10 mg/kg 投与群ではいずれの動物にも異常はみられなかった。10 mg/kg 投与群の 1 例（動物番号：2106）が妊娠 22 日に死亡した。授乳期間中のいずれの動物にも哺育状態に異常はみられなかった。

2) 回復期間

対照群及び 30 mg/kg 投与群のいずれの雄動物にも異常はみられなかった。

7.2 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. 1~3、Table 2-1~2-60、Appendix 2-1~2-210)

7.2.1 ホームケージ内観察 (Table 2-1~2-17、Appendix 2-1~2-60)

100 mg/kg 投与群では、投与 2 週の観察時に生存していた雄 1/1 例と雌 1/5 例で姿勢が丸まり、傾眠・時に覚醒する状態がみられた。

その他のいずれの動物にも異常はみられなかった。

7.2.2 手に持つての観察 (Table 2-18~2-34、Appendix 2-61~2-120)

100 mg/kg 投与群では、投与 2 週の観察時に生存していた雄 1/1 例と雌 2/5 例でケージから取り出す際に捕まえることが困難な状態及び軽度の粗毛がみられた。

雄では 30 mg/kg 投与群で投与 3、4、5 及び 6 週の観察時に流涎がみられた。

交配群雌では 30 mg/kg 投与群で妊娠 1、7 及び 14 日の観察時に流涎がみられた。

その他のいずれの動物にも被験物質投与に関連すると考えられる異常はみられなかった。

7.2.3 オープンフィールド内観察 (Table 2-35~2-51、Appendix 2-121~2-180)

100 mg/kg 投与群では、投与 1 週の観察時に雌 3/22 例で、投与 2 週の観察時に生存していた雄 1/1 例と雌 4/5 例でよろめき歩行が、雌 1/5 例で腹臥がみられた。また、立ち上がり回数に対照群と比べ有意な低値が投与 1 及び 2 週の観察時に雌で認められた。

その他のいずれの動物にも被験物質投与に関連すると考えられる異常はみられなかった。また、排糞の個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かった。なお、交配群雌の 10 mg/kg 投与群で妊娠 14 日の立ち上がり回数に有意な高値が認められたが、用量に関連しない変化であった。

7.2.4 機能検査 (Table 2-52~2-54、Appendix 2-181~2-190)

1) 投与期間終了週検査

対照群、10 及び 30 mg/kg 投与群の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みられず、着地開脚幅には対照群と 10 及び 30 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

対照群及び 30 mg/kg 投与群のいずれの雄動物にも聴覚反応、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みられず、着地開脚幅には雄の対照群と 30 mg/kg 投与群との間に有意差は認められなかった。

7.2.5 握力 (Table 2-55~2-57、Appendix 2-191~2-200)

1) 投与期間終了週測定

対照群と 10 及び 30 mg/kg 投与群との間に有意差は認められなかった。

2) 回復期間終了週測定

雄の対照群と 30 mg/kg 投与群との間に有意差は認められなかった。

7.2.6 自発運動量 (Fig. 1~3、Table 2-58~2-60、Appendix 2-201~2-210)

1) 投与期間終了週測定

対照群と 10 及び 30 mg/kg 投与群との間に有意差は認められなかった。

2) 回復期間終了週測定

雄の対照群と 30 mg/kg 投与群との間に有意差は認められなかった。

7.3 体重 (Fig. 4~6、Table 3-1~3-6、Appendix 3-1~3-20)

1) 投与期間

100 mg/kg 投与群では、雌雄とも投与 8 日の体重に対照群と比べ有意な低値（顕著な体重減少）が認められ、投与 12 日までに全例が瀕死期剖検あるいは死亡した。

雄の 30 mg/kg 投与群では投与期間を通じ体重が対照群を下回って推移し、体重増加量に対照群と比べて有意な低値が認められた。10 mg/kg 投与群と対照群との間に有意差は認められなかった。

交配群雌の 30 mg/kg 投与群では交配前投与期間中の体重増加量に対照群と比べて有意な低値が認められたが、妊娠及び授乳の各期間中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。10 mg/kg 投与群と対照群との間に有意差は認められな

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った。

2) 回復期間

雄の 30 mg/kg 投与群で回復期間中の体重増加量に対照群と比べ有意な高値が認められた。

7.4 摂餌量 (Fig. 7~9、Table 4-1~4-6、Appendix 4-1~4-20)

1) 投与期間

100 mg/kg 投与群では、雌雄とも投与 2 及び 8 日の摂餌量に対照群と比べ有意な低値が認められ、投与 12 日までに全例が瀕死期剖検あるいは死亡した。

10 及び 30 mg/kg 投与群の交配前、妊娠及び授乳の各期間中の摂餌量に対照群と比べ有意差は認められなかった。

2) 回復期間

雄の対照群と 30 mg/kg 投与群との間に有意差は認められなかった。

7.5 尿検査 (摂水量測定を含む) (Table 5-1~5-8、Appendix 5-1~5-18)

1) 投与期間終了週検査

定性項目については、対照群、10 及び 30 mg/kg 投与群のいずれの動物にも異常はみられなかった。

定量項目については、いずれの検査項目においても 10 及び 30 mg/kg 投与群と対照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

定性項目については、対照群及び 30 mg/kg 投与群のいずれの雄動物にも異常はみられなかった。

定量項目については、雄の 30 mg/kg 投与群で尿量並びにナトリウム、カリウム及び塩素の尿中排泄量に対照群と比べ有意な高値が認められた。

7.6 血液学検査 (Table 6-1~6-8、Appendix 6-1~6-24)

1) 投与期間終了時検査

雄では 30 mg/kg 投与群で対照群と比べヘモグロビン量、ヘマトクリット値、平均赤血球容積及び平均赤血球血色素量の有意な低値、10 mg/kg 投与群でヘモグロビン量及びヘマトクリット値の有意な低値が認められた。

交配群雌では 30 mg/kg 投与群でプロトロンビン時間に対照群と比べ有意な延長が認められたが、試験施設の背景データ (Mean±2S.D.: 12.4±1.2、n=15、2009/04-2013/03) の範囲内であり、他の血液凝固系パラメータに変動はないことから偶発性と判断した。

2) 回復期間終了時検査

30 mg/kg 投与群の雄ではいずれの検査項目においても対照群との間に有意差は認められなかった。

7.7 血液化学検査 (Table 7-1~7-8、Appendix 7-1~7-24)

1) 投与期間終了時検査

雄では 30 mg/kg 投与群で対照群と比べリン脂質に有意な高値が認められたが、試験施設の背景データ (Mean±2S.D. : 82±14、n=15、2009/04-2013/03) の範囲内であることから、生理的変動範囲内と判断した。

交配群雌では 30 mg/kg 投与群で対照群と比べ尿素窒素に有意な高値が認められたが、試験施設の背景データ (Mean±2S.D. : 14±4、n=15、2009/04-2013/03) の範囲内であることから、生理的変動範囲内と判断した。

2) 回復期間終了時検査

30 mg/kg 投与群の雄で総胆汁酸及びアルブミンに対照群と比べ有意な高値が認められたが、アルブミンは軽微な変化 (6%程度) であり、総胆汁酸は試験施設の背景データ (Mean±2S.D. : 13.0±10.6、n=15、2011/04-2013/03) の範囲内で、また、いずれも投与期間終了時検査に異常がみられないことから生理的変動範囲内と判断した。

7.8 器官重量 (Table 8-1~8-8、Appendix 8-1~8-42)

1) 投与期間終了時検査

雄及び交配群雌ではいずれの器官重量にも 10 及び 30 mg/kg 投与群と対照群との間に有意差は認められなかった。

2) 回復期間終了時検査

雄の 30 mg/kg 投与群ではいずれの器官重量にも対照群との間に有意差は認められなかった。

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

1) 死亡及び瀕死期剖検動物

100 mg/kg 投与群では被験物質投与の影響と考えられる変化として、低栄養状態、被毛の汚染、心臓の白色巣、脾臓の小型化、胃の拡張及び前胃白色巣、胸腺の小型化、膀胱の拡張及び子宮の小型化がみられた。Table に示したその他の所見は、その発現状況あるいは病理学的性状から被験物質投与と関係しない偶発性変化と判断した。

妊娠 22 日に死亡した 10 mg/kg 投与群の 1 例 (動物番号: 2106) では肺の暗赤色化、食道に泡沫液貯留及び胸水貯留、口腔から食道に羊膜組織の滞留がみられた。

2) 投与期間終了時検査

雄では 10 及び 30 mg/kg 投与群のいずれの器官/組織にも被験物質投与に起因すると考えられる変化はみられなかった。

交配群雌では 10 及び 30mg/kg 投与群で腺胃に暗赤色巣がみられたが、母動物には時折みられる変化であり、用量との相関性もみられないことから、被験物質投与と関係しない偶発性変化と判断した。

交尾不成立であった 10 mg/kg 投与群の雌 1 例 (動物番号: 2101) では肉眼的異常はみられなかった。

3) 回復期間終了時検査

雄の対照群及び 30 mg/kg 投与群では肉眼的異常はみられなかった。

7.10 病理組織学検査 (Table 10-1~10-22、Appendix 9-1~9-116)

1) 死亡及び瀕死期剖検動物

被験物質投与に起因する考えられる変化が心臓、胃、十二指腸、空腸、回腸（パイエル板）、膀胱、副腎、大腿骨（骨髄）、盲腸、結腸、直腸、脾臓、胸腺、顎下リンパ節、腸間膜リンパ節、膵臓、前立腺、子宮及び膣にみられた。

心臓 : 100 mg/kg 投与群の雌雄で限局性心筋炎の程度及び頻度が増加した。なお、本変化に部位特異性は認められなかった。

胃 : 100 mg/kg 投与群の雌雄で前胃扁平上皮細胞の過形成、前胃のびらん/潰瘍、胃底腺の単細胞壊死、腺胃の粘液の減少がみられ、さらに同群の雄では、腺頸部の延長みられた。

十二指腸、空腸、回腸（パイエル板） : 100 mg/kg 投与群の雌雄で十二指腸、空腸及び回腸に粘膜の変性/壊死（十二指腸は雌のみ）、回腸でパイエル板の萎縮がみられた。

膀胱 : 100 mg/kg 投与群の雌雄で粘膜の好塩基性化、被蓋上皮細胞の空胞化、内腔の拡張がみられ、雄のみで粘膜/粘膜下の細胞浸潤、びらん/潰瘍、粘膜下の出血がみられた。

副腎 : 100 mg/kg 投与群の雌雄で副腎の皮質細胞の肥大、雌で限局性出血がみられた。

大腿骨（骨髄） : 100 mg/kg 投与群の雌雄で骨髄細胞の減少がみられた。

盲腸、結腸、直腸 : 100 mg/kg 投与群の雌雄で盲腸、結腸及び直腸で杯細胞の減少、雄の直腸で粘膜の細胞浸潤がみられた。

脾臓、胸腺、顎下リンパ節、腸管膜リンパ節 : 100 mg/kg 投与群の雌雄で脾臓の萎縮、髄外造血の減少、胸腺の萎縮、顎下リンパ節で萎縮、腸間膜リンパ節で萎縮及び洞内組織球の活性化がみられた。
10 mg/kg 投与群の雌の死亡例 1 例で脾臓、顎下リンパ節、腸間膜リンパ節の萎縮がみられた。

膵臓 : 100 mg/kg 投与群の雌の膵臓でチモーゲン顆粒の減少がみられた。

前立腺、子宮、膣 : 100 mg/kg 投与群で前立腺の萎縮、出血、子宮で萎縮、膣で粘膜の萎縮及び粘膜/粘膜下の細胞浸潤がみられ

た。なお、前立腺の細胞浸潤は 100 mg/kg 投与群の中等度の 1 例のみ、同個体の膀胱の強い変化に伴う病変として、被験物質投与の影響とした。

100 mg/kg 投与群で肉眼的に皮下組織（頭頂部）に暗赤色巣、前肢の腫脹が各 1 例にみられ、組織学的には、頭頂部皮下の出血及び細胞浸潤、前肢の関節炎が認められた。同部位について、他の動物の組織学的検索は実施していないが、剖検時に同様の変化がみられていないことから、各個体に限った偶発性変化と考えられた。

2) 投与期間終了時検査

雄及び交配群雌では 10 及び 30 mg/kg 投与群のいずれの器官/組織にも被験物質投与に起因すると考えられる変化はみられなかった。交配群雌でみられた腺胃粘膜の限局性の軽微なびらん、一般毒性試験の対照群の雌雄や今回のような Reprotax 試験の交配群の雌（母動物）で背景的に時折みられる変化であり、その原因として、体重減少・投与手技・妊娠・出産・授乳などのストレスが考えられる。本試験では、対照群での発現はみられなかったが、同時期に試験施設で実施した試験では、対照群の少数例に同所見が観察されている。従って、本試験で観察された軽微な腺胃のびらんはその出現頻度から背景的にみられる範囲を超えているとは考え難く、偶発的な変化と判断した。なお、その他にもいくつかの器官/組織に組織学的変化がみられたが、その発現状況あるいは病理学的性状から被験物質投与と関係しない偶発性変化と判断した。

10 mg/kg 投与群の交尾不成立動物（動物番号：2001、2101）では、交尾不成立の原因と考えられる組織学的変化はみられなかった。不妊は低用量群の 1 例のみであり、偶発性にも発現しうることから、被験物質投与による影響は否定した。

3) 回復期間終了時検査

雄の 30 mg/kg 投与群で大腿骨（骨髄）に骨髄細胞の減少がみられたが、対照群との間に発生頻度及び程度の差はなかった。Table に示したその他の所見は、その発現状況あるいは病理学的性状から被験物質投与と関係しない偶発性変化と判断した。

7.11 性周期（Table 11、Appendix 10-1~10-4）

100 mg/kg 投与群で膣垢像が発情休止期を呈し、周期性がみられず性周期が停止した状態の性周期異常がみられ、性周期異常率に有意な高値が認められた。

その他の群では性周期異常の動物はみられず、発情期像発現回数には対照群と 10 及び 30 mg/kg 投与群との間に有意差は認められなかった。なお、10 mg/kg 投与群で平均性周期日数に有意な高値が認められたが、用量に関連しない変化であった。

7.12 交配成績（Table 12、Appendix 11-1~11-3）

10 mg/kg 投与群の 1 組（動物番号：2001 及び 2101）を除くほぼ全例の交尾が交配 4 日までに成立し、交尾までに要した日数、交尾率、授精率及び受胎率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かった。

7.13 分娩成績 (Table 13、Appendix 12-1~12-3) 並びに分娩及び哺育状態 (Table 1-5 及び 1-6、Appendix 1-17~1-24)

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は対照群と 10 及び 30 mg/kg 投与群との間に有意差は認められなかった。

妊娠動物の分娩状態では妊娠 22 日に死亡した 10 mg/kg 投与群の 1 例を除き妊娠 21 から 23 日に全例が分娩し、胎盤及び羊膜の処理は正常に行われ、哺育状態ではいずれの母動物にも児集め、営巣及び授乳行動に異常はみられなかった。出産児の外表観察で短尾が 10 mg/kg 投与群に 1 例、左後肢欠損が 30 mg/kg 投与群に 1 例みられたが、各 1 例のみでありいずれも偶発性と判断した。

7.14 出生児の生存率 (Table 14、Appendix 13-1~13-3)

出生率及び生後 4 日生存率には対照群と 10 及び 30 mg/kg 投与群との間に有意差は認められなかった。

7.15 出生児の性比 (Table 15、Appendix 14-1~14-3)

出産児並びに出生児の生後 0 及び 4 日の性比には対照群と 10 及び 30 mg/kg 投与群との間に有意差は認められなかった。

7.16 出生児の体重 (Table 16、Appendix 15-1~15-3)

生後 0 及び 4 日の雌雄体重並びに生後 0~4 日間の体重増加量には対照群と 10 及び 30 mg/kg 質投与群との間に有意差は認められなかった。

7.17 死亡児の肉眼観察所見 (Table 17、Appendix 16-1~16-3)

いずれの死亡児にも肉眼的異常はみられなかった。

7.18 出生児の生後 4 日肉眼観察所見 (Table 18、Appendix 17-1~17-3)

いずれの出生児にも肉眼的異常はみられなかった。

8. 考察

ジデカー1-イル(メチル)アミンの0(対照群:コーン油)、10、30及び100 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)、交配群雌には交配前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(42~50日間)、非交配群雌には6~15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30 mg/kg投与群の一部の雄動物については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。

8.1 反復投与毒性

8.1.1 死亡動物

100 mg/kg投与群の雌雄で自発運動の減少、よろめき歩行、腹臥/横臥、流涎、削瘦、過敏、痙攣、はいずり姿勢並びに全身状態の悪化がみられ、顕著な摂餌量の低値を伴った体重減少と全身状態の悪化に伴い投与6~12日の間に雌雄全例が瀕死期剖検あるいは死亡した。病理学検査では、肉眼的に全身状態の悪化に関連した所見に加え、前胃に白色巣、心臓に白色巣、膀胱の拡張がみられ、組織学的に心臓に限局性心筋炎、前胃扁平上皮細胞過形成、前胃のびらん/潰瘍、胃底腺単細胞壊死、腺胃粘液減少、腺頸部延長、十二指腸、空腸及び回腸に粘膜変性/壊死、回腸パイエル板萎縮、膀胱に粘膜好塩基性化、被蓋上皮細胞空胞化、内腔拡張、粘膜/粘膜下細胞浸潤、びらん/潰瘍、粘膜下出血、副腎に皮質細胞肥大及び限局性出血、大腿骨骨髓に骨髓細胞減少、盲腸、結腸及び直腸に杯細胞減少、直腸に粘膜細胞浸潤、脾臓に萎縮、髄外造血減少、胸腺に萎縮、顎下リンパ節に萎縮、腸間膜リンパ節に萎縮及び洞内組織球活性化、膵臓にチモーゲン顆粒減少、前立腺に萎縮、出血、膀胱の強い変化に伴う細胞浸潤、子宮に萎縮、腔に粘膜萎縮及び粘膜/粘膜下細胞浸潤がみられた。一般状態でみられた全身状態の悪化に伴う変化に関連した所見が詳細な一般状態でもみられた。また、過敏、痙攣、ケージから取り出す際に捕まえることが困難な状態がみられたことから外部刺激に対する過剰な反応が伺われ、中枢神経系への被験物質投与による影響が疑われた。各動物における死因/瀕死期殺に至る組織学的変化は不明であったが、全例が投与12日目までに死亡/瀕死期殺され、共通して体重の減少がみられ、一般状態の悪化が示唆されることから、被験物質の作用による死亡/瀕死状態と考えられた。

10 mg/kg投与群の1例が妊娠22日の分娩中に死亡した。剖検所見では肺の暗赤色化、食道に泡沫液貯留及び胸水貯留がみられ、口腔から食道に羊膜組織の滞留がみられたことから、分娩中に羊膜組織を詰まらせた可能性が考えられた。組織学的に脾臓、顎下リンパ節、腸間膜リンパ節の萎縮がみられたが、分娩障害に伴うストレス性変化と考えられた為、被験物質投与の影響とは判断しなかった。低用量群の1例のみの発現であり、当該母体の妊娠期間、胎児数は正常で、分娩遅延/異常の徴候もみられないことから、偶発的な死亡と判断した。

本試験では、100 mg/kg 投与群の雌雄全例が死亡/瀕死期殺され、病理組織学検査では被験物質投与の影響が 100 mg/kg 投与群のみにみられた。

心臓では、限局性心筋炎の程度及び頻度が増加した。心筋炎は様々な化学物質により誘発されることが知られているが、本試験における詳細は不明であった。

前胃にみられた扁平上皮細胞の過形成及びびらん/潰瘍は、粘膜への刺激性を有する物質によりしばしば誘発される。しかし、本試験では、被験液の pH あるいは刺激性の有無などが不明である為、前胃の変化が刺激性か否かは不明であったが、過形成を有する動物に必ずしもびらん等の炎症反応を伴っていない動物もみられることから、刺激性によって起こる変化でない可能性が疑われた。なお、本変化は、肉眼所見の白色巣に一致してみられた。腺胃では、腺頸部の延長がみられ、この変化は胃底腺の単細胞性壊死に対する反応性変化の可能性も考えられた。なお、胃底腺の単細胞壊死の発生機序については、明らかでなかった。

十二指腸、空腸、回腸（パイエル板）では、単細胞壊死が陰窩を主としてみられ、程度が強い例では、粘膜の好塩基性化に加え、顕著な粘膜の空胞化及び絨毛の短縮がみられることから、内容物による粘膜刺激への反応ではなく、血中を介した変化である可能性も考えられた。また、腸間膜リンパ節でみられた洞内組織球の活性化は、消化管粘膜の変性/壊死により、粘膜の防御機能が異常をきたした可能性が疑われ、それに伴う反応性変化と考えられた。

膀胱では、粘膜の好塩基性化、被蓋上皮細胞の空胞化、内腔の拡張、粘膜下の出血及び粘膜/粘膜下の細胞浸潤、びらん/潰瘍がみられた。膀胱では、尿が蓄積されるため、膀胱粘膜は、一般的に尿性状の変化や尿中に排泄される被験物質あるいはその代謝物による影響を受けやすい。100 mg/kg 投与群の尿性状及び尿中の被験物質あるいはその代謝物の存在は不明であったが、粘膜の好塩基性化は多数例にみられており、被験物質による膀胱粘膜への何らかの影響が疑われた。また、一部の動物にみられた内腔の拡張、びらん/潰瘍、粘膜の出血及び細胞浸潤は移行上皮及び被蓋上皮細胞の変化に伴う二次性変化の可能性が考えられた。なお、粘膜下の出血は剖検時にみられた赤色尿の貯留に関連するものと推察された。

大腿骨（骨髄）でみられた骨髄細胞の減少は、脾臓の髓外造血の減少との関連性は疑われるものの、造血細胞の構成比率に変動を示さない個体もみられた。また、一般状態の悪化に伴う骨髄細胞の減少も考えられたが、程度や発現状況において、状態悪化に伴う他の器官/組織の変化との相関性が明らかでないことから、発現機序は不明であった。脾臓の髓外造血の減少は、軽微な程度ではあるものの血液学検査における網状赤血球の減少との関連が疑われた。

その他、直腸の粘膜、膣の粘膜/粘膜下の好中球を主体とした細胞浸潤が、雌 1 例に副腎の限局性出血がみられたが、それらの発生機序は不明であった。

胸腺、脾臓、顎下リンパ節、腸間膜リンパ節、回腸パイエル板、前立腺、子宮、膣の萎縮、副腎の皮質細胞の肥大、胃の幽門部粘膜の粘液の減少、盲腸、結腸及び直腸の杯細胞の減少、膵臓のチモーゲン顆粒の減少は、栄養状態の悪化あるいはストレス

などを反映した二次性変化と考えられた。また、前立腺の出血（動物番号：4006、4012）及び中等度にみられた細胞浸潤（動物番号：4006）は膀胱における出血及び炎症性変化が上行性に波及したものと推察された。

8.1.2 生存動物

10及び30 mg/kg 投与群では、機能検査、握力、自発運動量、摂餌量、血液化学検査、剖検、器官重量及び病理組織学検査に被験物質投与の影響は認められなかった。

一般状態及び詳細な一般状態では、30 mg/kg 投与群の雄及び母動物で流涎がみられ、死亡動物でみられた神経症状と合わせて被験物質投与と関連づけられる変化と考えられた。投与終了とともに流涎は消失し、回復性がみられた。

体重では、30 mg/kg 投与群の雄で増加抑制が認められたが、回復期間中の増加量は対照群を上回り、回復性が認められた。30 mg/kg 投与群の雌にも交配前投与期間中に増加抑制が認められた。

尿検査では、30 mg/kg 投与群の雄で回復終了週検査時の尿量並びにナトリウム、カリウム及び塩素の尿中排泄量に高値が認められたが、いずれも試験施設の背景データ [Mean±2S.D., n=15, 2009/04-2013/03] (U.V.: 15.6±4.8, Na: 1.51±0.40, K: 4.85±1.12, Cl: 1.98±0.52) の範囲内であり、投与終了時には同様の変化はみられず、血中電解質濃度に変動は認められないことから、毒性学的意義はないと考えられた。

血液学検査では、雄の 30 mg/kg 投与群でヘモグロビン量、ヘマトクリット値、平均赤血球容積及び平均赤血球血色素量の低値が認められ、被験物質による血色素の産生に及ぼす影響が考えられることから、毒性影響と判断した。ヘモグロビン量及びヘマトクリット値の低値は 10 mg/kg 投与群にもみられたが、いずれも 2.5%程度の軽度な変化であり、他の赤血球パラメータに異常はなく、病理組織に造血系の異常を示唆する所見はみられていないことから、被験物質投与の影響と考えられるものの、毒性学的意義はないと判断した。

100mg/kg 投与群では全例が瀕死期剖検あるいは死亡したのに対し、被験物質の毒性の発現機序は明らかでないが、30mg/kg 投与群では前述の如く軽度な影響しかみられないことから、毒性-用量曲線が急勾配であることが示唆された。

8.2 生殖発生毒性

100 mg/kg 投与群で性周期異常率の高値が認められたが、急激な体重減少など全身状態の悪化に伴う 2 次的な変化と考えられた。

10 及び 30 mg/kg 投与群では、性周期、交尾までに要した日数、交尾率、授精率及び受胎率には被験物質投与の影響は認められなかった。更に、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、死産児の外表観察、出生児数及び出生率に被験物質投与の影響は認められず、授乳期間中の哺育状態にも異常が認められないことから、30 mg/kg 投与群においては雌雄動物の交尾能、授精能及び受胎能、母動物の妊娠維持、分娩及び哺育行動などの生殖機能への影響はないと判断した。

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出生児では、生後 0 日の外表観察、生後 0 及び 4 日の雌雄体重並びに性比、生後 4 日の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、30 mg/kg 投与群においては児の発生、発育及び生存性への影響はないと判断した。

これらの結果から、本試験条件下でジデカー1-イル（メチル）アミンを反復経口投与することにより、主な毒性変化として 100 mg/kg の雌雄で死亡がみられ、30 mg/kg の雌雄で流涎、体重増加抑制、雄でヘモグロビン量、ヘマトクリット値、平均赤血球容積及び平均赤血球血色素量に低値が認められた。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は雄で 10 mg/kg 未満、雌で 10 mg/kg、無毒性量は雌雄とも 10 mg/kg と判断した。また、雌雄親動物と児動物における生殖発生毒性に対する無影響量及び無毒性量はいずれも 30 mg/kg と判断した。

9. 文献

- [1] ██████████ ジデカー1-イル（メチル）アミンの GC 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：コーン油）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-2514、2012 年）

- [2] ██████████ ジデカー1-イル（メチル）アミンのラットを用いた 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-R034、2012 年）

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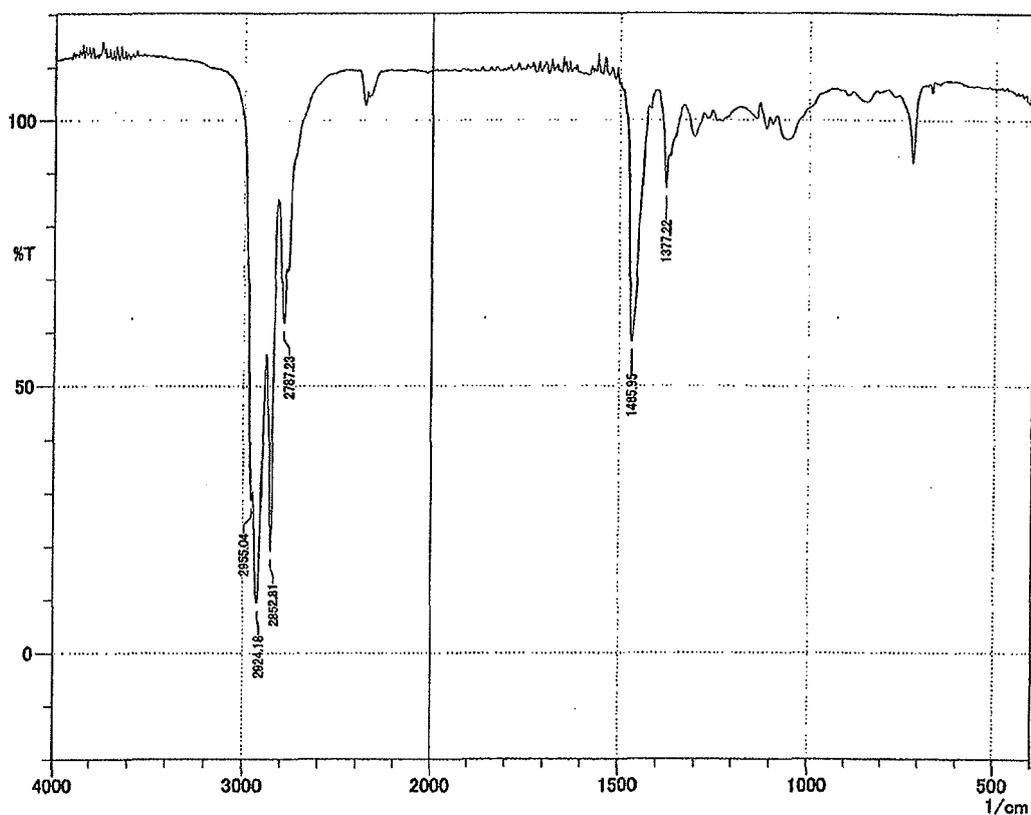
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試験成績書
[ジデカ-1-イル (メチル) アミンの特性]

ステージ : 被験物質の使用前
測定日 : 2012年7月20日
被験物質 : ジデカ-1-イル (メチル) アミン (ロット番号 : Z2J4C)
試験項目 : 赤外吸収スペクトルの確認 (液膜法)
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)

試験責任者
株式会社ポゾリサーチセンター 御殿場研究所

2012年7月30日

試験成績書

[ジデカ-1-イル (メチル) アミンの安定性]

ステージ : 投与期間終了後
測定日 : 2012年12月5日
被験物質 : ジデカ-1-イル (メチル) アミン (ロット番号 : Z2J4C)
試験項目 : 赤外吸収スペクトルの確認 (液膜法)
評価基準 : 安定性のスペクトルを特性のスペクトル (A-2514) 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。

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)

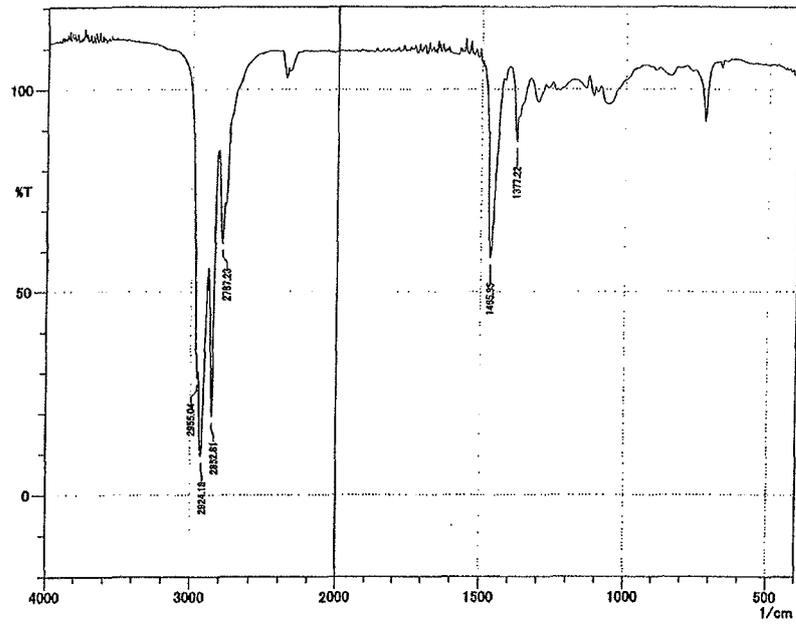
判定 : 適

2012年 12月 11日

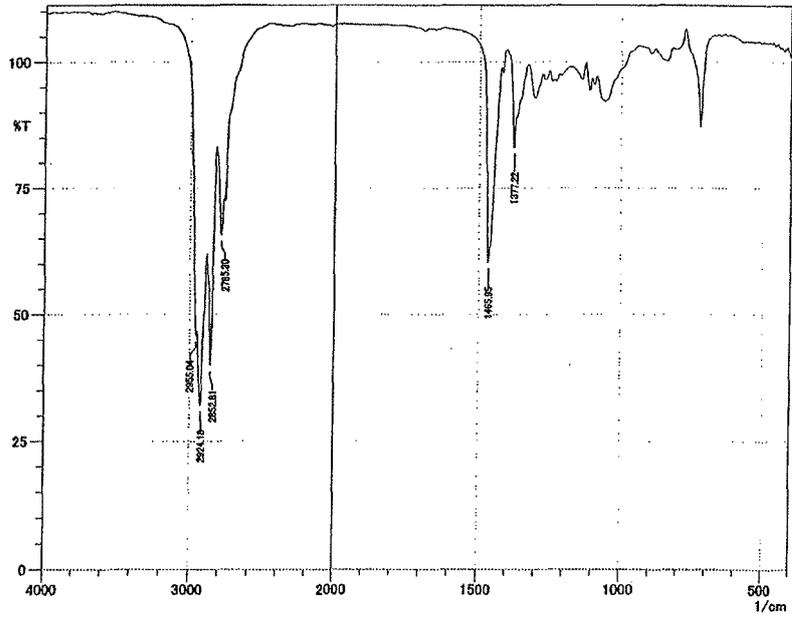

化学分析責任者
株式会社ボゾリサーチセンター 御殿場研究所

結果 : 赤外吸収スペクトル

(特性のスペクトル : A-2514)



(安定性のスペクトル)



試験成績書
(被験液中ジデカ-1-イル (メチル) アミンの安定性)

被験物質 : ジデカ-1-イル (メチル) アミン (ロット番号 ; Z2J4C)
形態 (媒体) : 溶液 (コーン油)
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	1.02	0.994
	1.05	1.016
	1.02	1.015
	平均値	1.01
残存率 (%)	-	98.1
200	201	203
	204	201
	203	198
	平均値	201
残存率 (%)	-	99.0

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)

2012 年 8 月 20 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
(被験液中ジデカ - 1 - イル (メチル) アミンの濃度)

ステージ : 初回投与
分析日 : 2012年9月27日

測定試料
被験物質 : ジデカ - 1 - イル (メチル) アミン
(ロット番号 ; Z2J4C)
形態 (媒体) : 溶液 (コーン油)
調製日 : 2012年9月27日

評価基準
濃度 : 表示値に対する割合 ; 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 (%)
2	1.92	96.0
6	5.76	96.0
20	19.2	96.0

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)

判定 : 適


化学分析責任者
株式会社ポゾリサーチセンター 御殿場研究所

20 13 年 1 月 8 日

試験成績書
(被験液中ジデカ - 1 - イル (メチル) アミンの濃度)

ステージ : 投与 6 週
分析日 : 2012 年 11 月 5 日

測定試料
被験物質 : ジデカ - 1 - イル (メチル) アミン
(ロット番号 ; Z2J4C)
形態 (媒体) : 溶液 (コーン油)
調製日 : 2012 年 11 月 5 日

評価基準
濃度 : 表示値に対する割合 ; 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 (%)
2	1.96	98.0
6	5.84	97.3

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)

判定 : 適


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

20 13 年 1 月 8 日

ジデカー1-イル（メチル）アミンのラットを用いた
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-R034

被験物質		媒体 ^{a)}	ジデカー1-イル（メチル）アミン				
投与量 (mg/kg)		0	10	50	250	500	1000
投与容量 (mL/kg)		5	5	5	5	5	5
使用動物数 (♂/♀)		5/5	5/5	5/5	5/5	5/5	5/5
死亡動物数 (♂/♀)		0/0	0/0	0/0	5/5	5/5	5/5
死亡発現時期		—	—	—	投与 5-10 日	投与 6-10 日	投与 6-10 日
一般 状態	生存	—	—	—			
	死亡				軟便、はいずり姿勢、腹臥/横臥、自発運動の減少、糞量の減少、よろめき歩行、下痢、被毛の汚れ（下腹部又は口腔周囲）、痙攣、呼吸数の減少、体温低下、過敏及び削瘦		
体重			—	増加抑制	↓↓（投与 4 日以降）		
摂餌量			—	低値傾向	↓↓（投与 4 日以降）		
血液学検査			—	平均赤血球血色素濃度：低値傾向（♀）	/	/	/
血液化学検査			—	グルコース：低値傾向（♂） AST：低値傾向（♀） 総コレステロール：高値傾向（♀）	/	/	/
器官 重量	絶対		—	胸腺：低値傾向（♂） 脾臓：高値傾向（♂）	/	/	/
	相対		—	胸腺：低値傾向（♂） 脾臓：高値傾向（♂）	/	/	/
剖検	生存	—	—	—			
	死亡				低栄養状態、被毛の汚れ（口腔周囲又は下腹部）、胸水貯留、胸腺又は脾臓の小型化、肺の暗赤色巢、肝臓の白色巢、副腎の大型化、胃の拡張、前胃又は腺胃の暗赤色巢、前胃の白色巢、隆起巢又は壁肥厚、盲腸の拡張、十二指腸から回腸の壁肥厚		

a)：コーン油

—：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)

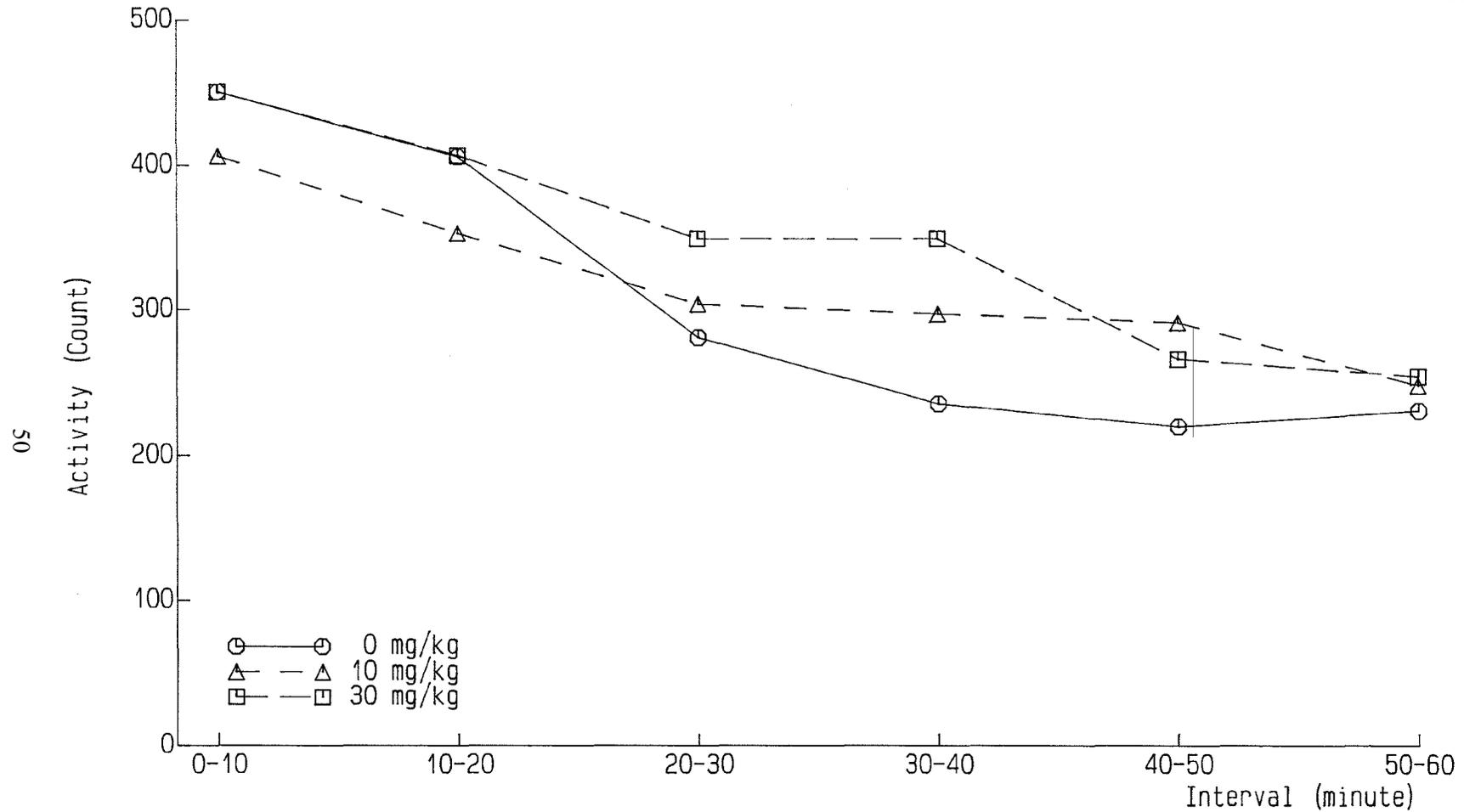


Fig.1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Motor activity of male rats (Week 6 of administration)

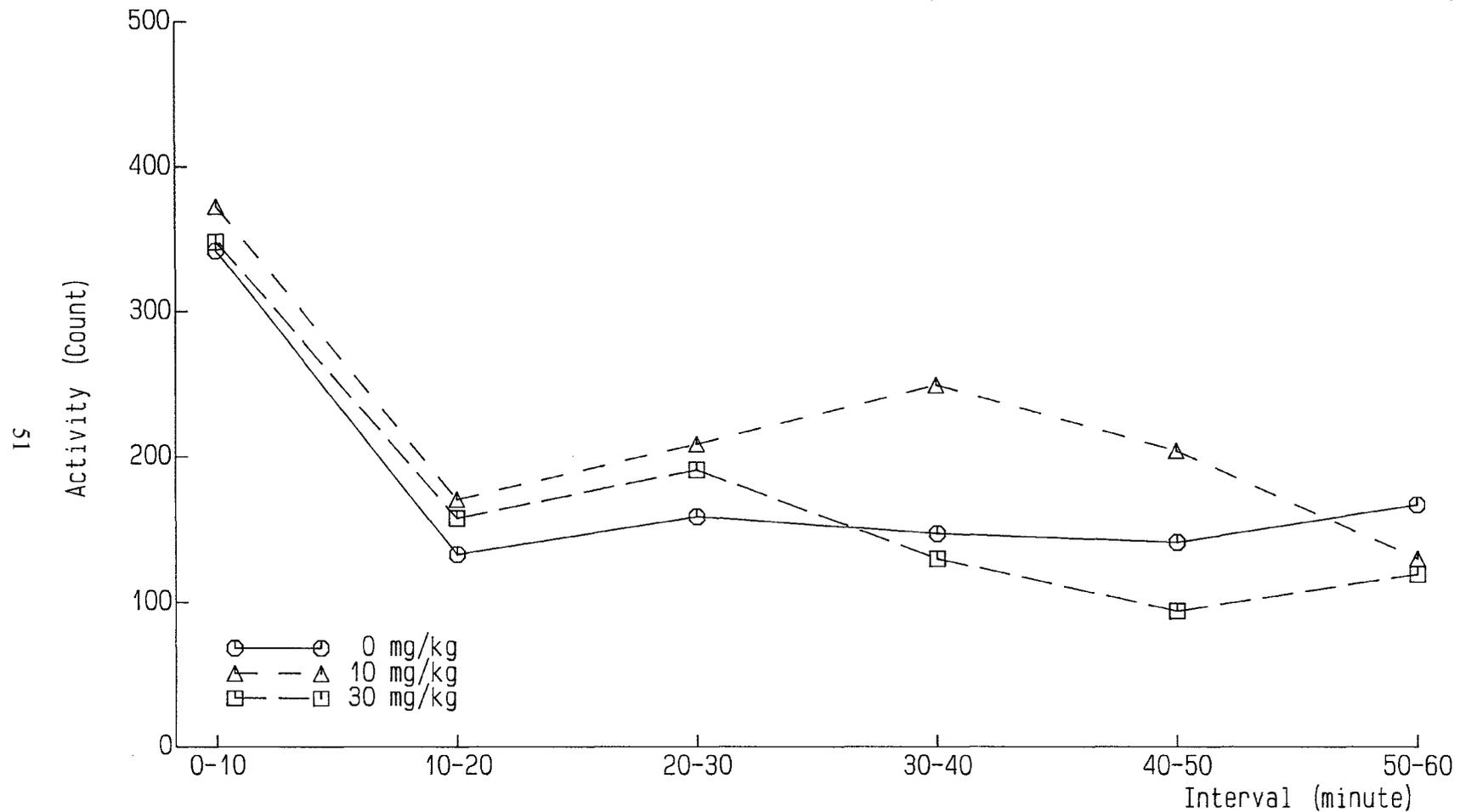


Fig.2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Motor activity of female rats (Main group, Lactation day 4)

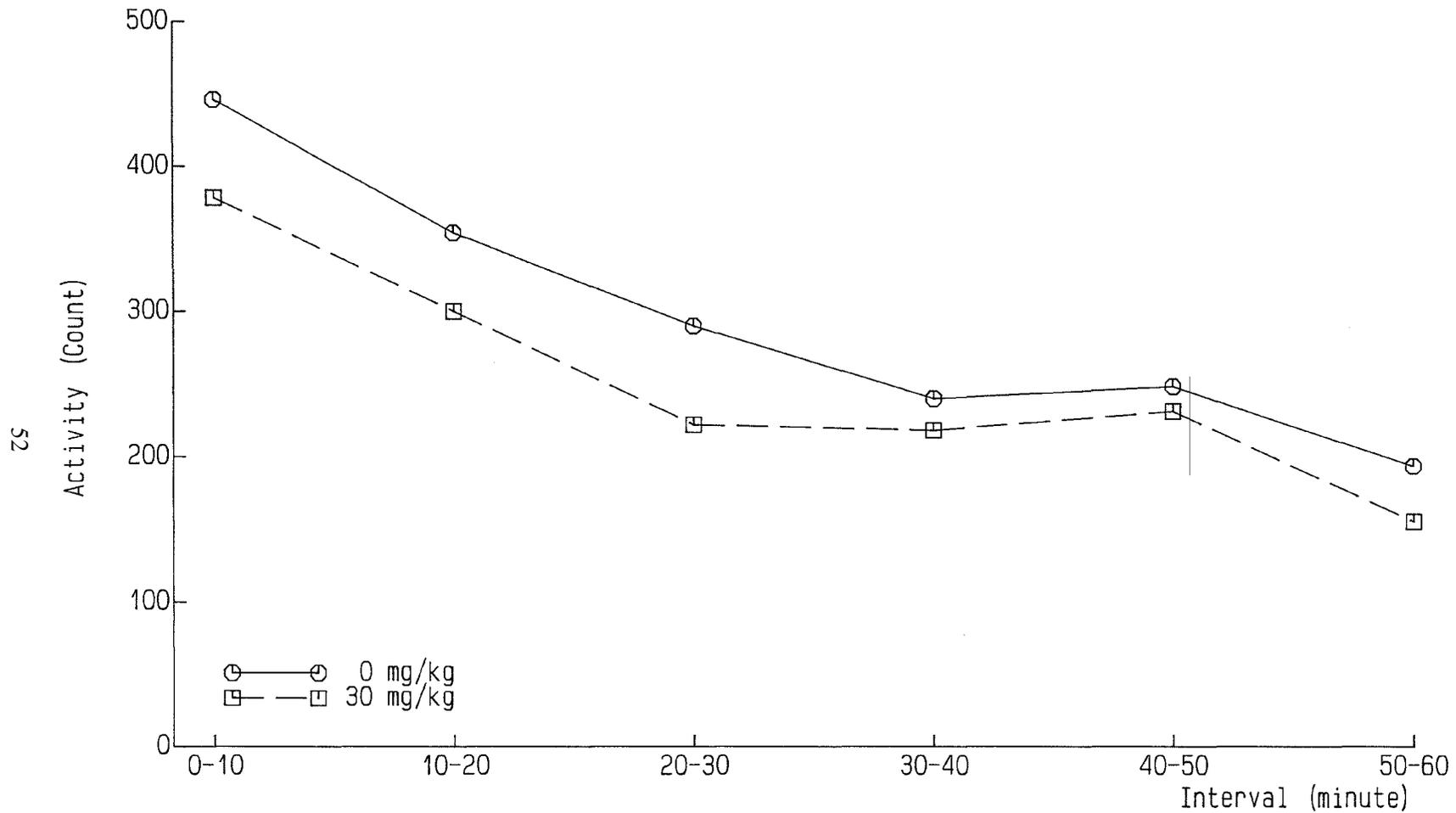


Fig.3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Motor activity of male rats (Week 2 of recovery)

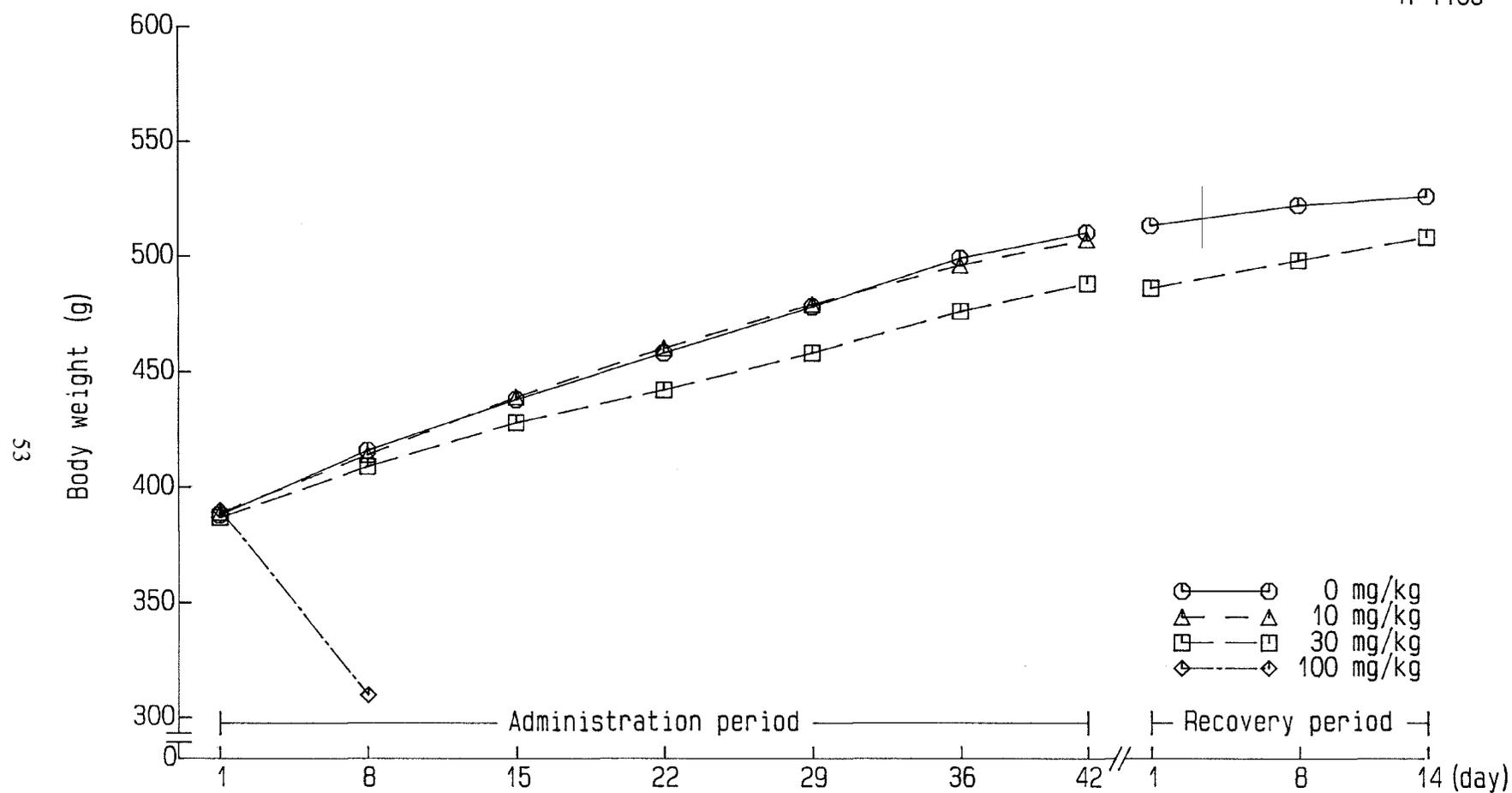


Fig.4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Body weight of male rats

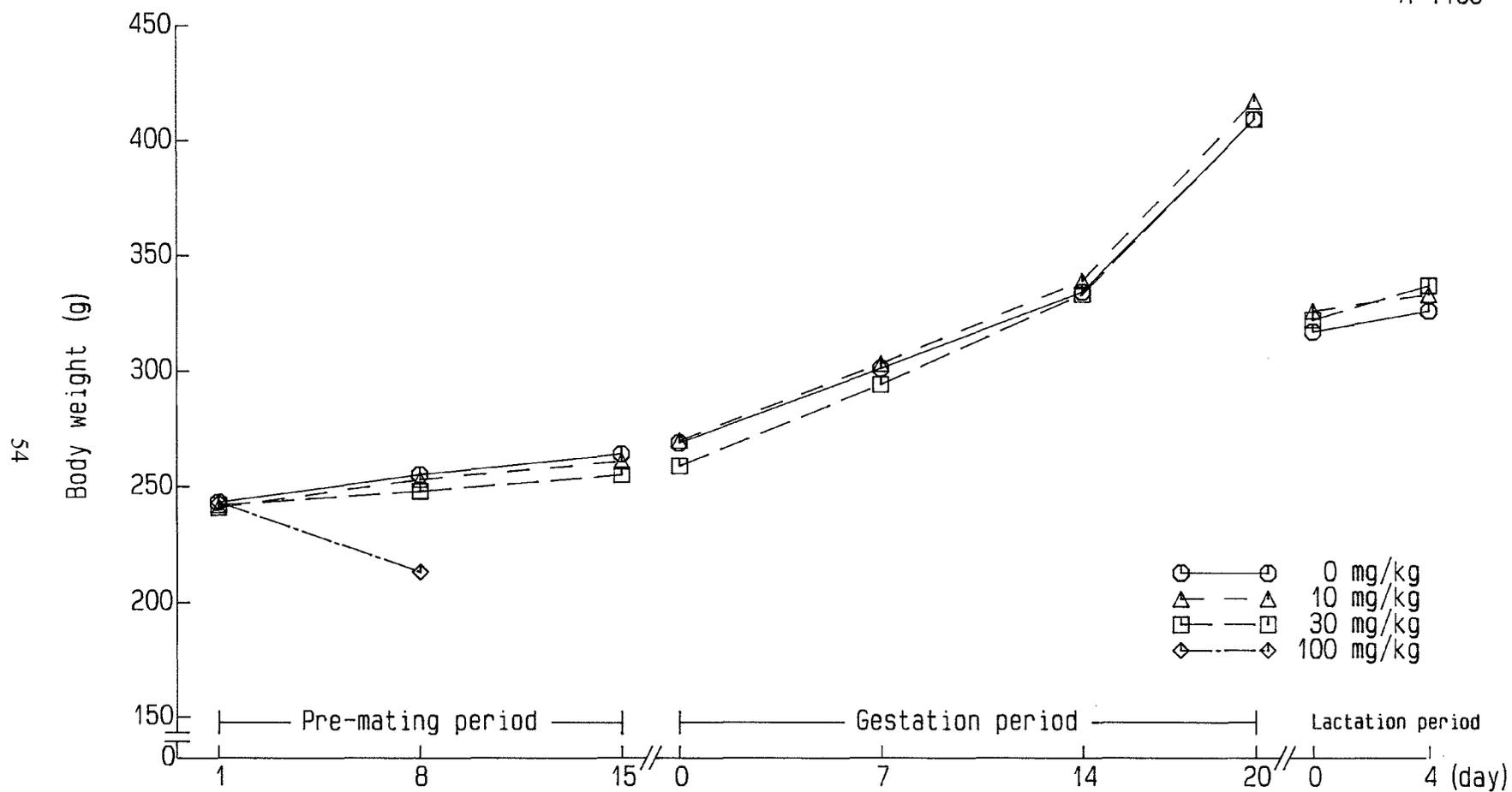


Fig.5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Body weight of female rats (Main group)

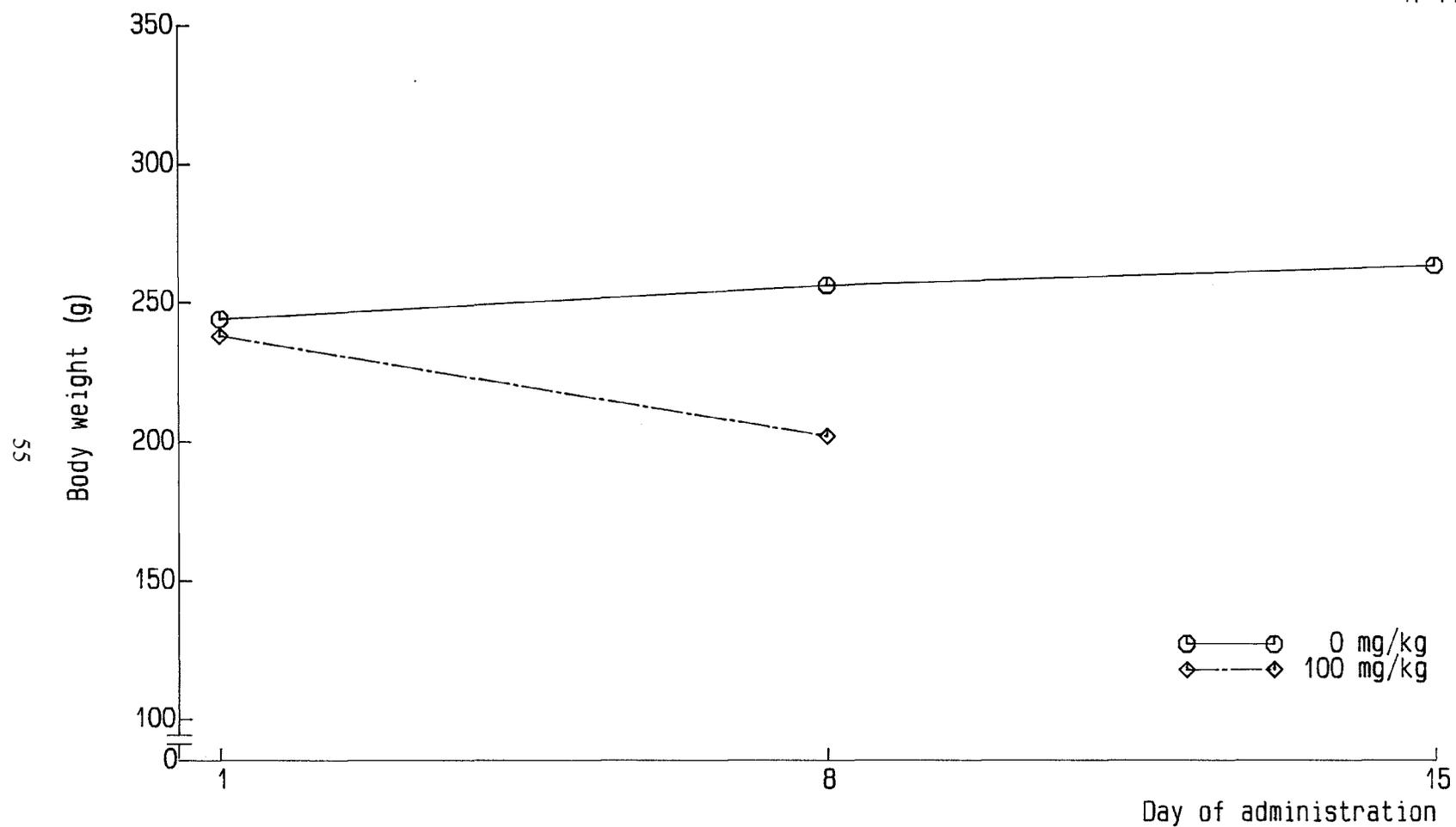


Fig.6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Body weight of female rats (Satellite group)

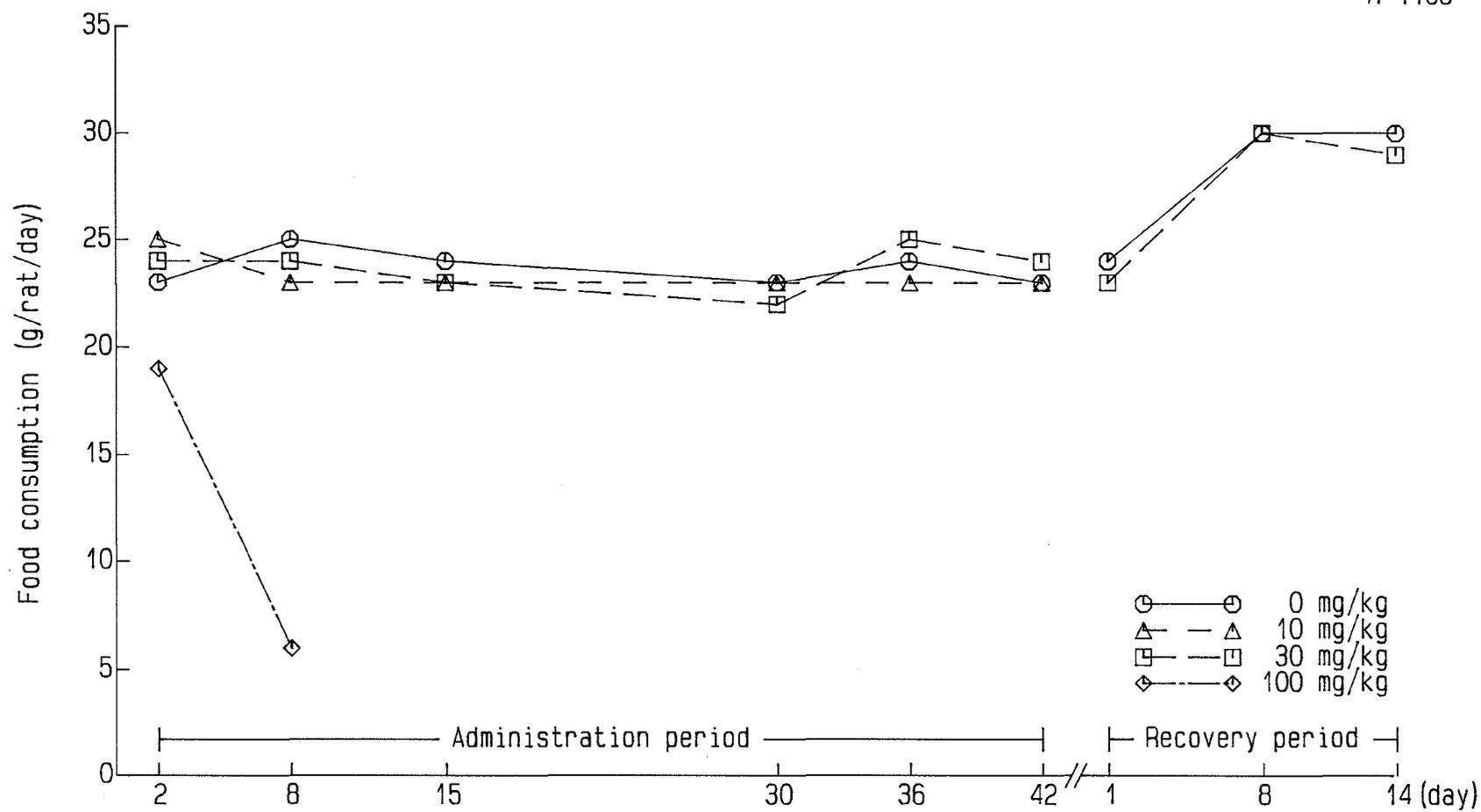


Fig.7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Food consumption of male rats

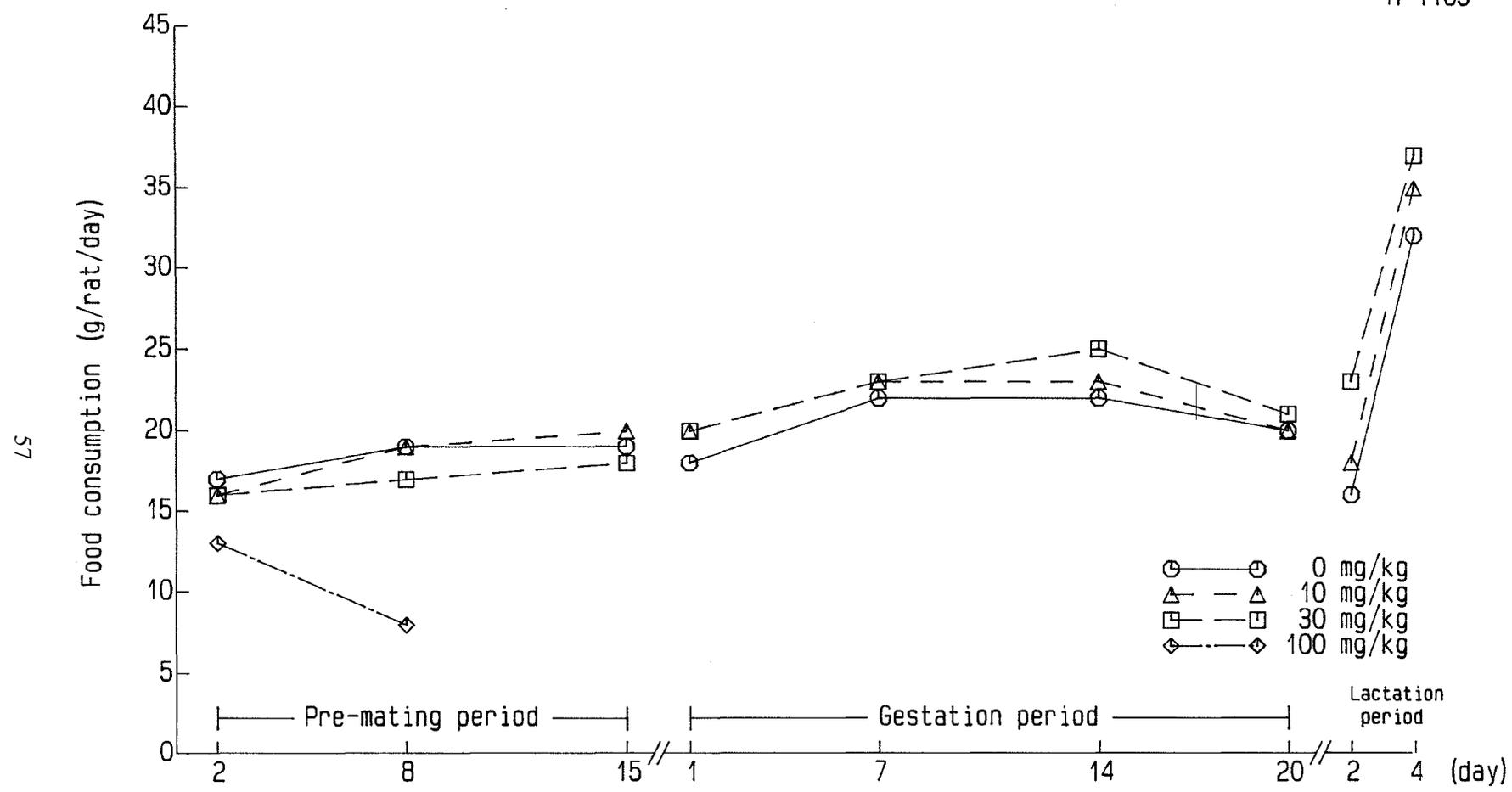


Fig.8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Food consumption of female rats (Main group)

85

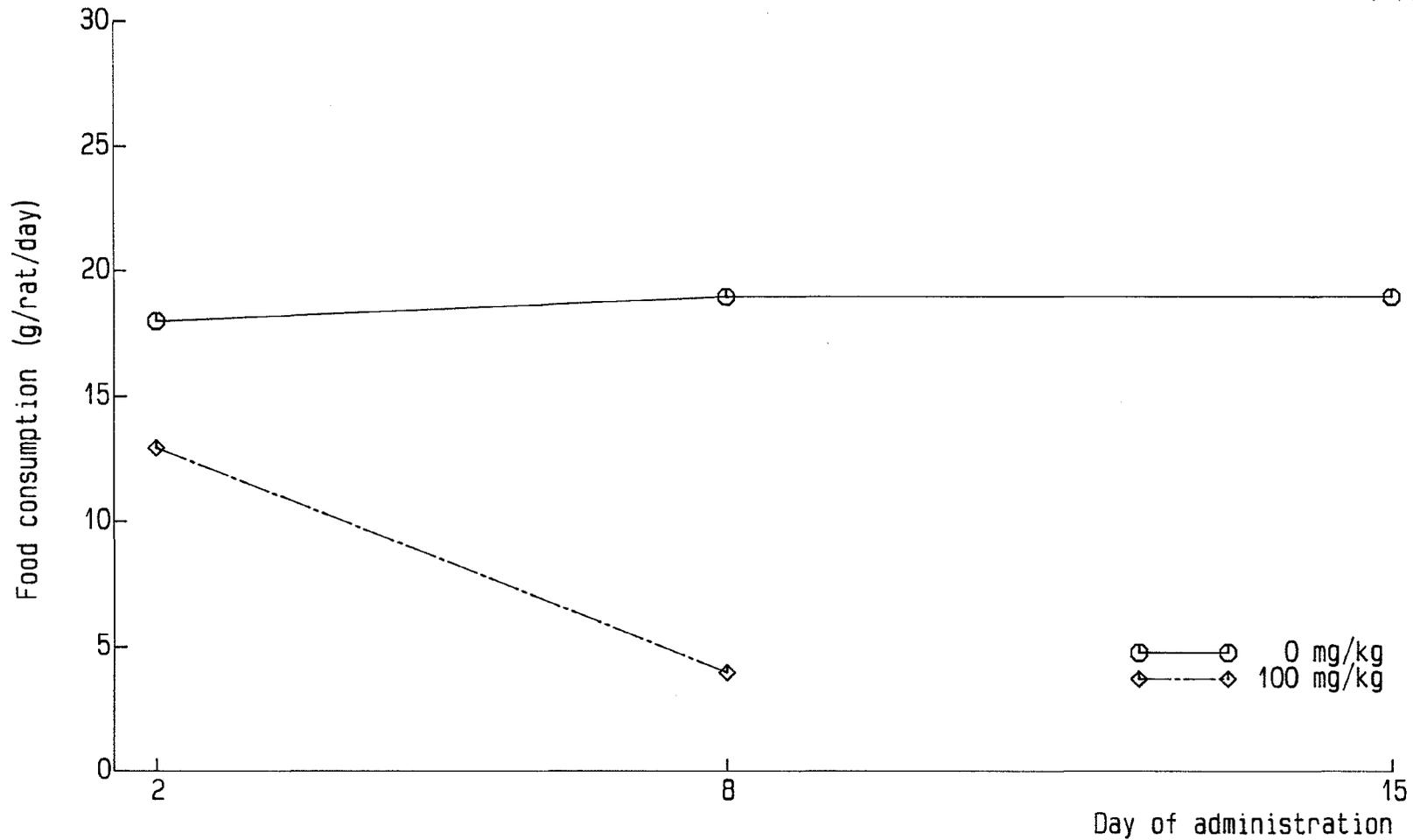


Fig.9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Food consumption of female rats (Satellite group)

Table 1-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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
10	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
30	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
100	No. of animals	12	12	12	12	12	12	10	10	8	7	2	0		
	No. of animals with abnormal findings	0	0	0	0	9	10	8	9	8	7	2			
	Decrease in spontaneous movement	0	0	0	0	3	6	3	3	6	2	1			
	Ataxia	0	0	0	0	1	1	1	3	4	1	1			
	Prone/Lateral position	0	0	0	0	2	4	5	5	1	5	2			
	Salivation	0	0	0	0	1	1	0	0	0	0	0			
	Emaciation	0	0	0	0	0	0	2	3	4	4	1			
	Hypersensitivity	0	0	0	0	5	2	1	2	5	1	0			
	Convulsion	0	0	0	0	4	2	3	0	1	1	0			
	Smudge of lower abdomen	0	0	0	0	0	1	1	3	5	3	0			
	Smudge of perioral	0	0	0	0	0	1	4	5	5	4	1			
	Hypothermia	0	0	0	0	0	2	0	1	1	5	2			
	Reddish urine	0	0	0	0	0	0	0	1	2	0	0			
	Soft feces	0	0	0	0	0	0	0	2	1	2	0			
	Decrease in feces	0	0	0	0	0	0	0	4	6	4	1			
	Creeping position	0	0	0	0	0	0	0	0	5	1	0			
	Swelling of fore limb	0	0	0	0	0	0	0	0	0	1	1			
Dead	0	0	0	0	0	0	0	1	0	0	0				
Sacrificed moribund	0	0	0	0	0	2	0	1	1	5	2				

Table 1-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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
10	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
30	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	3	5	5	5	3	3	6	5	2	2
	Salivation	0	0	0	0	3	5	5	5	3	3	6	5	2	2
100	No. of animals	0													
	No. of animals with abnormal findings														

Table 1-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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
10	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
30	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	No. of animals with abnormal findings	4	6	4	4	3	4	1	4	1	5	3	6	5	5	0
	Salivation	4	6	4	4	3	4	1	4	1	5	3	6	5	5	0
100	No. of animals	0														
	No. of animals with abnormal findings															

a): Day of necropsy

Table 1-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	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
30	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
100	No. of animals	12	12	12	12	12	12	11	10	6	4	1	1	0		
	No. of animals with abnormal findings	0	0	0	0	5	6	8	8	6	4	1	1			
	Decrease in spontaneous movement	0	0	0	0	5	0	3	0	1	1	0	1			
	Ataxia	0	0	0	0	3	2	4	1	2	0	0	0			
	Prone/Lateral position	0	0	0	0	0	4	4	5	1	3	0	0			
	Salivation	0	0	0	0	0	1	1	0	0	0	0	0			
	Emaciation	0	0	0	0	1	4	5	3	1	2	0	1			
	Hypersensitivity	0	0	0	0	0	1	5	0	1	1	0	0			
	Convulsion	0	0	0	0	0	2	2	2	0	2	0	0			
	Smudge of lower abdomen	0	0	0	0	0	0	1	0	0	0	0	0			
	Smudge of perioral	0	0	0	0	0	0	2	1	0	0	0	0			
	Hypothermia	0	0	0	0	0	1	1	1	1	3	0	1			
	Decrease in feces	0	0	0	0	0	0	0	3	4	3	1	1			
	Dead	0	0	0	0	0	0	0	2	1	0	0	0			
	Sacrificed moribund	0	0	0	0	0	1	1	2	1	3	0	1			

Table 1-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	12	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	0	0	0
10	No. of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	5	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	0	1
	Dead	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
30	No. of dams	12	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	1	1	0	1	2	2	2	2	1	1	1	2	1	1	1	1	1	1	0	0	0	0	0	
	Salivation	1	1	0	1	2	2	2	2	1	1	1	2	1	1	1	1	1	1	0	0	0	0	0	
100	No. of dams	0																							
	No. of dams with abnormal findings	0																							

a): Gestation day

Table 1-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	12	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0	0
10	No. of dams	10	10	10	10	10	10
	No. of dams with abnormal findings	0	0	0	0	0	0
30	No. of dams	12	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0	0
100	No. of dams	0					
	No. of dams with abnormal findings						

a): Lactation day

b): Day of necropsy

Table 1-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Clinical signs in female rats (Satellite group)

Dose mg/kg	Signs	Day of administration															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16a)
0	No. of animals	10	10	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	0	0
100	No. of animals	10	10	10	10	10	10	10	10	8	7	6	3	0			
	No. of animals with abnormal findings	0	0	0	0	4	5	6	9	8	7	6	3				
	Decrease in spontaneous movement	0	0	0	0	2	4	5	0	4	5	3	3				
	Ataxia	0	0	0	0	3	5	5	3	5	5	4	3				
	Prone/Lateral position	0	0	0	0	0	0	1	6	3	0	2	0				
	Salivation	0	0	0	0	0	1	0	0	0	0	0	0				
	Emaciation	0	0	0	0	1	4	4	3	5	5	4	3				
	Hypersensitivity	0	0	0	0	2	2	1	3	3	2	1	1				
	Convulsion	0	0	0	0	1	0	1	2	1	0	0	0				
	Smudge of lower abdomen	0	0	0	0	0	0	1	1	0	0	0	0				
	Smudge of perioral	0	0	0	0	0	0	0	0	1	0	0	0				
	Hypothermia	0	0	0	0	0	0	0	1	1	0	2	3				
	Soft feces	0	0	0	0	0	0	0	1	0	0	0	0				
	Decrease in feces	0	0	0	0	0	0	0	2	7	5	3	1				
	Creeping position	0	0	0	0	0	0	0	0	1	1	0	0				
	Dead	0	0	0	0	0	0	0	1	0	1	1	0				
Sacrificed moribund	0	0	0	0	0	0	0	1	1	0	2	3					

a): Day of necropsy

Table 1-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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
30	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

a): Day of necropsy

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

Parameter	Dose (mg/kg)	0	10	30	100
	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 didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 2 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	1
Posture					
Normal		12	12	12	0
Hunched		0	0	0	1d)
Convulsion					
None		12	12	12	1
Abnormal behavior					
None		12	12	12	1

a): Somnolent

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

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Posture					
Normal		12	12	12	
Convulsion					
None		12	12	12	
Abnormal behavior					
None		12	12	12	

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

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Posture					
Normal		12	12	12	
Convulsion					
None		12	12	12	
Abnormal behavior					
None		12	12	12	

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

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Posture					
Normal		12	12	12	
Convulsion					
None		12	12	12	
Abnormal behavior					
None		12	12	12	

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

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Posture					
Normal		12	12	12	
Convulsion					
None		12	12	12	
Abnormal behavior					
None		12	12	12	

Table 2-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	30	100
	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 didec-1-yl(methyl)amine 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	10	30	100
	No. of animals	12	12	12	1
Posture					
Normal		12	12	12	1
Convulsion					
None		12	12	12	1
Abnormal behavior					
None		12	12	12	1

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

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	11	12	0
Posture					
Normal		12	11	12	
Convulsion					
None		12	11	12	
Abnormal behavior					
None		12	11	12	

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

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	11	12	0
Posture					
Normal		12	11	12	
Convulsion					
None		12	11	12	
Abnormal behavior					
None		12	11	12	

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

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	11	12	0
Posture					
Normal		12	11	12	
Convulsion					
None		12	11	12	
Abnormal behavior					
None		12	11	12	

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

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	11	12	0
Posture					
Normal		12	11	12	
Convulsion					
None		12	11	12	
Abnormal behavior					
None		12	11	12	

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

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	10	12	0
Posture					
Normal		12	10	12	
Convulsion					
None		12	10	12	
Abnormal behavior					
None		12	10	12	

Table 2-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	100
	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 didec-1-yl(methyl)amine 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	100
	No. of animals	-----	-----
Posture			
Normal		10	3
Hunched		0	1d)
Convulsion			
None		10	4
Abnormal behavior			
None		10	4

a): Somnolent

Table 2-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	30
	No. of animals	----- 5	----- 5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	30
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 1 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	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	11	12	12
Soft		0	1	0	0
Reactivity to handling					
Easy		12	12	12	12

Table 2-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 2 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	1
Ease of removal from cage					
Easy		12	12	11	0
Some resistance/avoidance		0	0	1	0
Difficult		0	0	0	1
Fur condition					
Normal		12	12	12	0
Slight		0	0	0	1a)
Skin					
Normal		12	12	12	1
Secretions-Eye, Nose					
Absent		12	12	12	1
Exophthalmos					
Absent		12	12	12	1
Palpebral closure					
Normal		12	12	12	1
Mucosal membranes					
Normal		12	12	12	1
Lacrimation					
Normal		12	12	12	1
Piloerection					
Absent		12	12	12	1
Pupil size					
Normal		12	12	12	1
Salivation					
None		12	12	12	1
Abnormal respiration					
Absent		12	12	12	1
Vocalization					
None		12	12	12	1
Reactivity to handling					
Easy		12	10	12	1
Slightly awkward		0	2	0	0

a): Unkempt fur

Table 2-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 3 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Ease of removal from cage					
Easy		12	12	12	
Fur condition					
Normal		12	12	12	
Skin					
Normal		12	12	12	
Secretions-Eye, Nose					
Absent		12	12	12	
Exophthalmos					
Absent		12	12	12	
Palpebral closure					
Normal		12	12	12	
Mucosal membranes					
Normal		12	12	12	
Lacrimation					
Normal		12	12	12	
Piloerection					
Absent		12	12	12	
Pupil size					
Normal		12	12	12	
Salivation					
None		12	12	7	
Moderate		0	0	5	
Abnormal respiration					
Absent		12	12	12	
Vocalization					
None		11	12	11	
Soft		1	0	1	
Reactivity to handling					
Easy		12	12	12	

Table 2-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 4 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Ease of removal from cage					
Easy		12	12	12	
Fur condition					
Normal		12	12	12	
Skin					
Normal		12	12	12	
Secretions-Eye, Nose					
Absent		12	12	12	
Exophthalmos					
Absent		12	12	12	
Palpebral closure					
Normal		12	12	12	
Mucosal membranes					
Normal		12	12	12	
Lacrimation					
Normal		12	12	12	
Piloerection					
Absent		12	12	12	
Pupil size					
Normal		12	12	12	
Salivation					
None		12	12	6	
Slight		0	0	3	
Moderate		0	0	3	
Abnormal respiration					
Absent		12	12	12	
Vocalization					
None		12	12	12	
Reactivity to handling					
Easy		12	12	11	
Slightly awkward		0	0	1	

Table 2-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 5 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Ease of removal from cage					
Easy		12	12	12	
Fur condition					
Normal		12	12	12	
Skin					
Normal		12	12	12	
Secretions-Eye, Nose					
Absent		12	12	12	
Exophthalmos					
Absent		12	12	12	
Palpebral closure					
Normal		12	12	12	
Mucosal membranes					
Normal		12	12	12	
Lacrimation					
Normal		12	12	12	
Piloerection					
Absent		12	12	12	
Pupil size					
Normal		12	12	12	
Salivation					
None		12	12	7	
Slight		0	0	4	
Moderate		0	0	1	
Abnormal respiration					
Absent		12	12	12	
Vocalization					
None		12	12	12	
Reactivity to handling					
Easy		12	12	12	

Table 2-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 6 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Ease of removal from cage					
Easy		12	12	12	
Fur condition					
Normal		12	12	12	
Skin					
Normal		12	12	12	
Secretions-Eye, Nose					
Absent		12	12	12	
Exophthalmos					
Absent		12	12	12	
Palpebral closure					
Normal		12	12	12	
Mucosal membranes					
Normal		12	12	12	
Lacrimation					
Normal		12	12	12	
Piloerection					
Absent		12	12	12	
Pupil size					
Normal		12	12	12	
Salivation					
None		12	12	9	
Slight		0	0	3	
Abnormal respiration					
Absent		12	12	12	
Vocalization					
None		11	12	12	
Soft		1	0	0	
Reactivity to handling					
Easy		12	12	12	

Table 2-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	30	100
	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 didec-1-yl(methyl)amine 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	10	30	100
	No. of animals	12	12	12	1
Ease of removal from cage					
Easy		12	12	12	1
Fur condition					
Normal		12	12	12	1
Skin					
Normal		12	12	12	1
Secretions-Eye, Nose					
Absent		12	12	12	1
Exophthalmos					
Absent		12	12	12	1
Palpebral closure					
Normal		12	12	12	1
Mucosal membranes					
Normal		12	12	12	1
Lacrimation					
Normal		12	12	12	1
Piloerection					
Absent		12	12	12	1
Pupil size					
Normal		12	12	12	1
Salivation					
None		12	12	12	1
Abnormal respiration					
Absent		12	12	12	1
Vocalization					
None		12	12	12	1
Reactivity to handling					
Easy		12	12	12	1

Table 2-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	30	100
	No. of animals	12	11	12	0
Ease of removal from cage					
Easy		12	11	12	
Fur condition					
Normal		12	11	12	
Skin					
Normal		12	11	12	
Secretions-Eye, Nose					
Absent		12	11	12	
Exophthalmos					
Absent		12	11	12	
Palpebral closure					
Normal		12	11	12	
Mucosal membranes					
Normal		12	11	12	
Lacrimation					
Normal		12	11	12	
Piloerection					
Absent		12	11	12	
Pupil size					
Normal		12	11	12	
Salivation					
None		12	11	11	
Moderate		0	0	1	
Abnormal respiration					
Absent		12	11	12	
Vocalization					
None		12	11	12	
Reactivity to handling					
Easy		12	11	12	

Table 2-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	30	100
	No. of animals	12	11	12	0
Ease of removal from cage					
Easy		12	11	12	
Fur condition					
Normal		12	11	12	
Skin					
Normal		12	11	12	
Secretions-Eye, Nose					
Absent		12	11	12	
Exophthalmos					
Absent		12	11	12	
Palpebral closure					
Normal		12	11	12	
Mucosal membranes					
Normal		12	11	12	
Lacrimation					
Normal		12	11	12	
Piloerection					
Absent		12	11	12	
Pupil size					
Normal		12	11	12	
Salivation					
None		12	11	10	
Slight		0	0	1	
Moderate		0	0	1	
Abnormal respiration					
Absent		12	11	12	
Vocalization					
None		12	11	12	
Reactivity to handling					
Easy		12	11	12	

Table 2-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	30	100
	No. of animals	12	11	12	0
Ease of removal from cage					
Easy		12	11	12	
Fur condition					
Normal		12	11	12	
Skin					
Normal		12	11	12	
Secretions-Eye, Nose					
Absent		12	11	12	
Exophthalmos					
Absent		12	11	12	
Palpebral closure					
Normal		12	11	12	
Mucosal membranes					
Normal		12	11	12	
Lacrimation					
Normal		12	11	12	
Piloerection					
Absent		12	11	12	
Pupil size					
Normal		12	11	12	
Salivation					
None		12	11	11	
Slight		0	0	1	
Abnormal respiration					
Absent		12	11	12	
Vocalization					
None		12	11	12	
Reactivity to handling					
Easy		12	11	12	

Table 2-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	30	100
	No. of animals	12	11	12	0
Ease of removal from cage					
Easy		12	11	12	
Fur condition					
Normal		12	11	12	
Skin					
Normal		12	11	12	
Secretions-Eye, Nose					
Absent		12	11	12	
Exophthalmos					
Absent		12	11	12	
Palpebral closure					
Normal		12	11	12	
Mucosal membranes					
Normal		12	11	12	
Lacrimation					
Normal		12	11	12	
Piloerection					
Absent		12	11	12	
Pupil size					
Normal		12	11	12	
Salivation					
None		12	11	12	
Abnormal respiration					
Absent		12	11	12	
Vocalization					
None		12	11	12	
Reactivity to handling					
Easy		12	11	12	

Table 2-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	30	100
	No. of animals	12	10	12	0
Ease of removal from cage					
Easy		12	10	12	
Fur condition					
Normal		12	10	12	
Skin					
Normal		12	10	12	
Secretions-Eye, Nose					
Absent		12	10	12	
Exophthalmos					
Absent		12	10	12	
Palpebral closure					
Normal		12	10	12	
Mucosal membranes					
Normal		12	10	12	
Lacrimation					
Normal		12	10	12	
Piloerection					
Absent		12	10	12	
Pupil size					
Normal		12	10	12	
Salivation					
None		12	10	12	
Abnormal respiration					
Absent		12	10	12	
Vocalization					
None		12	10	12	
Reactivity to handling					
Easy		12	10	12	

Table 2-31 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	100
	No. of animals	-----	-----
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 2-32 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	100
	No. of animals	-----	-----
Ease of removal from cage		10	4
Easy		10	2
Difficult		0	2
Fur condition			
Normal		10	2
Slight		0	2a)
Skin			
Normal		10	4
Secretions-Eye, Nose			
Absent		10	4
Exophthalmos			
Absent		10	4
Palpebral closure			
Normal		10	4
Mucosal membranes			
Normal		10	4
Lacrimation			
Normal		10	4
Piloerection			
Absent		10	4
Pupil size			
Normal		10	4
Salivation			
None		10	4
Abnormal respiration			
Absent		10	4
Vocalization			
None		10	4
Reactivity to handling			
Easy		10	4

a): Unkempt fur

Table 2-33 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	30
	No. of animals	-----	-----
Ease of removal from cage			
Easy		5	5
Fur condition			
Normal		5	5
Skin			
Normal		5	5
Secretions-Eye, Nose			
Absent		5	5
Exophthalmos			
Absent		5	5
Palpebral closure			
Normal		5	5
Mucosal membranes			
Normal		5	5
Lacrimation			
Normal		5	5
Piloerection			
Absent		5	5
Pupil size			
Normal		5	5
Salivation			
None		5	5
Abnormal respiration			
Absent		5	5
Vocalization			
None		5	5
Reactivity to handling			
Easy		5	5

Table 2-34 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	30
	No. of animals	-----	-----
Ease of removal from cage			
Easy		4	5
Some resistance/avoidance		1	0
Fur condition			
Normal		5	5
Skin			
Normal		5	5
Secretions-Eye, Nose			
Absent		5	5
Exophthalmos			
Absent		5	5
Palpebral closure			
Normal		5	5
Mucosal membranes			
Normal		5	5
Lacrimation			
Normal		5	5
Piloerection			
Absent		5	5
Pupil size			
Normal		5	5
Salivation			
None		5	5
Abnormal respiration			
Absent		5	5
Vocalization			
None		5	5
Reactivity to handling			
Easy		5	5

Table 2-35 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 1 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	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	12	12
Rearing (Mean±S.D.)		4± 1	4± 2	4± 2	3± 1
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	11	12	12
Small amount		1	1	0	0

No significant difference in any treated groups from control group.

Table 2-36 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 2 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	1
Arousal					
Normal		12	12	12	1
Convulsion					
None		12	12	12	1
Abnormal behavior					
None		12	12	12	1
Stereotypy					
None		12	12	12	1
Gait					
Normal		12	12	12	0
Slight		0	0	0	1a)
Posture					
Normal		12	12	12	1
Grooming					
None		12	12	12	1
Rearing (Mean±S.D.)		4± 2	4± 2	4± 2	5± 0
Defecation count (Mean±S.D.)		1± 1	0± 0	0± 0	0± 0
Urination					
None		11	9	11	1
Small amount		1	3	1	0

No significant difference in any treated groups from control group.

a): Ataxia

Table 2-37 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 3 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Arousal					
Normal		12	12	12	
Convulsion					
None		12	12	12	
Abnormal behavior					
None		12	12	12	
Stereotypy					
None		12	12	12	
Gait					
No/minimal location		1	0	0	
Normal		11	12	12	
Posture					
Normal		12	12	12	
Grooming					
None		12	12	12	
Rearing (Mean±S.D.)		4± 2	3± 2	3± 2	
Defecation count (Mean±S.D.)		0± 0	0± 1	0± 0	
Urination					
None		11	11	10	
Small amount		1	1	2	

No significant difference in any treated groups from control group.

Table 2-38 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 4 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Arousal					
Normal		12	12	12	
Convulsion					
None		12	12	12	
Abnormal behavior					
None		12	12	12	
Stereotypy					
None		12	12	12	
Gait					
Normal		12	12	12	
Posture					
Normal		12	12	12	
Grooming					
None		12	12	12	
Rearing (Mean±S.D.)		3± 2	4± 3	4± 1	
Defecation count (Mean±S.D.)		0± 1	0± 0	0± 0	
Urination					
None		9	11	11	
Small amount		3	1	1	

No significant difference in any treated groups from control group.

Table 2-39 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 5 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Arousal					
Normal		12	12	12	
Convulsion					
None		12	12	12	
Abnormal behavior					
None		12	12	12	
Stereotypy					
None		12	12	12	
Gait					
Normal		12	12	12	
Posture					
Normal		12	12	12	
Grooming					
None		12	12	12	
Rearing (Mean±S.D.)		4± 2	5± 2	4± 2	
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	
Urination					
None		8	10	11	
Small amount		4	2	1	

No significant difference in any treated groups from control group.

Table 2-40 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 6 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	12	12	0
Arousal					
Normal		12	12	12	
Convulsion					
None		12	12	12	
Abnormal behavior					
None		12	12	12	
Stereotypy					
None		12	12	12	
Gait					
No/minimal location		1	0	1	
Normal		11	12	11	
Posture					
Normal		12	12	12	
Grooming					
None		12	12	12	
Rearing (Mean±S.D.)		4± 2	4± 2	4± 2	
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	
Urination					
None		10	10	10	
Small amount		2	2	2	

No significant difference in any treated groups from control group.

Table 2-41 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	30	100
	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	10
Slight		0	0	0	2a)
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		7± 3	8± 2	8± 2	4± 2**D
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	12	12	11
Small amount		0	0	0	1

** : $p < 0.01$ (Significant difference from control group)

D: Dunnett's test

a): Ataxia

Table 2-42 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	30	100
	No. of animals	12	12	12	1
Arousal					
Normal		12	12	12	1
Convulsion					
None		12	12	12	1
Abnormal behavior					
None		12	12	12	1
Stereotypy					
None		12	12	12	1
Gait					
Normal		12	12	12	1
Posture					
Normal		12	12	12	1
Grooming					
None		12	12	12	1
Rearing (Mean±S.D.)		7± 3	7± 2	6± 2	4± 0
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	12	12	1

No significant difference in any treated groups from control group.

Table 2-43 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 1)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	11	12	0
Arousal					
Normal		12	11	12	
Convulsion					
None		12	11	12	
Abnormal behavior					
None		12	11	12	
Stereotypy					
None		12	11	12	
Gait					
Normal		12	11	12	
Posture					
Normal		12	11	12	
Grooming					
None		12	11	12	
Rearing (Mean±S.D.)		5± 2	6± 2	5± 3	
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	
Urination					
None		12	11	11	
Small amount		0	0	1	

No significant difference in any treated groups from control group.

Table 2-44 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 7)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	11	12	0
Arousal					
Normal		12	11	12	
Convulsion					
None		12	11	12	
Abnormal behavior					
None		12	11	12	
Stereotypy					
None		12	11	12	
Gait					
Normal		12	11	12	
Posture					
Normal		12	11	12	
Grooming					
None		12	11	12	
Rearing (Mean±S.D.)		5± 2	6± 1	4± 2	
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	
Urination					
None		12	11	12	

No significant difference in any treated groups from control group.

Table 2-45 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 14)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	11	12	0
Arousal					
Normal		12	11	12	
Convulsion					
None		12	11	12	
Abnormal behavior					
None		12	11	12	
Stereotypy					
None		12	11	12	
Gait					
Normal		12	11	12	
Posture					
Normal		12	11	12	
Grooming					
None		12	11	12	
Rearing (Mean±S.D.)		3± 2	5± 2*D	5± 2	
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	
Urination					
None		12	11	12	

*: p<0.05 (Significant difference from control group)

D: Dunnett's test

Table 2-46 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 20)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	11	12	0
Arousal					
Normal		12	11	12	
Convulsion					
None		12	11	12	
Abnormal behavior					
None		12	11	12	
Stereotypy					
None		12	11	12	
Gait					
Normal		12	11	12	
Posture					
Normal		12	11	12	
Grooming					
None		12	11	12	
Rearing (Mean±S.D.)		4± 1	5± 1	4± 1	
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	
Urination					
None		12	11	12	

No significant difference in any treated groups from control group.

Table 2-47 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	12	10	12	0
Arousal					
Normal		12	10	12	
Convulsion					
None		12	10	12	
Abnormal behavior					
None		12	10	12	
Stereotypy					
None		12	10	12	
Gait					
Normal		12	10	12	
Posture					
Normal		12	10	12	
Grooming					
None		12	10	12	
Rearing (Mean±S.D.)		6± 1	6± 2	7± 2	
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	
Urination					
None		12	9	12	
Small amount		0	1	0	

No significant difference in any treated groups from control group.

Table 2-48 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	100
	No. of animals	-----	-----
Arousal			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10
Stereotypy			
None		10	10
Gait			
Normal		10	9
Slight		0	1a)
Posture			
Normal		10	10
Grooming			
None		10	10
Rearing (Mean±S.D.)		6± 2	4± 1**T
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	10

** : p<0.01 (Significant difference from control group)

T: Student's t-test

a): Ataxia

Table 2-49 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	100
	No. of animals	-----	-----
Arousal			
Normal		10	4
Convulsion			
None		10	4
Abnormal behavior			
None		10	4
Stereotypy			
None		10	4
Gait			
Normal		10	0
Slight		0	4a)
Posture			
Normal		10	3
Flattened		0	1b)
Grooming			
None		10	4
Rearing (Mean±S.D.)		6± 1	2± 2**T
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	4

** : $p < 0.01$ (Significant difference from control group)

T: Student's t-test

a): Ataxia

b): Prone position

Table 2-50 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	30
	No. of animals	----- 5	----- 5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean±S.D.)		3± 3	3± 3
Defecation count (Mean±S.D.)		0± 1	0± 0
Urination			
None		3	5
Small amount		2	0

No significant difference between treated group and control group.

Table 2-51 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	30
	No. of animals	----- 5	----- 5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean±S.D.)		3± 2	4± 3
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		3	4
Small amount		2	1

No significant difference between treated group and control group.

Table 2-52 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Manipulative test of male rats (Week 6 of administration)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	5	5	5	0
Auditory response					
Normal		5	5	5	
Approach response					
Normal		5	5	5	
Touch response					
Normal		5	5	5	
Tail pinch response					
Normal		5	5	5	
Pupillary reflex					
Pass, both		5	5	5	
Aerial righting reflex					
(Total score: Mean±S.D.)		0± 0	0± 0	0± 0	
Landing foot splay (mm: Mean±S.D.)		93±18	70±20	82±27	

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 didec-1-yl(methyl)amine by oral administration in rats
Manipulative test of female rats (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	10	30	100
	No. of animals	5	5	5	0
Auditory response					
Normal		5	5	5	
Approach response					
Normal		5	5	5	
Touch response					
Normal		5	5	5	
Tail pinch response					
Normal		5	5	5	
Pupillary reflex					
Pass, both		5	5	5	
Aerial righting reflex					
(Total score: Mean±S.D.)		0± 0	0± 0	0± 0	
Landing foot splay (mm: Mean±S.D.)		60±10	69±21	56±13	

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 didec-1-yl(methyl)amine by oral administration in rats
Manipulative test of male rats (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	30
	No. of animals	-----	-----
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean±S.D.)		0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		86±16	71±24

No significant difference between treated group and control group.

Table 2-55 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	1552	943
	S.D.	71	76
10	No.	5	5
	Mean	1620	981
	S.D.	52	78
30	No.	5	5
	Mean	1520	933
	S.D.	370	74
100	No.	0	0
	Mean		
	S.D.		

No.: No. of animals

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 didec-1-yl(methyl)amine 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	1278	673
	S.D.	249	82
10	No.	5	5
	Mean	1328	826
	S.D.	123	150
30	No.	5	5
	Mean	1168	800
	S.D.	231	121
100	No.	0	0
	Mean		
	S.D.		

No.: No. of animals

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 didec-1-yl(methyl)amine 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	1790	1121
	S.D.	227	72
30	No.	5	5
	Mean	1829	1140
	S.D.	328	127

No.: No. of animals

No significant difference between treated group and control group.

Table 2-58 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	450	406	281	236	220	231	1824
	S.D.	31	60	110	147	122	167	514
10	No.	5	5	5	5	5	5	5
	Mean	406	353	304	297	291	248	1899
	S.D.	60	67	61	86	88	140	372
30	No.	5	5	5	5	5	5	5
	Mean	450	407	349	349	266	254	2076
	S.D.	36	47	59	114	118	134	477
100	No.	0	0	0	0	0	0	0
	Mean							
	S.D.							

Unit: Count

No.: No. of animals

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 didec-1-yl(methyl)amine 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	342	133	159	147	141	167	1089
	S.D.	108	134	145	156	118	128	628
10	No.	5	5	5	5	5	5	5
	Mean	372	171	209	249	204	130	1335
	S.D.	119	88	84	141	43	100	274
30	No.	5	5	5	5	5	5	5
	Mean	348	158	191	130	94	119	1040
	S.D.	74	102	68	118	151	152	526
100	No.	0	0	0	0	0	0	0
	Mean							
	S.D.							

Unit: Count

No.: No. of animals

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 didec-1-yl(methyl)amine by oral administration in rats
Motor activity of male rats (Week 2 of recovery)

Dose mg/kg	Interval (minutes)							Total(0-60)
	0-10	10-20	20-30	30-40	40-50	50-60		
0	No.	5	5	5	5	5	5	5
	Mean	446	354	290	240	248	193	1771
	S.D.	38	41	87	137	121	54	289
30	No.	5	5	5	5	5	5	5
	Mean	378	300	222	218	231	155	1504
	S.D.	69	67	51	45	79	52	242

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 didec-1-yl(methyl)amine by oral administration in rats
Body weight of male rats (Administration period)

Dose mg/kg		Day of administration							Gain 1-42
		1	8	15	22	29	36	42	
0	No.	12	12	12	12	12	12	12	12
	Mean	388	416	438	458	478	499	510	122
	S.D.	14	21	22	27	28	32	36	27
10	No.	12	12	12	12	12	12	12	12
	Mean	389	414	439	460	479	496	507	118
	S.D.	14	17	21	19	25	27	32	22
30	No.	12	12	12	12	12	12	12	12
	Mean	387	409	428	442	458	476	488	101*
	S.D.	13	14	16	15	19	21	24	15D
100	No.	12	8	0a)					
	Mean	390	310**						
	S.D.	15	30D						

Unit: g

No.: No. of animals

a): One animal died and eleven animals were sacrificed by day 11 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 didec-1-yl(methyl)amine by oral administration in rats
Body weight of female rats during the pre-mating period (Main group)

Dose mg/kg		Day of administration			Gain 1-15
		1	8	15	
0	No.	12	12	12	12
	Mean	243	255	264	21
	S.D.	15	15	15	5
10	No.	12	12	12	12
	Mean	241	253	261	21
	S.D.	11	15	15	8
30	No.	12	12	12	12
	Mean	242	248	255	13*
	S.D.	16	17	19	9D
100	No.	12	7	0a)	
	Mean	243	213**		
	S.D.	12	26D		

Unit: g

No.: No. of animals

a): Three animals died and nine animals were sacrificed by day 12 of administration.

*: $p < 0.05$; **: $p < 0.01$ (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 didec-1-yl(methyl)amine by oral administration in rats
Body weight of dams during the gestation period (Main group)

Dose mg/kg		Administration				Gain 0-20
		0	7	14	20a)	
0	No.	12	12	12	12	12
	Mean	269	301	334	409	140
	S.D.	17	21	23	34	29
10	No.	11	11	11	11	11
	Mean	270	303	339	417	147
	S.D.	15	16	20	22	12
30	No.	12	12	12	12	12
	Mean	259	294	333	409	150
	S.D.	18	19	24	33	19
100	No.	0				
	Mean					
	S.D.					

Unit: g

No.: No. of dams

a): Gestation day

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 didec-1-yl(methyl)amine by oral administration in rats
Body weight of dams during the lactation period (Main group)

Dose mg/kg		Administration		Gain 0-4
		0	4a)	
0	No.	12	12	12
	Mean	317	326	9
	S.D.	29	23	18
10	No.	10b)	10	10
	Mean	326	333	7
	S.D.	25	20	11
30	No.	12	12	12
	Mean	322	337	15
	S.D.	22	23	15
100	No.	0		
	Mean			
	S.D.			

Unit: g

No.: No. of dams

a): Lactation day

b): One dam died on gestation day 22.

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 didec-1-yl(methyl)amine by oral administration in rats
Body weight of female rats (Satellite group)

Dose mg/kg		Day of administration			Gain 1-15
		1	8	15	
0	No.	10	10	10	10
	Mean	244	256	263	20
	S.D.	17	15	17	7
100	No.	10	8	0a)	
	Mean	238	202**		
	S.D.	14	20T		

Unit: g

No.: No. of animals

a): Three animals died and seven animals were sacrificed by day 12 of administration.

** : $p < 0.01$ (Significant difference from control group)

T: Student's t-test

Table 3-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Body weight of male rats (Recovery period)

Dose mg/kg		Day of recovery			Gain 1-14
		1	8	14	
0	No.	5	5	5	5
	Mean	513	522	526	13
	S.D.	43	45	43	5
30	No.	5	5	5	5
	Mean	486	498	508	22**
	S.D.	13	14	11	4T

Unit: g

No.: No. of animals

** : $p < 0.01$ (Significant difference from control group)

T: Student's t-test

Table 4-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	23	25	24	23	24	23
	S.D.	3	3	3	5	2	2
10	No.	12	12	12	12	12	12
	Mean	25	23	23	23	23	23
	S.D.	3	2	2	3	3	3
30	No.	12	12	12	12	12	12
	Mean	24	24	23	22	25	24
	S.D.	2	3	2	2	2	3
100	No.	12	8	0a)			
	Mean	19**	6**				
	S.D.	4D	4D				

Unit: g/rat/day

No.: No. of animals

a): One animal died and eleven animals were sacrificed by day 11 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 didec-1-yl(methyl)amine 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	12
	Mean	17	19	19
	S.D.	2	3	2
10	No.	12	12	12
	Mean	16	19	20
	S.D.	3	3	1
30	No.	12	12	12
	Mean	16	17	18
	S.D.	2	3	3
100	No.	12	7	0a)
	Mean	13**	8**	
	S.D.	2D	7D	

Unit: g/rat/day

No.: No. of animals

a): Three animals died and nine animals were sacrificed by day 12 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 didec-1-yl(methyl)amine 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.	12	12	12	12
	Mean	18	22	22	20
	S.D.	4	2	2	3
10	No.	11	11	11	11
	Mean	20	23	23	20
	S.D.	3	2	2	2
30	No.	12	12	12	12
	Mean	20	23	25	21
	S.D.	4	3	4	4
100	No.	0			
	Mean				
	S.D.				

Unit: g/rat/day

No.: No. of dams

a): Gestation day

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 didec-1-yl(methyl)amine by oral administration in rats
Food consumption of dams during the lactation period (Main group)

Dose mg/kg		Administration	
		2	4a)
0	No.	12	12
	Mean	16	32
	S.D.	9	9
10	No.	10b)	10
	Mean	18	35
	S.D.	8	5
30	No.	12	12
	Mean	23	37
	S.D.	5	7
100	No.	0	
	Mean		
	S.D.		

Unit: g/rat/day

No.: No. of dams

a): Lactation day

b): One dam died on gestation day 22.

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 didec-1-yl(methyl)amine by oral administration in rats
Food consumption of female rats (Satellite group)

Dose mg/kg		Day of administration		
		2	8	15
0	No.	10	10	10
	Mean	18	19	19
	S.D.	3	3	2
100	No.	10	8	0a)
	Mean	13**	4**	
	S.D.	3T	4T	

Unit: g/rat/day

No.: No. of animals

a): Three animals died and seven animals were sacrificed by day 12 of administration.

** : $p < 0.01$ (Significant difference from control group)

T: Student's t-test

Table 4-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	24	30	30
	S.D.	3	2	3
30	No.	5	5	5
	Mean	23	30	29
	S.D.	1	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 didec-1-yl(methyl)amine by oral administration in rats
Urinalysis of male rats (Week 6 of administration)

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	0	0	0	1	3	0	1	0	1	0	4	0	0	1	2	2	0	5	0	0	0	0	
10	5	0	0	0	0	1	0	0	2	2	0	1	1	3	0	1	0	2	1	1	5	0	0	0	0	
30	5	0	0	0	0	0	1	2	2	0	1	0	4	0	0	0	1	4	0	0	5	0	0	0	0	
100	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 didec-1-yl(methyl)amine 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
0	5	4	1	0	0	0	2	3	0	0	2	3	0	0	0	5	0	0
10	5	3	2	0	0	0	3	2	0	0	4	1	0	0	0	5	0	0
30	5	2	3	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0
100	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

Table 5-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	URINE SEDIMENT																																
		RBC					WBC					CRYSTALLIZATION																						
		SEC					SREC					Cast																						
PS					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	1	4	0	0	0	5	0	0	0	0
10	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	1	4	0	0	0	5	0	0	0	0
30	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	1	4	0	0	0	5	0	0	0	0
100	0																																	

SEC : Squamous Epithelial Cell - : Negative
 SREC : Small Round Epithelial Cell +- : Slight
 PS : Phosphate Salts + : Mild
 CO : Calcium Oxalate ++ : Moderate
 +++ : Severe

Table 5-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	31	7.6	2437	0.96	3.04	1.19
		S.D.	5	2.3	203	0.19	0.74	0.27
10	5	Mean	35	8.5	2104	0.64	2.39	0.81
		S.D.	10	6.7	659	0.27	1.12	0.35
30	5	Mean	41	12.1	1798	1.12	3.51	1.37
		S.D.	6	3.3	286	0.33	0.59	0.27
100	0	Mean						
		S.D.						

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 didec-1-yl(methyl)amine by oral administration in rats
Urinalysis of male 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	0	1	2	0	0	1	1	0	0	2	3	0	0	0	5	0	0	5	0	0	0	0
30	5	0	0	0	0	0	0	1	4	0	0	3	2	0	0	1	1	3	0	0	5	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 didec-1-yl(methyl)amine 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
0	5	2	3	0	0	0	4	1	0	0	4	1	0	0	0	5	0
30	5	1	4	0	0	0	5	0	0	0	5	0	0	0	0	5	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

Table 5-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	URINE SEDIMENT										CRYSTALLIZATION																						
		RBC			WBC			SEC			SREC			Cast			PS			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	4	1	0	0	5	0	0	0	0
30	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	5	0	0	0	0

SEC : Squamous Epithelial Cell - : Negative
 SREC : Small Round Epithelial Cell +- : Slight
 PS : Phosphate Salts + : Mild
 CO : Calcium Oxalate ++ : Moderate
 +++ : Severe

Table 5-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	37	10.4	2450	1.27	3.87	1.64
		S.D.	6	3.3	508	0.18	0.52	0.18
30	5	Mean	42	15.7*	2099	1.77*	5.49**	2.38**
		S.D.	5	2.9T	217	0.38T	0.93T	0.37T

*: p<0.05; **: p<0.01 (Significant difference from control group)

T: Student's t-test

Table 6-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Hematology of female rats (Satellite group, Day 15 of administration)

Dose mg/kg	No.		RBC	HGB	HCT	MCV	MCH	MCHC	Retic	PLT	PT	APTT	FIB
			10E4/ μ L	g/dL	%	fL	pg	g/dL	%	10E4/ μ L	s	s	mg/dL
0	10	Mean	832	15.5	44.8	53.8	18.6	34.6	2.2	102.5	11.5	17.4	206
		S.D.	32	0.4	1.4	1.5	0.5	0.4	0.5	9.3	0.3	1.9	17
100	0	Mean											
		S.D.											

Table 6-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Hematology of female rats (Satellite group, Day 15 of administration)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)					Differential leukocyte counts (10E2/ μ L)						
			10E2/ μ L	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	10	Mean	72.2	71.9	23.3	1.6	0.3	1.9	1.1	52.1	16.6	1.2	0.2	1.4	0.8
		S.D.	17.5	5.1	5.3	0.4	0.1	0.4	0.4	13.8	4.9	0.4	0.1	0.5	0.4
100	0	Mean													
		S.D.													

LUC: Large unstained cells

Table 6-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Hematology of male rats (End of administration)

Dose mg/kg	No.		RBC	HGB	HCT	MCV	MCH	MCHC	Retic	PLT	PT	APTT	FIB
			10E4/ μ L	g/dL	%	fL	pg	g/dL	%	10E4/ μ L	s	s	mg/dL
0	5	Mean	883	15.8	45.5	51.5	17.9	34.7	2.1	99.9	14.3	20.9	258
		S.D.	24	0.2	0.8	1.1	0.4	0.3	0.4	5.0	2.0	3.6	27
10	5	Mean	881	15.4*	44.4*	50.3	17.5	34.7	1.9	111.6	15.0	21.4	260
		S.D.	13	0.2D	0.7D	0.7	0.3	0.4	0.3	11.8	2.9	4.3	22
30	5	Mean	873	15.1**	43.4**	49.7*	17.3*	34.9	1.7	102.3	15.8	19.2	410
		S.D.	9	0.2D	0.4D	0.6D	0.2D	0.5	0.5	9.4	2.9	4.0	322
100	0	Mean											
		S.D.											

*: p<0.05; **: p<0.01 (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 didec-1-yl(methyl)amine by oral administration in rats
Hematology of male rats (End of administration)

Dose mg/kg	No.		WBC 10E2/ μ L	Differential leukocyte ratio (%)					Differential leukocyte counts (10E2/ μ L)						
				Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	76.1	75.3	20.9	1.2	0.2	2.0	0.4	57.2	16.0	0.9	0.2	1.5	0.3
		S.D.	20.5	6.0	5.8	0.3	0.1	0.5	0.1	15.3	6.4	0.2	0.1	0.5	0.1
10	5	Mean	61.5	70.4	25.2	1.8	0.2	1.9	0.5	43.3	15.5	1.1	0.1	1.2	0.3
		S.D.	16.7	9.0	8.9	0.7	0.0	0.3	0.2	13.6	6.7	0.6	0.1	0.4	0.2
30	5	Mean	98.8	59.8	35.1	1.0	0.2	2.2	1.6	49.9	42.4	0.8	0.2	2.7	2.8
		S.D.	58.7	22.5	19.5	0.4	0.1	1.1	2.5	10.4	51.7	0.2	0.1	3.2	5.4
100	0	Mean													
		S.D.													

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 didec-1-yl(methyl)amine by oral administration in rats
Hematology of female rats (Lactation day 5)

Dose mg/kg	No.		RBC	HGB	HCT	MCV	MCH	MCHC	Retic	PLT	PT	APTT	FIB
			10E4/ μ L	g/dL	%	fL	pg	g/dL	%	10E4/ μ L	s	s	mg/dL
0	5	Mean	721	13.4	39.3	54.5	18.5	34.0	6.9	136.9	11.6	13.4	299
		S.D.	46	0.8	2.6	0.7	0.3	0.5	2.0	17.9	0.4	1.1	104
10	5	Mean	745	13.7	40.0	53.6	18.4	34.3	5.9	149.3	11.8	15.6	293
		S.D.	31	0.8	2.3	1.4	0.7	0.6	1.2	27.6	0.4	1.1	22
30	5	Mean	741	13.7	40.5	54.6	18.6	33.9	6.5	143.9	12.4*	15.5	276
		S.D.	12	0.2	0.9	1.0	0.4	0.6	0.5	15.9	0.5D	2.0	56
100	0	Mean											
		S.D.											

*: p<0.05 (Significant difference from control group)

D: Dunnett's test

Table 6-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Hematology of female rats (Lactation day 5)

Dose mg/kg	No.		WBC 10E2/ μ L	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/ μ L)					
				Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	96.1	55.7	40.6	0.6	0.1	2.1	0.8	52.3	40.6	0.5	0.2	1.8	0.7
		S.D.	24.6	8.9	9.8	0.2	0.1	0.8	0.5	10.0	17.4	0.2	0.1	0.3	0.3
10	5	Mean	105.5	57.6	38.8	0.8	0.2	1.9	0.7	59.3	42.2	0.7	0.3	2.2	0.9
		S.D.	44.0	5.5	5.2	0.4	0.1	0.6	0.3	22.0	20.6	0.2	0.2	1.2	0.6
30	5	Mean	124.7	59.7	35.8	0.7	0.2	2.7	1.0	74.8	44.3	0.8	0.3	3.3	1.1
		S.D.	37.2	7.9	8.7	0.2	0.1	0.6	0.5	25.0	13.8	0.4	0.2	1.0	0.7
100	0	Mean													
		S.D.													

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

Table 6-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Hematology of male rats (End of recovery)

Dose mg/kg	No.		RBC	HGB	HCT	MCV	MCH	MCHC	Retic	PLT	PT	APTT	FIB
			10E4/ μ L	g/dL	%	fL	pg	g/dL	%	10E4/ μ L	s	s	mg/dL
0	5	Mean	909	15.8	45.8	50.3	17.4	34.5	1.7	99.8	16.9	19.5	301
		S.D.	32	0.6	2.3	1.6	0.5	0.4	0.2	15.2	1.9	3.3	33
30	5	Mean	923	15.8	45.5	49.4	17.1	34.7	1.6	108.1	16.0	19.8	283
		S.D.	51	0.6	1.8	2.5	1.0	0.5	0.2	11.0	1.8	3.4	14

No significant difference between treated group and control group.

Table 6-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Hematology of male rats (End of recovery)

Dose mg/kg	No.		WBC 10E2/ μ L	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/ μ L)					
				Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	83.8	75.1	20.1	1.6	0.3	2.3	0.6	62.6	17.4	1.2	0.3	1.9	0.4
		S.D.	24.7	6.4	6.5	0.6	0.0	0.4	0.3	17.1	10.3	0.3	0.1	0.5	0.2
30	5	Mean	94.7	80.2	15.6	1.3	0.4	2.0	0.5	77.4	13.3	1.2	0.4	2.0	0.5
		S.D.	34.0	5.6	5.7	0.3	0.1	0.2	0.1	31.5	2.3	0.5	0.2	0.8	0.2

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 didec-1-yl(methyl)amine by oral administration in rats
Blood chemistry of female rats (Satellite group, Day 15 of administration)

Dose mg/kg	No.		AST	ALT	LDH	r-GTP	ALP	TBA	T-CHO	TG	PL	T-BIL	GLU
			IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
0	10	Mean	64	28	47	1	305	11.3	49	13	97	0.1	133
		S.D.	6	5	7	0	70	3.9	8	5	14	0.0	15
100	0	Mean											
		S.D.											

Table 7-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Blood chemistry of female rats (Satellite group, Day 15 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	10	Mean	15	0.30	142	4.3	106	9.9	5.2	6.1	3.6	1.46
		S.D.	2	0.03	1	0.2	2	0.2	0.6	0.2	0.1	0.12
100	0	Mean										
		S.D.										

Table 7-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Blood chemistry of male rats (End of administration)

Dose mg/kg	No.		AST	ALT	LDH	r-GTP	ALP	TBA	T-CHO	TG	PL	T-BIL	GLU
			IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
0	5	Mean	64	28	51	1	444	14.3	45	21	75	0.1	149
		S.D.	7	2	12	0	121	8.0	7	7	7	0.0	8
10	5	Mean	66	31	57	1	433	6.3	52	23	82	0.1	152
		S.D.	7	4	19	1	45	2.7	9	14	9	0.0	16
30	5	Mean	61	31	47	1	438	13.9	53	29	90*	0.1	144
		S.D.	6	4	13	0	45	7.3	4	13	5D	0.0	4
100	0	Mean											
		S.D.											

*: p<0.05 (Significant difference from control group)

D: Dunnett's test

Table 7-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	13	0.25	143	4.7	106	9.5	5.7	5.6	3.2	1.30
		S.D.	1	0.03	1	0.2	2	0.2	0.4	0.1	0.1	0.06
10	5	Mean	13	0.26	143	4.4	107	9.6	5.8	5.7	3.1	1.23
		S.D.	2	0.03	1	0.3	2	0.4	0.5	0.2	0.1	0.05
30	5	Mean	13	0.26	143	4.6	106	10.0	5.9	5.9	3.1	1.12
		S.D.	2	0.05	0	0.2	2	0.4	0.5	0.2	0.3	0.22
100	0	Mean										
		S.D.										

No significant difference in any treated groups from control group.

Table 7-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Blood chemistry of female rats (Lactation day 5)

Dose mg/kg	No.		AST	ALT	LDH	r-GTP	ALP	TBA	T-CHO	TG	PL	T-BIL	GLU
			IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
0	5	Mean	98	55	39	1	222	10.8	62	34	111	0.1	130
		S.D.	30	22	8	0	93	2.8	20	13	29	0.0	7
10	5	Mean	75	44	44	1	227	8.3	51	26	99	0.1	122
		S.D.	12	13	7	0	89	2.0	7	6	13	0.1	9
30	5	Mean	85	50	46	1	246	14.7	54	38	111	0.1	125
		S.D.	21	6	9	0	37	7.6	19	12	37	0.0	5
100	0	Mean											
		S.D.											

No significant difference in any treated groups from control group.

Table 7-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	12	0.29	141	3.9	105	10.2	7.0	5.9	3.3	1.27
		S.D.	2	0.04	1	0.3	2	0.3	0.9	0.2	0.2	0.08
10	5	Mean	14	0.26	142	4.2	107	10.0	6.8	5.9	3.4	1.38
		S.D.	1	0.04	2	0.4	2	0.2	1.0	0.1	0.2	0.16
30	5	Mean	15*	0.26	141	4.4	107	10.1	6.6	5.9	3.3	1.32
		S.D.	2D	0.01	1	0.4	3	0.2	0.7	0.2	0.2	0.13
100	0	Mean										
		S.D.										

*: p<0.05 (Significant difference from control group)

D: Dunnett's test

Table 7-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Blood chemistry of male rats (End of recovery)

Dose mg/kg	No.		AST	ALT	LDH	r-GTP	ALP	TBA	T-CHO	TG	PL	T-BIL	GLU
			IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
0	5	Mean	58	30	40	1	341	7.9	48	37	83	0.1	143
		S.D.	8	3	5	0	67	2.5	9	19	13	0.0	18
30	5	Mean	74	41	51	2	399	27.6*	48	35	81	0.1	137
		S.D.	23	11	29	1	87	14.0AT	8	14	11	0.0	13

*: p<0.05 (Significant difference from control group)

AT: Aspin-Welch t-test

Table 7-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	15	0.24	141	4.4	105	9.4	5.7	5.8	3.1	1.18
		S.D.	1	0.03	1	0.1	1	0.2	0.3	0.2	0.0	0.09
30	5	Mean	15	0.23	142	4.5	105	9.7	5.9	6.0	3.3**	1.23
		S.D.	1	0.02	2	0.0	2	0.1	0.2	0.2	0.0T	0.14

** : p<0.01 (Significant difference from control group)

T: Student's t-test

Table 8-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Organ weight of male rats (End of administration)

Dose mg/kg		Body weight g	Brain	Pituitary	Thyroid (R+L)	Thymus	Heart	Liver	
			g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)	
Absolute	0	No.	7	7	7	7	7	7	
		Mean	483	2.10	13.0	21.4	299	1.41	12.54
		S.D.	30	0.08	1.5	3.5	42	0.09	1.18
	10	No.	12	12	12	12	12	12	12
		Mean	483	2.13	13.4	21.9	311	1.38	12.11
		S.D.	30	0.07	1.5	3.3	108	0.10	1.32
	30	No.	7	7	7	7	7	7	7
		Mean	466	2.05	13.0	20.2	266	1.43	12.49
		S.D.	28	0.08	1.9	1.9	50	0.19	1.67
	100	No.	0						
		Mean							
		S.D.							
Relative	0	No.	7	7	7	7	7	7	
		Mean	0.44	2.7	4.4	62	0.29	2.60	
		S.D.	0.02	0.3	0.7	9	0.03	0.17	
	10	No.	12	12	12	12	12	12	
		Mean	0.44	2.8	4.5	64	0.29	2.50	
		S.D.	0.03	0.3	0.7	22	0.01	0.16	
	30	No.	7	7	7	7	7	7	
		Mean	0.44	2.8	4.3	57	0.31	2.68	
		S.D.	0.02	0.3	0.5	10	0.03	0.29	
	100	No.							
		Mean							
		S.D.							

No significant difference in any treated groups from control group.

Table 8-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Organ weight of male rats (End of administration)

Dose mg/kg		Spleen	Kidney (R+L)	Adrenal (R+L)	Testis (R+L)	Epididymis (R+L)	Seminal vesicle	Prostate	
		g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)	
Absolute	0	No.	7	7	7	7	7	7	
		Mean	0.73	3.22	62	3.14	1236	1.72	1.32
		S.D.	0.11	0.27	6	0.14	79	0.25	0.13
	10	No.	12	12	12	12	12	12	12
		Mean	0.69	3.16	68	3.24	1302	1.77	1.32
		S.D.	0.10	0.38	9	0.18	119	0.26	0.17
	30	No.	7	7	7	7	7	7	7
		Mean	0.73	3.15	61	3.20	1280	1.67	1.36
		S.D.	0.14	0.21	9	0.15	76	0.37	0.14
	100	No.							
		Mean							
		S.D.							
Relative	0	No.	7	7	7	7	7	7	
		Mean	0.15	0.67	13	0.65	257	0.36	0.27
		S.D.	0.02	0.06	2	0.05	28	0.06	0.04
	10	No.	12	12	12	12	12	12	12
		Mean	0.14	0.65	14	0.67	270	0.37	0.27
		S.D.	0.02	0.07	2	0.06	28	0.06	0.03
	30	No.	7	7	7	7	7	7	7
		Mean	0.16	0.68	13	0.69	276	0.36	0.29
		S.D.	0.03	0.05	2	0.04	21	0.10	0.04
	100	No.							
		Mean							
		S.D.							

No significant difference in any treated groups from control group.

Table 8-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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)		
								No.	Mean
Absolute	0	No.	12	12	12	12	12	12	
		Mean	305	1.95	16.8	17.4	199	1.00	10.10
		S.D.	20	0.08	2.0	2.5	83	0.11	1.06
	10	No.	10	10	10	10	10	10	10
		Mean	306	1.97	17.3	17.3	192	1.03	10.26
		S.D.	19	0.05	1.4	2.3	66	0.09	0.90
	30	No.	12	12	12	12	12	12	12
		Mean	303	1.96	17.0	17.5	197	1.04	10.65
		S.D.	20	0.06	1.7	3.3	59	0.11	1.26
	100	No.	0						
		Mean							
		S.D.							
Relative	0	No.	12	12	12	12	12	12	
		Mean	0.64	5.5	5.7	65	0.33	3.31	
		S.D.	0.04	0.5	0.8	25	0.02	0.30	
	10	No.	10	10	10	10	10	10	10
		Mean	0.65	5.7	5.6	63	0.34	3.35	
		S.D.	0.04	0.6	0.7	22	0.04	0.22	
	30	No.	12	12	12	12	12	12	12
		Mean	0.65	5.6	5.8	65	0.34	3.52	
		S.D.	0.04	0.6	0.8	19	0.02	0.29	
	100	No.							
		Mean							
		S.D.							

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 didec-1-yl(methyl)amine by oral administration in rats
Organ weight of female rats (Main group, End of administration)

Dose mg/kg		Spleen	Kidney (R+L)	Adrenal (R+L)	Ovary (R+L)	Uterus	
		g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	
Absolute	0	No.	12	12	12	12	
		Mean	0.69	2.02	76	109.4	672
		S.D.	0.16	0.18	11	14.4	99
	10	No.	10	10	10	10	10
		Mean	0.61	2.11	85	109.8	705
		S.D.	0.08	0.18	10	16.6	129
	30	No.	12	12	12	12	12
		Mean	0.69	2.10	86	100.9	683
		S.D.	0.14	0.18	14	15.0	92
	100	No.					
		Mean					
		S.D.					
Relative	0	No.	12	12	12	12	
		Mean	0.23	0.66	25	35.9	221
		S.D.	0.05	0.04	4	4.0	33
	10	No.	10	10	10	10	10
		Mean	0.20	0.69	28	36.0	230
		S.D.	0.03	0.04	4	5.1	38
	30	No.	12	12	12	12	12
		Mean	0.23	0.70	28	33.3	225
		S.D.	0.04	0.05	4	4.3	20
	100	No.					
		Mean					
		S.D.					

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 didec-1-yl(methyl)amine by oral administration in rats
Organ weight of female rats (Satellite group, End of administration)

Dose		Body weight	Brain	Pituitary	Thyroid (R+L)	Thymus	Heart	Liver	
mg/kg		g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)	
Absolute	0	No.	10	10	10	10	10	10	
		Mean	249	1.92	17.5	19.6	366	0.87	7.07
		S.D.	16	0.04	2.2	3.5	86	0.12	0.67
	100	No.	0						
		Mean							
		S.D.							
Relative	0	No.		10	10	10	10	10	
		Mean		0.77	7.1	7.9	146	0.35	2.84
		S.D.		0.06	1.1	1.1	27	0.03	0.17
	100	No.							
		Mean							
		S.D.							

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

Dose			Spleen	Kidney	Adrenal	Ovary	Uterus
mg/kg			g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
Absolute	0	No.	10	10	10	10	10
		Mean	0.49	1.77	73	95.2	574
		S.D.	0.05	0.16	11	15.3	134
	100	No.					
		Mean					
		S.D.					
Relative	0	No.	10	10	10	10	10
		Mean	0.20	0.71	29	38.2	232
		S.D.	0.02	0.06	4	5.2	59
	100	No.					
		Mean					
		S.D.					

Table 8-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Organ weight of male rats (End of recovery)

Dose		Body weight	Brain	Pituitary	Thyroid (R+L)	Thymus	Heart	Liver	
mg/kg		g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)	
Absolute	0	No.	5	5	5	5	5	5	
		Mean	499	2.12	13.5	21.6	256	1.46	12.20
		S.D.	45	0.10	1.5	4.1	36	0.12	1.53
	30	No.	5	5	5	5	5	5	5
		Mean	477	2.09	11.8	19.0	250	1.48	11.97
		S.D.	13	0.11	0.9	5.1	60	0.17	0.62
Relative	0	No.		5	5	5	5	5	
		Mean		0.43	2.7	4.3	52	0.29	2.44
		S.D.		0.03	0.4	0.5	9	0.03	0.10
	30	No.		5	5	5	5	5	5
		Mean		0.44	2.5	4.0	52	0.31	2.51
		S.D.		0.03	0.2	1.1	13	0.03	0.08

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 didec-1-yl(methyl)amine by oral administration in rats
Organ weight of male rats (End of recovery)

Dose mg/kg		Spleen	Kidney	Adrenal	Testis	Epididymis	Seminal vesicle	Prostate	
		g(g/100g BW)	g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)	mg(mg/100g BW)	g(g/100g BW)	g(g/100g BW)	
Absolute	0	No.	5	5	5	5	5	5	
		Mean	0.70	3.25	61	3.19	1314	2.03	1.48
		S.D.	0.04	0.19	10	0.42	85	0.28	0.29
	30	No.	5	5	5	5	5	5	5
		Mean	0.72	3.35	52	3.26	1342	1.77	1.40
		S.D.	0.09	0.19	6	0.26	73	0.26	0.26
Relative	0	No.	5	5	5	5	5	5	
		Mean	0.14	0.65	12	0.64	265	0.41	0.30
		S.D.	0.02	0.05	3	0.12	33	0.08	0.07
	30	No.	5	5	5	5	5	5	5
		Mean	0.15	0.70	11	0.68	281	0.37	0.29
		S.D.	0.02	0.05	1	0.06	17	0.06	0.06

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 didec-1-yl(methyl)amine by oral administration in rats
Gross pathological findings (End of administration period (D42))

Organs	Sex:	M	M	M
	Dose (mg/kg) :	0	10	30
Findings	Number:	7	12	7
Epididymis				
Focus, white		0	1	0
Lung (bronchus)				
Focus, dark red		0	2	0
Spleen				
Focus, white		0	0	1

M : Male

Table 9-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Gross pathological findings (End of administration period (D15))

Organs	Sex:	F
	Dose (mg/kg):	0
Findings	Number:	10
All tissues		
Not remarkable		10

F : Female

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

Organs	Sex:	F	F	F
	Dose (mg/kg) :	0	10	30
Findings	Number:	12	10	12
Stomach				
Focus, raised		0	1	0
Focus, dark red, glandular stomach		0	2	3

F : Female

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

Organs	Sex:	M	M
	Dose (mg/kg):	0	30
Findings	Number:	5	5
All tissues			
Not remarkable		5	5

M : Male

Table 9-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Gross pathological findings (Not copulated)

Organs	Sex:	F
	Dose (mg/kg):	10
Findings	Number:	1
All tissues		
Not remarkable		1

F : Female

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

Organs	Sex:	M
Findings	Dose (mg/kg) :	100
	Number:	12
General descriptions		
Undernourishment		6
Smudge, fur		9
Heart		
Focus, white		1
Kidney		
Focus, white		1
Spleen		
Small		7
Stomach		
Distention		3
Focus, white, forestomach		8
Thymus		
Small		10
Urinary bladder		
Distention		3
Forelimb		
Swelling		1
Subcutis		
Focus, dark red		1

M : Male

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

Organs	Sex:	F	F
Findings	Dose (mg/kg) :	10	100
	Number:	1	22
General descriptions			
Undernourishment		0	18
Smudge, fur		0	4
Retention, aminion, oral cavity		1	0
Lung (bronchus)			
Discoloration, dark red		1	0
Focus, dark red		0	1
Spleen			
Small		0	10
Stomach			
Distention		0	5
Focus, white, forestomach		0	7
Thymus			
Small		0	17
Trachea			
Retention, foamy fluid		1	0
Uterus			
Small		0	1
Thoracic cavity			
Excess fluid		1	0

F : Female

Table 10-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	M	M	M
Findings	Dose (mg/kg):	0	10	30
	Number:	7	12	7
Adrenal				
Number examined		5	5	5
Not remarkable		5	5	5
Bone+Bone marrow, femoral				
Number examined		5	5	5
Not remarkable		5	5	5
Cerebellum(Pons)				
Number examined		5	1	5
Not remarkable		5	1	5
Cerebrum				
Number examined		5	1	5
Not remarkable		5	1	5
Epididymis				
Number examined		5	1	5
Not remarkable		4	1	5
Hypospermia		1	0	0
minimal		1	0	0
Cell debris, luminal		1	0	0
mild		1	0	0
Eye				
Number examined		5	1	5
Not remarkable		5	1	5
Heart				
Number examined		5	5	5
Not remarkable		3	2	4
Myocarditis, focal		2	3	1
minimal		2	3	1
Intestine, duodenum				
Number examined		5	1	5
Not remarkable		5	1	5
Intestine, jejunum				
Number examined		5	5	5
Not remarkable		5	5	5
Intestine, ileum(Peyer's patch)				
Number examined		5	5	5
Not remarkable		5	5	5
Intestine, cecum				
Number examined		5	5	5
Not remarkable		4	4	5
Cell infiltration		1	1	0
mild		1	1	0
Decrease, goblet cell		1	1	0
mild		1	1	0
Intestine, colon				
Number examined		5	5	5
Not remarkable		5	5	5
Intestine, rectum				
Number examined		5	5	5
Not remarkable		5	5	5

M : Male

Table 10-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	M	M	M
	Dose (mg/kg) :	0	10	30
Findings	Number:	7	12	7
Kidney				
Number examined		5	1	5
Not remarkable		3	1	3
Cyst		0	0	1
minimal		0	0	1
Regeneration, tubular		2	0	1
minimal		2	0	1
Liver				
Number examined		5	1	5
Not remarkable		0	0	1
Microgranuloma		5	1	4
minimal		5	1	4
Lung (bronchus)				
Number examined		5	1	5
Not remarkable		2	0	3
Hemorrhage, focal		2	0	0
minimal		2	0	0
Cell infiltration		0	0	1
mild		0	0	1
Aggregation, alveolar macrophage		2	1	1
minimal		2	1	1
Lymph node, mesenteric				
Number examined		5	5	5
Not remarkable		5	5	5
Lymph node, submandibular				
Number examined		5	5	5
Not remarkable		5	5	5
Pancreas				
Number examined		5	1	5
Not remarkable		5	1	5
Parathyroid				
Number examined		5	1	5
Not remarkable		5	1	5
Pituitary				
Number examined		5	1	5
Not remarkable		5	1	5
Prostate				
Number examined		5	5	5
Not remarkable		2	3	5
Cell infiltration		3	2	0
minimal		2	2	0
mild		1	0	0
Salivary gland, submandibular				
Number examined		5	1	5
Not remarkable		5	1	5
Sciatic nerve				
Number examined		5	1	5
Not remarkable		5	1	5
Seminal vesicle (coagulating gland)				
Number examined		5	1	5
Not remarkable		5	1	5

M : Male

Table 10-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	M	M	M
	Dose (mg/kg) :	0	10	30
Findings	Number:	7	12	7
Skeletal muscle, femoral				
Number examined		5	1	5
Not remarkable		5	1	5
Spinal cord, thoracic				
Number examined		5	1	5
Not remarkable		5	1	5
Spleen				
Number examined		5	5	5
Not remarkable		1	3	1
Necrosis, focal		0	0	1
moderate		0	0	1
Hematopoiesis, extramedullary		4	2	3
minimal		4	1	3
mild		0	1	0
Stomach				
Number examined		5	5	5
Not remarkable		5	5	5
Testis				
Number examined		5	1	5
Not remarkable		4	1	5
Degeneration, spermatid		1	0	0
mild		1	0	0
Vacuolation, seminiferous tubular		1	0	0
mild		1	0	0
Thymus				
Number examined		5	5	5
Not remarkable		5	5	5
Thyroid				
Number examined		5	1	5
Not remarkable		5	1	5
Trachea				
Number examined		5	1	5
Not remarkable		5	1	5
Urinary bladder				
Number examined		5	5	5
Not remarkable		5	5	5

M : Male

Table 10-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of administration period (D15))

Organs	Sex:	F
Findings	Dose (mg/kg) :	0
	Number:	10
Adrenal		
Number examined		10
Not remarkable		10
Bone+Bone marrow, femoral		
Number examined		10
Not remarkable		10
Cerebellum(Pons)		
Number examined		10
Not remarkable		10
Cerebrum		
Number examined		10
Not remarkable		10
Eye		
Number examined		10
Not remarkable		10
Heart		
Number examined		10
Not remarkable		8
Myocarditis, focal		2
minimal		2
Intestine, duodenum		
Number examined		10
Not remarkable		10
Intestine, jejunum		
Number examined		10
Not remarkable		10
Intestine, ileum(Peyer's patch)		
Number examined		10
Not remarkable		10
Intestine, cecum		
Number examined		10
Not remarkable		8
Cell infiltration		2
mild		2
Decrease, goblet cell		2
mild		2
Intestine, colon		
Number examined		10
Not remarkable		10
Intestine, rectum		
Number examined		10
Not remarkable		10
Kidney		
Number examined		10
Not remarkable		10
Liver		
Number examined		10
Not remarkable		6
Microgranuloma		4
minimal		4

F : Female

Table 10-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of administration period (D15))

Organs	Sex:	F
Findings	Dose (mg/kg) :	0
	Number:	10
Lung (bronchus)		
Number examined		10
Not remarkable		9
Aggregation, alveolar macrophage		1
minimal		1
Lymph node, mesenteric		
Number examined		10
Not remarkable		10
Lymph node, submandibular		
Number examined		10
Not remarkable		10
Ovary		
Number examined		10
Not remarkable		10
Pancreas		
Number examined		10
Not remarkable		10
Parathyroid		
Number examined		10
Not remarkable		10
Pituitary		
Number examined		10
Not remarkable		10
Salivary gland, submandibular		
Number examined		10
Not remarkable		10
Sciatic nerve		
Number examined		10
Not remarkable		10
Skeletal muscle, femoral		
Number examined		10
Not remarkable		10
Spinal cord, thoracic		
Number examined		10
Not remarkable		10
Spleen		
Number examined		10
Not remarkable		6
Hematopoiesis, extramedullary		4
minimal		4
Stomach		
Number examined		10
Not remarkable		10

F : Female

Table 10-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of administration period (D15))

Organs	Sex:	F
Findings	Dose (mg/kg):	0
	Number:	10
Thymus		
Number examined		10
Not remarkable		10
Thyroid		
Number examined		10
Not remarkable		10
Trachea		
Number examined		10
Not remarkable		10
Urinary bladder		
Number examined		10
Not remarkable		10
Uterus		
Number examined		10
Not remarkable		10
Vagina		
Number examined		10
Not remarkable		10

F : Female

Table 10-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of administration period (L4))

Organs	Sex:	F	F	F
Findings	Dose (mg/kg):	0	10	30
	Number:	12	10	12
Adrenal				
Number examined		5	5	5
Not remarkable		5	5	5
Bone+Bone marrow, femoral				
Number examined		5	5	5
Not remarkable		5	5	5
Cerebellum(Pons)				
Number examined		5	0	5
Not remarkable		5	0	5
Cerebrum				
Number examined		5	0	5
Not remarkable		5	0	5
Eye				
Number examined		5	0	5
Not remarkable		5	0	5
Heart				
Number examined		5	5	5
Not remarkable		5	5	4
Myocarditis, focal		0	0	1
minimal		0	0	1
Intestine, duodenum				
Number examined		5	5	5
Not remarkable		5	5	5
Intestine, jejunum				
Number examined		5	5	5
Not remarkable		5	5	5
Intestine, ileum(Peyer's patch)				
Number examined		5	5	5
Not remarkable		5	5	5
Intestine, cecum				
Number examined		5	5	5
Not remarkable		5	5	5
Intestine, colon				
Number examined		5	5	5
Not remarkable		5	5	5
Intestine, rectum				
Number examined		5	5	5
Not remarkable		5	5	5
Kidney				
Number examined		5	0	5
Not remarkable		5	0	5
Liver				
Number examined		5	0	5
Not remarkable		2	0	2
Hematopoiesis, extramedullary		0	0	1
minimal		0	0	1
Microgranuloma		3	0	2
minimal		3	0	2

F : Female

Table 10-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of administration period (L4))

Organs	Sex:	F	F	F
Findings	Dose (mg/kg): Number:	0 12	10 10	30 12
Lung (bronchus)				
Number examined		5	0	5
Not remarkable		4	0	3
Cell infiltration		1	0	1
minimal		1	0	1
Aggregation, alveolar macrophage		0	0	1
minimal		0	0	1
Lymph node, mesenteric				
Number examined		5	5	5
Not remarkable		5	5	5
Lymph node, submandibular				
Number examined		5	5	5
Not remarkable		5	5	5
Ovary				
Number examined		5	0	5
Not remarkable		5	0	5
Pancreas				
Number examined		5	5	5
Not remarkable		5	5	5
Parathyroid				
Number examined		5	0	5
Not remarkable		5	0	5
Pituitary				
Number examined		5	0	5
Not remarkable		5	0	5
Salivary gland, submandibular				
Number examined		5	0	5
Not remarkable		5	0	5
Sciatic nerve				
Number examined		5	0	5
Not remarkable		5	0	5
Skeletal muscle, femoral				
Number examined		5	0	5
Not remarkable		5	0	5
Spinal cord, thoracic				
Number examined		5	0	5
Not remarkable		5	0	5
Spleen				
Number examined		5	5	5
Hematopoiesis, extramedullary		5	5	5
minimal		0	3	0
mild		5	2	5
Stomach				
Number examined		5	5	5
Not remarkable		5	4	3
Erosion, glandular stomach		0	1	2
minimal		0	1	2

F : Female

Table 10-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of administration period (L4))

Organs	Sex:	F	F	F
Findings	Dose (mg/kg):	0	10	30
	Number:	12	10	12
Thymus				
Number examined		5	5	5
Not remarkable		5	5	5
Thyroid				
Number examined		5	0	5
Not remarkable		5	0	5
Trachea				
Number examined		5	0	5
Not remarkable		5	0	5
Urinary bladder				
Number examined		5	5	5
Not remarkable		5	5	5
Uterus				
Number examined		5	5	5
Not remarkable		5	5	5
Vagina				
Number examined		5	5	5
Not remarkable		5	5	5

F : Female

Table 10-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of recovery period)

Organs	Sex:	M	M
	Dose (mg/kg) :	0	30
Findings	Number:	5	5
Adrenal			
Number examined		5	5
Not remarkable		5	5
Bone+Bone marrow, femoral			
Number examined		5	5
Not remarkable		4	4
Hypocellularity, bone marrow		1	1
minimal		1	1
Heart			
Number examined		5	5
Not remarkable		4	5
Myocarditis, focal		1	0
minimal		1	0
Intestine, jejunum			
Number examined		5	5
Not remarkable		5	5
Intestine, ileum(Peyer's patch)			
Number examined		5	5
Not remarkable		5	5
Intestine, cecum			
Number examined		5	5
Not remarkable		5	5
Intestine, colon			
Number examined		5	5
Not remarkable		5	5
Intestine, rectum			
Number examined		5	5
Not remarkable		5	5
Lymph node, mesenteric			
Number examined		5	5
Not remarkable		5	5
Lymph node, submandibular			
Number examined		5	5
Not remarkable		5	5
Prostate			
Number examined		5	5
Not remarkable		4	3
Cell infiltration		1	2
minimal		1	2
Spleen			
Number examined		5	5
Not remarkable		2	3
Hematopoiesis, extramedullary		3	2
minimal		3	2
Stomach			
Number examined		5	5
Not remarkable		5	5

M : Male

Table 10-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (End of recovery period)

Organs	Sex:	M	M
	Dose (mg/kg) :	0	30
Findings	Number:	5	5
Thymus			
	Number examined	5	5
	Not remarkable	5	5
Urinary bladder			
	Number examined	5	5
	Not remarkable	5	5

M : Male

Table 10-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (Not copulated)

Organs	Sex:	F
Findings	Dose (mg/kg) :	10
	Number:	1
Adrenal		
Number examined		1
Not remarkable		1
Bone+Bone marrow, femoral		
Number examined		1
Not remarkable		1
Cerebellum(Pons)		
Number examined		1
Not remarkable		1
Cerebrum		
Number examined		1
Not remarkable		1
Eye		
Number examined		1
Not remarkable		1
Heart		
Number examined		1
Not remarkable		1
Intestine, duodenum		
Number examined		1
Not remarkable		1
Intestine, jejunum		
Number examined		1
Not remarkable		1
Intestine, ileum(Peyer's patch)		
Number examined		1
Not remarkable		1
Intestine, cecum		
Number examined		1
Not remarkable		1
Intestine, colon		
Number examined		1
Not remarkable		1
Intestine, rectum		
Number examined		1
Not remarkable		1
Kidney		
Number examined		1
Not remarkable		1
Liver		
Number examined		1
Not remarkable		1
Lung (bronchus)		
Number examined		1
Not remarkable		1

F : Female

Table 10-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (Not copulated)

Organs	Sex:	F
Findings	Dose (mg/kg) :	10
	Number:	1
Lymph node, mesenteric		
Number examined		1
Not remarkable		1
Lymph node, submandibular		
Number examined		1
Not remarkable		1
Ovary		
Number examined		1
Not remarkable		1
Pancreas		
Number examined		1
Not remarkable		1
Parathyroid		
Number examined		1
Not remarkable		1
Pituitary		
Number examined		1
Not remarkable		1
Salivary gland, submandibular		
Number examined		1
Not remarkable		1
Sciatic nerve		
Number examined		1
Not remarkable		1
Skeletal muscle, femoral		
Number examined		1
Not remarkable		1
Spinal cord, thoracic		
Number examined		1
Not remarkable		1
Spleen		
Number examined		1
Not remarkable		1
Stomach		
Number examined		1
Not remarkable		1
Thymus		
Number examined		1
Not remarkable		1
Thyroid		
Number examined		1
Not remarkable		1
Trachea		
Number examined		1
Not remarkable		1

F : Female

Table 10-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (Not copulated)

Organs	Sex:	F
Findings	Dose (mg/kg):	10
	Number:	1
Urinary bladder		
Number examined		1
Not remarkable		1
Uterus		
Number examined		1
Not remarkable		1
Vagina		
Number examined		1
Not remarkable		1

F : Female

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

Organs	Sex:	M
Findings	Dose (mg/kg):	100
	Number:	12
Adrenal		
Number examined		12
Hypertrophy, cortical cell		12
mild		12
Bone+Bone marrow, femoral		
Number examined		12
Not remarkable		6
Hypocellularity, bone marrow		6
minimal		4
mild		2
Cerebellum(Pons)		
Number examined		12
Not remarkable		12
Cerebrum		
Number examined		12
Not remarkable		12
Epididymis		
Number examined		12
Not remarkable		12
Eye		
Number examined		12
Not remarkable		12
Heart		
Number examined		12
Not remarkable		2
Myocarditis, focal		10
minimal		5
mild		5
Intestine, duodenum		
Number examined		11
Not remarkable		11
Sample autolysed		1
Intestine, jejunum		
Number examined		12
Not remarkable		9
Degeneration/necrosis, mucosal		3
minimal		2
mild		1
Intestine, ileum(Peyer's patch)		
Number examined		11
Not remarkable		5
Sample autolysed		1
Atrophy, Peyer's patch		6
mild		5
moderate		1
Degeneration/necrosis, mucosal		1
moderate		1
Intestine, cecum		
Number examined		11
Not remarkable		1
Sample autolysed		1
Cell infiltration		1
mild		1

M : Male

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

Organs	Sex:	M
Findings	Dose (mg/kg):	100
	Number:	12
Intestine, cecum (continued)		
Decrease, goblet cell		10
mild		10
Intestine, colon		
Number examined		12
Not remarkable		5
Decrease, goblet cell		7
minimal		6
mild		1
Intestine, rectum		
Number examined		11
Not remarkable		6
Sample autolysed		1
Cell infiltration, mucosal		4
minimal		4
Decrease, goblet cell		4
minimal		2
mild		2
Kidney		
Number examined		12
Not remarkable		10
Regeneration, tubular		2
minimal		1
mild		1
Mineralization		1
mild		1
Cell infiltration		1
mild		1
Liver		
Number examined		12
Not remarkable		9
Microgranuloma		3
minimal		3
Lung (bronchus)		
Number examined		12
Not remarkable		9
Hemorrhage, focal		2
minimal		2
Aggregation, alveolar macrophage		2
minimal		2
Lymph node, mesenteric		
Number examined		12
Not remarkable		3
Atrophy		3
minimal		3
Activation, histiocyte, sinus		8
mild		8
Lymph node, submandibular		
Number examined		12
Not remarkable		7
Atrophy		5
minimal		5

M : Male

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

Organs	Sex:	M
Findings	Dose (mg/kg) :	100
	Number:	12
Pancreas		
Number examined		12
Not remarkable		12
Parathyroid		
Number examined		11
Not remarkable		11
No sample		1
Pituitary		
Number examined		12
Not remarkable		12
Prostate		
Number examined		12
Not remarkable		4
Atrophy		3
mild		3
Hemorrhage		2
mild		2
Cell infiltration		5
minimal		3
mild		1
moderate		1
Salivary gland, submandibular		
Number examined		12
Not remarkable		12
Sciatic nerve		
Number examined		12
Not remarkable		12
Seminal vesicle (coagulating gland)		
Number examined		11
Not remarkable		11
Sample autolysed		1
Skeletal muscle, femoral		
Number examined		12
Not remarkable		12
Spinal cord, thoracic		
Number examined		12
Not remarkable		12
Spleen		
Number examined		12
Not remarkable		5
Atrophy		7
minimal		4
mild		3
Stomach		
Number examined		12
Not remarkable		1
Hyperplasia, squamous, forestomach		8
minimal		1
mild		7
Erosion/Ulcer, forestomach		1
mild		1

M : Male

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

Organs	Sex:	M
Findings	Dose (mg/kg):	100
	Number:	12
Stomach (continued)		
Decrease, mucus, glandular stomach		10
minimal		5
mild		5
Elongate, glandular neck		1
mild		1
Single cell necrosis, gastric gland		5
minimal		2
mild		3
Testis		
Number examined		12
Not remarkable		12
Thymus		
Number examined		12
Atrophy		12
moderate		7
severe		5
Thyroid		
Number examined		12
Not remarkable		12
Trachea		
Number examined		12
Not remarkable		12
Urinary bladder		
Number examined		12
Dilatation, lumina		8
minimal		3
mild		5
Erosion/ulcer		1
mild		1
Basophilic change, mucosal		9
minimal		9
Vacuolation, umbrella cell		1
minimal		1
Hemorrhage, submucosal		2
minimal		1
moderate		1
Cell infiltration, mucosal/submucosal		3
minimal		1
mild		2
Forelimb		
Number examined		1
Arthritis		1
moderate		1
Subcutis		
Number examined		1
Hemorrhage, subcutaneous		1
mild		1
Cell infiltration, subcutaneous		1
mild		1

M : Male

Table 10-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	F	F
Findings	Dose (mg/kg) :	10	100
	Number:	1	22
Adrenal			
Number examined		1	22
Not remarkable		1	4
Hemorrhage, focal		0	1
mild		0	1
Hypertrophy, cortical cell		0	18
mild		0	18
Bone+Bone marrow, femoral			
Number examined		1	22
Not remarkable		1	17
Hypocellularity, bone marrow		0	5
minimal		0	2
mild		0	3
Cerebellum (Pons)			
Number examined		1	22
Not remarkable		1	22
Cerebrum			
Number examined		1	22
Not remarkable		1	22
Eye			
Number examined		1	22
Not remarkable		1	21
Dysplasia, retinal		0	1
minimal		0	1
Heart			
Number examined		1	22
Not remarkable		1	7
Myocarditis, focal		0	15
minimal		0	10
mild		0	5
Intestine, duodenum			
Number examined		0	20
Not remarkable		0	15
Sample autolysed		1	2
Degeneration/necrosis, mucosal		0	5
minimal		0	3
mild		0	2
Intestine, jejunum			
Number examined		0	19
Not remarkable		0	12
Sample autolysed		1	3
Degeneration/necrosis, mucosal		0	7
minimal		0	4
mild		0	2
moderate		0	1
Intestine, ileum (Peyer's patch)			
Number examined		0	19
Not remarkable		0	13
Sample autolysed		1	3
Atrophy, Peyer's patch		0	5
mild		0	3
moderate		0	2

F : Female

Table 10-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	F	F
	Dose (mg/kg) :	10	100
Findings	Number:	1	22
Intestine, ileum(Peyer's patch) (continued)			
Degeneration/necrosis, mucosal		0	4
minimal		0	2
mild		0	1
moderate		0	1
Intestine, cecum			
Number examined		0	19
Not remarkable		0	3
Sample autolysed		1	3
Cell infiltration		0	2
mild		0	2
Decrease, goblet cell		0	16
mild		0	16
Intestine, colon			
Number examined		0	20
Not remarkable		0	4
Sample autolysed		1	2
Decrease, goblet cell		0	16
minimal		0	12
mild		0	4
Intestine, rectum			
Number examined		0	21
Not remarkable		0	7
Sample autolysed		1	1
Decrease, goblet cell		0	14
minimal		0	9
mild		0	5
Kidney			
Number examined		1	22
Not remarkable		1	21
Regeneration, tubular		0	1
minimal		0	1
Liver			
Number examined		1	22
Not remarkable		0	12
Necrosis, focal		1	1
minimal		1	1
Microgranuloma		0	10
minimal		0	10
Lung (bronchus)			
Number examined		1	22
Not remarkable		1	22
Lymph node, mesenteric			
Number examined		1	22
Not remarkable		0	8
Atrophy		1	6
minimal		1	6
Activation, histiocyte, sinus		0	14
mild		0	14
Lymph node, submandibular			
Number examined		1	22
Not remarkable		0	19
Atrophy		1	3
minimal		0	1
mild		1	2

F : Female

Table 10-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	F	F
	Dose (mg/kg) :	10	100
Findings	Number:	1	22
Ovary			
Number examined		1	22
Not remarkable		1	22
Pancreas			
Number examined		1	22
Not remarkable		1	20
Decrease, zymogen granule		0	2
mild		0	2
Parathyroid			
Number examined		1	22
Not remarkable		1	22
Pituitary			
Number examined		1	22
Not remarkable		1	22
Salivary gland, submandibular			
Number examined		1	22
Not remarkable		1	22
Sciatic nerve			
Number examined		1	22
Not remarkable		1	22
Skeletal muscle, femoral			
Number examined		1	22
Not remarkable		1	22
Spinal cord, thoracic			
Number examined		1	22
Not remarkable		1	22
Spleen			
Number examined		1	22
Not remarkable		0	10
Atrophy		1	12
minimal		0	7
mild		1	5
Stomach			
Number examined		1	19
Not remarkable		1	6
Sample autolysed		0	3
Erosion, glandular stomach		0	1
mild		0	1
Hyperplasia, squamous, forestomach		0	9
minimal		0	2
mild		0	7
Erosion/Ulcer, forestomach		0	4
mild		0	4
Decrease, mucus, glandular stomach		0	10
minimal		0	6
mild		0	4
Single cell necrosis, gastric gland		0	5
minimal		0	4
mild		0	1

F : Female

Table 10-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Histopathological findings (Found dead and Moribund sacrifice)

Organs	Sex:	F	F
Findings	Dose (mg/kg): Number:	10 1	100 22
Thymus			
Number examined		1	22
Not remarkable		1	0
Atrophy		0	22
mild		0	2
moderate		0	5
severe		0	15
Thyroid			
Number examined		1	22
Not remarkable		1	22
Trachea			
Number examined		1	22
Not remarkable		1	22
Urinary bladder			
Number examined		1	22
Not remarkable		1	1
Dilatation, lumina		0	1
minimal		0	1
Basophilic change, mucosal		0	20
minimal		0	20
Vacuolation, umbrella cell		0	1
mild		0	1
Uterus			
Number examined		1	22
Not remarkable		1	16
Atrophy		0	6
mild		0	6
Vagina			
Number examined		1	22
Not remarkable		1	2
Atrophy, mucosal		0	9
mild		0	9
Cell infiltration, mucosal/submucosal		0	18
minimal		0	10
mild		0	8

F : Female

Table 11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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±S.D.	Mean duration of cycles Mean±S.D.	Index of animals with abnormal estrous cycle (%) ^a
		0	1	2	3	4			
0	12	0	0	0	3	9	3.8±0.5	4.0±0.0	0/12(0.0)
10	12	0	0	0	4	8	3.7±0.5	4.3±0.4*ST	0/12(0.0)
30	12	0	0	0	4	8	3.7±0.5	4.1±0.2	0/12(0.0)
100	0								5/12(41.7)*F

a): (No. of animals with abnormal estrous cycle / No. of animals examined)×100

*: p<0.05 (Significant difference from control group)

ST: Steel's test

F: Fisher's exact test

Table 12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Mating and fertility of animals

Dose mg/kg	Male				Female			
	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	2.9±2.5	12/12(100.0)	12/12(100.0)	12	2.9±2.5	12/12(100.0)	12/12(100.0)
10	12	2.7±1.5	11/12(91.7)	11/11(100.0)	12	2.7±1.5	11/12(91.7)	11/11(100.0)
30	12	2.4±1.2	12/12(100.0)	12/12(100.0)	12	2.4±1.2	12/12(100.0)	12/12(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 didec-1-yl(methyl)amine 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 abnormalities (%)f)
0	Total	12	12	100.0		189	165			3	152	0
	Mean				22.0	15.8	13.8	85.4	92.8	(3.1)	12.7	(0.0)
	S.D.				0.4	3.6	4.7	20.4	9.9	(7.3)	4.9	(0.0)
10	Total	11g)	10	90.9		166	154			0	141	1h)
	Mean				21.9	16.6	15.4	93.3	91.6	(0.0)	14.1	(0.7)
	S.D.				0.3	1.9	1.3	7.4	12.6	(0.0)	2.2	(2.1)
30	Total	12	12	100.0		175	168			1	151	1i)
	Mean				22.0	14.6	14.0	95.8	89.9	(0.6)	12.6	(0.7)
	S.D.				0.0	1.4	2.0	6.8	9.8	(1.9)	2.5	(2.4)

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 dam died on gestation day 22.

h): Brachyury

i): Absent, left hind limb

No significant difference in any treated groups from control group.

Table 14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	12	152	155		12	152	146	
	Mean		12.7	12.9	96.9		12.7	12.2	97.1
	S.D.		4.9	4.8	7.3		4.9	4.4	5.0
10	Total	10	141	141		10	140c)	130	
	Mean		14.1	14.1	100.0		14.0	13.0	91.2
	S.D.		2.2	2.2	0.0		2.2	3.4	17.0
30	Total	12	151	152		12	150c)	149	
	Mean		12.6	12.7	99.4		12.5	12.4	99.4
	S.D.		2.5	2.6	1.9		2.6	2.6	2.2

a): (No. of liveborns / No. of delivered pups)×100

b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

c): One pup with external abnormality was excluded.

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 didec-1-yl(methyl)amine by oral administration in rats
Sex ratio of pups

Dose mg/kg	No. of dams		Liveborns		Stillborns		Sex ratio of delivered pups	Sex ratio of liveborns	No. of dams	Postnatal day 4		Sex ratio of live pups on day 4
			No. of males	No. of females	No. of males	No. of females	a)	b)		No. of males	No. of females	c)
0	12	Total	71	81	2	1			12	68	78	
		Mean	5.9	6.8	0.2	0.1	0.46	0.45		5.7	6.5	0.45
		S.D.	3.2	3.2	0.4	0.3	0.17	0.17		3.1	3.1	0.17
10	10	Total	80	61	0	0			10	72	58	
		Mean	8.0	6.1	0.0	0.0	0.57	0.57		7.2	5.8	0.53
		S.D.	1.8	2.2	0.0	0.0	0.13	0.13		2.7	2.1	0.16
30	12	Total	73	78	0	1			12	72	77	
		Mean	6.1	6.5	0.0	0.1	0.48	0.48		6.0	6.4	0.48
		S.D.	2.8	2.6	0.0	0.3	0.20	0.20		2.9	2.7	0.20

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

No significant difference in any treated groups from control group.

Table 16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Body weight of pups

Dose mg/kg		Male			Female		
		0	4a)	Gain	0	4a)	Gain
0	No.	12	12	12	12	12	12
	Mean	6.7	10.4	3.7	6.4	10.1	3.7
	S.D.	0.5	1.9	1.5	0.5	1.8	1.4
10	No.	10	10	10	10	10	10
	Mean	6.5	9.8	3.4	6.2	9.3	3.1
	S.D.	0.4	1.4	1.2	0.5	1.3	0.9
30	No.	11b)	11	11	12	12	12
	Mean	6.9	10.7	3.8	6.5	10.1	3.6
	S.D.	0.6	1.0	0.6	0.6	0.9	0.4

Unit: g

No.: No. of dams

a): Postnatal day

b): Male pups were not born in one dam.

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 didec-1-yl(methyl)amine by oral administration in rats
Externally for gross abnormalities in dead pups

	Dose (mg/kg)	0	10	30
Male				
No. of pups examined		0	5	1
No. of pups with abnormal findings		0	0	0
Female				
No. of pups examined		1	2	0
No. of pups with abnormal findings		0	0	0

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

	Dose (mg/kg)	0	10	30
Male				
No. of pups examined		68	72	72
No. of pups with abnormal findings		0	0	0
Female				
No. of pups examined		78	58	77
No. of pups with abnormal findings		0	0	0

Appendix 1-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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
 didec-1-yl(methyl)amine 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
 didec-1-yl(methyl)amine 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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in male rats (Administration period)
 Dose (mg/kg): 10

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in male rats (Administration period)
 Dose (mg/kg): 10

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in male rats (Administration period)
 Dose (mg/kg): 10

Animal number	Day of administration														43a)
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	
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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in male rats (Administration period)
 Dose (mg/kg): 30

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in male rats (Administration period)
 Dose (mg/kg): 30

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

-: No abnormal findings

E: Salivation

Appendix 1-9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in male rats (Administration period)
 Dose (mg/kg): 30

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

a): Day of necropsy
 -: No abnormal findings
 E: Salivation

Appendix 1-10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in male rats (Administration period)
 Dose (mg/kg): 100

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4001	-	-	-	-	DEH	DHIJKx								
4002	-	-	-	-	AG	A	A	ABO	AGIJOP	DHKx				
4003	-	-	-	-	AG	A	DH	+						
4004	-	-	-	-	G	-	-	-	BG	DJKx				
4005	-	-	-	-	-	AE	DHJ	ABGJO	BG	ABGQ	ABDKQx			
4006	-	-	-	-	-	A	A	DG	ADFHIJKMOPx					
4007	-	-	-	-	-	A	DJ	ABFJNO	ABFGIJOP	DFIJKNOx				
4008	-	-	-	-	A	D	DFIJ	DFIJNO	AFIJOP	DFIJKOx				
4009	-	-	-	-	B	DGH	DPHJ	DFJ	AFJNOP	AFJNOP	DFJKOx			
4010	-	-	-	-	GH	-	-	DIJKx						
4011	-	-	-	-	GH	DKx								
4012	-	-	-	-	DH	ABG	ABG	DIM	ABGIMO	DFIKOx				

-: No abnormal findings
 A: Decrease in spontaneous movement
 B: Ataxia
 D: Prone/Lateral position
 E: Salivation
 F: Emaciation
 G: Hypersensitivity
 H: Convulsion
 I: Smudge of lower abdomen
 J: Smudge of perioral
 K: Hypothermia
 M: Reddish urine
 N: Soft feces
 O: Decrease in feces
 P: Creeping position
 Q: Swelling of fore limb
 +: Dead
 x: Sacrificed moribund

Appendix 1-11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 100

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														

Appendix 1-12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 100

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

a): Day of necropsy

Appendix 1-13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-14

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in female rats during the pre-mating period (Main group)
 Dose (mg/kg): 10

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in female rats during the pre-mating period (Main group)
 Dose (mg/kg): 30

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in female rats during the pre-mating period (Main group)
 Dose (mg/kg): 100

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
4101	-	-	-	-	-	BG	BG	B	BG	DHKx					
4102	-	-	-	-	A	BF	ABFG	DFHOx							
4103	-	-	-	-	A	DH	DF	+							
4104	-	-	-	-	-	-	BG	DF	+						
4105	-	-	-	-	-	-	AG	DJKx							
4106	-	-	-	-	-	-	-	DHO	DKOx						
4107	-	-	-	-	-	-	-	-	O	GHO	O	AFKOx			
4108	-	-	-	-	-	-	-	-	O	ADFKOx					
4109	-	-	-	-	AB	DEF	DEFHJ	+							
4110	-	-	-	-	AB	DFHKx									
4111	-	-	-	-	-	-	ABDFH	DFO	ABFO	DFKOx					
4112	-	-	-	-	ABF	DF	DFGIJKx								

-: No abnormal findings
 A: Decrease in spontaneous movement
 B: Ataxia
 D: Prone/Lateral position
 E: Salivation
 F: Emaciation
 G: Hypersensitivity
 H: Convulsion
 I: Smudge of lower abdomen
 J: Smudge of perioral
 K: Hypothermia
 O: Decrease in feces
 +: Dead
 x: Sacrificed moribund

Appendix 1-17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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
1104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d

a): Gestation day

-: 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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in dams during the gestation period (Main group)
 Dose (mg/kg): 10

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	Not copulated																							
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d

a): Gestation day

-: No abnormal findings

+: Dead

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in dams during the gestation period (Main group)
 Dose (mg/kg): 30

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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	/d
3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
3107	-	-	-	-	E	E	E	-	-	-	E	-	-	-	-	-	-	-	-	-	-	-	-	/d
3108	-	-	-	-	-	-	-	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	/d
3109	E	E	-	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	-	-	-	-	-	d
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d

a): Gestation day

-: No abnormal findings

E: Salivation

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in dams during the gestation period (Main group)
 Dose (mg/kg): 100

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)																										
4102b)																										
4103c)																										
4104c)																										
4105b)																										
4106b)																										
4107b)																										
4108b)																										
4109c)																										
4110b)																										
4111b)																										
4112b)																										

a): Gestation day
 b): Sacrificed moribund
 c): Dead

Appendix 1-21

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	-	-	-	-	-	-
1104	-	-	-	-	-	-
1105	-	-	-	-	-	-
1106	-	-	-	-	-	-
1107	-	-	-	-	-	-
1108	-	-	-	-	-	-
1109	-	-	-	-	-	-
1110	-	-	-	-	-	-
1111	-	-	-	-	-	-
1112	-	-	-	-	-	-

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

Appendix 1-22

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in dams during the lactation period (Main group)
 Dose (mg/kg): 10

Dam number	Administration					
	0	1	2	3	4a)	5b)
2101	Not copulated					
2102	-	-	-	-	-	-
2103	-	-	-	-	-	-
2104	-	-	-	-	-	-
2105	-	-	-	-	-	-
2106c)	-	-	-	-	-	-
2107	-	-	-	-	-	-
2108	-	-	-	-	-	-
2109	-	-	-	-	-	-
2110	-	-	-	-	-	-
2111	-	-	-	-	-	-
2112	-	-	-	-	-	-

a): Lactation day
 b): Day of necropsy
 c): Died on gestation day 22
 -: No abnormal findings

Appendix 1-23

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in dams during the lactation period (Main group)
 Dose (mg/kg): 30

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in dams during the lactation period (Main group)
 Dose (mg/kg): 100

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

a): Lactation day
 b): Day of necropsy
 c): Sacrificed moribund
 d): Dead

Appendix 1-25

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in female rats (Satellite group)
 Dose (mg/kg): 0

Animal number	Day of administration															16a)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
1113	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1114	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1115	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1116	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1117	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1118	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1119	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1121	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1122	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
 -: No abnormal findings

Appendix 1-26

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual clinical signs in female rats (Satellite group)
 Dose (mg/kg): 100

Animal number	Day of administration															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16a)
4113	-	-	-	-	-	-	-	-	BFO	ABFO	ABDFKOx					
4114	-	-	-	-	-	-	AB	DKx								
4115	-	-	-	-	-	-	-	BH	BG	BG	B	ABFKOx				
4116	-	-	-	-	-	-	-	DG	ADGHOP	AFOP	+					
4117	-	-	-	-	F	BFG	DFH	DF	ABFGO	ABFGO	ABFG	ABFGKx				
4118	-	-	-	-	-	ABE	AB	B	ABO	ABFO	DFKOx					
4119	-	-	-	-	AB	ABF	ABF	DFGHO	DFO	+						
4120	-	-	-	-	-	-	-	BDG	DFJKOx							
4121	-	-	-	-	ABGH	ABFG	ABFG	+								
4122	-	-	-	-	BG	ABF	ABFI	DFINO	ABFO	ABFO	ABFO	ABFKx				

a): Day of necropsy

-: No abnormal findings

A: Decrease in spontaneous movement

B: Ataxia

D: Prone/Lateral position

E: Salivation

F: Emaciation

G: Hypersensitivity

H: Convulsion

I: Smudge of lower abdomen

J: Smudge of perioral

K: Hypothermia

N: Soft feces

O: Decrease in feces

P: Creeping position

+: Dead

x: Sacrificed moribund

Appendix 1-27

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 1-28

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual clinical signs in male rats (Recovery period)
Dose (mg/kg): 30

Animal number	Day of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
3008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 2-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 1 of administration)
 Dose (mg/kg): 10

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 1 of administration)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 1 of administration)
 Dose (mg/kg): 100

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 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 2 of administration)
 Dose (mg/kg): 10

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 2 of administration)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 2 of administration)
 Dose (mg/kg): 100

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

Appendix 2-9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 3 of administration)
 Dose (mg/kg): 10

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 3 of administration)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 3 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S

Posture a)
 Convulsion b)
 Abnormal behavior c)

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 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 4 of administration)
 Dose (mg/kg): 10

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 4 of administration)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 4 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S

Posture a)
 Convulsion b)
 Abnormal behavior c)

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 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 5 of administration)
 Dose (mg/kg): 10

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 5 of administration)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 5 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S

Posture a)
 Convulsion b)
 Abnormal behavior c)

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 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 6 of administration)
 Dose (mg/kg): 10

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 6 of administration)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 6 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S

Posture a)
 Convulsion b)
 Abnormal behavior c)

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
 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Week 1 of administration)
 Dose (mg/kg): 10

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Week 1 of administration)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Week 1 of administration)
 Dose (mg/kg): 100

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
 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Week 2 of administration)
 Dose (mg/kg): 10

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Week 2 of administration)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Week 2 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S		S	D	S	S	S
Posture a)	N											
Convulsion b)	0											
Abnormal behavior c)	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 2-33

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	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 2-34

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 1)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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

NC: Not copulated

Appendix 2-35

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 1)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 1)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S

Posture a)
 Convulsion b)
 Abnormal behavior c)

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 2-37

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	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 2-38

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 7)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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

NC: Not copulated

Appendix 2-39

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 7)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 7)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S

Posture a)
 Convulsion b)
 Abnormal behavior c)

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 2-41

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	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 2-42

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 14)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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

NC: Not copulated

Appendix 2-43

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 14)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 14)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S

Posture a)
 Convulsion b)
 Abnormal behavior c)

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 2-45

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	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 2-46

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 20)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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

NC: Not copulated

Appendix 2-47

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 20)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Gestation day 20)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S

Posture a)
 Convulsion b)
 Abnormal behavior c)

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 2-49

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	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 2-50

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Lactation day 4)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC					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

NC: Not copulated

D: Dead

Appendix 2-51

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Lactation day 4)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Main group, Lactation day 4)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S

Posture a)
 Convulsion b)
 Abnormal behavior c)

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 2-53

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Satellite group, Week 1 of administration)
 Dose (mg/kg): 100

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 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: home cage observation
 (Satellite group, Week 2 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
		S		D		S	D	S	D	
Posture a)	Hd)		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) Somnolent
 D: Dead
 S: Sacrificed moribund

Appendix 2-57

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 2-58

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 1 of recovery)
 Dose (mg/kg): 30

Parameter	Animal number (3008-3012)				
	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 2-59

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 2-60

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: home cage observation
 (Week 2 of recovery)
 Dose (mg/kg): 30

Parameter	Animal number (3008-3012)				
	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 2-61

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 2-62

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 1 of administration)
 Dose (mg/kg): 10

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	1	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 2-63

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 1 of administration)
 Dose (mg/kg): 30

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 2-64

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 1 of administration)
 Dose (mg/kg): 100

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 2-65

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 2-66

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 2 of administration)
 Dose (mg/kg): 10

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	1	1	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 2-67

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 2 of administration)
 Dose (mg/kg): 30

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	1	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 2-68

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 2 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S		S	S	S	S	S	S	S
Ease of removal from cage a)					2							
Fur condition b)					1o)							
Skin c)					0							
Secretions-Eye, Nose d)					0							
Exophthalmos e)					0							
Palpebral closure f)					0							
Mucosal membranes g)					0							
Lacrimation h)					0							
Piloerection i)					0							
Pupil size j)					0							
Salivation k)					0							
Abnormal respiration l)					0							
Vocalization m)					0							
Reactivity to handling n)					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) Unkempt fur
 D: Dead
 S: Sacrificed moribund

Appendix 2-69

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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)	1	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 2-70

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 3 of administration)
 Dose (mg/kg): 10

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 2-71

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 3 of administration)
 Dose (mg/kg): 30

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	2	0	0	0	0	2	2	2	0	0	2
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	1	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 2-72

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 3 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S
Ease of removal from cage a)												
Fur condition b)												
Skin c)												
Secretions-Eye, Nose d)												
Exophthalmos e)												
Palpebral closure f)												
Mucosal membranes g)												
Lacrimation h)												
Piloerection i)												
Pupil size j)												
Salivation k)												
Abnormal respiration l)												
Vocalization m)												
Reactivity to handling n)												

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 2-73

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 2-74

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 4 of administration)
 Dose (mg/kg): 10

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 4 of administration)
 Dose (mg/kg): 30

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	1	0	1	1	2	2	0	0	2
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	1	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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 4 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S

Ease of removal from cage a)
 Fur condition b)
 Skin c)
 Secretions-Eye, Nose d)
 Exophthalmos e)
 Palpebral closure f)
 Mucosal membranes g)
 Lacrimation h)
 Piloerection i)
 Pupil size j)
 Salivation k)
 Abnormal respiration l)
 Vocalization m)
 Reactivity to handling n)

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 2-77

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 2-78

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 5 of administration)
 Dose (mg/kg): 10

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 2-79

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 5 of administration)
 Dose (mg/kg): 30

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	1	1	1	2	0	0	1
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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 5 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S

Ease of removal from cage a)
 Fur condition b)
 Skin c)
 Secretions-Eye, Nose d)
 Exophthalmos e)
 Palpebral closure f)
 Mucosal membranes g)
 Lacrimation h)
 Piloerection i)
 Pupil size j)
 Salivation k)
 Abnormal respiration l)
 Vocalization m)
 Reactivity to handling n)

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
 didec-1-yl(methyl)amine 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)	1	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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 6 of administration)
 Dose (mg/kg): 10

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 6 of administration)
 Dose (mg/kg): 30

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	1	1	1	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 2-84

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 6 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S

Ease of removal from cage a)
 Fur condition b)
 Skin c)
 Secretions-Eye, Nose d)
 Exophthalmos e)
 Palpebral closure f)
 Mucosal membranes g)
 Lacrimation h)
 Piloerection i)
 Pupil size j)
 Salivation k)
 Abnormal respiration l)
 Vocalization m)
 Reactivity to handling n)

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
 didec-1-yl(methyl)amine 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	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
 didec-1-yl(methyl)amine 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): 10

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 2-87

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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): 30

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 2-88

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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): 100

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)	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 2-89

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 2-90

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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): 10

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 2-91

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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): 30

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 2-92

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S		S	D	S	S	S
Ease of removal from cage a)							0					
Fur condition b)							0					
Skin c)							0					
Secretions-Eye, Nose d)							0					
Exophthalmos e)							0					
Palpebral closure f)							0					
Mucosal membranes g)							0					
Lacrimation h)							0					
Piloerection i)							0					
Pupil size j)							0					
Salivation k)							0					
Abnormal respiration l)							0					
Vocalization m)							0					
Reactivity to handling n)							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 2-93

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 1)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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

NC: Not copulated

Appendix 2-95

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 1)
 Dose (mg/kg): 30

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	2	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 2-96

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 1)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S
Ease of removal from cage a)												
Fur condition b)												
Skin c)												
Secretions-Eye, Nose d)												
Exophthalmos e)												
Palpebral closure f)												
Mucosal membranes g)												
Lacrimation h)												
Piloerection i)												
Pupil size j)												
Salivation k)												
Abnormal respiration l)												
Vocalization m)												
Reactivity to handling n)												

- 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
 didec-1-yl(methyl)amine 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	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 2-98

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 7)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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

NC: Not copulated

Appendix 2-99

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 7)
 Dose (mg/kg): 30

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	1	2	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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 7)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S

Ease of removal from cage a)
 Fur condition b)
 Skin c)
 Secretions-Eye, Nose d)
 Exophthalmos e)
 Palpebral closure f)
 Mucosal membranes g)
 Lacrimation h)
 Piloerection i)
 Pupil size j)
 Salivation k)
 Abnormal respiration l)
 Vocalization m)
 Reactivity to handling n)

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 2-101

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 14)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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

NC: Not copulated

Appendix 2-103

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 14)
 Dose (mg/kg): 30

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	1	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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 14)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S
Ease of removal from cage a)												
Fur condition b)												
Skin c)												
Secretions-Eye, Nose d)												
Exophthalmos e)												
Palpebral closure f)												
Mucosal membranes g)												
Lacrimation h)												
Piloerection i)												
Pupil size j)												
Salivation k)												
Abnormal respiration l)												
Vocalization m)												
Reactivity to handling n)												

- 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 2-105

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	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 2-106

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 20)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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
 NC: Not copulated

Appendix 2-107

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 20)
 Dose (mg/kg): 30

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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Gestation day 20)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S
Ease of removal from cage a)												
Fur condition b)												
Skin c)												
Secretions-Eye, Nose d)												
Exophthalmos e)												
Palpebral closure f)												
Mucosal membranes g)												
Lacrimation h)												
Piloerection i)												
Pupil size j)												
Salivation k)												
Abnormal respiration l)												
Vocalization m)												
Reactivity to handling n)												

- 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 2-109

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	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 2-110

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Lactation day 4)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC					D						
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
 NC: Not copulated
 D: Dead

Appendix 2-111

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Lactation day 4)
 Dose (mg/kg): 30

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: in-the-hand observation
 (Main group, Lactation day 4)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S
Ease of removal from cage a)												
Fur condition b)												
Skin c)												
Secretions-Eye, Nose d)												
Exophthalmos e)												
Palpebral closure f)												
Mucosal membranes g)												
Lacrimation h)												
Piloerection i)												
Pupil size j)												
Salivation k)												
Abnormal respiration l)												
Vocalization m)												
Reactivity to handling n)												

- 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 2-113

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	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 2-114

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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): 100

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 2-115

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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 2-116

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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): 100

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
	S		D		S	D	S	D		
Ease of removal from cage a)	0		2		2					0
Fur condition b)	1o)		0		0					1o)
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

o) Unkempt fur

D: Dead

S: Sacrificed moribund

Appendix 2-117 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 2-118 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 1 of recovery)
 Dose (mg/kg): 30

Parameter	Animal number (3008-3012)				
	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 2-119 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	1	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 2-120 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: in-the-hand observation
 (Week 2 of recovery)
 Dose (mg/kg): 30

Parameter	Animal number (3008-3012)				
	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 2-121

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	6	4	3	4	4	6	3	5	3	3	5	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	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 2-122

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 1 of administration)
 Dose (mg/kg): 10

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	7	2	0	5	2	7	5	6	2	3	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	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 2-123

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 1 of administration)
 Dose (mg/kg): 30

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	3	6	4	3	8	5	6	3	3	4	4	4
Defecation count	0	0	0	0	0	0	1	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 2-124

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 1 of administration)
 Dose (mg/kg): 100

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	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	5	4	0	4	2	5	2	2	2	3	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 2-125

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	4	4	6	3	1	3	2	5	6	2	6	5
Defecation count	0	0	0	0	0	2	3	0	0	1	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 2-126

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 2 of administration)
 Dose (mg/kg): 10

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	2	1	7	1	1	4	4	5	3	6
Defecation count	1	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	1	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 2-127

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 2 of administration)
 Dose (mg/kg): 30

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	3	2	6	5	6	4	4	1	7	2	0	4
Defecation count	0	0	0	0	0	0	1	0	0	0	1	0
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 2-128

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 2 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S		S	S	S	S	S	S	S
Arousal a)	0											
Convulsion b)	0											
Abnormal behavior c)	0											
Stereotypy d)	0											
Gait e)	1i)											
Posture f)	N											
Grooming g)	0											
Rearing	5											
Defecation count	0											
Urination h)	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
 i) Ataxia
 D: Dead
 S: Sacrificed moribund

Appendix 2-129

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	U	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	3	1	2	5	2	3	4	4	0	6	8
Defecation count	0	0	0	0	0	0	0	0	0	1	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 2-130

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 3 of administration)
 Dose (mg/kg): 10

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	5	1	5	1	1	2	2	5	0	3
Defecation count	0	0	0	0	0	0	0	0	0	2	0	0
Urination h)	0	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 2-131

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 3 of administration)
 Dose (mg/kg): 30

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	3	6	5	1	4	1	3	2	7	2	1	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	1	1	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 2-132

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 3 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S
Arousal a)												
Convulsion b)												
Abnormal behavior c)												
Stereotypy d)												
Gait e)												
Posture f)												
Grooming g)												
Rearing												
Defecation count												
Urination h)												

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 2-133

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	3	2	4	0	3	4	4	3	5	0	6	6
Defecation count	0	0	0	0	0	0	0	0	0	2	0	0
Urination h)	0	0	0	0	0	1	0	0	1	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 2-134

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 4 of administration)
 Dose (mg/kg): 10

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	6	3	4	5	1	1	7	3	3	0	10
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	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 2-135

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 4 of administration)
 Dose (mg/kg): 30

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	5	4	2	5	5	3	4	6	5	2	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	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 2-136

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 4 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S
Arousal a)												
Convulsion b)												
Abnormal behavior c)												
Stereotypy d)												
Gait e)												
Posture f)												
Grooming g)												
Rearing												
Defecation count												
Urination h)												

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 2-137

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	5	2	4	1	5	4	5	4	6	0	4	3
Defecation count	0	0	0	0	0	0	0	0	0	1	0	0
Urination h)	0	0	0	1	0	1	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

Appendix 2-138

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 5 of administration)
 Dose (mg/kg): 10

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	8	4	6	5	4	3	8	7	4	2	8
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	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 2-139

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 5 of administration)
 Dose (mg/kg): 30

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	3	6	1	4	6	5	2	6	4	0	4
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 2-140

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 5 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S
Arousal a)												
Convulsion b)												
Abnormal behavior c)												
Stereotypy d)												
Gait e)												
Posture f)												
Grooming g)												
Rearing												
Defecation count												
Urination h)												

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 2-141

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	U	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	2	4	3	6	2	7	4	5	0	3	5
Defecation count	0	0	0	0	0	0	0	0	0	1	0	0
Urination h)	0	0	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

Appendix 2-142

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 6 of administration)
 Dose (mg/kg): 10

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	1	6	3	5	5	5	3	4	3	5	2	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	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 2-143

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 6 of administration)
 Dose (mg/kg): 30

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	U
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	5	4	1	6	4	2	3	7	4	0	3
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	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 2-144

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 6 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	S	S	S	S	S	S	S	S	S

Arousal a)
 Convulsion b)
 Abnormal behavior c)
 Stereotypy d)
 Gait e)
 Posture f)
 Grooming g)
 Rearing
 Defecation count
 Urination h)

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 2-145

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	8	4	13	5	9	5	9	7	6	9	8	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 2-146

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Week 1 of administration)
 Dose (mg/kg): 10

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	10	6	8	9	10	9	8	9	5	8	9	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	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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Week 1 of administration)
 Dose (mg/kg): 30

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	12	8	6	7	9	9	9	6	9	8	6	9
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 2-148

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Week 1 of administration)
 Dose (mg/kg): 100

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	1i)	0	0	0	0	0	0	0	1i)
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	8	1	4	5	4	4	5	1	7	2
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	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
 i) Ataxia

Appendix 2-149

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	3	5	14	8	6	7	9	6	5	5	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 2-150

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Week 2 of administration)
 Dose (mg/kg): 10

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	11	4	7	7	6	7	9	7	4	6	11	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	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 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Week 2 of administration)
 Dose (mg/kg): 30

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	6	9	9	6	5	8	4	7	8	3	2
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 2-152

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Week 2 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S		S	D	S	S	S
Arousal a)	0											
Convulsion b)	0											
Abnormal behavior c)	0											
Stereotypy d)	0											
Gait e)	0											
Posture f)	N											
Grooming g)	0											
Rearing	4											
Defecation count	0											
Urination h)	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 didec-1-yl(methyl)amine 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	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	2	4	6	5	9	7	5	4	5	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 2-154

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 1)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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	8	5	5	5	5	7	6	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
 NC: Not copulated

Appendix 2-155

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 1)
 Dose (mg/kg): 30

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	5	6	11	6	4	9	4	3	3	3	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	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 2-156

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 1)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S

Arousal a)
 Convulsion b)
 Abnormal behavior c)
 Stereotypy d)
 Gait e)
 Posture f)
 Grooming g)
 Rearing
 Defecation count
 Urination h)

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 didec-1-yl(methyl)amine 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	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	8	5	5	4	7	6	5	5	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 2-158

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 7)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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	7	5	6	7	6	6	5	4	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
 NC: Not copulated

Appendix 2-159

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 7)
 Dose (mg/kg): 30

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	5	3	8	5	3	6	3	4	5	0	2
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 2-160

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 7)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S

Arousal a)
 Convulsion b)
 Abnormal behavior c)
 Stereotypy d)
 Gait e)
 Posture f)
 Grooming g)
 Rearing
 Defecation count
 Urination h)

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 didec-1-yl(methyl)amine 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	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	5	6	3	3	3	4	5	4	1	1	2
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 2-162

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 14)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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	5	3	5	4	9	4	5	5	5	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

NC: Not copulated

Appendix 2-163

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 14)
 Dose (mg/kg): 30

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	4	3	3	6	5	4	5	5	8	8	0	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 2-164

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 14)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S
Arousal a)												
Convulsion b)												
Abnormal behavior c)												
Stereotypy d)												
Gait e)												
Posture f)												
Grooming g)												
Rearing												
Defecation count												
Urination h)												

- 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 didec-1-yl(methyl)amine 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	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	5	5	6	3	4	3	2	5	3	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 2-166

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 20)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC											
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	6	5	2	5	6	7	4	5	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
 NC: Not copulated

Appendix 2-167

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 20)
 Dose (mg/kg): 30

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	4	4	5	4	3	5	6	5	4	3	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 2-168

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Gestation day 20)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S
Arousal a)												
Convulsion b)												
Abnormal behavior c)												
Stereotypy d)												
Gait e)												
Posture f)												
Grooming g)												
Rearing												
Defecation count												
Urination h)												

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 didec-1-yl(methyl)amine 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	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	4	6	6	8	9	5	5	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 2-170

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Lactation day 4)
 Dose (mg/kg): 10

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	NC					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		8	8	4	7		6	7	4	5	8	7
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

NC: Not copulated

D: Dead

Appendix 2-171

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Lactation day 4)
 Dose (mg/kg): 30

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	7	7	11	5	5	7	6	6	8	5	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 2-172

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Main group, Lactation day 4)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S
Arousal a)												
Convulsion b)												
Abnormal behavior c)												
Stereotypy d)												
Gait e)												
Posture f)												
Grooming g)												
Rearing												
Defecation count												
Urination h)												

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 2-173

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	4	6	5	7	7	5	7	9	6	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 2-174

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Satellite group, Week 1 of administration)
 Dose (mg/kg): 100

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	1i) 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	6	3	4	2	4	6	4	5	3
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
 i) Ataxia

Appendix 2-175

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	7	6	6	5	6	6	4	6	7	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 2-176

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in female rats: open field observation
 (Satellite group, Week 2 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
	S		D		S	D	S	D		
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)	1i)		1i)		1i)					1i)
Posture f)	N		N		N					Fj)
Grooming g)	0		0		0					0
Rearing	2		3		4					0
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
 i) Ataxia
 j) Prone position
 D: Dead
 S: Sacrificed moribund

Appendix 2-177

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	4	6	0	1	5
Defecation count	0	0	2	0	0
Urination h)	0	1	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 2-178

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 1 of recovery)
 Dose (mg/kg): 30

Parameter	Animal number (3008-3012)				
	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	2	7	3	0	3
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 2-179

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	6	0	2	5
Defecation count	0	0	0	0	0
Urination h)	0	1	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 2-180

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual detailed clinical signs in male rats: open field observation
 (Week 2 of recovery)
 Dose (mg/kg): 30

Parameter	Animal number (3008-3012)				
	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	1	8	4	0	5
Defecation count	0	0	0	0	0
Urination h)	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 2-181

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	69	117	85	99

- 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 2-182

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual manipulative test of male rats (Week 6 of administration)
 Dose (mg/kg): 10

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)	47	57	100	77	68

- 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 2-183

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual manipulative test of male rats (Week 6 of administration)
 Dose (mg/kg): 30

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)	101	49	107	95	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

Appendix 2-184

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual manipulative test of male rats (Week 6 of administration)
 Dose (mg/kg): 100

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
	S	S	S	S	S

Auditory response a)
 Approach response b)
 Touch response c)
 Tail pinch response d)
 Pupillary reflex e)
 Aerial righting reflex
 (Total score)
 Landing foot splay (mm)

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 2-185

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual manipulative test of female rats (Main group, Lactation day 4)
 Dose (mg/kg): 0

Parameter	Animal number (1101-1112)				
	1	5	6	7	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)	65	51	57	52	76

- 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 2-186

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual manipulative test of female rats (Main group, Lactation day 4)
 Dose (mg/kg): 10

Parameter	Animal number (2102-2112)				
	2	3	5	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)	86	69	91	59	40

- 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 2-187

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual manipulative test of female rats (Main group, Lactation day 4)
 Dose (mg/kg): 30

Parameter	Animal number (3101-3111)				
	1	2	4	7	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)	59	36	72	53	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 2-188

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual manipulative test of female rats (Main group, Lactation day 4)
 Dose (mg/kg): 100

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
	S	S	D	D	S	S	S	S	D	S	S	S
Auditory response a)												
Approach response b)												
Touch response c)												
Tail pinch response d)												
Pupillary reflex e)												
Aerial righting reflex (Total score)												
Landing foot splay (mm)												

- 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
 S: Sacrificed moribund

Appendix 2-189

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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)	101	98	94	67	72

- 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 2-190

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual manipulative test of male rats (Week 2 of recovery)
 Dose (mg/kg): 30

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)	69	47	105	84	50

- 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 2-191

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine 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	1641	1013
1009	1468	898
1010	1548	1007
1011	1603	835
1012	1502	961
Mean	1552	943
S.D.	71	76

Appendix 2-192

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 10

Animal number	Fore limb g	Hind limb g
2008	1576	877
2009	1558	977
2010	1680	946
2011	1629	1085
2012	1659	1018
Mean	1620	981
S.D.	52	78

Appendix 2-193

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 30

Animal number	Fore limb g	Hind limb g
3008	1887	911
3009	1297	850
3010	990	959
3011	1645	899
3012	1780	1045
Mean	1520	933
S.D.	370	74

Appendix 2-194

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 100

Animal number	Fore limb g	Hind limb g
4008S		
4009S		
4010S		
4011S		
4012S		
Mean		
S.D.		

S: Sacrificed moribund

Appendix 2-195

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine 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
1101	1226	633
1105	1516	564
1106	1422	774
1107	876	728
1112	1352	667
Mean	1278	673
S.D.	249	82

Appendix 2-196

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 10

Animal number	Fore limb g	Hind limb g
2102	1110	837
2103	1369	969
2105	1364	977
2111	1412	692
2112	1383	657
Mean	1328	826
S.D.	123	150

Appendix 2-197

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 30

Animal number	Fore limb g	Hind limb g
3101	1001	788
3102	1241	959
3104	1176	675
3107	914	881
3111	1508	697
Mean	1168	800
S.D.	231	121

Appendix 2-198

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 100

Animal number	Fore limb g	Hind limb g
4101S		
4102S		
4103D		
4104D		
4105S		
4106S		
4107S		
4108S		
4109D		
4110S		
4111S		
4112S		
Mean		
S.D.		

D: Dead
S: Sacrificed moribund

Appendix 2-199

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine 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	2172	1148
1009	1712	999
1010	1779	1175
1011	1569	1112
1012	1719	1169
Mean	1790	1121
S.D.	227	72

Appendix 2-200

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Individual grip strength of male rats (Week 2 of recovery)
Dose (mg/kg): 30

Animal number	Fore limb g	Hind limb g
3008	2119	1138
3009	1341	1039
3010	1643	1190
3011	2014	1326
3012	2029	1007
Mean	1829	1140
S.D.	328	127

Appendix 2-201

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of male rats (Week 6 of administration)
 Dose (mg/kg): 0

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
1008	446	392	420	404	328	348	2338
1009	489	412	306	360	261	389	2217
1010	474	489	324	196	181	110	1774
1011	428	321	226	176	303	308	1762
1012	415	417	128	42	26	1	1029
Mean	450	406	281	236	220	231	1824
S.D.	31	60	110	147	122	167	514

Unit: Count

Appendix 2-202

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of male rats (Week 6 of administration)
 Dose (mg/kg): 10

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
2008	477	405	224	206	157	60	1529
2009	311	249	276	206	306	210	1558
2010	423	373	294	347	297	320	2054
2011	418	327	347	330	291	216	1929
2012	401	409	380	394	404	435	2423
Mean	406	353	304	297	291	248	1899
S.D.	60	67	61	86	88	140	372

Unit: Count

Appendix 2-203

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of male rats (Week 6 of administration)
 Dose (mg/kg): 30

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
3008	481	453	409	384	369	313	2409
3009	435	410	365	311	278	281	2080
3010	466	430	340	451	261	196	2144
3011	473	415	380	432	351	420	2471
3012	393	328	253	169	71	62	1276
Mean	450	407	349	349	266	254	2076
S.D.	36	47	59	114	118	134	477

Unit: Count

Appendix 2-204

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of male rats (Week 6 of administration)
 Dose (mg/kg): 100

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
4008S							
4009S							
4010S							
4011S							
4012S							
Mean							
S.D.							

Unit: Count

S: Sacrificed moribund

Appendix 2-205

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of female rats (Main group, Lactation day 4)
 Dose (mg/kg): 0

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
1101	390	136	342	84	45	337	1334
1105	487	360	267	405	317	250	2086
1106	200	76	143	37	139	20	615
1107	348	18	16	179	24	78	663
1112	286	74	26	31	182	150	749
Mean	342	133	159	147	141	167	1089
S.D.	108	134	145	156	118	128	628

Unit: Count

Appendix 2-206

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of female rats (Main group, Lactation day 4)
 Dose (mg/kg): 10

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
2102	497	249	245	198	247	159	1595
2103	390	102	60	23	170	141	886
2105	269	54	247	333	166	277	1346
2111	473	234	231	352	182	36	1508
2112	230	218	260	340	255	38	1341
Mean	372	171	209	249	204	130	1335
S.D.	119	88	84	141	43	100	274

Unit: Count

Appendix 2-207

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of female rats (Main group, Lactation day 4)
 Dose (mg/kg): 30

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
3101	430	208	267	319	361	293	1878
3102	370	52	194	140	59	278	1093
3104	326	82	104	2	13	11	538
3107	383	305	244	80	23	2	1037
3111	233	142	145	107	13	13	653
Mean	348	158	191	130	94	119	1040
S.D.	74	102	68	118	151	152	526

Unit: Count

Appendix 2-208

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of female rats (Main group, Lactation day 4)
 Dose (mg/kg): 100

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
4101S							
4102S							
4103D							
4104D							
4105S							
4106S							
4107S							
4108S							
4109D							
4110S							
4111S							
4112S							
Mean							
S.D.							

Unit: Count

D: Dead

S: Sacrificed moribund

Appendix 2-209

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of male rats (Week 2 of recovery)
 Dose (mg/kg): 0

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
1008	450	376	319	372	275	183	1975
1009	459	328	392	229	319	214	1941
1010	417	304	224	76	339	210	1570
1011	403	351	179	140	39	250	1362
1012	500	410	338	384	270	106	2008
Mean	446	354	290	240	248	193	1771
S.D.	38	41	87	137	121	54	289

Unit: Count

Appendix 2-210

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual motor activity of male rats (Week 2 of recovery)
 Dose (mg/kg): 30

Animal number	Interval (minutes)						Total (0-60)
	0-10	10-20	20-30	30-40	40-50	50-60	
3008	376	352	290	291	312	187	1808
3009	315	293	173	195	104	98	1178
3010	434	259	262	172	274	209	1610
3011	459	380	195	208	218	101	1561
3012	304	215	190	223	249	181	1362
Mean	378	300	222	218	231	155	1504
S.D.	69	67	51	45	79	52	242

Unit: Count

Appendix 3-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of male rats (Administration period)
 Dose (mg/kg): 0

Animal number	Day of administration							Gain 1-42
	1	8	15	22	29	36	42	
1001	391	426	455	483	509	534	547	156
1002	380	398	418	439	464	485	498	118
1003	401	434	450	475	488	504	515	114
1004	381	403	427	440	470	500	519	138
1005	372	386	408	416	430	449	458	86
1006	407	439	460	479	502	527	534	127
1007	373	402	419	439	461	472	480	107
1008	398	431	447	462	483	495	505	107
1009	380	407	436	462	476	495	511	131
1010	375	399	419	438	457	484	498	123
1011	414	456	484	513	536	569	589	175
1012	389	408	434	445	454	468	465	76
Mean	388	416	438	458	478	499	510	122
S.D.	14	21	22	27	28	32	36	27

Unit: g

Appendix 3-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of male rats (Administration period)
 Dose (mg/kg): 10

Animal number	Day of administration							Gain 1-42
	1	8	15	22	29	36	42	
2001	404	420	442	465	481	490	498	94
2002	381	397	418	441	449	459	464	83
2003	393	424	453	471	494	511	527	134
2004	382	405	428	450	465	488	506	124
2005	416	452	481	500	533	556	579	163
2006	388	412	429	464	494	501	512	124
2007	390	416	437	454	475	492	503	113
2008	400	428	466	484	499	525	529	129
2009	365	384	406	432	437	452	451	86
2010	382	410	432	446	470	494	513	131
2011	374	404	429	444	460	483	489	115
2012	388	416	445	464	485	498	508	120
Mean	389	414	439	460	479	496	507	118
S.D.	14	17	21	19	25	27	32	22

Unit: g

Appendix 3-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of male rats (Administration period)
 Dose (mg/kg): 30

Animal number	Day of administration							Gain 1-42
	1	8	15	22	29	36	42	
3001	380	402	421	439	457	476	483	103
3002	399	420	449	463	477	497	505	106
3003	375	391	407	415	419	428	434	59
3004	406	424	441	462	478	499	512	106
3005	368	392	409	437	457	473	480	112
3006	388	427	444	454	475	490	494	106
3007	414	428	454	461	484	504	528	114
3008	388	414	427	431	447	474	482	94
3009	388	413	433	445	459	480	493	105
3010	380	407	422	437	457	473	496	116
3011	383	399	411	429	442	463	477	94
3012	378	395	419	430	446	460	469	91
Mean	387	409	428	442	458	476	488	101
S.D.	13	14	16	15	19	21	24	15

Unit: g

Appendix 3-4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of male rats (Administration period)
 Dose (mg/kg): 100

Animal number	Day of administration							Gain 1-42
	1	8	15	22	29	36	42	
4001S (Day 6)	395							
4002S (Day 10)	386	322						
4003D (Day 8)	413							
4004S (Day 10)	375	362						
4005S (Day 11)	383	305						
4006S (Day 9)	388	323						
4007S (Day 10)	372	284						
4008S (Day 10)	385	279						
4009S (Day 11)	372	274						
4010S (Day 8)	418							
4011S (Day 6)	391							
4012S (Day 10)	399	327						
Mean	390	310						
S.D.	15	30						

Unit: g

S: Sacrificed moribund

D: Dead

(): Day of death or moribund sacrifice

Appendix 3-5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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			Gain 1-15
	1	8	15	
1101	254	254	265	11
1102	236	252	263	27
1103	258	273	281	23
1104	250	261	266	16
1105	231	248	253	22
1106	259	266	278	19
1107	232	246	257	25
1108	267	287	296	29
1109	242	254	263	21
1110	220	238	238	18
1111	229	247	255	26
1112	234	236	250	16
Mean	243	255	264	21
S.D.	15	15	15	5

Unit: g

Appendix 3-6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of female rats during the pre-mating period (Main group)
 Dose (mg/kg): 10

Animal number	Day of administration			Gain 1-15
	1	8	15	
2101	243	241	254	11
2102	238	258	265	27
2103	228	229	247	19
2104	254	260	274	20
2105	237	252	255	18
2106	234	240	243	9
2107	238	259	264	26
2108	257	279	284	27
2109	227	235	237	10
2110	252	267	271	19
2111	229	248	258	29
2112	251	272	282	31
Mean	241	253	261	21
S.D.	11	15	15	8

Unit: g

Appendix 3-7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of female rats during the pre-mating period (Main group)
 Dose (mg/kg): 30

Animal number	Day of administration			Gain 1-15
	1	8	15	
3101	255	265	276	21
3102	231	213	231	0
3103	245	239	239	-6
3104	253	258	268	15
3105	260	270	277	17
3106	225	235	243	18
3107	216	238	240	24
3108	237	245	245	8
3109	240	251	250	10
3110	230	238	240	10
3111	271	274	289	18
3112	243	255	259	16
Mean	242	248	255	13
S.D.	16	17	19	9

Unit: g

Appendix 3-8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of female rats during the pre-mating period (Main group)
 Dose (mg/kg): 100

Animal number	Day of administration			Gain 1-15
	1	8	15	
4101S (Day 10)	245	216		
4102S (Day 8)	222	182		
4103D (Day 8)	256			
4104D (Day 9)	250	201		
4105S (Day 8)	252			
4106S (Day 9)	243	197		
4107S (Day 12)	252	250		
4108S (Day 10)	263	246		
4109D (Day 8)	232			
4110S (Day 6)	232			
4111S (Day 10)	238	202		
4112S (Day 7)	233			
Mean	243	213		
S.D.	12	26		

Unit: g

S: Sacrificed moribund

D: Dead

(): Day of death or moribund sacrifice

Appendix 3-9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of dams during the gestation period (Main group)
 Dose (mg/kg): 0

Dam number	Administration				Gain 0-20
	0	7	14	20a)	
1101	276	308	328	365	89
1102	280	319	355	436	156
1103	287	328	369	465	178
1104	281	308	336	372	91
1105	259	283	308	387	128
1106	284	323	367	459	175
1107	256	289	319	397	141
1108	292	328	356	444	152
1109	268	298	331	413	145
1110	237	264	301	391	154
1111	256	283	317	376	120
1112	253	284	322	404	151
Mean	269	301	334	409	140
S.D.	17	21	23	34	29

Unit: g

a): Gestation day

Appendix 3-10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of dams during the gestation period (Main group)
 Dose (mg/kg): 10

Dam number	Administration				Gain 0-20
	0	7	14	20a)	
2101	Not copulated				
2102	270	302	335	416	146
2103	252	291	332	405	153
2104	289	312	348	438	149
2105	261	298	329	414	153
2106	255	288	320	397	142
2107	272	300	327	404	132
2108	295	332	369	450	155
2109	247	275	301	372	125
2110	272	318	349	437	165
2111	269	302	355	428	159
2112	284	318	361	423	139
Mean	270	303	339	417	147
S.D.	15	16	20	22	12

Unit: g

a): Gestation day

Appendix 3-11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of dams during the gestation period (Main group)
 Dose (mg/kg): 30

Dam number	Administration				Gain 0-20
	0	7	14	20a)	
3101	280	310	352	445	165
3102	233	264	291	362	129
3103	250	273	312	381	131
3104	271	305	341	410	139
3105	271	323	358	434	163
3106	251	295	347	439	188
3107	238	282	320	371	133
3108	258	290	330	401	143
3109	259	298	340	424	165
3110	238	266	295	363	125
3111	292	318	367	454	162
3112	266	302	342	421	155
Mean	259	294	333	409	150
S.D.	18	19	24	33	19

Unit: g

a): Gestation day

Appendix 3-12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of dams during the gestation period (Main group)
 Dose (mg/kg): 100

Dam number	Administration				Gain 0-20
	0	7	14	20a)	
4101S					
4102S					
4103D					
4104D					
4105S					
4106S					
4107S					
4108S					
4109D					
4110S					
4111S					
4112S					
Mean					
S.D.					

Unit: g

a): Gestation day

S: Sacrificed moribund

D: Dead

Appendix 3-13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of dams during the lactation period (Main group)
 Dose (mg/kg): 0

Dam number	Administration		Gain 0-4
	0	4a)	
1101	340	323	-17
1102	348	335	-13
1103	345	348	3
1104	356	354	-2
1105	290	303	13
1106	339	349	10
1107	282	286	4
1108	322	362	40
1109	302	309	7
1110	269	313	44
1111	315	319	4
1112	300	316	16
Mean	317	326	9
S.D.	29	23	18

Unit: g

a): Lactation day

Appendix 3-14

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of dams during the lactation period (Main group)
 Dose (mg/kg): 10

Dam number	Administration		Gain 0-4
	0	4a)	
2101	Not copulated		
2102	326	321	-5
2103	302	327	25
2104	323	319	-4
2105	330	344	14
2106b)			
2107	308	311	3
2108	353	355	2
2109	291	311	20
2110	315	326	11
2111	337	345	8
2112	377	371	-6
Mean	326	333	7
S.D.	25	20	11

Unit: g

a): Lactation day

b): Died on gestation day 22

Appendix 3-15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of dams during the lactation period (Main group)
 Dose (mg/kg): 30

Dam number	Administration		Gain 0-4
	0	4a)	
3101	342	351	9
3102	276	304	28
3103	307	309	2
3104	325	330	5
3105	324	362	38
3106	320	350	30
3107	323	324	1
3108	341	337	-4
3109	347	349	2
3110	288	303	15
3111	338	376	38
3112	332	349	17
Mean	322	337	15
S.D.	22	23	15

Unit: g

a): Lactation day

Appendix 3-16

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of dams during the lactation period (Main group)
 Dose (mg/kg): 100

Dam number	Administration		Gain 0-4
	0	4a)	
4101S			
4102S			
4103D			
4104D			
4105S			
4106S			
4107S			
4108S			
4109D			
4110S			
4111S			
4112S			
Mean			
S.D.			

Unit: g

a): Lactation day

S: Sacrificed moribund

D: Dead

Appendix 3-17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of female rats (Satellite group)
 Dose (mg/kg): 0

Animal number	Day of administration			Gain 1-15
	1	8	15	
1113	228	245	248	20
1114	269	274	291	22
1115	239	256	264	25
1116	269	274	282	13
1117	241	251	257	16
1118	218	238	249	31
1119	251	261	274	23
1120	250	268	269	19
1121	229	230	234	5
1122	242	262	266	24
Mean	244	256	263	20
S.D.	17	15	17	7

Unit: g

Appendix 3-18

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of female rats (Satellite group)
 Dose (mg/kg): 100

Animal number	Day of administration			Gain 1-15
	1	8	15	
4113S (Day 11)	242	198		
4114S (Day 8)	228			
4115S (Day 12)	226	220		
4116D (Day 11)	246	230		
4117S (Day 12)	219	176		
4118S (Day 11)	259	219		
4119D (Day 10)	236	190		
4120S (Day 9)	229	201		
4121D (Day 8)	262			
4122S (Day 12)	229	178		
Mean	238	202		
S.D.	14	20		

Unit: g

S: Sacrificed moribund

D: Dead

(): Day of death or moribund sacrifice

Appendix 3-19

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual body weight of male rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery			Gain 1-14
	1	8	14	
1008	506	520	522	16
1009	508	510	514	6
1010	497	502	515	18
1011	586	598	599	13
1012	470	480	482	12
Mean	513	522	526	13
S.D.	43	45	43	5

Unit: g

Appendix 3-20

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual body weight of male rats (Recovery period)
Dose (mg/kg): 30

Animal number	Day of recovery			Gain 1-14
	1	8	14	
3008	481	493	502	21
3009	497	507	515	18
3010	502	517	523	21
3011	477	490	503	26
3012	471	482	497	26
Mean	486	498	508	22
S.D.	13	14	11	4

Unit: g

Appendix 4-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	21	27	24	22	25	24
1002	19	22	20	21	23	24
1003	26	28	20	22	21	25
1004	25	26	27	25	27	26
1005	20	21	20	18	23	20
1006	21	24	22	22	25	22
1007	25	28	23	19	22	20
1008	25	27	23	21	22	22
1009	22	27	28	24	23	24
1010	25	23	23	23	24	27
1011	30	30	30	35	27	26
1012	22	22	24	18	21	21
Mean	23	25	24	23	24	23
S.D.	3	3	3	5	2	2

Unit: g/rat/day

Appendix 4-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of male rats (Administration period)
 Dose (mg/kg): 10

Animal number	Day of administration					
	2	8	15	30	36	42
2001	23	24	21	19	22	21
2002	26	18	21	15	18	19
2003	25	23	25	22	24	22
2004	27	23	26	29	28	26
2005	30	25	24	26	26	28
2006	22	23	23	24	23	20
2007	24	23	21	22	23	24
2008	26	23	25	25	25	24
2009	19	22	21	22	21	23
2010	25	25	25	24	27	25
2011	23	24	24	23	23	22
2012	25	26	25	23	20	22
Mean	25	23	23	23	23	23
S.D.	3	2	2	3	3	3

Unit: g/rat/day

Appendix 4-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of male rats (Administration period)
 Dose (mg/kg): 30

Animal number	Day of administration					
	2	8	15	30	36	42
3001	23	21	22	18	23	22
3002	27	28	25	23	27	25
3003	21	22	20	20	22	20
3004	23	22	25	23	25	25
3005	23	23	26	19	24	19
3006	26	29	24	22	25	24
3007	24	22	23	23	26	26
3008	24	23	22	23	26	24
3009	21	26	21	20	25	28
3010	20	23	21	23	22	23
3011	27	25	24	25	26	28
3012	24	22	21	20	23	22
Mean	24	24	23	22	25	24
S.D.	2	3	2	2	2	3

Unit: g/rat/day

Appendix 4-4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of male rats (Administration period)
 Dose (mg/kg): 100

Animal number	Day of administration					
	2	8	15	30	36	42
4001S (Day 6)	14					
4002S (Day 10)	17	11				
4003D (Day 8)	17					
4004S (Day 10)	25	13				
4005S (Day 11)	19	1				
4006S (Day 9)	23	5				
4007S (Day 10)	13	3				
4008S (Day 10)	21	4				
4009S (Day 11)	20	4				
4010S (Day 8)	24					
4011S (Day 6)	16					
4012S (Day 10)	20	10				
Mean	19	6				
S.D.	4	4				

Unit: g/rat/day

S: Sacrificed moribund

D: Dead

(): Day of death or moribund sacrifice

Appendix 4-5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	17	14	20
1102	17	17	19
1103	16	20	15
1104	16	22	16
1105	20	20	18
1106	17	17	19
1107	19	19	21
1108	20	23	20
1109	12	21	18
1110	15	21	21
1111	18	18	17
1112	17	12	18
Mean	17	19	19
S.D.	2	3	2

Unit: g/rat/day

Appendix 4-6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 10

Animal number	Day of administration		
	2	8	15
2101	16	16	21
2102	13	22	20
2103	16	12	19
2104	18	16	22
2105	18	19	19
2106	12	20	18
2107	17	22	20
2108	20	23	19
2109	14	18	17
2110	12	19	19
2111	15	23	21
2112	19	22	20
Mean	16	19	20
S.D.	3	3	1

Unit: g/rat/day

Appendix 4-7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 30

Animal number	Day of administration		
	2	8	15
3101	19	14	22
3102	17	10	16
3103	17	16	13
3104	16	15	20
3105	13	21	21
3106	12	17	19
3107	17	18	16
3108	12	19	15
3109	17	18	14
3110	13	17	19
3111	18	15	19
3112	17	18	20
Mean	16	17	18
S.D.	2	3	3

Unit: g/rat/day

Appendix 4-8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of female rats during the pre-mating period (Main group)
 Dose (mg/kg): 100

Animal number	Day of administration	
	2	8 15
4101S (Day 10)	14	16
4102S (Day 8)	11	0
4103D (Day 8)	13	
4104D (Day 9)	11	3
4105S (Day 8)	11	
4106S (Day 9)	12	0
4107S (Day 12)	13	18
4108S (Day 10)	18	10
4109D (Day 8)	14	
4110S (Day 6)	13	
4111S (Day 10)	13	6
4112S (Day 7)	13	
Mean	13	8
S.D.	2	7

Unit: g/rat/day

S: Sacrificed moribund

D: Dead

(): Day of death or moribund sacrifice

Appendix 4-9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	25	20	21	17
1102	14	26	24	19
1103	20	25	23	19
1104	19	19	23	18
1105	17	20	19	18
1106	20	25	28	24
1107	17	20	21	18
1108	20	22	25	22
1109	10	22	21	19
1110	16	23	22	22
1111	16	19	21	16
1112	18	21	20	25
Mean	18	22	22	20
S.D.	4	2	2	3

Unit: g/rat/day
 a): Gestation day

Appendix 4-10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of dams during the gestation period (Main group)
 Dose (mg/kg): 10

Dam number	Administration			
	1	7	14	20a)
2101	Not copulated			
2102	17	21	22	19
2103	16	22	24	19
2104	22	24	22	20
2105	18	23	23	22
2106	18	23	22	18
2107	21	24	23	21
2108	22	25	27	20
2109	16	20	20	22
2110	20	25	21	18
2111	26	23	26	23
2112	22	24	20	23
Mean	20	23	23	20
S.D.	3	2	2	2

Unit: g/rat/day
 a): Gestation day

Appendix 4-11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of dams during the gestation period (Main group)
 Dose (mg/kg): 30

Dam number	Administration			
	1	7	14	20a)
3101	23	22	24	30
3102	24	24	20	18
3103	10	17	22	18
3104	22	26	24	20
3105	23	27	27	19
3106	23	23	33	23
3107	22	25	24	27
3108	15	20	26	16
3109	22	26	30	23
3110	17	20	19	17
3111	19	20	29	21
3112	16	24	24	22
Mean	20	23	25	21
S.D.	4	3	4	4

Unit: g/rat/day

a): Gestation day

Appendix 4-12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of dams during the gestation period (Main group)
 Dose (mg/kg): 100

Dam number	Administration			
	1	7	14	20a)
4101S				
4102S				
4103D				
4104D				
4105S				
4106S				
4107S				
4108S				
4109D				
4110S				
4111S				
4112S				
Mean				
S.D.				

Unit: g/rat/day
 a): Gestation day
 S: Sacrificed moribund
 D: Dead

Appendix 4-13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine 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	11	19
1102	11	29
1103	10	39
1104	13	23
1105	19	34
1106	24	38
1107	1	27
1108	29	52
1109	8	28
1110	29	42
1111	18	26
1112	24	31
Mean	16	32
S.D.	9	9

Unit: g/rat/day
a): Lactation day

Appendix 4-14

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of dams during the lactation period (Main group)
 Dose (mg/kg): 10

Dam number	Administration	
	2	4a)
2101	Not copulated	
2102	22	38
2103	22	39
2104	0	39
2105	28	36
2106b)		
2107	18	38
2108	20	32
2109	23	35
2110	10	29
2111	22	42
2112	13	25
Mean	18	35
S.D.	8	5

Unit: g/rat/day

a): Lactation day

b): Died on gestation day 22

Appendix 4-15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Individual food consumption of dams during the lactation period (Main group)
Dose (mg/kg): 30

Dam number	Administration	
	2	4a)
3101	21	37
3102	23	34
3103	21	29
3104	23	36
3105	24	45
3106	38	46
3107	17	30
3108	20	36
3109	26	39
3110	22	33
3111	25	50
3112	20	34
Mean	23	37
S.D.	5	7

Unit: g/rat/day
a): Lactation day

Appendix 4-16

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of dams during the lactation period (Main group)
 Dose (mg/kg): 100

Dam number	Administration	
	2	4a)
4101S		
4102S		
4103D		
4104D		
4105S		
4106S		
4107S		
4108S		
4109D		
4110S		
4111S		
4112S		
Mean		
S.D.		

Unit: g/rat/day
 a): Lactation day
 S: Sacrificed moribund
 D: Dead

Appendix 4-17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual food consumption of female rats (Satellite group)
Dose (mg/kg): 0

Animal number	Day of administration		
	2	8	15
1113	19	20	19
1114	20	18	23
1115	16	21	20
1116	21	16	19
1117	14	21	18
1118	18	18	19
1119	21	15	18
1120	19	24	18
1121	15	16	17
1122	14	24	22
Mean	18	19	19
S.D.	3	3	2

Unit: g/rat/day

Appendix 4-18

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual food consumption of female rats (Satellite group)
 Dose (mg/kg): 100

Animal number	Day of administration		
	2	8	15
4113S (Day 11)	8	1	
4114S (Day 8)	14		
4115S (Day 12)	11	10	
4116D (Day 11)	14	4	
4117S (Day 12)	10	0	
4118S (Day 11)	20	3	
4119D (Day 10)	11	0	
4120S (Day 9)	14	9	
4121D (Day 8)	10		
4122S (Day 12)	13	3	
Mean	13	4	
S.D.	3	4	

Unit: g/rat/day

S: Sacrificed moribund

D: Dead

(): Day of death or moribund sacrifice

Appendix 4-19

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine 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	20	29	26
1009	26	30	29
1010	24	29	33
1011	27	33	32
1012	22	29	28
Mean	24	30	30
S.D.	3	2	3

Unit: g/rat/day

Appendix 4-20

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual food consumption of male rats (Recovery period)
Dose (mg/kg): 30

Animal number	Day of recovery		
	1	8	14
3008	22	27	29
3009	24	31	28
3010	23	33	28
3011	24	32	32
3012	22	28	28
Mean	23	30	29
S.D.	1	3	2

Unit: g/rat/day

Appendix 5-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	8.0	++	+	-	-	+	+	Y
1009	8.0	+-	+-	-	+-	-	+-	Y
1010	7.5	++	++	-	-	+	+	Y
1011	>=9.0	++	+	-	-	-	+-	Y
1012	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		

Appendix 5-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 - : Negative
 SREC : Small Round Epithelial Cell +- : Slight
 PS : Phosphate Salts + : Mild
 CO : Calcium Oxalate ++ : Moderate
 +++ : Severe

Appendix 5-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	32	8.1	2320	1.12	2.93	1.18
1009	38	11.0	2164	1.08	4.03	1.54
1010	31	4.6	2482	0.63	1.99	0.82
1011	25	7.1	2698	0.94	3.30	1.31
1012	30	7.2	2522	1.01	2.94	1.08
Mean	31	7.6	2437	0.96	3.04	1.19
S.D.	5	2.3	203	0.19	0.74	0.27

Appendix 5-4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 10

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	8.5	+-	-	-	-	-	+-	Y
2011	7.0	++	++	-	-	+	+-	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			

Appendix 5-5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual urinalysis of male rats (Week 6 of administration)
 Dose (mg/kg): 10

Animal number	URINE SEDIMENT					CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
2008	-	-	+-	-	-	+-	-
2009	-	-	+-	-	-	+-	-
2010	-	-	+-	-	-	+-	-
2011	-	-	+-	-	-	-	-
2012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell - : Negative
 SREC : Small Round Epithelial Cell +- : Slight
 PS : Phosphate Salts + : Mild
 CO : Calcium Oxalate ++ : Moderate
 +++ : Severe

Appendix 5-6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual water intake and urinalysis of male rats (Week 6 of administration)
 Dose (mg/kg): 10

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
2008	32	6.6	2056	0.58	2.06	0.70
2009	29	5.2	2682	0.82	2.15	0.98
2010	52	19.7	1128	0.99	3.97	1.26
2011	31	2.4	2744	0.31	0.93	0.31
2012	30	8.4	1908	0.52	2.86	0.82
Mean	35	8.5	2104	0.64	2.39	0.81
S.D.	10	6.7	659	0.27	1.12	0.35

Appendix 5-7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 30

Animal number	pH	1) Pro- tein	2) Ketone body	3) Glu- cose	4) Occult blood	5) Bili- rubin	6) Urobi- linogen	7) Color
3008	8.0	-	+-	-	-	-	+-	Y
3009	8.5	+	+	-	-	-	+-	Y
3010	7.5	+	+	-	+-	-	+-	Y
3011	8.5	+	+	-	+-	-	+-	Y
3012	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			

Appendix 5-8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual urinalysis of male rats (Week 6 of administration)
 Dose (mg/kg): 30

Animal number	URINE SEDIMENT					CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
3008	-	-	+-	-	-	+-	-
3009	-	-	+-	-	-	+-	-
3010	-	-	+-	-	-	+-	-
3011	-	-	+-	-	-	+-	-
3012	-	-	+-	-	-	-	-

SEC : Squamous Epithelial Cell - : Negative
 SREC : Small Round Epithelial Cell +- : Slight
 PS : Phosphate Salts + : Mild
 CO : Calcium Oxalate ++ : Moderate
 +++ : Severe

Appendix 5-9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual water intake and urinalysis of male rats (Week 6 of administration)
 Dose (mg/kg): 30

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
3008	47	12.4	1854	0.99	4.02	1.44
3009	47	16.1	1380	1.13	3.43	1.29
3010	35	9.5	2038	1.16	3.09	1.27
3011	38	8.3	2064	0.70	2.80	1.08
3012	36	14.4	1652	1.61	4.19	1.79
Mean	41	12.1	1798	1.12	3.51	1.37
S.D.	6	3.3	286	0.33	0.59	0.27

Appendix 5-10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual urinalysis of male rats (Week 6 of administration)
 Dose (mg/kg): 100

Animal number	pH	1) Pro- tein	2) Ketone body	3) Glu- cose	4) Occult blood	5) Bili- rubin	6) Urobi- linogen	7) Color
4008S								
4009S								
4010S								
4011S								
4012S								
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				
S: Sacrificed moribund								

Appendix 5-11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual urinalysis of male rats (Week 6 of administration)
 Dose (mg/kg): 100

Animal number	URINE SEDIMENT					CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4008S							
4009S							
4010S							
4011S							
4012S							

SEC : Squamous Epithelial Cell - : Negative
 SREC : Small Round Epithelial Cell +- : Slight
 PS : Phosphate Salts + : Mild
 CO : Calcium Oxalate ++ : Moderate
 +++ : Severe

S: Sacrificed moribund

Appendix 5-12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual water intake and urinalysis of male rats (Week 6 of administration)
 Dose (mg/kg): 100

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
4008S						
4009S						
4010S						
4011S						
4012S						
Mean						
S.D.						

S: Sacrificed moribund

Appendix 5-13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	6.5	++	+	-	-	+	+	Y
1009	>=9.0	+	+	-	+-	-	+-	Y
1010	7.0	++	+	-	-	-	+-	Y
1011	8.5	++	+	-	+-	-	+-	Y
1012	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		

Appendix 5-14

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 - : Negative
 SREC : Small Round Epithelial Cell +- : Slight
 PS : Phosphate Salts + : Mild
 CO : Calcium Oxalate ++ : Moderate
 +++ : Severe

Appendix 5-15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	45	15.1	1716	1.33	3.89	1.63
1009	40	9.1	2422	1.15	3.63	1.66
1010	34	7.0	2930	1.04	3.22	1.37
1011	32	8.3	2926	1.33	3.96	1.68
1012	33	12.5	2258	1.50	4.64	1.88
Mean	37	10.4	2450	1.27	3.87	1.64
S.D.	6	3.3	508	0.18	0.52	0.18

Appendix 5-16

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual urinalysis of male rats (Week 2 of recovery)
 Dose (mg/kg): 30

Animal number	pH	1) Pro- tein	2) Ketone body	3) Glu- cose	4) Occult blood	5) Bili- rubin	6) Urobi- linogen	7) Color
3008	8.0	+	+	-	-	-	+-	Y
3009	8.5	+-	-	-	+-	-	+-	Y
3010	8.5	+	+	-	+-	-	+-	Y
3011	8.5	+-	+-	-	+-	-	+-	Y
3012	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			

Appendix 5-17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual urinalysis of male rats (Week 2 of recovery)
 Dose (mg/kg): 30

Animal number	URINE SEDIMENT					CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
3008	-	-	+-	-	-	+-	-
3009	-	-	+-	-	-	+-	-
3010	-	-	+-	-	-	+-	-
3011	-	-	+-	-	-	+-	-
3012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell - : Negative
 SREC : Small Round Epithelial Cell +- : Slight
 PS : Phosphate Salts + : Mild
 CO : Calcium Oxalate ++ : Moderate
 +++ : Severe

Appendix 5-18

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual water intake and urinalysis of male rats (Week 2 of recovery)
 Dose (mg/kg): 30

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
3008	46	14.8	1962	1.60	4.75	2.10
3009	47	20.8	1932	2.41	6.55	2.87
3010	36	14.4	2010	1.41	4.76	2.13
3011	42	15.0	2464	1.65	6.46	2.67
3012	37	13.5	2126	1.76	4.95	2.11
Mean	42	15.7	2099	1.77	5.49	2.38
S.D.	5	2.9	217	0.38	0.93	0.37

Appendix 6-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Satellite group, Day 15 of administration)
 Dose (mg/kg): 0

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
1113	846	15.6	45.5	53.8	18.4	34.3	1.6	99.1	11.7	18.1	201
1114	821	15.6	44.9	54.6	19.0	34.9	2.6	89.5	11.0	18.4	233
1115	803	15.3	44.2	55.0	19.1	34.6	1.8	100.6	12.0	19.9	180
1116	794	15.4	44.9	56.5	19.4	34.3	2.5	91.9	11.2	14.8	223
1117	872	15.8	45.1	51.7	18.2	35.1	2.5	98.4	11.5	16.9	200
1118	814	15.4	43.8	53.7	18.9	35.1	2.0	111.4	11.5	16.0	212
1119	833	15.8	45.7	54.8	18.9	34.5	2.9	102.6	11.3	15.2	200
1120	897	16.1	47.6	53.1	18.0	33.9	1.9	105.4	11.6	20.1	188
1121	822	14.5	42.7	51.9	17.7	34.1	2.1	121.6	11.4	18.6	193
1122	818	15.1	43.1	52.7	18.5	35.0	1.6	104.7	11.9	16.3	225
Mean	832	15.5	44.8	53.8	18.6	34.6	2.2	102.5	11.5	17.4	206
S.D.	32	0.4	1.4	1.5	0.5	0.4	0.5	9.3	0.3	1.9	17

Appendix 6-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Satellite group, Day 15 of administration)
 Dose (mg/kg): 0

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/ μ L)					
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1113	88.6	70.4	25.3	1.3	0.3	2.0	0.6	62.4	22.4	1.2	0.3	1.8	0.5
1114	94.4	72.9	22.5	1.0	0.3	1.9	1.5	68.7	21.2	0.9	0.3	1.8	1.4
1115	63.1	72.5	22.0	1.9	0.2	2.1	1.2	45.7	13.9	1.2	0.2	1.3	0.8
1116	72.5	76.4	20.0	1.1	0.3	1.4	0.8	55.4	14.5	0.8	0.2	1.0	0.6
1117	66.7	75.1	19.7	2.3	0.3	1.7	1.0	50.1	13.1	1.5	0.2	1.1	0.6
1118	51.6	72.1	24.1	1.4	0.2	1.1	1.0	37.3	12.4	0.7	0.1	0.6	0.5
1119	91.6	73.5	21.4	1.6	0.4	2.0	1.1	67.3	19.6	1.5	0.3	1.8	1.0
1120	79.4	78.8	14.8	2.0	0.3	2.4	1.7	62.6	11.8	1.6	0.2	1.9	1.3
1121	40.3	65.1	29.8	1.7	0.2	2.0	1.2	26.3	12.0	0.7	0.1	0.8	0.5
1122	73.4	61.8	33.5	2.0	0.1	2.1	0.4	45.4	24.6	1.5	0.1	1.5	0.3
Mean	72.2	71.9	23.3	1.6	0.3	1.9	1.1	52.1	16.6	1.2	0.2	1.4	0.8
S.D.	17.5	5.1	5.3	0.4	0.1	0.4	0.4	13.8	4.9	0.4	0.1	0.5	0.4

LUC: Large unstained cells

Appendix 6-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Satellite group, Day 15 of administration)
 Dose (mg/kg): 100

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
4113S	908Z	16.7Z	49.4Z	54.4Z	18.4Z	33.8Z	0.2Z	104.9Z	13.9Z	16.4Z	480Z
4114S	898Z	16.2Z	47.3Z	52.6Z	18.0Z	34.3Z	0.5Z	133.5Z	12.6Z	11.7Z	259Z
4115S	815Z	14.2Z	43.3Z	53.1Z	17.4Z	32.8Z	1.0Z	126.8Z	13.4Z	12.6Z	316Z
4116D											
4117S	776Z	13.6Z	40.8Z	52.6Z	17.5Z	33.3Z	0.8Z	79.9Z	10.3Z	7.7Z	216Z
4118S	1019Z	18.0Z	53.2Z	52.2Z	17.6Z	33.7Z	0.2Z	86.1Z	13.6Z	13.0Z	225Z
4119D											
4120S	997Z	18.3Z	52.4Z	52.6Z	18.3Z	34.9Z	1.1Z	119.0Z	-	-	-
4121D											
4122S	807Z	13.8Z	41.1Z	50.9Z	17.1Z	33.6Z	0.6Z	97.9Z	14.9Z	25.3Z	253Z
Mean											
S.D.											

-: Not done. A sufficient amount of blood sample was not obtained due to severe moribundity.

D: Dead

S: Sacrificed moribund

Z: Data was excluded from statistical analysis.

Appendix 6-4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Satellite group, Day 15 of administration)
 Dose (mg/kg): 100

Animal number	WBC	Differential leukocyte ratio (%)					Differential leukocyte counts (10E2/ μ L)						
	10E2/ μ L	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4113S	120.4Z	38.2Z	53.6Z	0.4Z	0.3Z	4.7Z	2.8Z	46.0Z	64.5Z	0.5Z	0.4Z	5.6Z	3.3Z
4114S	81.0Z	10.8Z	84.2Z	0.1Z	0.1Z	3.6Z	1.2Z	8.7Z	68.2Z	0.1Z	0.1Z	2.9Z	1.0Z
4115S	89.8Z	75.2Z	17.6Z	1.6Z	0.4Z	2.9Z	2.3Z	67.5Z	15.8Z	1.5Z	0.4Z	2.6Z	2.1Z
4116D													
4117S	153.6Z	66.8Z	26.7Z	0.7Z	0.4Z	4.2Z	1.2Z	102.7Z	41.0Z	1.0Z	0.6Z	6.4Z	1.9Z
4118S	153.6Z	35.0Z	58.1Z	0.1Z	0.5Z	5.3Z	1.0Z	53.7Z	89.3Z	0.1Z	0.7Z	8.2Z	1.5Z
4119D													
4120S	101.7Z	23.5Z	65.2Z	0.2Z	0.5Z	5.7Z	4.9Z	23.9Z	66.3Z	0.2Z	0.5Z	5.8Z	5.0Z
4121D													
4122S	90.5Z	60.4Z	33.4Z	1.0Z	0.3Z	4.0Z	0.9Z	54.7Z	30.2Z	0.9Z	0.3Z	3.6Z	0.8Z
Mean													
S.D.													

LUC: Large unstained cells

D: Dead

S: Sacrificed moribund

Z: Data was excluded from statistical analysis.

Appendix 6-5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of administration)
 Dose (mg/kg): 0

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
1001	895	15.6	44.8	50.0	17.4	34.9	1.5	103.6	12.1	20.3	240
1002	846	15.5	44.8	53.0	18.4	34.6	2.6	106.6	17.6	25.8	287
1003	874	15.9	45.4	52.0	18.2	35.1	2.0	97.0	13.6	16.8	245
1004	905	16.1	46.7	51.6	17.8	34.5	2.1	97.7	14.2	23.1	231
1005	897	15.7	45.7	50.9	17.5	34.3	2.2	94.6	13.9	18.7	288
Mean	883	15.8	45.5	51.5	17.9	34.7	2.1	99.9	14.3	20.9	258
S.D.	24	0.2	0.8	1.1	0.4	0.3	0.4	5.0	2.0	3.6	27

Appendix 6-6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of administration)
 Dose (mg/kg): 0

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)					Differential leukocyte counts (10E2/ μ L)						
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1001	70.7	81.4	15.0	1.0	0.1	2.0	0.5	57.5	10.6	0.7	0.1	1.4	0.3
1002	108.6	74.8	21.3	0.9	0.4	2.1	0.5	81.2	23.1	1.0	0.4	2.3	0.5
1003	82.0	69.7	26.8	1.3	0.3	1.6	0.4	57.2	22.0	1.0	0.2	1.3	0.3
1004	56.9	69.2	26.4	1.0	0.2	2.7	0.5	39.4	15.0	0.6	0.1	1.5	0.3
1005	62.5	81.3	14.9	1.7	0.2	1.6	0.3	50.8	9.3	1.1	0.1	1.0	0.2
Mean	76.1	75.3	20.9	1.2	0.2	2.0	0.4	57.2	16.0	0.9	0.2	1.5	0.3
S.D.	20.5	6.0	5.8	0.3	0.1	0.5	0.1	15.3	6.4	0.2	0.1	0.5	0.1

LUC: Large unstained cells

Appendix 6-7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of administration)
 Dose (mg/kg): 10

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
2001	882	15.2	44.4	50.3	17.3	34.3	2.1	105.0	13.3	19.3	226
2002	871	15.5	44.1	50.6	17.8	35.2	1.6	97.1	13.4	17.5	255
2003	866	15.3	43.7	50.4	17.7	35.1	1.8	127.8	14.7	20.1	262
2004	893	15.2	44.0	49.2	17.0	34.5	1.9	117.7	20.0	28.6	270
2005	895	15.7	45.6	51.0	17.6	34.5	2.3	110.4	13.6	21.4	286
Mean	881	15.4	44.4	50.3	17.5	34.7	1.9	111.6	15.0	21.4	260
S.D.	13	0.2	0.7	0.7	0.3	0.4	0.3	11.8	2.9	4.3	22

Appendix 6-8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of administration)
 Dose (mg/kg): 10

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)					Differential leukocyte counts (10E2/ μ L)						
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
2001	71.9	81.5	14.8	0.7	0.2	2.0	0.7	58.6	10.7	0.5	0.2	1.4	0.5
2002	34.3	73.9	22.0	1.8	0.1	1.6	0.7	25.3	7.5	0.6	0.0	0.5	0.2
2003	63.3	71.6	23.2	2.4	0.2	2.4	0.2	45.3	14.7	1.5	0.1	1.5	0.1
2004	77.7	68.2	27.0	2.5	0.2	1.7	0.4	53.0	21.0	1.9	0.2	1.3	0.3
2005	60.3	57.0	38.9	1.4	0.2	1.9	0.4	34.4	23.5	0.9	0.1	1.2	0.2
Mean	61.5	70.4	25.2	1.8	0.2	1.9	0.5	43.3	15.5	1.1	0.1	1.2	0.3
S.D.	16.7	9.0	8.9	0.7	0.0	0.3	0.2	13.6	6.7	0.6	0.1	0.4	0.2

LUC: Large unstained cells

Appendix 6-9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of administration)
 Dose (mg/kg): 30

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
3001	871	15.1	43.3	49.7	17.4	35.0	1.5	102.8	20.1	25.4	301
3002	886	15.0	43.8	49.4	17.0	34.4	1.8	112.7	12.1	15.9	232
3003	878	15.3	43.0	49.0	17.4	35.6	1.5	88.5	16.5	20.1	251
3004	866	15.2	43.8	50.6	17.6	34.8	2.4	98.8	14.6	15.4	284
3005	864	14.9	43.2	50.0	17.2	34.5	1.1	108.9	15.5	19.0	984*
Mean	873	15.1	43.4	49.7	17.3	34.9	1.7	102.3	15.8	19.2	410
S.D.	9	0.2	0.4	0.6	0.2	0.5	0.5	9.4	2.9	4.0	322

*: Re-analyzed value

Appendix 6-10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of administration)
 Dose (mg/kg): 30

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/ μ L)					
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
3001	76.5	78.1	18.5	1.4	0.2	1.4	0.3	59.8	14.2	1.1	0.1	1.1	0.3
3002	73.0	69.5	27.1	1.1	0.3	1.7	0.3	50.7	19.8	0.8	0.2	1.2	0.3
3003	78.9	74.0	22.2	1.0	0.3	1.6	0.9	58.3	17.5	0.8	0.3	1.3	0.7
3004	62.3	54.7	41.5	0.9	0.2	2.2	0.6	34.1	25.8	0.5	0.1	1.4	0.4
3005	203.1	22.9	66.3	0.4	0.2	4.1	6.1	46.6	134.6	0.8	0.3	8.3	12.5
Mean	98.8	59.8	35.1	1.0	0.2	2.2	1.6	49.9	42.4	0.8	0.2	2.7	2.8
S.D.	58.7	22.5	19.5	0.4	0.1	1.1	2.5	10.4	51.7	0.2	0.1	3.2	5.4

LUC: Large unstained cells

Appendix 6-11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of administration)
 Dose (mg/kg): 100

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
4001S	955Z	18.3Z	52.9Z	55.4Z	19.2Z	34.6Z	0.8Z	111.2Z	18.1Z	24.3Z	795Z
4002S	1064Z	19.0Z	57.3Z	53.9Z	17.9Z	33.1Z	0.3Z	79.4Z	16.9Z	29.1Z	225Z
4003D											
4004S	1009Z	17.6Z	53.2Z	52.7Z	17.4Z	33.0Z	0.5Z	108.1Z	18.5Z	26.7Z	418Z
4005S	858Z	15.4Z	46.4Z	54.1Z	18.0Z	33.2Z	1.1Z	85.0Z	13.5Z	16.9Z	524Z
4006S	882Z	15.3Z	45.0Z	51.0Z	17.4Z	34.1Z	0.5Z	80.9Z	-	-	-
4007S	944Z	16.7Z	50.9Z	53.9Z	17.7Z	32.9Z	0.9Z	96.3Z	-	-	-
4008S	986Z	18.5Z	55.7Z	56.5Z	18.7Z	33.2Z	0.8Z	85.7Z	21.1Z	30.7Z	543Z
4009S	1288Z*	21.6Z*	68.2Z*	52.9Z*	16.8Z*	31.8Z*	0.5Z*	128.2Z*	-	-	-
4010S	882Z	17.2Z	51.1Z	57.9Z	19.6Z	33.8Z	0.5Z	127.9Z	14.5Z	18.7Z	306Z
4011S	968Z	17.8Z	51.8Z	53.5Z	18.4Z	34.3Z	0.5Z	92.6Z	19.5Z	27.7Z	356Z
4012S	672Z	12.0Z	36.6Z	54.4Z	17.8Z	32.7Z	2.3Z	129.7Z	12.2Z	15.4Z	429Z
Mean											
S.D.											

*: Re-analyzed value

-: Not done. A sufficient amount of blood sample was not obtained due to severe moribundity.

D: Dead

S: Sacrificed moribund

Z: Data was excluded from statistical analysis.

Appendix 6-12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of administration)
 Dose (mg/kg): 100

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)					Differential leukocyte counts (10E2/ μ L)						
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4001S	151.6Z	14.4Z	78.2Z	0.2Z	0.4Z	4.2Z	2.7Z	21.9Z	118.5Z	0.2Z	0.6Z	6.3Z	4.0Z
4002S	72.7Z	31.5Z	62.4Z	0.1Z	0.2Z	4.9Z	1.0Z	22.9Z	45.3Z	0.1Z	0.2Z	3.5Z	0.7Z
4003D													
4004S	110.2Z	17.7Z	74.0Z	0.1Z	0.4Z	4.8Z	3.1Z	19.5Z	81.5Z	0.1Z	0.4Z	5.3Z	3.4Z
4005S	128.6Z	47.7Z	41.4Z	0.4Z	0.3Z	6.3Z	3.9Z	61.4Z	53.3Z	0.5Z	0.4Z	8.1Z	5.0Z
4006S	239.5Z	6.6Z	88.8Z	0.1Z	0.1Z	2.6Z	1.9Z	15.8Z	212.7Z	0.1Z	0.2Z	6.2Z	4.6Z
4007S	136.3Z	15.0Z	78.5Z	0.1Z	0.2Z	4.2Z	2.0Z	20.4Z	107.0Z	0.2Z	0.2Z	5.7Z	2.7Z
4008S	160.6Z	41.1Z	54.7Z	0.4Z	0.3Z	2.5Z	1.0Z	65.9Z	87.8Z	0.7Z	0.5Z	4.0Z	1.6Z
4009S	233.8Z*	13.4Z*	80.9Z*	0.2Z*	0.2Z*	5.1Z*	0.3Z*	31.2Z*	189.0Z*	0.4Z*	0.4Z*	12.0Z*	0.6Z*
4010S	140.1Z	16.9Z	75.5Z	0.3Z	0.3Z	5.1Z	2.0Z	23.6Z	105.8Z	0.4Z	0.5Z	7.1Z	2.7Z
4011S	196.6Z	19.1Z	75.2Z	0.1Z	0.3Z	4.3Z	1.1Z	37.5Z	147.8Z	0.2Z	0.5Z	8.5Z	2.1Z
4012S	120.0Z	56.8Z	35.8Z	0.3Z	0.3Z	5.3Z	1.5Z	68.2Z	43.0Z	0.3Z	0.3Z	6.3Z	1.8Z
Mean													
S.D.													

LUC: Large unstained cells

*: Re-analyzed value

D: Dead

S: Sacrificed moribund

Z: Data was excluded from statistical analysis.

Appendix 6-13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Lactation day 5)
 Dose (mg/kg): 0

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
1101	759	14.2	41.9	55.2	18.7	33.8	4.4	128.1	11.3	12.5	228
1105	695	12.9	37.3	53.6	18.6	34.7	8.1	165.8	11.2	13.9	384
1106	744	13.8	40.9	55.0	18.5	33.7	6.4	135.0	11.8	13.1	227
1107	653	12.3	35.8	54.8	18.8	34.3	9.6	117.8	11.6	15.1	437
1112	756	13.6	40.7	53.8	18.1	33.5	6.2	137.7	12.2	12.4	219
Mean	721	13.4	39.3	54.5	18.5	34.0	6.9	136.9	11.6	13.4	299
S.D.	46	0.8	2.6	0.7	0.3	0.5	2.0	17.9	0.4	1.1	104

Appendix 6-14

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Lactation day 5)
 Dose (mg/kg): 0

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/ μ L)					
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1101	61.2	68.6	26.4	0.5	0.1	3.1	1.2	42.0	16.2	0.3	0.1	1.9	0.7
1105	122.9	47.9	49.6	0.5	0.2	1.3	0.4	58.9	61.0	0.6	0.3	1.5	0.5
1106	102.9	61.5	34.7	0.9	0.2	1.9	0.9	63.3	35.7	0.9	0.2	2.0	0.9
1107	111.6	50.1	47.8	0.3	0.1	1.4	0.3	55.9	53.3	0.3	0.2	1.5	0.4
1112	82.1	50.4	44.6	0.7	0.1	2.7	1.4	41.4	36.7	0.5	0.1	2.2	1.1
Mean	96.1	55.7	40.6	0.6	0.1	2.1	0.8	52.3	40.6	0.5	0.2	1.8	0.7
S.D.	24.6	8.9	9.8	0.2	0.1	0.8	0.5	10.0	17.4	0.2	0.1	0.3	0.3

LUC: Large unstained cells

Appendix 6-15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Lactation day 5)
 Dose (mg/kg): 10

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
2101NC	819Z	15.0Z	41.8Z	51.0Z	18.3Z	36.0Z	1.9Z	95.6Z	10.6Z	12.3Z	185Z
2102	742	12.9	38.3	51.6	17.4	33.7	6.5	155.4	12.2	16.2	306
2103	798	14.8	43.6	54.6	18.6	34.0	5.7	131.7	11.7	15.6	278
2105	717	13.2	37.9	52.9	18.3	34.7	5.4	118.8	12.0	15.5	271
2111	726	13.3	39.1	53.8	18.3	34.0	7.6	191.4	11.2	13.9	325
2112	743	14.4	40.9	55.1	19.4	35.2	4.3	149.4	12.1	17.0	286
Mean	745	13.7	40.0	53.6	18.4	34.3	5.9	149.3	11.8	15.6	293
S.D.	31	0.8	2.3	1.4	0.7	0.6	1.2	27.6	0.4	1.1	22

NC: Not copulated

Z: Data was excluded from statistical analysis.

Appendix 6-16

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Lactation day 5)
 Dose (mg/kg): 10

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/ μ L)					
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
2101NC	91.4Z	83.8Z	12.2Z	1.3Z	0.3Z	1.5Z	0.9Z	76.6Z	11.2Z	1.2Z	0.3Z	1.4Z	0.8Z
2102	162.4	52.6	43.1	0.7	0.3	2.5	0.9	85.4	69.9	1.1	0.5	4.0	1.5
2103	108.0	61.4	35.1	0.6	0.3	2.1	0.5	66.3	37.8	0.7	0.3	2.3	0.6
2105	88.4	53.2	43.3	0.6	0.1	2.4	0.4	47.0	38.3	0.6	0.1	2.1	0.4
2111	125.2	55.6	40.9	0.6	0.2	1.5	1.2	69.6	51.2	0.7	0.3	1.9	1.5
2112	43.6	65.1	31.6	1.5	0.1	1.1	0.6	28.4	13.8	0.6	0.1	0.5	0.3
Mean	105.5	57.6	38.8	0.8	0.2	1.9	0.7	59.3	42.2	0.7	0.3	2.2	0.9
S.D.	44.0	5.5	5.2	0.4	0.1	0.6	0.3	22.0	20.6	0.2	0.2	1.2	0.6

LUC: Large unstained cells

NC: Not copulated

Z: Data was excluded from statistical analysis.

Appendix 6-17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Lactation day 5)
 Dose (mg/kg): 30

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
3101	749	14.0	41.5	55.3	18.7	33.8	6.5	137.1	12.5	16.0	234
3102	729	13.8	39.8	54.6	18.9	34.6	6.6	134.1	12.8	16.1	218
3104	757	13.7	41.3	54.5	18.1	33.1	6.5	133.8	11.6	16.0	327
3107	729	13.8	40.6	55.7	19.0	34.1	7.0	171.5	12.7	12.0	256
3111	743	13.4	39.4	53.1	18.1	34.1	5.7	142.8	12.5	17.3	344
Mean	741	13.7	40.5	54.6	18.6	33.9	6.5	143.9	12.4	15.5	276
S.D.	12	0.2	0.9	1.0	0.4	0.6	0.5	15.9	0.5	2.0	56

Appendix 6-18

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Lactation day 5)
 Dose (mg/kg): 30

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/ μ L)					
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
3101	153.9	59.8	35.9	1.0	0.2	2.5	0.7	92.0	55.2	1.5	0.4	3.8	1.0
3102	89.2	46.7	49.9	0.6	0.1	2.2	0.5	41.7	44.5	0.5	0.1	1.9	0.4
3104	147.6	62.3	34.1	0.5	0.3	2.3	0.6	91.9	50.3	0.7	0.4	3.3	0.9
3107	79.2	68.1	26.0	0.5	0.2	3.6	1.6	54.0	20.6	0.4	0.1	2.9	1.2
3111	153.4	61.5	33.2	0.7	0.2	3.0	1.4	94.3	50.9	1.0	0.4	4.6	2.2
Mean	124.7	59.7	35.8	0.7	0.2	2.7	1.0	74.8	44.3	0.8	0.3	3.3	1.1
S.D.	37.2	7.9	8.7	0.2	0.1	0.6	0.5	25.0	13.8	0.4	0.2	1.0	0.7

LUC: Large unstained cells

Appendix 6-19

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Lactation day 5)
 Dose (mg/kg): 100

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
4101S	867Z	16.6Z	47.7Z	55.0Z	19.1Z	34.7Z	1.1Z	147.5Z	13.9Z	17.0Z	203Z
4102S	920Z	16.7Z	48.4Z	52.6Z	18.1Z	34.4Z	0.9Z	134.9Z	13.3Z	13.0Z	605Z
4103D											
4104D											
4105S	940Z	16.0Z	47.8Z	50.8Z	17.1Z	33.6Z	1.1Z	136.4Z	13.4Z	16.2Z	332Z
4106S	1163Z	20.4Z	61.6Z	53.0Z	17.5Z	33.1Z	0.3Z	95.5Z	-	-	-
4107S	821Z	15.4Z	46.2Z	56.3Z	18.8Z	33.4Z	1.5Z	137.6Z	12.3Z	13.4Z	192Z
4108S	936Z	16.0Z	47.3Z	50.5Z	17.1Z	33.9Z	1.4Z	125.4Z	14.3Z	19.2Z	371Z
4109D											
4110S	982Z	17.8Z	51.2Z	52.1Z	18.1Z	34.7Z	0.5Z	107.6Z	12.8Z	15.8Z	229Z
4111S	948Z	17.8Z	50.9Z	53.7Z	18.8Z	35.0Z	0.4Z	118.5Z	13.8Z	14.9Z	258Z
4112S	1344Z*	24.2Z*	71.4Z*	53.2Z*	17.9Z*	33.7Z*	0.9Z*	180.0Z*	-	-	-
Mean											
S.D.											

*: Re-analyzed value

-: Not done. A sufficient amount of blood sample was not obtained due to severe moribundity.

D: Dead

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of female rats (Lactation day 5)
 Dose (mg/kg): 100

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)					Differential leukocyte counts (10E2/ μ L)						
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4101S	170.1Z	40.9Z	52.1Z	0.2Z	0.5Z	3.8Z	2.6Z	69.6Z	88.6Z	0.3Z	0.8Z	6.4Z	4.4Z
4102S	149.9Z	25.0Z	66.0Z	0.1Z	0.2Z	4.9Z	3.7Z	37.5Z	99.0Z	0.2Z	0.3Z	7.4Z	5.5Z
4103D													
4104D													
4105S	110.8Z	29.5Z	64.7Z	0.2Z	0.2Z	3.8Z	1.7Z	32.7Z	71.7Z	0.2Z	0.2Z	4.2Z	1.9Z
4106S	93.7Z	19.5Z	74.3Z	0.1Z	0.3Z	3.6Z	2.1Z	18.3Z	69.6Z	0.1Z	0.3Z	3.4Z	2.0Z
4107S	102.4Z	72.0Z	23.1Z	0.3Z	0.4Z	3.4Z	0.8Z	73.8Z	23.6Z	0.3Z	0.4Z	3.5Z	0.8Z
4108S	84.1Z	32.9Z	59.6Z	0.2Z	0.3Z	5.1Z	1.9Z	27.7Z	50.1Z	0.2Z	0.2Z	4.3Z	1.6Z
4109D													
4110S	109.4Z	20.1Z	73.9Z	0.1Z	0.3Z	4.2Z	1.4Z	22.0Z	80.9Z	0.1Z	0.3Z	4.6Z	1.5Z
4111S	124.5Z	39.2Z	48.2Z	1.7Z	0.4Z	5.4Z	5.0Z	48.8Z	60.1Z	2.1Z	0.5Z	6.8Z	6.3Z
4112S	78.4Z*	16.1Z*	73.4Z*	0.5Z*	0.5Z*	8.1Z*	1.4Z*	12.6Z*	57.4Z*	0.4Z*	0.4Z*	6.4Z*	1.2Z*
Mean													
S.D.													

LUC: Large unstained cells

*: Re-analyzed value

D: Dead

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of recovery)
 Dose (mg/kg): 0

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
1008	949	16.3	47.5	50.0	17.2	34.3	1.6	98.2	16.0	19.1	304
1009	906	15.2	44.2	48.8	16.8	34.4	1.5	98.8	17.9	22.2	253
1010	898	16.3	47.5	52.9	18.2	34.4	2.0	78.5	18.9	23.0	323
1011	865	15.0	42.6	49.3	17.3	35.1	1.5	121.2	14.0	14.6	339
1012	929	16.1	47.1	50.6	17.3	34.2	1.7	102.3	17.7	18.7	288
Mean	909	15.8	45.8	50.3	17.4	34.5	1.7	99.8	16.9	19.5	301
S.D.	32	0.6	2.3	1.6	0.5	0.4	0.2	15.2	1.9	3.3	33

Appendix 6-22

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of recovery)
 Dose (mg/kg): 0

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/ μ L)					
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1008	67.4	78.6	16.0	1.9	0.3	2.8	0.4	53.0	10.8	1.3	0.2	1.9	0.3
1009	97.7	83.3	13.0	0.8	0.3	2.0	0.7	81.4	12.7	0.7	0.3	1.9	0.6
1010	120.8	66.8	29.4	1.2	0.3	2.0	0.3	80.7	35.6	1.4	0.4	2.5	0.3
1011	69.2	75.4	18.3	2.2	0.3	2.7	1.0	52.2	12.7	1.5	0.2	1.9	0.7
1012	64.0	71.5	23.9	1.9	0.3	1.9	0.4	45.8	15.3	1.2	0.2	1.2	0.2
Mean	83.8	75.1	20.1	1.6	0.3	2.3	0.6	62.6	17.4	1.2	0.3	1.9	0.4
S.D.	24.7	6.4	6.5	0.6	0.0	0.4	0.3	17.1	10.3	0.3	0.1	0.5	0.2

LUC: Large unstained cells

Appendix 6-23

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of recovery)
 Dose (mg/kg): 30

Animal number	RBC 10E4/ μ L	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/ μ L	PT s	APTT s	FIB mg/dL
3008	885	15.6	45.0	50.9	17.6	34.7	1.9	113.5	16.2	20.6	274
3009	967	15.1	43.8	45.3	15.6	34.5	1.7	117.6	16.0	23.1	269
3010	975	16.2	47.4	48.6	16.6	34.1	1.6	110.7	16.8	21.0	284
3011	858	15.5	43.7	51.0	18.1	35.4	1.5	109.5	13.1	14.0	282
3012	928	16.5	47.4	51.1	17.8	34.8	1.5	89.3	18.0	20.3	305
Mean	923	15.8	45.5	49.4	17.1	34.7	1.6	108.1	16.0	19.8	283
S.D.	51	0.6	1.8	2.5	1.0	0.5	0.2	11.0	1.8	3.4	14

Appendix 6-24

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual hematology of male rats (End of recovery)
 Dose (mg/kg): 30

Animal number	WBC 10E2/ μ L	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/ μ L)					
		Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
3008	114.0	84.8	11.1	1.3	0.3	1.9	0.5	96.8	12.7	1.5	0.3	2.2	0.6
3009	125.0	85.9	9.7	1.0	0.5	2.4	0.6	107.3	12.1	1.3	0.6	3.0	0.7
3010	118.9	81.0	14.5	1.5	0.5	1.9	0.5	96.3	17.2	1.8	0.6	2.3	0.6
3011	56.2	72.4	23.6	0.9	0.2	2.1	0.7	40.7	13.3	0.5	0.1	1.2	0.4
3012	59.3	77.0	18.9	1.7	0.4	1.8	0.3	45.7	11.2	1.0	0.2	1.1	0.2
Mean	94.7	80.2	15.6	1.3	0.4	2.0	0.5	77.4	13.3	1.2	0.4	2.0	0.5
S.D.	34.0	5.6	5.7	0.3	0.1	0.2	0.1	31.5	2.3	0.5	0.2	0.8	0.2

LUC: Large unstained cells

Appendix 7-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Satellite group, Day 15 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 $\mu\text{mol/L}$	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1113	69	30	51	1	333	18.6	45	11	92	0.1	124
1114	65	29	40	2	379	8.5	58	19	108	0.1	147
1115	61	28	45	2	224	12.5	42	11	87	0.1	131
1116	56	24	45	1	264	10.5	64	23	119	0.1	161
1117	62	23	46	1	316	10.0	46	10	86	0.1	126
1118	63	27	45	1	455	10.0	37	8	79	0.1	121
1119	67	23	42	1	247	6.0	45	14	86	0.1	149
1120	63	29	56	1	268	10.2	45	9	93	0.1	116
1121	76	39	60	1	314	9.1	57	15	114	0.1	137
1122	58	25	36	1	254	17.3	53	12	106	0.1	121
Mean	64	28	47	1	305	11.3	49	13	97	0.1	133
S.D.	6	5	7	0	70	3.9	8	5	14	0.0	15

Appendix 7-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Satellite group, Day 15 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	14	0.26	141	4.1	105	9.8	6.0	6.0	3.4	1.31
1114	13	0.30	140	4.2	103	9.9	5.8	5.8	3.6	1.64
1115	16	0.28	141	4.5	106	9.8	5.5	6.0	3.5	1.40
1116	15	0.32	141	4.6	106	10.2	5.2	6.1	3.6	1.44
1117	15	0.32	141	4.4	106	9.6	4.7	6.0	3.5	1.40
1118	16	0.28	143	4.2	109	10.1	4.4	6.2	3.6	1.38
1119	16	0.34	142	4.4	105	9.7	5.0	5.7	3.4	1.48
1120	15	0.30	142	4.4	109	10.0	5.6	6.2	3.6	1.38
1121	13	0.27	142	4.5	107	9.9	4.3	6.2	3.9	1.70
1122	18	0.29	142	4.0	107	10.0	5.8	6.3	3.7	1.42
Mean	15	0.30	142	4.3	106	9.9	5.2	6.1	3.6	1.46
S.D.	2	0.03	1	0.2	2	0.2	0.6	0.2	0.1	0.12

Appendix 7-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Satellite group, Day 15 of administration)
 Dose (mg/kg): 100

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA $\mu\text{mol/L}$	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4113S	150Z	115Z	70Z	1Z	374Z	9.1Z	45Z	43Z	104Z	0.1Z	181Z
4114S	212Z	97Z	461Z	1Z	265Z	22.2Z	52Z	22Z	107Z	0.2Z	129Z
4115S	88Z	25Z	46Z	2Z	554Z	5.8Z	41Z	48Z	78Z	0.1Z	172Z
4116D											
4117S	108Z	47Z	53Z	1Z	514Z	4.9Z	63Z	166Z	138Z	0.1Z	136Z
4118S	170Z	178Z	67Z	1Z	230Z	18.3Z	32Z	15Z	60Z	0.1Z	124Z
4119D											
4120S	232Z	154Z	156Z	1Z	413Z	13.3Z	25Z	35Z	55Z	0.1Z	133Z
4121D											
4122S	105Z	35Z	50Z	1Z	384Z	4.3Z	57Z	16Z	88Z	0.1Z	128Z
Mean											
S.D.											

D: Dead

S: Sacrificed moribund

Z: Data was excluded from statistical analysis.

Appendix 7-4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Satellite group, Day 15 of administration)
 Dose (mg/kg): 100

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
4113S	15Z	0.19Z	145Z	4.7Z	110Z	10.2Z	6.4Z	5.2Z	2.9Z	1.26Z
4114S	41Z	0.29Z	144Z	4.7Z	103Z	10.4Z	8.9Z	6.3Z	3.7Z	1.42Z
4115S	31Z	0.27Z	147Z	5.0Z	112Z	10.0Z	5.0Z	5.5Z	3.0Z	1.20Z
4116D										
4117S	34Z	0.28Z	140Z	4.9Z	102Z	10.7Z	6.2Z	5.0Z	2.8Z	1.27Z
4118S	22Z	0.22Z	148Z	3.9Z	115Z	9.0Z	7.7Z	4.0Z	2.5Z	1.67Z
4119D										
4120S	24Z	0.26Z	139Z	5.1Z	106Z	9.7Z	9.6Z	5.2Z	3.0Z	1.36Z
4121D										
4122S	29Z	0.26Z	144Z	5.6Z	108Z	9.5Z	5.1Z	4.7Z	2.6Z	1.24Z
Mean										
S.D.										

D: Dead

S: Sacrificed moribund

Z: Data was excluded from statistical analysis.

Appendix 7-5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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 $\mu\text{mol/L}$	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1001	64	26	42	1	539	21.3	56	17	87	0.1	139
1002	68	32	66	1	413	13.5	44	19	71	0.1	146
1003	71	29	45	1	540	6.4	44	16	72	0.1	146
1004	61	28	61	1	480	6.7	38	34	69	0.0	159
1005	54	26	39	1	250	23.7	43	21	75	0.1	156
Mean	64	28	51	1	444	14.3	45	21	75	0.1	149
S.D.	7	2	12	0	121	8.0	7	7	7	0.0	8

Appendix 7-6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	14	0.28	141	4.8	104	9.8	5.8	5.8	3.2	1.23
1002	11	0.22	143	4.6	107	9.3	5.9	5.6	3.2	1.33
1003	13	0.28	143	4.8	107	9.7	6.2	5.5	3.1	1.29
1004	14	0.24	143	4.7	106	9.4	5.4	5.5	3.1	1.29
1005	14	0.21	144	4.4	108	9.4	5.1	5.7	3.3	1.38
Mean	13	0.25	143	4.7	106	9.5	5.7	5.6	3.2	1.30
S.D.	1	0.03	1	0.2	2	0.2	0.4	0.1	0.1	0.06

Appendix 7-7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of male rats (End of administration)
 Dose (mg/kg): 10

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA $\mu\text{mol/L}$	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
2001	72	32	90	0	389	6.0	53	18	81	0.1	156
2002	61	25	52	1	384	5.2	56	8	82	0.1	141
2003	60	33	53	0	443	11.0	59	35	89	0.0	173
2004	75	37	41	1	486	4.9	37	16	67	0.1	133
2005	64	29	47	1	461	4.2	54	40	89	0.1	157
Mean	66	31	57	1	433	6.3	52	23	82	0.1	152
S.D.	7	4	19	1	45	2.7	9	14	9	0.0	16

Appendix 7-8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of male rats (End of administration)
 Dose (mg/kg): 10

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	12	0.24	143	4.8	106	9.5	5.7	5.9	3.2	1.19
2002	14	0.30	143	4.2	108	9.0	5.6	5.5	3.1	1.29
2003	14	0.29	144	4.4	109	10.1	5.1	5.9	3.2	1.19
2004	15	0.24	142	4.4	107	9.7	6.1	5.7	3.1	1.19
2005	10	0.23	145	4.0	105	9.5	6.5	5.5	3.1	1.29
Mean	13	0.26	143	4.4	107	9.6	5.8	5.7	3.1	1.23
S.D.	2	0.03	1	0.3	2	0.4	0.5	0.2	0.1	0.05

Appendix 7-9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of male rats (End of administration)
 Dose (mg/kg): 30

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA $\mu\text{mol/L}$	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
3001	60	32	39	1	467	10.1	55	19	90	0.1	147
3002	65	38	63	1	448	17.5	59	51	99	0.1	150
3003	65	28	30	1	447	6.5	53	19	86	0.1	143
3004	64	29	48	1	469	24.8	50	26	88	0.1	143
3005	51	27	56	2	360	10.4	49	30	88	0.1	139
Mean	61	31	47	1	438	13.9	53	29	90	0.1	144
S.D.	6	4	13	0	45	7.3	4	13	5	0.0	4

Appendix 7-10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of male rats (End of administration)
 Dose (mg/kg): 30

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	16	0.34	143	4.3	108	9.9	5.2	6.0	3.2	1.14
3002	12	0.22	143	4.7	106	10.0	5.6	6.0	3.3	1.22
3003	13	0.26	143	4.6	105	9.6	6.0	5.8	3.1	1.15
3004	10	0.20	144	4.7	108	9.7	6.0	5.6	3.2	1.33
3005	14	0.26	143	4.8	105	10.6	6.6	6.0	2.6	0.76
Mean	13	0.26	143	4.6	106	10.0	5.9	5.9	3.1	1.12
S.D.	2	0.05	0	0.2	2	0.4	0.5	0.2	0.3	0.22

Appendix 7-11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of male rats (End of administration)
 Dose (mg/kg): 100

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
4001S	157Z	55Z	95Z	2Z	351Z	14.9Z	58Z	33Z	99Z	0.1Z	136Z
4002S	166Z	87Z	180Z	1Z	1091Z	9.4Z	55Z	56Z	93Z	0.1Z	223Z
4003D											
4004S	169Z	72Z	204Z	1Z	694Z	5.1Z	53Z	64Z	110Z	0.1Z	183Z
4005S	94Z	33Z	78Z	1Z	645Z	4.0Z	61Z	18Z	99Z	0.1Z	194Z
4006S	93Z	37Z	111Z	2Z	607Z	7.6Z	84Z	56Z	159Z	0.1Z	141Z
4007S	128Z	99Z	128Z	2Z	408Z	5.0Z	48Z	74Z	72Z	0.3Z	142Z
4008S	97Z	82Z	75Z	1Z	387Z	3.5Z	57Z	58Z	103Z	0.1Z	137Z
4009S	114Z	135Z	333Z	2Z	512Z	15.2Z	50Z	103Z	90Z	0.3Z	289Z
4010S	115Z	72Z	135Z	1Z	565Z	9.8Z	60Z	30Z	111Z	0.1Z	181Z
4011S	139Z	77Z	160Z	8Z	868Z	19.6Z	51Z	32Z	96Z	0.1Z	328Z
4012S	100Z	46Z	53Z	1Z	870Z	9.1Z	60Z	13Z	98Z	0.1Z	158Z
Mean											
S.D.											

D: Dead

S: Sacrificed moribund

Z: Data was excluded from statistical analysis.

Appendix 7-12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of male rats (End of administration)
 Dose (mg/kg): 100

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
4001S	111Z	0.52Z	143Z	4.9Z	106Z	9.1Z	8.8Z	4.4Z	2.4Z	1.20Z
4002S	26Z	0.18Z	143Z	5.0Z	107Z	9.6Z	8.2Z	4.6Z	2.7Z	1.42Z
4003D										
4004S	27Z	0.20Z	142Z	5.0Z	106Z	9.7Z	7.3Z	4.9Z	2.7Z	1.23Z
4005S	10Z	0.17Z	141Z	4.6Z	103Z	9.6Z	6.7Z	4.8Z	2.3Z	0.92Z
4006S	155Z	3.24Z	137Z	6.2Z	100Z	10.5Z	16.2Z	4.7Z	2.5Z	1.14Z
4007S	107Z	0.98Z	148Z	6.3Z	110Z	11.3Z	16.6Z	6.2Z	3.2Z	1.07Z
4008S	25Z	0.24Z	143Z	4.1Z	109Z	9.3Z	7.3Z	4.1Z	2.2Z	1.16Z
4009S	102Z	0.70Z	140Z	7.1Z	107Z	11.3Z	15.9Z	5.4Z	3.0Z	1.25Z
4010S	22Z	0.19Z	143Z	4.6Z	106Z	9.3Z	6.0Z	4.9Z	2.7Z	1.23Z
4011S	37Z	0.52Z	140Z	4.9Z	103Z	9.3Z	8.8Z	4.7Z	2.7Z	1.35Z
4012S	65Z	0.33Z	152Z	4.6Z	118Z	9.4Z	8.0Z	4.5Z	2.3Z	1.05Z
Mean										
S.D.										

D: Dead

S: Sacrificed moribund

Z: Data was excluded from statistical analysis.

Appendix 7-13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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
1101	61	30	35	1	150	11.8	49	12	86	0.1	129
1105	136	76	43	1	362	11.9	67	42	126	0.1	131
1106	77	44	31	1	152	10.6	54	41	99	0.1	135
1107	119	80	34	1	271	13.6	95	41	154	0.1	119
1112	98	44	50	1	175	6.1	46	34	89	0.0	138
Mean	98	55	39	1	222	10.8	62	34	111	0.1	130
S.D.	30	22	8	0	93	2.8	20	13	29	0.0	7

Appendix 7-14

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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
1101	10	0.28	142	4.0	107	9.9	5.6	5.8	3.2	1.23
1105	14	0.31	140	3.6	103	10.6	7.6	6.2	3.6	1.38
1106	11	0.23	143	3.8	107	10.3	6.8	6.0	3.3	1.22
1107	9	0.32	141	3.8	103	10.5	7.8	5.6	3.2	1.33
1112	14	0.30	141	4.4	106	9.9	7.1	5.7	3.1	1.19
Mean	12	0.29	141	3.9	105	10.2	7.0	5.9	3.3	1.27
S.D.	2	0.04	1	0.3	2	0.3	0.9	0.2	0.2	0.08

Appendix 7-15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Lactation day 5)
 Dose (mg/kg): 10

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA $\mu\text{mol/L}$	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
2101NC	64Z	42Z	57Z	1Z	438Z	6.7Z	72Z	53Z	137Z	0.1Z	156Z
2102	85	57	45	1	140	8.0	56	33	120	0.1	122
2103	70	49	54	1	153	10.4	41	28	84	0.1	136
2105	81	42	41	1	315	10.3	50	22	98	0.1	120
2111	82	50	42	1	197	6.9	50	30	92	0.0	110
2112	55	23	36	1	328	6.1	59	17	101	0.0	123
Mean	75	44	44	1	227	8.3	51	26	99	0.1	122
S.D.	12	13	7	0	89	2.0	7	6	13	0.1	9

NC: Not copulated

Z: Data was excluded from statistical analysis.

Appendix 7-16

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Lactation day 5)
 Dose (mg/kg): 10

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
2101NC	21Z	0.26Z	139Z	3.9Z	101Z	10.5Z	5.1Z	6.5Z	3.7Z	1.32Z
2102	13	0.32	140	4.0	105	10.2	6.2	6.1	3.6	1.44
2103	13	0.22	143	4.3	106	10.1	8.0	5.8	3.5	1.52
2105	15	0.30	140	3.6	104	9.8	5.5	6.0	3.3	1.22
2111	15	0.25	142	4.2	109	9.9	7.2	5.9	3.2	1.19
2112	12	0.23	144	4.7	109	10.0	7.0	5.8	3.5	1.52
Mean	14	0.26	142	4.2	107	10.0	6.8	5.9	3.4	1.38
S.D.	1	0.04	2	0.4	2	0.2	1.0	0.1	0.2	0.16

NC: Not copulated

Z: Data was excluded from statistical analysis.

Appendix 7-17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Lactation day 5)
 Dose (mg/kg): 30

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA $\mu\text{mol/L}$	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
3101	96	45	50	1	245	8.2	30	36	70	0.1	122
3102	70	42	39	1	211	27.9	65	31	126	0.1	128
3104	72	50	35	1	307	12.4	59	27	114	0.1	125
3107	70	56	45	1	238	11.9	39	40	82	0.1	131
3111	117	56	59	1	228	13.3	77	57	163	0.1	118
Mean	85	50	46	1	246	14.7	54	38	111	0.1	125
S.D.	21	6	9	0	37	7.6	19	12	37	0.0	5

Appendix 7-18

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Lactation day 5)
 Dose (mg/kg): 30

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	15	0.25	140	4.6	109	9.9	7.5	5.7	3.3	1.38
3102	17	0.26	140	3.7	107	10.0	6.4	5.7	3.4	1.48
3104	12	0.25	140	4.6	109	10.1	5.5	5.9	3.4	1.36
3107	17	0.28	143	4.6	107	10.1	6.6	5.8	3.1	1.15
3111	14	0.26	140	4.3	102	10.4	6.8	6.3	3.5	1.25
Mean	15	0.26	141	4.4	107	10.1	6.6	5.9	3.3	1.32
S.D.	2	0.01	1	0.4	3	0.2	0.7	0.2	0.2	0.13

Appendix 7-19

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Lactation day 5)
 Dose (mg/kg): 100

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
4101S	133Z	176Z	85Z	1Z	279Z	5.2Z	25Z	26Z	63Z	0.1Z	141Z
4102S	152Z	123Z	75Z	1Z	519Z	8.4Z	33Z	19Z	64Z	0.1Z	144Z
4103D											
4104D											
4105S	140Z	72Z	158Z	2Z	331Z	13.5Z	32Z	15Z	65Z	0.1Z	176Z
4106S	166Z	111Z	119Z	2Z	-	-	-	-	-	-	-
4107S	74Z	30Z	63Z	1Z	1003Z	45.8Z	42Z	13Z	94Z	0.1Z	140Z
4108S	87Z	40Z	88Z	1Z	495Z	4.8Z	37Z	30Z	88Z	0.1Z	209Z
4109D											
4110S	100Z	98Z	54Z	1Z	280Z	3.0Z	39Z	27Z	82Z	0.1Z	159Z
4111S	228Z	179Z	84Z	1Z	181Z	15.2Z	33Z	17Z	75Z	0.1Z	113Z
4112S	149Z	65Z	204Z	2Z	-	-	-	-	-	-	-
Mean											
S.D.											

-: Not done. A sufficient amount of blood sample was not obtained due to severe moribundity.

D: Dead

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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of female rats (Lactation day 5)
 Dose (mg/kg): 100

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
4101S	20Z	0.21Z	145Z	4.7Z	109Z	9.1Z	7.1Z	4.6Z	2.6Z	1.30Z
4102S	20Z	0.25Z	142Z	4.1Z	102Z	9.2Z	7.1Z	4.7Z	2.4Z	1.04Z
4103D										
4104D										
4105S	18Z	0.32Z	145Z	3.2Z	106Z	9.4Z	7.6Z	5.2Z	3.0Z	1.36Z
4106S	-	-	-	-	-	-	-	-	-	-
4107S	21Z	0.29Z	143Z	4.2Z	107Z	10.4Z	7.1Z	6.2Z	3.8Z	1.58Z
4108S	16Z	0.19Z	142Z	4.9Z	108Z	10.2Z	7.2Z	5.6Z	3.5Z	1.67Z
4109D										
4110S	23Z	0.19Z	143Z	4.2Z	105Z	10.0Z	6.4Z	5.7Z	3.3Z	1.38Z
4111S	28Z	0.23Z	146Z	4.9Z	111Z	10.1Z	7.7Z	5.7Z	3.4Z	1.48Z
4112S	-	-	-	-	-	-	-	-	-	-
Mean										
S.D.										

-: Not done. A sufficient amount of blood sample was not obtained due to severe moribundity.

D: Dead

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
 didec-1-yl(methyl)amine 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 $\mu\text{mol/L}$	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1008	53	26	40	1	298	9.8	52	29	80	0.1	129
1009	57	32	43	1	318	5.9	32	22	62	0.1	145
1010	69	31	33	1	369	6.9	51	63	94	0.1	146
1011	50	32	41	1	444	5.7	55	52	92	0.1	170
1012	63	27	45	1	278	11.3	49	20	85	0.1	126
Mean	58	30	40	1	341	7.9	48	37	83	0.1	143
S.D.	8	3	5	0	67	2.5	9	19	13	0.0	18

Appendix 7-22

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	14	0.23	141	4.3	103	9.3	5.8	5.9	3.2	1.19
1009	16	0.20	141	4.5	105	9.3	5.8	5.9	3.1	1.11
1010	16	0.27	141	4.3	106	9.2	6.0	5.5	3.1	1.29
1011	16	0.25	142	4.5	105	9.7	5.4	5.6	3.1	1.24
1012	14	0.23	142	4.4	106	9.6	5.3	6.0	3.1	1.07
Mean	15	0.24	141	4.4	105	9.4	5.7	5.8	3.1	1.18
S.D.	1	0.03	1	0.1	1	0.2	0.3	0.2	0.0	0.09

Appendix 7-23

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of male rats (End of recovery)
 Dose (mg/kg): 30

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA $\mu\text{mol/L}$	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
3008	59	32	36	2	419	12.7	45	32	74	0.1	125
3009	114	58	101	1	298	37.7	42	26	72	0.1	153
3010	65	46	47	1	460	42.0	61	56	99	0.1	147
3011	73	36	34	2	498	33.1	46	21	80	0.1	126
3012	59	31	35	2	322	12.7	45	38	80	0.1	133
Mean	74	41	51	2	399	27.6	48	35	81	0.1	137
S.D.	23	11	29	1	87	14.0	8	14	11	0.0	13

Appendix 7-24

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual blood chemistry of male rats (End of recovery)
 Dose (mg/kg): 30

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
3008	15	0.21	140	4.5	103	9.7	6.2	5.6	3.3	1.43
3009	16	0.25	141	4.4	103	9.5	6.2	6.2	3.2	1.07
3010	14	0.22	142	4.5	104	9.7	5.7	6.2	3.3	1.14
3011	14	0.22	144	4.5	105	9.6	5.8	5.9	3.3	1.27
3012	16	0.24	143	4.5	108	9.8	5.8	6.0	3.3	1.22
Mean	15	0.23	142	4.5	105	9.7	5.9	6.0	3.3	1.23
S.D.	1	0.02	2	0.0	2	0.1	0.2	0.2	0.0	0.14

Appendix 8-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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)
1001	522	2.23	13.2	9.4	9.7	19.1	306
1002	471	2.14	14.2	12.8	11.4	24.2	257
1003	487	2.03	13.9	10.7	10.0	20.7	351
1004	489	2.14	10.7	15.3	12.8	28.1	236
Absolute 1005	436	2.05	11.0	9.4	9.8	19.2	316
1006	515	2.14	14.2	12.0	7.4	19.4	339
1007	458	1.99	13.7	9.5	9.5	19.0	291
Mean	483	2.10	13.0	11.3	10.1	21.4	299
S.D.	30	0.08	1.5	2.2	1.7	3.5	42
1001		0.43	2.5	1.8	1.9	3.7	59
1002		0.45	3.0	2.7	2.4	5.1	55
1003		0.42	2.9	2.2	2.1	4.3	72
1004		0.44	2.2	3.1	2.6	5.7	48
Relative 1005		0.47	2.5	2.2	2.2	4.4	72
1006		0.42	2.8	2.3	1.4	3.8	66
1007		0.43	3.0	2.1	2.1	4.1	64
Mean		0.44	2.7	2.3	2.1	4.4	62
S.D.		0.02	0.3	0.4	0.4	0.7	9

Appendix 8-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 0

Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
1001	1.42	13.26	0.91	1.63	1.64	3.27
1002	1.46	12.66	0.71	1.82	1.70	3.52
1003	1.32	11.38	0.69	1.40	1.51	2.91
1004	1.27	12.33	0.66	1.55	1.50	3.05
Absolute 1005	1.41	11.00	0.77	1.43	1.46	2.89
1006	1.52	14.55	0.80	1.75	1.80	3.55
1007	1.47	12.60	0.56	1.64	1.68	3.32

Mean	1.41	12.54	0.73	1.60	1.61	3.22
S.D.	0.09	1.18	0.11	0.16	0.13	0.27

1001	0.27	2.54	0.17	0.31	0.31	0.63
1002	0.31	2.69	0.15	0.39	0.36	0.75
1003	0.27	2.34	0.14	0.29	0.31	0.60
1004	0.26	2.52	0.13	0.32	0.31	0.62
Relative 1005	0.32	2.52	0.18	0.33	0.33	0.66
1006	0.30	2.83	0.16	0.34	0.35	0.69
1007	0.32	2.75	0.12	0.36	0.37	0.72

Mean	0.29	2.60	0.15	0.33	0.33	0.67
S.D.	0.03	0.17	0.02	0.03	0.03	0.06

Appendix 8-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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)
1001	28	32	60	1.63	1.53	3.16
1002	36	31	67	1.45	1.52	2.97
1003	30	34	64	1.55	1.51	3.06
1004	33	33	66	1.61	1.61	3.22
Absolute 1005	27	28	55	1.51	1.48	2.99
1006	25	27	52	1.58	1.63	3.21
1007	34	35	69	1.70	1.67	3.37

Mean	30	31	62	1.58	1.56	3.14
S.D.	4	3	6	0.08	0.07	0.14
1001	5	6	11	0.31	0.29	0.61
1002	8	7	14	0.31	0.32	0.63
1003	6	7	13	0.32	0.31	0.63
1004	7	7	13	0.33	0.33	0.66
Relative 1005	6	6	13	0.35	0.34	0.69
1006	5	5	10	0.31	0.32	0.62
1007	7	8	15	0.37	0.36	0.74

Mean	6	7	13	0.33	0.32	0.65
S.D.	1	1	2	0.02	0.02	0.05

Appendix 8-4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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)
1001	553	519	1072	1.87	1.32
1002	609	626	1235	1.88	1.48
1003	631	584	1215	1.87	1.31
1004	658	632	1290	1.62	1.38
Absolute 1005	617	643	1260	1.72	1.41
1006	655	613	1268	1.21	1.07
1007	682	627	1309	1.89	1.27
Mean	629	606	1236	1.72	1.32
S.D.	42	43	79	0.25	0.13
1001	106	99	205	0.36	0.25
1002	129	133	262	0.40	0.31
1003	130	120	249	0.38	0.27
1004	135	129	264	0.33	0.28
Relative 1005	142	147	289	0.39	0.32
1006	127	119	246	0.23	0.21
1007	149	137	286	0.41	0.28
Mean	131	126	257	0.36	0.27
S.D.	14	15	28	0.06	0.04

Appendix 8-5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 10

Animal number	Body weight	Brain	Pituitary	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus
	g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
2001	477	2.13	14.0	11.4	10.3	21.7	339
2002	451	2.11	13.4	9.6	7.0	16.6	301
2003	506	2.01	11.4	10.5	11.5	22.0	408
2004	473	2.10	13.7	14.6	13.9	28.5	261
2005	551	2.20	14.3	9.6	12.4	22.0	277
2006	493	2.17	15.5	10.7	11.1	21.8	158
2007	479	2.23	12.1	11.1	10.3	21.4	419
Absolute 2008	505	2.09	16.2	14.5	11.3	25.8	208
2009	429	2.13	12.9	11.7	10.2	21.9	211
2010	484	2.21	14.2	11.8	12.3	24.1	399
2011	471	2.04	11.1	9.8	8.0	17.8	233
2012	482	2.16	12.5	10.5	8.5	19.0	523
Mean	483	2.13	13.4	11.3	10.6	21.9	311
S.D.	30	0.07	1.5	1.7	2.0	3.3	108
2001		0.45	2.9	2.4	2.2	4.5	71
2002		0.47	3.0	2.1	1.6	3.7	67
2003		0.40	2.3	2.1	2.3	4.3	81
2004		0.44	2.9	3.1	2.9	6.0	55
2005		0.40	2.6	1.7	2.3	4.0	50
2006		0.44	3.1	2.2	2.3	4.4	32
2007		0.47	2.5	2.3	2.2	4.5	87
Relative 2008		0.41	3.2	2.9	2.2	5.1	41
2009		0.50	3.0	2.7	2.4	5.1	49
2010		0.46	2.9	2.4	2.5	5.0	82
2011		0.43	2.4	2.1	1.7	3.8	49
2012		0.45	2.6	2.2	1.8	3.9	109
Mean		0.44	2.8	2.4	2.2	4.5	64
S.D.		0.03	0.3	0.4	0.4	0.7	22

Appendix 8-6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 10

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)
2001	1.43	11.88	0.81	1.55	1.48	3.03
2002	1.25	10.31	0.56	1.29	1.32	2.61
2003	1.49	14.05	0.66	1.38	1.38	2.76
2004	1.30	11.94	0.64	1.59	1.56	3.15
2005	1.43	14.07	0.89	1.76	1.89	3.65
2006	1.52	13.52	0.65	1.95	2.00	3.95
2007	1.39	11.20	0.58	1.51	1.48	2.99
2008	1.48	12.17	0.69	1.63	1.82	3.45
2009	1.18	9.98	0.63	1.63	1.67	3.30
2010	1.38	12.43	0.73	1.57	1.59	3.16
2011	1.32	11.28	0.62	1.39	1.41	2.80
2012	1.44	12.53	0.82	1.53	1.52	3.05
Mean	1.38	12.11	0.69	1.57	1.59	3.16
S.D.	0.10	1.32	0.10	0.18	0.21	0.38
2001	0.30	2.49	0.17	0.32	0.31	0.64
2002	0.28	2.29	0.12	0.29	0.29	0.58
2003	0.29	2.78	0.13	0.27	0.27	0.55
2004	0.27	2.52	0.14	0.34	0.33	0.67
2005	0.26	2.55	0.16	0.32	0.34	0.66
2006	0.31	2.74	0.13	0.40	0.41	0.80
2007	0.29	2.34	0.12	0.32	0.31	0.62
2008	0.29	2.41	0.14	0.32	0.36	0.68
2009	0.28	2.33	0.15	0.38	0.39	0.77
2010	0.29	2.57	0.15	0.32	0.33	0.65
2011	0.28	2.39	0.13	0.30	0.30	0.59
2012	0.30	2.60	0.17	0.32	0.32	0.63
Mean	0.29	2.50	0.14	0.33	0.33	0.65
S.D.	0.01	0.16	0.02	0.04	0.04	0.07

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Appendix 8-7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 10

Animal number	Adrenal	Adrenal	Adrenal	Testis	Testis	Testis
	(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	(R) g(g/100g BW)	(L) g(g/100g BW)	(R+L) g(g/100g BW)
2001	35	38	73	1.54	1.56	3.10
2002	31	32	63	1.57	1.57	3.14
2003	32	35	67	1.67	1.73	3.40
2004	34	39	73	1.67	1.64	3.31
2005	34	37	71	1.50	1.51	3.01
2006	35	38	73	1.81	1.77	3.58
2007	22	24	46	1.61	1.66	3.27
2008	33	36	69	1.63	1.64	3.27
2009	28	30	58	1.74	1.66	3.40
2010	37	37	74	1.49	1.53	3.02
2011	40	42	82	1.52	1.53	3.05
2012	33	34	67	1.63	1.66	3.29
Mean	33	35	68	1.62	1.62	3.24
S.D.	5	5	9	0.10	0.08	0.18
2001	7	8	15	0.32	0.33	0.65
2002	7	7	14	0.35	0.35	0.70
2003	6	7	13	0.33	0.34	0.67
2004	7	8	15	0.35	0.35	0.70
2005	6	7	13	0.27	0.27	0.55
2006	7	8	15	0.37	0.36	0.73
2007	5	5	10	0.34	0.35	0.68
2008	7	7	14	0.32	0.32	0.65
2009	7	7	14	0.41	0.39	0.79
2010	8	8	15	0.31	0.32	0.62
2011	8	9	17	0.32	0.32	0.65
2012	7	7	14	0.34	0.34	0.68
Mean	7	7	14	0.34	0.34	0.67
S.D.	1	1	2	0.03	0.03	0.06

Appendix 8-8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 10

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)
2001	584	540	1124	1.68	1.38
2002	645	594	1239	1.59	1.01
2003	712	693	1405	1.87	1.18
2004	730	697	1427	2.12	1.33
2005	652	669	1321	1.66	1.52
2006	833	722	1555	1.86	1.52
2007	601	623	1224	1.52	1.31
2008	661	653	1314	2.36	1.50
2009	682	671	1353	1.87	1.40
2010	603	619	1222	1.54	1.39
2011	634	607	1241	1.56	1.21
2012	613	588	1201	1.63	1.10
Mean	663	640	1302	1.77	1.32
S.D.	70	53	119	0.26	0.17
2001	122	113	236	0.35	0.29
2002	143	132	275	0.35	0.22
2003	141	137	278	0.37	0.23
2004	154	147	302	0.45	0.28
2005	118	121	240	0.30	0.28
2006	169	146	315	0.38	0.31
2007	125	130	256	0.32	0.27
2008	131	129	260	0.47	0.30
2009	159	156	315	0.44	0.33
2010	125	128	252	0.32	0.29
2011	135	129	263	0.33	0.26
2012	127	122	249	0.34	0.23
Mean	137	133	270	0.37	0.27
S.D.	16	12	28	0.06	0.03

Appendix 8-9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 30

Animal number	Body weight	Brain	Pituitary	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus
	g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
3001	457	2.00	12.0	10.3	7.2	17.5	337
3002	487	2.00	13.4	11.9	9.2	21.1	265
3003	412	1.98	9.9	11.3	9.3	20.6	169
3004	478	2.06	12.9	10.9	10.7	21.6	283
Absolute 3005	455	2.08	12.8	11.9	10.0	21.9	283
3006	471	2.04	15.8	11.2	10.1	21.3	259
3007	499	2.22	14.4	8.9	8.7	17.6	264
Mean	466	2.05	13.0	10.9	9.3	20.2	266
S.D.	28	0.08	1.9	1.0	1.1	1.9	50
3001		0.44	2.6	2.3	1.6	3.8	74
3002		0.41	2.8	2.4	1.9	4.3	54
3003		0.48	2.4	2.7	2.3	5.0	41
3004		0.43	2.7	2.3	2.2	4.5	59
Relative 3005		0.46	2.8	2.6	2.2	4.8	62
3006		0.43	3.4	2.4	2.1	4.5	55
3007		0.44	2.9	1.8	1.7	3.5	53
Mean		0.44	2.8	2.4	2.0	4.3	57
S.D.		0.02	0.3	0.3	0.3	0.5	10

Appendix 8-10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 30

Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
3001	1.20	11.69	0.70	1.36	1.42	2.78
3002	1.73	14.22	0.71	1.59	1.49	3.08
3003	1.27	9.43	0.60	1.55	1.59	3.14
3004	1.47	13.02	0.88	1.69	1.60	3.29
Absolute 3005	1.29	14.32	0.96	1.47	1.55	3.02
3006	1.50	12.40	0.70	1.69	1.70	3.39
3007	1.58	12.33	0.59	1.69	1.65	3.34

Mean	1.43	12.49	0.73	1.58	1.57	3.15
S.D.	0.19	1.67	0.14	0.13	0.09	0.21

3001	0.26	2.56	0.15	0.30	0.31	0.61
3002	0.36	2.92	0.15	0.33	0.31	0.63
3003	0.31	2.29	0.15	0.38	0.39	0.76
3004	0.31	2.72	0.18	0.35	0.33	0.69
Relative 3005	0.28	3.15	0.21	0.32	0.34	0.66
3006	0.32	2.63	0.15	0.36	0.36	0.72
3007	0.32	2.47	0.12	0.34	0.33	0.67

Mean	0.31	2.68	0.16	0.34	0.34	0.68
S.D.	0.03	0.29	0.03	0.03	0.03	0.05

Appendix 8-11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 30

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)
3001	30	31	61	1.62	1.60	3.22
3002	26	29	55	1.74	1.70	3.44
3003	27	30	57	1.57	1.56	3.13
3004	35	34	69	1.54	1.49	3.03
Absolute 3005	37	41	78	1.53	1.53	3.06
3006	27	29	56	1.59	1.59	3.18
3007	27	27	54	1.69	1.68	3.37

Mean	30	32	61	1.61	1.59	3.20
S.D.	4	5	9	0.08	0.08	0.15
3001	7	7	13	0.35	0.35	0.70
3002	5	6	11	0.36	0.35	0.71
3003	7	7	14	0.38	0.38	0.76
3004	7	7	14	0.32	0.31	0.63
Relative 3005	8	9	17	0.34	0.34	0.67
3006	6	6	12	0.34	0.34	0.68
3007	5	5	11	0.34	0.34	0.68

Mean	6	7	13	0.35	0.34	0.69
S.D.	1	1	2	0.02	0.02	0.04

Appendix 8-12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 30

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)
3001	686	663	1349	2.03	1.47
3002	665	634	1299	1.75	1.18
3003	601	609	1210	2.13	1.36
3004	687	697	1384	1.08	1.56
Absolute 3005	648	662	1310	1.82	1.35
3006	590	586	1176	1.53	1.21
3007	619	615	1234	1.37	1.41

Mean	642	638	1280	1.67	1.36
S.D.	40	38	76	0.37	0.14
3001	150	145	295	0.44	0.32
3002	137	130	267	0.36	0.24
3003	146	148	294	0.52	0.33
3004	144	146	290	0.23	0.33
Relative 3005	142	145	288	0.40	0.30
3006	125	124	250	0.32	0.26
3007	124	123	247	0.27	0.28

Mean	138	137	276	0.36	0.29
S.D.	10	11	21	0.10	0.04

Appendix 8-13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 100

Animal number	Body weight	Brain	Pituitary	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus
	g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
4001S	323Z	1.91Z	9.6Z	7.3Z	7.2Z	14.5Z	162Z
4002S	293Z	2.05Z	8.8Z	9.4Z	9.9Z	19.3Z	77Z
4003D	339Z	2.26Z	13.9Z	8.6Z	9.9Z	18.5Z	303Z
4004S	326Z	2.11Z	9.8Z	9.2Z	8.4Z	17.6Z	78Z
4005S	318Z	2.02Z	9.4Z	9.5Z	9.2Z	18.7Z	113Z
4006S	313Z	1.89Z	5.7Z	7.4Z	8.1Z	15.5Z	69Z
4007S	262Z	1.92Z	7.9Z	7.4Z	4.0Z	11.4Z	25Z
Absolute 4008S	260Z	1.89Z	9.8Z	8.9Z	8.9Z	17.8Z	44Z
4009S	253Z	2.06Z	10.3Z	8.4Z	6.4Z	14.8Z	44Z
4010S	343Z	2.11Z	12.0Z	9.8Z	7.2Z	17.0Z	151Z
4011S	324Z	2.02Z	11.2Z	6.4Z	6.1Z	12.5Z	130Z
4012S	293Z	1.96Z	9.6Z	7.2Z	8.6Z	15.8Z	63Z

Mean							
S.D.							

4001S		0.59Z	3.0Z	2.3Z	2.2Z	4.5Z	50Z
4002S		0.70Z	3.0Z	3.2Z	3.4Z	6.6Z	26Z
4003D		0.67Z	4.1Z	2.5Z	2.9Z	5.5Z	89Z
4004S		0.65Z	3.0Z	2.8Z	2.6Z	5.4Z	24Z
4005S		0.64Z	3.0Z	3.0Z	2.9Z	5.9Z	36Z
4006S		0.60Z	1.8Z	2.4Z	2.6Z	5.0Z	22Z
4007S		0.73Z	3.0Z	2.8Z	1.5Z	4.4Z	10Z
Relative 4008S		0.73Z	3.8Z	3.4Z	3.4Z	6.8Z	17Z
4009S		0.81Z	4.1Z	3.3Z	2.5Z	5.8Z	17Z
4010S		0.62Z	3.5Z	2.9Z	2.1Z	5.0Z	44Z
4011S		0.62Z	3.5Z	2.0Z	1.9Z	3.9Z	40Z
4012S		0.67Z	3.3Z	2.5Z	2.9Z	5.4Z	22Z

Mean							
S.D.							

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-14

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 100

Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
4001S	1.37Z	9.37Z	0.27Z	1.14Z	1.15Z	2.29Z
4002S	1.22Z	8.24Z	0.36Z	1.09Z	1.11Z	2.20Z
4003D	1.96Z	14.27Z	0.53Z	1.53Z	1.53Z	3.06Z
4004S	1.46Z	9.57Z	0.40Z	1.19Z	1.18Z	2.37Z
4005S	1.35Z	11.00Z	0.60Z	1.36Z	1.32Z	2.68Z
4006S	1.41Z	9.88Z	0.30Z	1.80Z	1.75Z	3.55Z
4007S	1.23Z	7.77Z	0.20Z	1.07Z	1.01Z	2.08Z
Absolute 4008S	1.32Z	8.51Z	0.26Z	1.22Z	1.16Z	2.38Z
4009S	1.36Z	8.25Z	0.23Z	1.07Z	1.04Z	2.11Z
4010S	1.87Z	11.08Z	0.35Z	1.27Z	1.24Z	2.51Z
4011S	1.38Z	9.29Z	0.37Z	1.20Z	1.12Z	2.32Z
4012S	1.20Z	9.07Z	0.50Z	1.71Z	1.63Z	3.34Z

Mean						
S.D.						
4001S	0.42Z	2.90Z	0.08Z	0.35Z	0.36Z	0.71Z
4002S	0.42Z	2.81Z	0.12Z	0.37Z	0.38Z	0.75Z
4003D	0.58Z	4.21Z	0.16Z	0.45Z	0.45Z	0.90Z
4004S	0.45Z	2.94Z	0.12Z	0.37Z	0.36Z	0.73Z
4005S	0.42Z	3.46Z	0.19Z	0.43Z	0.42Z	0.84Z
4006S	0.45Z	3.16Z	0.10Z	0.58Z	0.56Z	1.13Z
4007S	0.47Z	2.97Z	0.08Z	0.41Z	0.39Z	0.79Z
Relative 4008S	0.51Z	3.27Z	0.10Z	0.47Z	0.45Z	0.92Z
4009S	0.54Z	3.26Z	0.09Z	0.42Z	0.41Z	0.83Z
4010S	0.55Z	3.23Z	0.10Z	0.37Z	0.36Z	0.73Z
4011S	0.43Z	2.87Z	0.11Z	0.37Z	0.35Z	0.72Z
4012S	0.41Z	3.10Z	0.17Z	0.58Z	0.56Z	1.14Z

Mean						
S.D.						

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 100

	Animal number	Adrenal	Adrenal	Adrenal	Testis	Testis	Testis
		(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	(R) g(g/100g BW)	(L) g(g/100g BW)	(R+L) g(g/100g BW)
Absolute	4001S	53Z	54Z	107Z	1.33Z	1.38Z	2.71Z
	4002S	48Z	41Z	89Z	1.36Z	1.37Z	2.73Z
	4003D	69Z	68Z	137Z	1.45Z	1.40Z	2.85Z
	4004S	41Z	39Z	80Z	1.38Z	1.36Z	2.74Z
	4005S	35Z	36Z	71Z	1.48Z	1.54Z	3.02Z
	4006S	48Z	47Z	95Z	1.37Z	1.38Z	2.75Z
	4007S	30Z	36Z	66Z	1.30Z	1.29Z	2.59Z
	4008S	40Z	40Z	80Z	1.41Z	1.39Z	2.80Z
	4009S	42Z	40Z	82Z	1.50Z	1.48Z	2.98Z
	4010S	57Z	60Z	117Z	1.46Z	1.48Z	2.94Z
	4011S	34Z	34Z	68Z	1.36Z	1.33Z	2.69Z
	4012S	43Z	46Z	89Z	1.22Z	1.18Z	2.40Z
Mean							
S.D.							
Relative	4001S	16Z	17Z	33Z	0.41Z	0.43Z	0.84Z
	4002S	16Z	14Z	30Z	0.46Z	0.47Z	0.93Z
	4003D	20Z	20Z	40Z	0.43Z	0.41Z	0.84Z
	4004S	13Z	12Z	25Z	0.42Z	0.42Z	0.84Z
	4005S	11Z	11Z	22Z	0.47Z	0.48Z	0.95Z
	4006S	15Z	15Z	30Z	0.44Z	0.44Z	0.88Z
	4007S	11Z	14Z	25Z	0.50Z	0.49Z	0.99Z
	4008S	15Z	15Z	31Z	0.54Z	0.53Z	1.08Z
	4009S	17Z	16Z	32Z	0.59Z	0.58Z	1.18Z
	4010S	17Z	17Z	34Z	0.43Z	0.43Z	0.86Z
	4011S	10Z	10Z	21Z	0.42Z	0.41Z	0.83Z
	4012S	15Z	16Z	30Z	0.42Z	0.40Z	0.82Z
Mean							
S.D.							

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-16

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of administration)
 Dose (mg/kg): 100

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)
4001S	356Z	375Z	731Z	0.37Z	0.47Z
4002S	482Z	425Z	907Z	1.22Z	0.63Z
4003D	535Z	477Z	1012Z	1.05Z	0.69Z
4004S	422Z	421Z	843Z	1.21Z	0.59Z
4005S	464Z	456Z	920Z	0.67Z	0.67Z
4006S	450Z	440Z	890Z	0.95Z	1.00Z
4007S	356Z	381Z	737Z	1.01Z	0.54Z
Absolute 4008S	395Z	393Z	788Z	0.71Z	0.63Z
4009S	412Z	403Z	815Z	1.37Z	0.65Z
4010S	457Z	432Z	889Z	0.76Z	0.49Z
4011S	426Z	408Z	834Z	0.49Z	0.80Z
4012S	388Z	374Z	762Z	0.93Z	0.56Z
Mean					
S.D.					
4001S	110Z	116Z	226Z	0.11Z	0.15Z
4002S	165Z	145Z	310Z	0.42Z	0.22Z
4003D	158Z	141Z	299Z	0.31Z	0.20Z
4004S	129Z	129Z	259Z	0.37Z	0.18Z
4005S	146Z	143Z	289Z	0.21Z	0.21Z
4006S	144Z	141Z	284Z	0.30Z	0.32Z
4007S	136Z	145Z	281Z	0.39Z	0.21Z
Relative 4008S	152Z	151Z	303Z	0.27Z	0.24Z
4009S	163Z	159Z	322Z	0.54Z	0.26Z
4010S	133Z	126Z	259Z	0.22Z	0.14Z
4011S	131Z	126Z	257Z	0.15Z	0.25Z
4012S	132Z	128Z	260Z	0.32Z	0.19Z
Mean					
S.D.					

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 0

Animal number	Body weight	Brain	Pituitary	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus
	g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
1101	309	2.04	16.3	8.4	7.5	15.9	254
1102	316	1.91	15.3	9.3	9.0	18.3	267
1103	329	1.96	14.7	10.7	10.4	21.1	153
1104	320	1.99	19.8	11.4	7.9	19.3	325
1105	292	1.85	14.8	8.4	10.2	18.6	166
1106	325	1.97	19.7	9.9	7.3	17.2	331
1107	269	1.87	15.5	8.4	6.3	14.7	87
Absolute 1108	330	2.00	20.2	7.5	8.9	16.4	167
1109	296	2.11	16.8	11.3	7.2	18.5	83
1110	280	1.93	16.0	10.9	9.7	20.6	147
1111	307	1.87	17.0	9.1	5.6	14.7	181
1112	289	1.95	15.6	6.3	6.7	13.0	225
Mean	305	1.95	16.8	9.3	8.1	17.4	199
S.D.	20	0.08	2.0	1.6	1.6	2.5	83
1101		0.66	5.3	2.7	2.4	5.1	82
1102		0.60	4.8	2.9	2.8	5.8	84
1103		0.60	4.5	3.3	3.2	6.4	47
1104		0.62	6.2	3.6	2.5	6.0	102
1105		0.63	5.1	2.9	3.5	6.4	57
1106		0.61	6.1	3.0	2.2	5.3	102
1107		0.70	5.8	3.1	2.3	5.5	32
Relative 1108		0.61	6.1	2.3	2.7	5.0	51
1109		0.71	5.7	3.8	2.4	6.3	28
1110		0.69	5.7	3.9	3.5	7.4	53
1111		0.61	5.5	3.0	1.8	4.8	59
1112		0.67	5.4	2.2	2.3	4.5	78
Mean		0.64	5.5	3.1	2.6	5.7	65
S.D.		0.04	0.5	0.5	0.5	0.8	25

Appendix 8-18

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 0

Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
1101	0.98	8.61	0.69	0.96	0.97	1.93
1102	1.01	9.31	0.66	1.08	1.06	2.14
1103	1.04	12.44	1.02	1.08	1.09	2.17
1104	1.18	9.81	0.53	1.13	1.13	2.26
1105	0.86	10.19	0.54	0.91	0.86	1.77
1106	1.17	11.26	0.88	1.09	1.13	2.22
1107	0.85	9.96	0.60	0.88	0.81	1.69
Absolute 1108	1.06	11.23	0.69	1.04	1.05	2.09
1109	0.96	9.81	0.92	1.10	1.05	2.15
1110	0.89	9.40	0.57	1.01	0.98	1.99
1111	0.95	9.20	0.56	0.97	0.96	1.93
1112	1.00	9.99	0.67	0.97	0.96	1.93
Mean	1.00	10.10	0.69	1.02	1.00	2.02
S.D.	0.11	1.06	0.16	0.08	0.10	0.18
1101	0.32	2.79	0.22	0.31	0.31	0.62
1102	0.32	2.95	0.21	0.34	0.34	0.68
1103	0.32	3.78	0.31	0.33	0.33	0.66
1104	0.37	3.07	0.17	0.35	0.35	0.71
1105	0.29	3.49	0.18	0.31	0.29	0.61
1106	0.36	3.46	0.27	0.34	0.35	0.68
1107	0.32	3.70	0.22	0.33	0.30	0.63
Relative 1108	0.32	3.40	0.21	0.32	0.32	0.63
1109	0.32	3.31	0.31	0.37	0.35	0.73
1110	0.32	3.36	0.20	0.36	0.35	0.71
1111	0.31	3.00	0.18	0.32	0.31	0.63
1112	0.35	3.46	0.23	0.34	0.33	0.67
Mean	0.33	3.31	0.23	0.34	0.33	0.66
S.D.	0.02	0.30	0.05	0.02	0.02	0.04

Appendix 8-19

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 0

Animal number	Adrenal	Adrenal	Adrenal	Ovary	Ovary	Ovary	Uterus
	(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	mg(mg/100g BW)
1101	33	34	67	53.0	49.5	102.5	553
1102	23	35	58	35.2	51.3	86.5	740
1103	47	50	97	58.6	68.1	126.7	710
1104	39	39	78	70.9	50.5	121.4	549
1105	40	45	85	49.8	58.4	108.2	549
1106	39	40	79	65.0	57.3	122.3	745
1107	33	35	68	46.4	59.7	106.1	674
Absolute 1108	43	46	89	84.5	49.3	133.8	703
1109	36	41	77	54.4	51.6	106.0	832
1110	42	41	83	52.5	57.9	110.4	640
1111	32	32	64	42.3	56.2	98.5	794
1112	33	38	71	49.1	41.5	90.6	575
Mean	37	40	76	55.1	54.3	109.4	672
S.D.	6	5	11	13.3	6.8	14.4	99
1101	11	11	22	17.2	16.0	33.2	179
1102	7	11	18	11.1	16.2	27.4	234
1103	14	15	29	17.8	20.7	38.5	216
1104	12	12	24	22.2	15.8	37.9	172
1105	14	15	29	17.1	20.0	37.1	188
1106	12	12	24	20.0	17.6	37.6	229
1107	12	13	25	17.2	22.2	39.4	251
Relative 1108	13	14	27	25.6	14.9	40.5	213
1109	12	14	26	18.4	17.4	35.8	281
1110	15	15	30	18.8	20.7	39.4	229
1111	10	10	21	13.8	18.3	32.1	259
1112	11	13	25	17.0	14.4	31.3	199
Mean	12	13	25	18.0	17.9	35.9	221
S.D.	2	2	4	3.7	2.5	4.0	33

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Appendix 8-20

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 10

Animal number	Body weight	Brain	Pituitary	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus
	g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
2101a)	291Z	1.98Z	23.7Z	9.0Z	9.8Z	18.8Z	219Z
2102	291	1.91	15.8	6.6	5.7	12.3	145
2103	282	1.99	18.2	7.6	9.6	17.2	233
2104	301	2.05	17.5	8.6	10.2	18.8	145
2105	310	1.96	15.5	9.7	8.6	18.3	270
2106b)	396Z	1.96Z	19.4Z	12.0Z	9.1Z	21.1Z	341Z
2107	291	1.90	17.4	8.3	8.8	17.1	249
Absolute 2108	337	1.96	18.9	9.5	8.5	18.0	136
2109	293	2.01	17.3	7.7	6.6	14.3	153
2110	299	1.94	19.4	9.5	10.3	19.8	84
2111	318	1.91	17.5	7.7	11.1	18.8	233
2112	338	2.04	15.4	10.3	7.6	17.9	269
Mean	306	1.97	17.3	8.6	8.7	17.3	192
S.D.	19	0.05	1.4	1.2	1.7	2.3	66
2101a)		0.68Z	8.1Z	3.1Z	3.4Z	6.5Z	75Z
2102		0.66	5.4	2.3	2.0	4.2	50
2103		0.71	6.5	2.7	3.4	6.1	83
2104		0.68	5.8	2.9	3.4	6.2	48
2105		0.63	5.0	3.1	2.8	5.9	87
2106b)		0.49Z	4.9Z	3.0Z	2.3Z	5.3Z	86Z
2107		0.65	6.0	2.9	3.0	5.9	86
Relative 2108		0.58	5.6	2.8	2.5	5.3	40
2109		0.69	5.9	2.6	2.3	4.9	52
2110		0.65	6.5	3.2	3.4	6.6	28
2111		0.60	5.5	2.4	3.5	5.9	73
2112		0.60	4.6	3.0	2.2	5.3	80
Mean		0.65	5.7	2.8	2.9	5.6	63
S.D.		0.04	0.6	0.3	0.6	0.7	22

a): Not copulated

b): Died on gestation day 22

Z: Data was excluded from statistical analysis.

Appendix 8-21

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 10

Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
2101a)	0.84Z	9.72Z	0.52Z	0.93Z	0.85Z	1.78Z
2102	0.97	9.87	0.58	0.93	0.94	1.87
2103	1.18	8.89	0.55	0.97	0.94	1.91
2104	1.15	10.72	0.66	1.14	1.09	2.23
2105	0.96	9.80	0.67	1.04	1.08	2.12
2106b)	1.09Z	13.52Z	0.47Z	1.00Z	1.01Z	2.01Z
2107	0.96	10.81	0.45	1.02	1.01	2.03
Absolute 2108	1.13	11.86	0.58	1.16	1.15	2.31
2109	0.97	9.30	0.70	1.04	1.00	2.04
2110	0.92	9.84	0.59	1.00	0.92	1.92
2111	1.00	11.16	0.72	1.20	1.19	2.39
2112	1.07	10.31	0.64	1.10	1.16	2.26

Mean	1.03	10.26	0.61	1.06	1.05	2.11
S.D.	0.09	0.90	0.08	0.09	0.10	0.18

2101a)	0.29Z	3.34Z	0.18Z	0.32Z	0.29Z	0.61Z
2102	0.33	3.39	0.20	0.32	0.32	0.64
2103	0.42	3.15	0.20	0.34	0.33	0.68
2104	0.38	3.56	0.22	0.38	0.36	0.74
2105	0.31	3.16	0.22	0.34	0.35	0.68
2106b)	0.28Z	3.41Z	0.12Z	0.25Z	0.26Z	0.51Z
2107	0.33	3.71	0.15	0.35	0.35	0.70
Relative 2108	0.34	3.52	0.17	0.34	0.34	0.69
2109	0.33	3.17	0.24	0.35	0.34	0.70
2110	0.31	3.29	0.20	0.33	0.31	0.64
2111	0.31	3.51	0.23	0.38	0.37	0.75
2112	0.32	3.05	0.19	0.33	0.34	0.67

Mean	0.34	3.35	0.20	0.35	0.34	0.69
S.D.	0.04	0.22	0.03	0.02	0.02	0.04

a): Not copulated

b): Died on gestation day 22

Z: Data was excluded from statistical analysis.

Appendix 8-22

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 10

	Animal number	Adrenal	Adrenal	Adrenal	Ovary	Ovary	Ovary	Uterus
		(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	mg(mg/100g BW)
Absolute	2101a)	31Z	35Z	66Z	35.6Z	35.1Z	70.7Z	483Z
	2102	42	47	89	49.3	46.6	95.9	559
	2103	38	42	80	52.6	55.2	107.8	666
	2104	45	39	84	68.7	56.4	125.1	889
	2105	50	52	102	45.8	50.1	95.9	599
	2106b)	39Z	38Z	77Z	87.2Z	58.3Z	145.5Z	c)
	2107	45	48	93	55.5	55.5	111.0	621
	2108	40	45	85	49.2	36.7	85.9	635
	2109	41	43	84	53.6	51.6	105.2	641
	2110	39	39	78	57.4	45.7	103.1	673
	2111	46	46	92	62.0	68.3	130.3	903
	2112	32	34	66	70.7	67.3	138.0	862
	Mean	42	44	85	56.5	53.3	109.8	705
S.D.	5	5	10	8.3	9.6	16.6	129	
Relative	2101a)	11Z	12Z	23Z	12.2Z	12.1Z	24.3Z	166Z
	2102	14	16	31	16.9	16.0	33.0	192
	2103	13	15	28	18.7	19.6	38.2	236
	2104	15	13	28	22.8	18.7	41.6	295
	2105	16	17	33	14.8	16.2	30.9	193
	2106b)	10Z	10Z	19Z	22.0Z	14.7Z	36.7Z	
	2107	15	16	32	19.1	19.1	38.1	213
	2108	12	13	25	14.6	10.9	25.5	188
	2109	14	15	29	18.3	17.6	35.9	219
	2110	13	13	26	19.2	15.3	34.5	225
	2111	14	14	29	19.5	21.5	41.0	284
	2112	9	10	20	20.9	19.9	40.8	255
	Mean	14	14	28	18.5	17.5	36.0	230
S.D.	2	2	4	2.5	3.0	5.1	38	

a): Not copulated

b): Died on gestation day 22

c): It was not measured since containing conceptus.

Z: Data was excluded from statistical analysis.

Appendix 8-23

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 30

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)
3101	325	1.92	14.7	12.8	12.1	24.9	258
3102	262	1.86	16.2	7.8	6.6	14.4	128
3103	288	1.93	14.4	7.2	8.1	15.3	269
3104	304	1.95	16.3	8.9	8.6	17.5	126
3105	316	1.91	17.4	8.0	11.9	19.9	178
3106	314	2.02	19.3	8.6	7.7	16.3	169
3107	304	2.06	16.3	8.6	7.8	16.4	191
Absolute 3108	303	2.02	17.5	8.3	7.9	16.2	317
3109	307	1.94	17.1	9.4	9.6	19.0	198
3110	272	1.96	16.0	8.0	5.3	13.3	161
3111	328	1.98	18.3	11.0	10.6	21.6	217
3112	308	1.98	20.2	8.0	7.6	15.6	150
Mean	303	1.96	17.0	8.9	8.7	17.5	197
S.D.	20	0.06	1.7	1.6	2.0	3.3	59
3101		0.59	4.5	3.9	3.7	7.7	79
3102		0.71	6.2	3.0	2.5	5.5	49
3103		0.67	5.0	2.5	2.8	5.3	93
3104		0.64	5.4	2.9	2.8	5.8	41
3105		0.60	5.5	2.5	3.8	6.3	56
3106		0.64	6.1	2.7	2.5	5.2	54
3107		0.68	5.4	2.8	2.6	5.4	63
Relative 3108		0.67	5.8	2.7	2.6	5.3	105
3109		0.63	5.6	3.1	3.1	6.2	64
3110		0.72	5.9	2.9	1.9	4.9	59
3111		0.60	5.6	3.4	3.2	6.6	66
3112		0.64	6.6	2.6	2.5	5.1	49
Mean		0.65	5.6	2.9	2.8	5.8	65
S.D.		0.04	0.6	0.4	0.5	0.8	19

Appendix 8-24

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 30

Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
3101	1.07	10.60	0.76	1.04	1.04	2.08
3102	0.85	8.92	0.54	0.96	0.90	1.86
3103	1.00	10.54	0.67	1.05	1.07	2.12
3104	1.06	9.35	0.74	1.00	0.98	1.98
3105	1.13	11.70	0.58	1.25	1.19	2.44
3106	1.13	12.73	0.67	1.09	1.13	2.22
3107	0.96	9.62	0.66	0.98	0.90	1.88
3108	0.94	11.43	0.85	1.15	1.10	2.25
3109	1.04	10.80	0.58	1.04	1.06	2.10
3110	0.92	8.79	0.58	0.95	0.95	1.90
3111	1.22	11.94	0.65	1.07	1.01	2.08
3112	1.16	11.43	1.02	1.16	1.18	2.34
Mean	1.04	10.65	0.69	1.06	1.04	2.10
S.D.	0.11	1.26	0.14	0.09	0.10	0.18
3101	0.33	3.26	0.23	0.32	0.32	0.64
3102	0.32	3.40	0.21	0.37	0.34	0.71
3103	0.35	3.66	0.23	0.36	0.37	0.74
3104	0.35	3.08	0.24	0.33	0.32	0.65
3105	0.36	3.70	0.18	0.40	0.38	0.77
3106	0.36	4.05	0.21	0.35	0.36	0.71
3107	0.32	3.16	0.22	0.32	0.30	0.62
3108	0.31	3.77	0.28	0.38	0.36	0.74
3109	0.34	3.52	0.19	0.34	0.35	0.68
3110	0.34	3.23	0.21	0.35	0.35	0.70
3111	0.37	3.64	0.20	0.33	0.31	0.63
3112	0.38	3.71	0.33	0.38	0.38	0.76
Mean	0.34	3.52	0.23	0.35	0.35	0.70
S.D.	0.02	0.29	0.04	0.03	0.03	0.05

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Appendix 8-25

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 30

	Animal number	Adrenal	Adrenal	Adrenal	Ovary	Ovary	Ovary	Uterus
		(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	mg(mg/100g BW)
Absolute	3101	56	58	114	62.7	49.9	112.6	743
	3102	31	31	62	41.1	44.4	85.5	571
	3103	38	44	82	45.6	43.1	88.7	597
	3104	43	44	87	57.5	50.0	107.5	725
	3105	42	49	91	59.1	55.0	114.1	803
	3106	38	45	83	50.7	45.0	95.7	748
	3107	40	41	81	70.8	66.4	137.2	713
	3108	50	52	102	55.8	36.3	92.1	683
	3109	36	38	74	42.8	47.9	90.7	565
	3110	35	37	72	45.2	41.5	86.7	531
	3111	45	45	90	42.9	57.8	100.7	776
	3112	49	48	97	52.8	46.7	99.5	740
		Mean	42	44	86	52.3	48.7	100.9
	S.D.	7	7	14	9.2	8.0	15.0	92
Relative	3101	17	18	35	19.3	15.4	34.6	229
	3102	12	12	24	15.7	16.9	32.6	218
	3103	13	15	28	15.8	15.0	30.8	207
	3104	14	14	29	18.9	16.4	35.4	238
	3105	13	16	29	18.7	17.4	36.1	254
	3106	12	14	26	16.1	14.3	30.5	238
	3107	13	13	27	23.3	21.8	45.1	235
	3108	17	17	34	18.4	12.0	30.4	225
	3109	12	12	24	13.9	15.6	29.5	184
	3110	13	14	26	16.6	15.3	31.9	195
	3111	14	14	27	13.1	17.6	30.7	237
	3112	16	16	31	17.1	15.2	32.3	240
		Mean	14	15	28	17.2	16.1	33.3
	S.D.	2	2	4	2.7	2.3	4.3	20

Appendix 8-26

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 100

Animal number	Body weight	Brain	Pituitary	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus
	g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
4101S	199Z	1.86Z	9.4Z	4.1Z	4.0Z	8.1Z	111Z
4102S	179Z	1.76Z	10.7Z	6.2Z	3.9Z	10.1Z	87Z
4103D	177Z	1.86Z	12.4Z	8.0Z	7.3Z	15.3Z	83Z
4104D	197Z	1.87Z	15.3Z	8.2Z	6.5Z	14.7Z	207Z
4105S	209Z	1.87Z	13.8Z	9.7Z	5.3Z	15.0Z	179Z
4106S	187Z	1.94Z	12.4Z	4.1Z	5.6Z	9.7Z	96Z
4107S	224Z	1.91Z	14.0Z	5.4Z	5.6Z	11.0Z	214Z
Absolute 4108S	216Z	1.88Z	12.7Z	6.4Z	4.2Z	10.6Z	119Z
4109D	190Z	1.91Z	12.3Z	6.8Z	6.3Z	13.1Z	87Z
4110S	198Z	1.90Z	11.0Z	3.9Z	5.1Z	9.0Z	104Z
4111S	179Z	1.80Z	10.7Z	6.9Z	4.2Z	11.1Z	68Z
4112S	185Z	1.86Z	10.1Z	4.9Z	4.1Z	9.0Z	76Z

Mean							
S.D.							

4101S		0.93Z	4.7Z	2.1Z	2.0Z	4.1Z	56Z
4102S		0.98Z	6.0Z	3.5Z	2.2Z	5.6Z	49Z
4103D		1.05Z	7.0Z	4.5Z	4.1Z	8.6Z	47Z
4104D		0.95Z	7.8Z	4.2Z	3.3Z	7.5Z	105Z
4105S		0.89Z	6.6Z	4.6Z	2.5Z	7.2Z	86Z
4106S		1.04Z	6.6Z	2.2Z	3.0Z	5.2Z	51Z
4107S		0.85Z	6.3Z	2.4Z	2.5Z	4.9Z	96Z
Relative 4108S		0.87Z	5.9Z	3.0Z	1.9Z	4.9Z	55Z
4109D		1.01Z	6.5Z	3.6Z	3.3Z	6.9Z	46Z
4110S		0.96Z	5.6Z	2.0Z	2.6Z	4.5Z	53Z
4111S		1.01Z	6.0Z	3.9Z	2.3Z	6.2Z	38Z
4112S		1.01Z	5.5Z	2.6Z	2.2Z	4.9Z	41Z

Mean							
S.D.							

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-27

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 100

	Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
		g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
Absolute	4101S	8.12Z	6.56Z	0.38Z	0.72Z	0.65Z	1.37Z
	4102S	0.85Z	6.01Z	0.27Z	0.69Z	0.69Z	1.38Z
	4103D	0.85Z	5.95Z	0.17Z	0.80Z	0.82Z	1.62Z
	4104D	1.08Z	10.58Z	0.32Z	0.92Z	0.88Z	1.80Z
	4105S	1.06Z	6.63Z	0.28Z	0.80Z	0.74Z	1.54Z
	4106S	0.79Z	6.63Z	0.21Z	0.80Z	0.76Z	1.56Z
	4107S	0.97Z	7.99Z	0.51Z	0.90Z	0.82Z	1.72Z
	4108S	1.00Z	7.79Z	0.41Z	0.91Z	0.92Z	1.83Z
	4109D	1.01Z	6.92Z	0.18Z	0.78Z	0.75Z	1.53Z
	4110S	0.98Z	6.15Z	0.21Z	0.70Z	0.68Z	1.38Z
	4111S	0.73Z	5.80Z	0.22Z	0.68Z	0.68Z	1.36Z
	4112S	0.77Z	5.81Z	0.18Z	0.82Z	0.79Z	1.61Z
Mean							
S.D.							
Relative	4101S	4.08Z	3.30Z	0.19Z	0.36Z	0.33Z	0.69Z
	4102S	0.47Z	3.36Z	0.15Z	0.39Z	0.39Z	0.77Z
	4103D	0.48Z	3.36Z	0.10Z	0.45Z	0.46Z	0.92Z
	4104D	0.55Z	5.37Z	0.16Z	0.47Z	0.45Z	0.91Z
	4105S	0.51Z	3.17Z	0.13Z	0.38Z	0.35Z	0.74Z
	4106S	0.42Z	3.55Z	0.11Z	0.43Z	0.41Z	0.83Z
	4107S	0.43Z	3.57Z	0.23Z	0.40Z	0.37Z	0.77Z
	4108S	0.46Z	3.61Z	0.19Z	0.42Z	0.43Z	0.85Z
	4109D	0.53Z	3.64Z	0.09Z	0.41Z	0.39Z	0.81Z
	4110S	0.49Z	3.11Z	0.11Z	0.35Z	0.34Z	0.70Z
	4111S	0.41Z	3.24Z	0.12Z	0.38Z	0.38Z	0.76Z
	4112S	0.42Z	3.14Z	0.10Z	0.44Z	0.43Z	0.87Z
Mean							
S.D.							

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-28

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Main group, End of administration)
 Dose (mg/kg): 100

	Animal number	Adrenal	Adrenal	Adrenal	Ovary	Ovary	Ovary	Uterus
		(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	mg(mg/100g BW)
Absolute	4101S	51Z	53Z	104Z	47.5Z	51.0Z	98.5Z	274Z
	4102S	46Z	54Z	100Z	47.8Z	46.2Z	94.0Z	320Z
	4103D	61Z	67Z	128Z	39.0Z	41.9Z	80.9Z	462Z
	4104D	66Z	75Z	141Z	53.1Z	51.3Z	104.4Z	312Z
	4105S	40Z	48Z	88Z	36.5Z	32.8Z	69.3Z	541Z
	4106S	63Z	77Z	140Z	44.0Z	45.4Z	89.4Z	240Z
	4107S	49Z	55Z	104Z	43.1Z	45.0Z	88.1Z	377Z
	4108S	49Z	52Z	101Z	42.3Z	45.6Z	87.9Z	438Z
	4109D	75Z	90Z	165Z	40.4Z	31.0Z	71.4Z	279Z
	4110S	45Z	43Z	88Z	24.9Z	39.2Z	64.1Z	303Z
	4111S	56Z	65Z	121Z	26.0Z	29.7Z	55.7Z	373Z
	4112S	40Z	44Z	84Z	28.2Z	23.7Z	51.9Z	308Z

	Mean							
	S.D.							
Relative	4101S	26Z	27Z	52Z	23.9Z	25.6Z	49.5Z	138Z
	4102S	26Z	30Z	56Z	26.7Z	25.8Z	52.5Z	179Z
	4103D	34Z	38Z	72Z	22.0Z	23.7Z	45.7Z	261Z
	4104D	34Z	38Z	72Z	27.0Z	26.0Z	53.0Z	158Z
	4105S	19Z	23Z	42Z	17.5Z	15.7Z	33.2Z	259Z
	4106S	34Z	41Z	75Z	23.5Z	24.3Z	47.8Z	128Z
	4107S	22Z	25Z	46Z	19.2Z	20.1Z	39.3Z	168Z
	4108S	23Z	24Z	47Z	19.6Z	21.1Z	40.7Z	203Z
	4109D	39Z	47Z	87Z	21.3Z	16.3Z	37.6Z	147Z
	4110S	23Z	22Z	44Z	12.6Z	19.8Z	32.4Z	153Z
	4111S	31Z	36Z	68Z	14.5Z	16.6Z	31.1Z	208Z
	4112S	22Z	24Z	45Z	15.2Z	12.8Z	28.1Z	166Z

	Mean							
	S.D.							

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-29

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Satellite group, End of administration)
 Dose (mg/kg): 0

Animal number	Body weight	Brain	Pituitary	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus
	g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
1113	237	1.86	14.6	12.5	9.1	21.6	318
1114	274	1.93	18.1	13.8	11.1	24.9	407
1115	249	1.90	15.4	9.5	8.4	17.9	432
1116	272	1.88	18.0	14.7	6.2	20.9	551
1117	240	2.00	17.7	10.5	6.2	16.7	333
1118	235	1.92	16.4	8.8	7.9	16.7	298
Absolute 1119	254	1.94	19.4	13.9	7.7	21.6	389
1120	252	1.90	14.7	7.3	9.0	16.3	368
1121	224	1.97	21.1	8.5	6.7	15.2	237
1122	250	1.88	19.5	11.5	12.6	24.1	331
Mean	249	1.92	17.5	11.1	8.5	19.6	366
S.D.	16	0.04	2.2	2.6	2.1	3.5	86
1113		0.78	6.2	5.3	3.8	9.1	134
1114		0.70	6.6	5.0	4.1	9.1	149
1115		0.76	6.2	3.8	3.4	7.2	173
1116		0.69	6.6	5.4	2.3	7.7	203
1117		0.83	7.4	4.4	2.6	7.0	139
1118		0.82	7.0	3.7	3.4	7.1	127
Relative 1119		0.76	7.6	5.5	3.0	8.5	153
1120		0.75	5.8	2.9	3.6	6.5	146
1121		0.88	9.4	3.8	3.0	6.8	106
1122		0.75	7.8	4.6	5.0	9.6	132
Mean		0.77	7.1	4.4	3.4	7.9	146
S.D.		0.06	1.1	0.9	0.8	1.1	27

Appendix 8-30

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Satellite group, End of administration)
 Dose (mg/kg): 0

Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
1113	0.83	6.15	0.45	0.88	0.86	1.74
1114	1.15	7.73	0.54	1.05	1.11	2.16
1115	0.74	6.78	0.50	0.87	0.90	1.77
1116	0.96	8.37	0.54	0.85	0.86	1.71
1117	0.77	6.59	0.50	0.80	0.79	1.59
1118	0.83	7.00	0.57	0.85	0.88	1.73
Absolute 1119	0.87	7.49	0.53	0.87	0.85	1.72
1120	0.90	6.52	0.44	0.84	0.80	1.64
1121	0.77	6.68	0.40	0.91	0.90	1.81
1122	0.84	7.36	0.47	0.94	0.92	1.86
Mean	0.87	7.07	0.49	0.89	0.89	1.77
S.D.	0.12	0.67	0.05	0.07	0.09	0.16
1113	0.35	2.59	0.19	0.37	0.36	0.73
1114	0.42	2.82	0.20	0.38	0.41	0.79
1115	0.30	2.72	0.20	0.35	0.36	0.71
1116	0.35	3.08	0.20	0.31	0.32	0.63
1117	0.32	2.75	0.21	0.33	0.33	0.66
1118	0.35	2.98	0.24	0.36	0.37	0.74
Relative 1119	0.34	2.95	0.21	0.34	0.33	0.68
1120	0.36	2.59	0.17	0.33	0.32	0.65
1121	0.34	2.98	0.18	0.41	0.40	0.81
1122	0.34	2.94	0.19	0.38	0.37	0.74
Mean	0.35	2.84	0.20	0.36	0.36	0.71
S.D.	0.03	0.17	0.02	0.03	0.03	0.06

Appendix 8-31

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Satellite group, End of administration)
 Dose (mg/kg): 0

	Animal number	Adrenal	Adrenal	Adrenal	Ovary	Ovary	Ovary	Uterus
		(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	mg(mg/100g BW)
Absolute	1113	37	37	74	39.5	41.8	81.3	522
	1114	38	44	82	53.8	64.9	118.7	629
	1115	30	34	64	45.6	49.6	95.2	465
	1116	32	37	69	43.5	49.7	93.2	572
	1117	31	33	64	54.1	57.0	111.1	683
	1118	36	35	71	51.4	44.6	96.0	855
	1119	51	50	101	59.5	45.7	105.2	643
	1120	33	33	66	44.6	48.9	93.5	443
	1121	35	36	71	34.2	29.3	63.5	527
	1122	33	35	68	44.1	49.9	94.0	403
	Mean	36	37	73	47.0	48.1	95.2	574
	S.D.	6	5	11	7.6	9.3	15.3	134
	Relative	1113	16	16	31	16.7	17.6	34.3
1114		14	16	30	19.6	23.7	43.3	230
1115		12	14	26	18.3	19.9	38.2	187
1116		12	14	25	16.0	18.3	34.3	210
1117		13	14	27	22.5	23.8	46.3	285
1118		15	15	30	21.9	19.0	40.9	364
1119		20	20	40	23.4	18.0	41.4	253
1120		13	13	26	17.7	19.4	37.1	176
1121		16	16	32	15.3	13.1	28.3	235
1122		13	14	27	17.6	20.0	37.6	161
Mean		14	15	29	18.9	19.3	38.2	232
S.D.		2	2	4	2.8	3.1	5.2	59

Appendix 8-32

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Satellite group, End of administration)
 Dose (mg/kg): 100

Animal number	Body weight	Brain	Pituitary	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus
	g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)
4113S	177Z	1.93Z	13.5Z	9.3Z	6.0Z	15.3Z	59Z
4114S	191Z	1.80Z	12.0Z	6.1Z	5.8Z	11.9Z	94Z
4115S	223Z	1.99Z	12.0Z	6.3Z	5.7Z	12.0Z	120Z
4116D	198Z	1.81Z	12.2Z	4.8Z	4.6Z	9.4Z	74Z
4117S	213Z	1.88Z	11.9Z	6.4Z	7.2Z	13.6Z	65Z
4118S	185Z	1.91Z	9.1Z	4.9Z	4.3Z	9.2Z	89Z
Absolute 4119D	175Z	2.03Z	9.6Z	6.5Z	4.6Z	11.1Z	68Z
4120S	191Z	1.98Z	12.2Z	6.4Z	4.1Z	10.5Z	104Z
4121D	208Z	1.96Z	15.9Z	11.9Z	9.9Z	21.8Z	137Z
4122S	185Z	1.75Z	10.3Z	5.5Z	4.0Z	9.5Z	33Z

Mean							
S.D.							

4113S		1.09Z	7.6Z	5.3Z	3.4Z	8.6Z	33Z
4114S		0.94Z	6.3Z	3.2Z	3.0Z	6.2Z	49Z
4115S		0.89Z	5.4Z	2.8Z	2.6Z	5.4Z	54Z
4116D		0.91Z	6.2Z	2.4Z	2.3Z	4.7Z	37Z
4117S		0.88Z	5.6Z	3.0Z	3.4Z	6.4Z	31Z
4118S		1.03Z	4.9Z	2.6Z	2.3Z	5.0Z	48Z
Relative 4119D		1.16Z	5.5Z	3.7Z	2.6Z	6.3Z	39Z
4120S		1.04Z	6.4Z	3.4Z	2.1Z	5.5Z	54Z
4121D		0.94Z	7.6Z	5.7Z	4.8Z	10.5Z	66Z
4122S		0.95Z	5.6Z	3.0Z	2.2Z	5.1Z	18Z

Mean							
S.D.							

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-33

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Satellite group, End of administration)
 Dose (mg/kg): 100

	Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)	
		g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	
Absolute	4113S	0.89Z	6.02Z	0.30Z	0.74Z	0.69Z	1.43Z	
	4114S	0.94Z	6.37Z	0.21Z	0.83Z	0.85Z	1.68Z	
	4115S	0.80Z	7.92Z	0.43Z	0.83Z	0.80Z	1.63Z	
	4116D	0.80Z	7.02Z	0.15Z	0.90Z	0.78Z	1.68Z	
	4117S	0.74Z	12.03Z	0.47Z	0.71Z	0.76Z	1.47Z	
	4118S	1.02Z	6.28Z	0.30Z	0.79Z	0.79Z	1.58Z	
	4119D	0.88Z	7.05Z	0.19Z	0.80Z	0.74Z	1.54Z	
	4120S	0.76Z	5.60Z	0.27Z	0.75Z	0.71Z	1.46Z	
	4121D	1.26Z	10.51Z	0.38Z	1.19Z	1.07Z	2.26Z	
	4122S	0.73Z	7.43Z	0.23Z	0.74Z	0.74Z	1.48Z	

	Mean							
S.D.								
Relative	4113S	0.50Z	3.40Z	0.17Z	0.42Z	0.39Z	0.81Z	
	4114S	0.49Z	3.34Z	0.11Z	0.43Z	0.45Z	0.88Z	
	4115S	0.36Z	3.55Z	0.19Z	0.37Z	0.36Z	0.73Z	
	4116D	0.40Z	3.55Z	0.08Z	0.45Z	0.39Z	0.85Z	
	4117S	0.35Z	5.65Z	0.22Z	0.33Z	0.36Z	0.69Z	
	4118S	0.55Z	3.39Z	0.16Z	0.43Z	0.43Z	0.85Z	
	4119D	0.50Z	4.03Z	0.11Z	0.46Z	0.42Z	0.88Z	
	4120S	0.40Z	2.93Z	0.14Z	0.39Z	0.37Z	0.76Z	
	4121D	0.61Z	5.05Z	0.18Z	0.57Z	0.51Z	1.09Z	
	4122S	0.39Z	4.02Z	0.12Z	0.40Z	0.40Z	0.80Z	

	Mean							
S.D.								

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-34

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of female rats (Satellite group, End of administration)
 Dose (mg/kg): 100

	Animal number	Adrenal	Adrenal	Adrenal	Ovary	Ovary	Ovary	Uterus	
		(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	mg(mg/100g BW)	
Absolute	4113S	42Z	46Z	88Z	36.3Z	34.5Z	70.8Z	267Z	
	4114S	48Z	56Z	104Z	32.4Z	50.0Z	82.4Z	364Z	
	4115S	50Z	54Z	104Z	29.6Z	31.6Z	61.2Z	256Z	
	4116D	75Z	74Z	149Z	48.5Z	48.4Z	96.9Z	268Z	
	4117S	33Z	38Z	71Z	25.2Z	20.7Z	45.9Z	227Z	
	4118S	43Z	46Z	89Z	35.2Z	33.0Z	68.2Z	275Z	
	4119D	69Z	62Z	131Z	29.7Z	33.5Z	63.2Z	268Z	
	4120S	48Z	49Z	97Z	38.1Z	44.6Z	82.7Z	467Z	
	4121D	61Z	74Z	135Z	50.1Z	41.9Z	92.0Z	475Z	
	4122S	44Z	49Z	93Z	36.2Z	39.2Z	75.4Z	183Z	

	Mean								
	S.D.								
Relative	4113S	24Z	26Z	50Z	20.5Z	19.5Z	40.0Z	151Z	
	4114S	25Z	29Z	54Z	17.0Z	26.2Z	43.1Z	191Z	
	4115S	22Z	24Z	47Z	13.3Z	14.2Z	27.4Z	115Z	
	4116D	38Z	37Z	75Z	24.5Z	24.4Z	48.9Z	135Z	
	4117S	15Z	18Z	33Z	11.8Z	9.7Z	21.5Z	107Z	
	4118S	23Z	25Z	48Z	19.0Z	17.8Z	36.9Z	149Z	
	4119D	39Z	35Z	75Z	17.0Z	19.1Z	36.1Z	153Z	
	4120S	25Z	26Z	51Z	19.9Z	23.4Z	43.3Z	245Z	
	4121D	29Z	36Z	65Z	24.1Z	20.1Z	44.2Z	228Z	
	4122S	24Z	26Z	50Z	19.6Z	21.2Z	40.8Z	99Z	

	Mean								
	S.D.								

S: Sacrificed moribund

D: Dead

Z: Data was excluded from statistical analysis.

Appendix 8-35

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of recovery)
 Dose (mg/kg): 0

Animal number	Body weight	Brain	Pituitary	Thyroid (R)	Thyroid (L)	Thyroid (R+L)	Thymus	
	g	g(g/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	mg(mg/100g BW)	
Absolute	1008	498	2.07	13.2	10.5	9.3	19.8	202
	1009	487	2.26	16.1	9.2	9.2	18.4	303
	1010	481	2.08	12.2	11.2	11.7	22.9	259
	1011	575	2.19	12.7	14.7	13.5	28.2	255
	1012	456	2.02	13.4	10.9	7.6	18.5	259
	Mean	499	2.12	13.5	11.3	10.3	21.6	256
	S.D.	45	0.10	1.5	2.0	2.3	4.1	36
Relative	1008		0.42	2.7	2.1	1.9	4.0	41
	1009		0.46	3.3	1.9	1.9	3.8	62
	1010		0.43	2.5	2.3	2.4	4.8	54
	1011		0.38	2.2	2.6	2.3	4.9	44
	1012		0.44	2.9	2.4	1.7	4.1	57
	Mean		0.43	2.7	2.3	2.0	4.3	52
	S.D.		0.03	0.4	0.3	0.3	0.5	9

Appendix 8-36

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of recovery)
 Dose (mg/kg): 0

Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
1008	1.49	11.86	0.68	1.45	1.59	3.04
1009	1.25	12.19	0.73	1.79	1.64	3.43
1010	1.48	11.81	0.75	1.65	1.60	3.25
Absolute 1011	1.52	14.68	0.67	1.73	1.70	3.43
1012	1.54	10.48	0.67	1.52	1.56	3.08

Mean	1.46	12.20	0.70	1.63	1.62	3.25
S.D.	0.12	1.53	0.04	0.14	0.05	0.19

1008	0.30	2.38	0.14	0.29	0.32	0.61
1009	0.26	2.50	0.15	0.37	0.34	0.70
1010	0.31	2.46	0.16	0.34	0.33	0.68
Relative 1011	0.26	2.55	0.12	0.30	0.30	0.60
1012	0.34	2.30	0.15	0.33	0.34	0.68

Mean	0.29	2.44	0.14	0.33	0.33	0.65
S.D.	0.03	0.10	0.02	0.03	0.02	0.05

Appendix 8-37

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of recovery)
 Dose (mg/kg): 0

Animal number	Adrenal	Adrenal	Adrenal	Testis	Testis	Testis
	(R) mg(mg/100g BW)	(L) mg(mg/100g BW)	(R+L) mg(mg/100g BW)	(R) g(g/100g BW)	(L) g(g/100g BW)	(R+L) g(g/100g BW)
1008	24	24	48	1.84	1.86	3.70
1009	25	28	53	1.43	1.49	2.92
1010	33	35	68	1.42	1.42	2.84
Absolute 1011	30	31	61	1.47	1.43	2.90
1012	36	37	73	1.79	1.81	3.60

Mean	30	31	61	1.59	1.60	3.19
S.D.	5	5	10	0.21	0.22	0.42

1008	5	5	10	0.37	0.37	0.74
1009	5	6	11	0.29	0.31	0.60
1010	7	7	14	0.30	0.30	0.59
Relative 1011	5	5	11	0.26	0.25	0.50
1012	8	8	16	0.39	0.40	0.79

Mean	6	6	12	0.32	0.33	0.64
S.D.	1	1	3	0.06	0.06	0.12

Appendix 8-38

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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)
1008	725	696	1421	2.02	1.72
1009	653	630	1283	1.74	1.66
1010	690	678	1368	2.47	1.66
Absolute 1011	598	602	1200	1.86	1.08
1012	660	637	1297	2.08	1.27

Mean	665	649	1314	2.03	1.48
S.D.	47	38	85	0.28	0.29

1008	146	140	285	0.41	0.35
1009	134	129	263	0.36	0.34
1010	143	141	284	0.51	0.35
Relative 1011	104	105	209	0.32	0.19
1012	145	140	284	0.46	0.28

Mean	134	131	265	0.41	0.30
S.D.	18	15	33	0.08	0.07

Appendix 8-39

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of recovery)
 Dose (mg/kg): 30

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)
3008	470	2.27	12.5	7.7	5.5	13.2	293
3009	490	2.08	10.6	7.0	7.2	14.2	204
3010	493	2.06	12.1	11.1	11.1	22.2	277
Absolute 3011	470	2.08	12.6	11.4	9.6	21.0	169
3012	463	1.96	11.0	12.0	12.6	24.6	306
Mean	477	2.09	11.8	9.8	9.2	19.0	250
S.D.	13	0.11	0.9	2.3	2.9	5.1	60
3008		0.48	2.7	1.6	1.2	2.8	62
3009		0.42	2.2	1.4	1.5	2.9	42
3010		0.42	2.5	2.3	2.3	4.5	56
Relative 3011		0.44	2.7	2.4	2.0	4.5	36
3012		0.42	2.4	2.6	2.7	5.3	66
Mean		0.44	2.5	2.1	1.9	4.0	52
S.D.		0.03	0.2	0.5	0.6	1.1	13

Appendix 8-40

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of recovery)
 Dose (mg/kg): 30

Animal number	Heart	Liver	Spleen	Kidney (R)	Kidney (L)	Kidney (R+L)
	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)	g(g/100g BW)
3008	1.36	11.59	0.75	1.60	1.59	3.19
3009	1.59	12.84	0.75	1.68	1.57	3.25
3010	1.73	12.36	0.82	1.63	1.72	3.35
Absolute 3011	1.35	11.33	0.66	1.62	1.67	3.29
3012	1.36	11.71	0.60	1.85	1.83	3.68

Mean	1.48	11.97	0.72	1.68	1.68	3.35
S.D.	0.17	0.62	0.09	0.10	0.11	0.19

3008	0.29	2.47	0.16	0.34	0.34	0.68
3009	0.32	2.62	0.15	0.34	0.32	0.66
3010	0.35	2.51	0.17	0.33	0.35	0.68
Relative 3011	0.29	2.41	0.14	0.34	0.36	0.70
3012	0.29	2.53	0.13	0.40	0.40	0.79

Mean	0.31	2.51	0.15	0.35	0.35	0.70
S.D.	0.03	0.08	0.02	0.03	0.03	0.05

Appendix 8-41

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of recovery)
 Dose (mg/kg): 30

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)
3008	30	25	55	1.77	1.69	3.46
3009	21	22	43	1.55	1.60	3.15
3010	28	29	57	1.76	1.77	3.53
Absolute 3011	23	26	49	1.44	1.43	2.87
3012	26	28	54	1.68	1.63	3.31

Mean	26	26	52	1.64	1.62	3.26
S.D.	4	3	6	0.14	0.13	0.26

3008	6	5	12	0.38	0.36	0.74
3009	4	4	9	0.32	0.33	0.64
3010	6	6	12	0.36	0.36	0.72
Relative 3011	5	6	10	0.31	0.30	0.61
3012	6	6	12	0.36	0.35	0.71

Mean	5	5	11	0.35	0.34	0.68
S.D.	1	1	1	0.03	0.03	0.06

Appendix 8-42

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual organ weight of male rats (End of recovery)
 Dose (mg/kg): 30

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)
3008	684	641	1325	1.59	1.05
3009	651	675	1326	1.47	1.30
3010	715	677	1392	1.72	1.53
Absolute 3011	631	606	1237	2.03	1.37
3012	697	731	1428	2.05	1.76
Mean	676	666	1342	1.77	1.40
S.D.	34	47	73	0.26	0.26
3008	146	136	282	0.34	0.22
3009	133	138	271	0.30	0.27
3010	145	137	282	0.35	0.31
Relative 3011	134	129	263	0.43	0.29
3012	151	158	308	0.44	0.38
Mean	142	140	281	0.37	0.29
S.D.	8	11	17	0.06	0.06

Appendix 9-1(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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:

Epididymis	Hypospermia: minimal, bilateral Cell debris, luminal: mild, bilateral
Heart	Myocarditis, focal: minimal
Intestine, cecum	Cell infiltration: mild, mucosal mononuclear Decrease, goblet cell: mild
Kidney	Regeneration, tubular: minimal
Liver	Microgranuloma: minimal
Lung (bronchus)	Hemorrhage, focal: minimal Aggregation, alveolar macrophage: minimal
Prostate	Cell infiltration: mild, lymphocytic ventral
Spleen	Hematopoiesis, extramedullary: minimal
Testis	Degeneration, spermatid: mild, bilateral Vacuolation, 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, colon, Intestine, rectum, Lymph node, mesenteric
Lymph node, submandibular, Parathyroid, Pancreas, Pituitary
Salivary gland, submandibular, Sciatic nerve, Stomach, Skeletal muscle, femoral
Seminal vesicle(coagulating gland), Spinal cord, thoracic, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 9-2(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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

Lung (bronchus) Aggregation, alveolar macrophage: 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, 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 didec-1-yl(methyl)amine 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:

Liver Microgranuloma: minimal

Prostate Cell infiltration: minimal, lymphocytic 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 9-4(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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:

Heart Myocarditis,focal: minimal

Liver Microgranuloma: minimal

Spleen Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
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 9-5(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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:

Liver Microgranuloma: minimal

Lung (bronchus) Hemorrhage, focal: minimal

Prostate Cell infiltration: minimal, lymphocytic ventral

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, Salivary gland, submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle, femoral, Seminal vesicle(coagulating gland), Spinal cord, thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-6(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine 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:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Heart, Intestine, jejunum
Intestine, ileum(Peyer's patch), Intestine, cecum, Intestine, colon
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular, Prostate
Spleen, Stomach, Thymus, Urinary bladder

Appendix 9-9(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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:

Prostate Cell infiltration: minimal, lymphocytic
ventral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Heart, Intestine, jejunum
Intestine, ileum(Peyer's patch), Intestine, cecum, Intestine, colon
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular, Spleen
Stomach, Thymus, Urinary bladder

Appendix 9-10(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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:

Spleen Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Heart, Intestine,jejunum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Prostate
Stomach, Thymus, Urinary bladder

Appendix 9-11(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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:

Bone+Bone marrow, femoral Hypocellularity, bone marrow: minimal

Spleen Hematopoiesis, extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Heart, Intestine, jejunum, Intestine, ileum (Peyer's patch)
Intestine, cecum, Intestine, colon, Intestine, rectum, Lymph node, mesenteric
Lymph node, submandibular, Prostate, Stomach, Thymus, Urinary bladder

Appendix 9-12(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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:

Heart Myocarditis,focal: minimal

Spleen Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Intestine,jejunum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Prostate
Stomach, Thymus, Urinary bladder

Appendix 9-13(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2001 Male 10 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine,cecum	Cell infiltration: mild, mucosal mononuclear Decrease,goblet cell: mild
Liver	Microgranuloma: minimal
Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Prostate	Cell infiltration: minimal, lymphocytic ventral

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,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, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-14(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2002 Male 10 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Heart Myocarditis,focal: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Intestine,jejunum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Prostate
Spleen, Stomach, Thymus, Urinary bladder

Appendix 9-15(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2003 Male 10 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Heart Myocarditis,focal: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Intestine,jejunum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Prostate
Spleen, Stomach, Thymus, Urinary bladder

Appendix 9-16(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2004 Male 10 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Lung (bronchus) Focus, dark red: 1 present
2x2mm

Other tissues Not remarkable

Histopathology:

Spleen Hematopoiesis, extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Heart, Intestine, jejunum
Intestine, ileum (Peyer's patch), Intestine, cecum, Intestine, colon
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular, Prostate
Stomach, Thymus, Urinary bladder

Appendix 9-17(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2005 Male 10 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Lung (bronchus) Focus, dark red: 1 present
1x1mm

Other tissues Not remarkable

Histopathology:

Heart Myocarditis, focal: minimal

Prostate Cell infiltration: minimal, lymphocytic
ventral

Spleen Hematopoiesis, extramedullary: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Intestine, jejunum
Intestine, ileum (Peyer's patch), Intestine, cecum, Intestine, colon
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular, Stomach
Thymus, Urinary bladder

Appendix 9-18(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2006 Male 10 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Epididymis Focus, white: 1 present, right cauda, 5x5mm

Other 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2007 Male 10 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2008 Male 10 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2009 Male 10 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2010 Male 10 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2011 Male 10 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2012 Male 10 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3001 Male 30 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Regeneration, tubular: minimal

Liver Microgranuloma: 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, Spleen, Stomach
Skeletal muscle, femoral, Seminal vesicle(coagulating gland), Spinal cord, thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-26(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3002 Male 30 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All 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 9-27(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3003 Male 30 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Cyst: minimal

Liver Microgranuloma: minimal

Lung (bronchus) Aggregation, alveolar macrophage: 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, 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 9-28(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3004 Male 30 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All 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 9-29(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3005 Male 30 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Spleen Focus,white: 1 present
15x10mm

Other tissues Not remarkable

Histopathology:

Heart Myocarditis,focal: minimal

Lung(bronchus) Cell infiltration: mild, focal, inflammatory

Spleen Necrosis,focal: moderate

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
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, Stomach
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-30(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3006 Male 30 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3007 Male 30 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3008 Male 30 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Bone+Bone marrow, femoral Hypocellularity, bone marrow: minimal

Following tissues : Not remarkable

Adrenal, Heart, Intestine, jejunum, Intestine, ileum(Peyer's patch)
Intestine, cecum, Intestine, colon, Intestine, rectum, Lymph node, mesenteric
Lymph node, submandibular, Prostate, Spleen, Stomach, Thymus, Urinary bladder

Appendix 9-33(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3009 Male 30 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Prostate Cell infiltration: minimal, inflammatory
dorsolateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Heart, Intestine, jejunum
Intestine, ileum(Peyer's patch), Intestine, cecum, Intestine, colon
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular, Spleen
Stomach, Thymus, Urinary bladder

Appendix 9-34(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3010 Male 30 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, Heart, Intestine,jejunum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Prostate
Stomach, Thymus, Urinary bladder

Appendix 9-35(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3011 Male 30 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Prostate Cell infiltration: minimal, lymphocytic
ventral

Spleen Hematopoiesis,extramedullary: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Heart, Intestine,jejunum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Stomach
Thymus, Urinary bladder

Appendix 9-36(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3012 Male 30 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Heart, Intestine, jejunum
Intestine, ileum(Peyer's patch), Intestine, cecum, Intestine, colon
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular, Prostate
Spleen, Stomach, Thymus, Urinary bladder

Appendix 9-37(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4001 Male 100 mg/kg Day 6 Moribund sacrifice

Gross pathology:

General descriptions	Smudge, fur: lower abdominal, perioral
Stomach	Focus, white, forestomach: many 1x1mm
Thymus	Small: mild
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Heart	Myocarditis, focal: minimal
Intestine, jejunum	Degeneration/necrosis, mucosal: minimal
Intestine, ileum (Peyer's patch)	Atrophy, Peyer's patch: mild Degeneration/necrosis, mucosal: moderate
Intestine, cecum	Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: mild
Intestine, rectum	Cell infiltration, mucosal: minimal, neutrophilic Decrease, goblet cell: mild
Lymph node, submandibular	Atrophy: minimal
Liver	Microgranuloma: minimal
Lung (bronchus)	Hemorrhage, focal: minimal
Prostate	Atrophy: mild with single cell necrosis
Spleen	Atrophy: mild
Stomach	Hyperplasia, squamous, forestomach: minimal Decrease, mucus, glandular stomach: minimal, pyloric Single cell necrosis, gastric gland: mild
Thymus	Atrophy: severe
Urinary bladder	Dilatation, lumina: mild Vacuolation, umbrella cell: minimal
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Epididymis, Eye
Intestine, duodenum, Kidney, Lymph node, mesenteric, Parathyroid, Pancreas
Pituitary, Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Seminal vesicle (coagulating gland), Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-38(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4002 Male 100 mg/kg Day 10 Moribund sacrifice

Gross pathology:

General descriptions	Undernourishment Smudge, fur: lower abdominal, perioral
Kidney	Focus, white: 1 present, left 4x3mm
Spleen	Small: mild
Thymus	Small: mild
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Bone+Bone marrow, femoral	Hypocellularity, bone marrow: minimal
Heart	Myocarditis, focal: mild
Intestine, ileum (Peyer's patch)	Atrophy, Peyer's patch: mild
Intestine, cecum	Cell infiltration: mild, mucosal mononuclear Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: minimal
Kidney	Regeneration, tubular: mild with tubular dilatation and hyaline cast Mineralization: mild, cortical Cell infiltration: mild, mononuclear
Lymph node, mesenteric	Activation, histiocyte, sinus: mild
Prostate	Atrophy: mild
Spleen	Atrophy: minimal
Stomach	Decrease, mucus, glandular stomach: minimal, pyloric Single cell necrosis, gastric gland: minimal
Thymus	Atrophy: moderate
Urinary bladder	Basophilic change, mucosal: minimal
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Cerebellum (Pons), Cerebrum, Epididymis, Eye, Intestine, duodenum
Intestine, jejunum, Intestine, rectum, Lymph node, submandibular, Liver
Lung (bronchus), Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular
Sciatic nerve, Skeletal muscle, femoral, Seminal vesicle (coagulating gland)
Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-39(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4003 Male 100 mg/kg Day 8 Found dead

Gross pathology:

Spleen	Small: mild
Stomach	Focus, white, forestomach: many 1x1mm
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Heart	Myocarditis, focal: minimal
Intestine, duodenum	Sample autolysed
Intestine, ileum(Peyer's patch)	Sample autolysed
Intestine, cecum	Sample autolysed
Intestine, rectum	Sample autolysed
Lymph node, mesenteric	Atrophy: minimal
Parathyroid	No sample
Prostate	Cell infiltration: minimal, lymphocytic dorsolateral
Stomach	Hyperplasia, squamous, forestomach: mild Decrease, mucus, glandular stomach: mild, pyloric
Seminal vesicle(coagulating gland)	Sample autolysed
Thymus	Atrophy: moderate
Urinary bladder	Dilatation, lumina: mild
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Intestine, jejunum, Intestine, colon, Kidney, Lymph node, submandibular, Liver
Lung(bronchus), Pancreas, Pituitary, Salivary gland, submandibular, Sciatic nerve
Spleen, Skeletal muscle, femoral, Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-40(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4004 Male 100 mg/kg Day 10 Moribund sacrifice

Gross pathology:

General descriptions	Smudge, fur: perioral
Heart	Focus, white: 1 present 10x7mm
Spleen	Small: mild
Stomach	Distention: Retention, content Focus, white, forestomach: many 1x1-2x2mm
Thymus	Small: mild
Urinary bladder	Distention: mild, uroschesis
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Heart	Myocarditis, focal: mild
Intestine, ileum (Peyer's patch)	Atrophy, Peyer's patch: mild
Intestine, cecum	Decrease, goblet cell: mild
Intestine, rectum	Cell infiltration, mucosal: minimal, neutrophilic
Lymph node, mesenteric	Activation, histiocyte, sinus: mild
Lymph node, submandibular	Atrophy: minimal
Stomach	Hyperplasia, squamous, forestomach: mild Decrease, mucus, glandular stomach: minimal, pyloric Single cell necrosis, gastric gland: mild
Thymus	Atrophy: moderate
Urinary bladder	Dilatation, lumina: minimal Basophilic change, mucosal: minimal
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Epididymis, Eye
Intestine, duodenum, Intestine, jejunum, Intestine, colon, Kidney, Liver
Lung (bronchus), Parathyroid, Pancreas, Pituitary, Prostate
Salivary gland, submandibular, Sciatic nerve, Spleen, Skeletal muscle, femoral
Seminal vesicle (coagulating gland), Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-41(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4005 Male 100 mg/kg Day 11 Moribund sacrifice

Gross pathology:

Forelimb Swelling: right

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Bone+Bone marrow, femoral Hypocellularity, bone marrow: minimal

Forelimb Arthritis: moderate

Intestine, cecum Decrease, goblet cell: mild

Lung (bronchus) Hemorrhage, focal: minimal
Aggregation, alveolar macrophage: minimal

Prostate Cell infiltration: minimal, inflammatory
dorsolateral

Thymus Atrophy: moderate

Urinary bladder Basophilic change, mucosal: minimal

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Cerebellum (Pons), Cerebrum, Epididymis, Eye, Heart, Intestine, duodenum
Intestine, jejunum, Intestine, ileum (Peyer's patch), Intestine, colon
Intestine, rectum, Kidney, Lymph node, mesenteric, Lymph node, submandibular, Liver
Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle, femoral, Seminal vesicle (coagulating gland)
Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-42 (1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4006 Male 100 mg/kg Day 9 Moribund sacrifice

Gross pathology:

General descriptions	Undernourishment Smudge, fur: lower abdominal, perioral
Stomach	Distention: Retention, content Focus, white, forestomach: many less than 1x1mm
Urinary bladder	Distention: moderate, uroschisis reddish
Other tissues	Not remarkable
Histopathology:	
Adrenal	Hypertrophy, cortical cell: mild
Bone+Bone marrow, femoral	Hypocellularity, bone marrow: minimal
Heart	Myocarditis, focal: mild
Intestine, cecum	Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: minimal
Lymph node, mesenteric	Activation, histiocyte, sinus: mild
Prostate	Hemorrhage: mild Cell infiltration: moderate, neutrophilic ventral and dorsolateral
Spleen	Atrophy: minimal
Stomach	Hyperplasia, squamous, forestomach: mild No finding correlating with distention in gross findings Decrease, mucus, glandular stomach: mild, pyloric
Thymus	Atrophy: severe
Urinary bladder	Dilatation, lumina: mild Erosion/ulcer: mild Basophilic change, mucosal: minimal with focal hyperplasia of transitional cell Hemorrhage, submucosal: moderate Cell infiltration, mucosal/submucosal: mild, neutrophilic
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Cerebellum (Pons), Cerebrum, Epididymis, Eye, Intestine, duodenum
Intestine, jejunum, Intestine, ileum (Peyer's patch), Intestine, rectum, Kidney
Lymph node, submandibular, Liver, Lung (bronchus), Parathyroid, Pancreas
Pituitary, Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Seminal vesicle (coagulating gland), Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-43(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4007 Male 100 mg/kg Day 10 Moribund sacrifice

Gross pathology:

General descriptions	Undernourishment Smudge, fur: lower abdominal, perioral
Subcutis	Focus, dark red: 1 present, parietal 15x15mm
Spleen	Small: mild
Stomach	Distention: moderate Retention, reddish content
Thymus	Small: severe
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Intestine, jejunum	Degeneration/necrosis, mucosal: minimal
Intestine, ileum (Peyer's patch)	Atrophy, Peyer's patch: moderate
Intestine, cecum	Decrease, goblet cell: mild
Lymph node, mesenteric	Activation, histiocyte, sinus: mild
Lymph node, submandibular	Atrophy: minimal
Subcutis	Hemorrhage, subcutaneous: mild Cell infiltration, subcutaneous: mild, inflammatory
Spleen	Atrophy: mild
Stomach	Decrease, mucus, glandular stomach: mild, pyloric No finding correlating with distention in gross findings Elongate, glandular neck: mild
Thymus	Atrophy: severe
Urinary bladder	Basophilic change, mucosal: minimal
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Epididymis, Eye, Heart
Intestine, duodenum, Intestine, colon, Intestine, rectum, Kidney, Liver
Lung (bronchus), Parathyroid, Pancreas, Pituitary, Prostate
Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Seminal vesicle (coagulating gland), Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-44(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4008 Male 100 mg/kg Day 10 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment
Smudge, fur:
lower abdominal, perioral

Spleen Small: mild

Stomach Focus, white, forestomach: many
less than 1x1mm

Thymus Small: moderate

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Bone+Bone marrow, femoral Hypocellularity, bone marrow: mild

Heart Myocarditis, focal: minimal

Intestine, cecum Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: minimal

Intestine, rectum Cell infiltration, mucosal: minimal, neutrophilic
Decrease, goblet cell: mild

Lymph node, mesenteric Activation, histiocyte, sinus: mild

Spleen Atrophy: minimal

Stomach Hyperplasia, squamous, forestomach: mild
Decrease, mucus, glandular stomach: minimal, pyloric

Thymus Atrophy: severe

Urinary bladder Dilatation, lumina: minimal
Basophilic change, mucosal: minimal

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Cerebellum(Pons), Cerebrum, Epididymis, Eye, Intestine, duodenum
Intestine, jejunum, Intestine, ileum(Peyer's patch), Kidney
Lymph node, submandibular, Liver, Lung(bronchus), Parathyroid, Pancreas
Pituitary, Prostate, Salivary gland, submandibular, Sciatic nerve
Skeletal muscle, femoral, Seminal vesicle(coagulating gland), Spinal cord, thoracic
Testis, Trachea, Thyroid

Appendix 9-45(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4009 Male 100 mg/kg Day 11 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment
Smudge, fur:
perioral

Spleen Small: mild

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Bone+Bone marrow, femoral Hypocellularity, bone marrow: mild

Heart Myocarditis, focal: mild

Intestine, jejunum Degeneration/necrosis, mucosal: mild

Intestine, ileum(Peyer's patch) Atrophy, Peyer's patch: mild

Intestine, cecum Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: minimal

Intestine, rectum Decrease, goblet cell: minimal

Lymph node, mesenteric Atrophy: minimal
Activation, histiocyte, sinus: mild

Lymph node, submandibular Atrophy: minimal

Liver Microgranuloma: minimal

Prostate Cell infiltration: mild, inflammatory
dorsolateral

Spleen Atrophy: mild

Stomach Decrease, mucus, glandular stomach: mild, pyloric

Thymus Atrophy: severe

Urinary bladder Basophilic change, mucosal: minimal

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Cerebellum(Pons), Cerebrum, Epididymis, Eye, Intestine, duodenum, Kidney
Lung(bronchus), Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular
Sciatic nerve, Skeletal muscle, femoral, Seminal vesicle(coagulating gland)
Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-46(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4010 Male 100 mg/kg Day 8 Moribund sacrifice

Gross pathology:

General descriptions Smudge, fur:
lower abdominal, perioral

Spleen Small: mild

Stomach Focus, white, forestomach: many
1x1mm

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Heart Myocarditis, focal: mild

Intestine, ileum (Peyer's patch) Atrophy, Peyer's patch: mild

Intestine, cecum Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: minimal

Kidney Regeneration, tubular: minimal

Lymph node, submandibular Atrophy: minimal

Lung (bronchus) Aggregation, alveolar macrophage: minimal

Stomach Hyperplasia, squamous, forestomach: mild
Decrease, mucus, glandular stomach: minimal, pyloric
Single cell necrosis, gastric gland: minimal

Thymus Atrophy: moderate

Urinary bladder Dilatation, lumina: mild

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Epididymis, Eye
Intestine, duodenum, Intestine, jejunum, Intestine, rectum, Lymph node, mesenteric
Liver, Parathyroid, Pancreas, Pituitary, Prostate, Salivary gland, submandibular
Sciatic nerve, Spleen, Skeletal muscle, femoral, Seminal vesicle (coagulating gland)
Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-47(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4011 Male 100 mg/kg Day 6 Moribund sacrifice

Gross pathology:

Stomach Focus, white, forestomach: many
1x1mm

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Heart Myocarditis, focal: minimal

Intestine, rectum Cell infiltration, mucosal: minimal, neutrophilic
Decrease, goblet cell: minimal

Lymph node, mesenteric Activation, histiocyte, sinus: mild

Prostate Cell infiltration: minimal, inflammatory
dorsolateral

Spleen Atrophy: minimal

Stomach Hyperplasia, squamous, forestomach: mild
Decrease, mucus, glandular stomach: mild, pyloric
Single cell necrosis, gastric gland: mild

Thymus Atrophy: moderate

Urinary bladder Dilatation, lumina: minimal
Basophilic change, mucosal: minimal
Cell infiltration, mucosal/submucosal: minimal, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch)
Intestine, cecum, Intestine, colon, Kidney, Lymph node, submandibular, Liver
Lung(bronchus), Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular
Sciatic nerve, Skeletal muscle, femoral, Seminal vesicle(coagulating gland)
Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-48(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4012 Male 100 mg/kg Day 10 Moribund sacrifice

Gross pathology:

General descriptions	Undernourishment Smudge, fur: lower abdominal
Stomach	Focus, white, forestomach: many less than 1x1mm
Thymus	Small: moderate
Urinary bladder	Distention: moderate, uroschisis reddish
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Bone+Bone marrow, femoral	Hypocellularity, bone marrow: minimal
Heart	Myocarditis, focal: minimal
Intestine, cecum	Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: minimal
Lymph node, mesenteric	Atrophy: minimal Activation, histiocyte, sinus: mild
Liver	Microgranuloma: minimal
Prostate	Atrophy: mild with single cell necrosis Hemorrhage: mild
Stomach	Hyperplasia, squamous, forestomach: mild Erosion/Ulcer, forestomach: mild
Thymus	Atrophy: moderate
Urinary bladder	Dilatation, lumina: mild Basophilic change, mucosal: minimal with focal hyperplasia of transitional cell Hemorrhage, submucosal: minimal Cell infiltration, mucosal/submucosal: mild, neutrophilic
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Cerebellum(Pons), Cerebrum, Epididymis, Eye, Intestine, duodenum
Intestine, jejunum, Intestine, ileum(Peyer's patch), Intestine, rectum, Kidney
Lymph node, submandibular, Lung(bronchus), Parathyroid, Pancreas, Pituitary
Salivary gland, submandibular, Sciatic nerve, Spleen, Skeletal muscle, femoral
Seminal vesicle(coagulating gland), Spinal cord, thoracic, Testis, Trachea, Thyroid

Appendix 9-49(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1101 Female 0 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All 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 9-50(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1102 Female 0 mg/kg Day 51 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1103 Female 0 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-52(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1104 Female 0 mg/kg Day 47 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-53(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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:

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 9-54(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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:

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 9-55(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1107 Female 0 mg/kg Day 44 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 9-56(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1108 Female 0 mg/kg Day 44 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 didec-1-yl(methyl)amine 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1110 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-59(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1111 Female 0 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-60(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1112 Female 0 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Lung(bronchus) Cell infiltration: minimal, focal, inflammatory

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, Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-61(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1113 Female 0 mg/kg Day 16 End of administration period (D15)

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, 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 9-62(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1114 Female 0 mg/kg Day 16 End of administration period (D15)

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine,cecum Cell infiltration: mild, mucosal
mononuclear
Decrease,goblet cell: mild

Liver Microgranuloma: 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,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 9-63(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1115 Female 0 mg/kg Day 16 End of administration period (D15)

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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1116 Female 0 mg/kg Day 16 End of administration period (D15)

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: 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, 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 9-65(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1117 Female 0 mg/kg Day 16 End of administration period (D15)

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 9-66(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1118 Female 0 mg/kg Day 16 End of administration period (D15)

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 9-67(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1119 Female 0 mg/kg Day 16 End of administration period (D15)

Gross pathology:

All tissues Not remarkable

Histopathology:

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
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-68(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1120 Female 0 mg/kg Day 16 End of administration period (D15)

Gross pathology:

All tissues Not remarkable

Histopathology:

Heart Myocarditis,focal: minimal

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
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-69(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1121 Female 0 mg/kg Day 16 End of administration period (D15)

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine,cecum Cell infiltration: mild, mucosal
mononuclear
Decrease,goblet cell: 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,colon, 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, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-70(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 1122 Female 0 mg/kg Day 16 End of administration period (D15)

Gross pathology:

All tissues Not remarkable

Histopathology:

Heart Myocarditis,focal: minimal

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
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-71(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2101 Female 10 mg/kg Day 54 Not copulated

Gross pathology:

All tissues Not remarkable

Histopathology:

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
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-72(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2102 Female 10 mg/kg Day 45 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, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Pancreas
Stomach, Thymus, Urinary bladder, Uterus, Vagina

Appendix 9-73 (1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2103 Female 10 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, Heart, Intestine,duodenum, Intestine,jejenum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Pancreas
Stomach, Thymus, Urinary bladder, Uterus, Vagina

Appendix 9-74(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2104 Female 10 mg/kg Day 47 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-75(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2105 Female 10 mg/kg Day 44 End of administration period (L4)

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present
4x1mm

Other tissues Not remarkable

Histopathology:

Spleen Hematopoiesis, extramedullary: mild

Stomach Erosion, glandular stomach: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Heart, Intestine, duodenum, Intestine, jejunum
Intestine, ileum (Peyer's patch), Intestine, cecum, Intestine, colon
Intestine, rectum, Lymph node, mesenteric, Lymph node, submandibular, Pancreas
Thymus, Urinary bladder, Uterus, Vagina

Appendix 9-76(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2106 Female 10 mg/kg Day 40 Found dead

Gross pathology:

General descriptions	Retention, aminion, oral cavity: to esophagus
Thoracic cavity	Excess fluid: clear 0.5mL
Lung (bronchus)	Discoloration, dark red
Trachea	Retention, foamy fluid
Other tissues	Not remarkable

Histopathology:

Intestine, duodenum	Sample autolysed
Intestine, jejunum	Sample autolysed
Intestine, ileum (Peyer's patch)	Sample autolysed
Intestine, cecum	Sample autolysed
Intestine, colon	Sample autolysed
Intestine, rectum	Sample autolysed
Lymph node, mesenteric	Atrophy: minimal
Lymph node, submandibular	Atrophy: mild
Liver	Necrosis, focal: minimal
Lung (bronchus)	Unremarkable
Spleen	Atrophy: mild
Trachea	Unremarkable
Cause of demise	Unclear

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Eye, Heart
Kidney, Ovary, Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular
Sciatic nerve, Stomach, Skeletal muscle, femoral, Spinal cord, thoracic
Thymus, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-77(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2107 Female 10 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-78(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2108 Female 10 mg/kg Day 46 End of administration period (L4)

Gross pathology:

Stomach Focus, raised: 1 present, serosal
1x1x1mm
Focus, dark red, glandular stomach: 1 present
1x1mm

Other 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2109 Female 10 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2110 Female 10 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2111 Female 10 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, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Pancreas
Stomach, Thymus, Urinary bladder, Uterus, Vagina

Appendix 9-82(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 2112 Female 10 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, Heart, Intestine,duodenum, Intestine,jejenum
Intestine,ileum(Peyer's patch), Intestine,cecum, Intestine,colon
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Pancreas
Stomach, Thymus, Urinary bladder, Uterus, Vagina

Appendix 9-83(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3101 Female 30 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Heart Myocarditis,focal: minimal

Liver Microgranuloma: minimal

Lung(bronchus) Cell infiltration: minimal, focal, mononuclear

Spleen Hematopoiesis,extramedullary: 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, Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-84(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3102 Female 30 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All 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 9-85(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3103 Female 30 mg/kg Day 46 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3104 Female 30 mg/kg Day 43 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 9-87(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3105 Female 30 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-88(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3106 Female 30 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3107 Female 30 mg/kg Day 43 End of administration period (L4)

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present
1x1mm

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 9-90(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3108 Female 30 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-91(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3109 Female 30 mg/kg Day 46 End of administration period (L4)

Gross pathology:

Stomach Focus, dark red, glandular stomach: 2 present
1x1mm, 3x1mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-92(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3110 Female 30 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-93(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3111 Female 30 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Hematopoiesis,extramedullary: minimal

Lung(bronchus) Aggregation,alveolar macrophage: 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, Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-94(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 3112 Female 30 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 didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4101 Female 100 mg/kg Day 10 Moribund sacrifice

Gross pathology:

General descriptions	Undernourishment
Stomach	Focus, white, forestomach: many less than 2x2mm
Thymus	Small: mild
Other tissues	Not remarkable
Histopathology:	
Adrenal	Hypertrophy, cortical cell: mild
Intestine, cecum	Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: minimal
Intestine, rectum	Decrease, goblet cell: minimal
Lymph node, mesenteric	Activation, histiocyte, sinus: mild
Liver	Microgranuloma: minimal
Stomach	Hyperplasia, squamous, forestomach: mild Decrease, mucus, glandular stomach: minimal, pyloric
Thymus	Atrophy: moderate
Urinary bladder	Basophilic change, mucosal: minimal
Vagina	Cell infiltration, mucosal/submucosal: mild, neutrophilic
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch), Kidney
Lymph node, submandibular, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland, submandibular, Sciatic nerve, Spleen
Skeletal muscle, femoral, Spinal cord, thoracic, Trachea, Thyroid, Uterus

Appendix 9-96(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4102 Female 100 mg/kg Day 8 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Bone+Bone marrow, femoral Hypocellularity, bone marrow: minimal

Heart Myocarditis, focal: minimal

Intestine, jejunum Degeneration/necrosis, mucosal: minimal

Intestine, cecum Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: minimal

Intestine, rectum Decrease, goblet cell: minimal

Lymph node, mesenteric Activation, histiocyte, sinus: mild

Liver Microgranuloma: minimal

Pancreas Decrease, zymogen granule: mild

Thymus Atrophy: severe

Urinary bladder Basophilic change, mucosal: minimal
with increased mitosis

Vagina Cell infiltration, mucosal/submucosal: minimal, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Cerebellum(Pons), Cerebrum, Eye, Intestine, duodenum
Intestine, ileum(Peyer's patch), Kidney, Lymph node, submandibular, Lung(bronchus)
Ovary, Parathyroid, Pituitary, Salivary gland, submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle, femoral, Spinal cord, thoracic, Trachea, Thyroid
Uterus

Appendix 9-97(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4103 Female 100 mg/kg Day 8 Found dead

Gross pathology:

General descriptions	Undernourishment
Spleen	Small: mild
Stomach	Distention: mild retention, liquid material
Thymus	Small: moderate
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Heart	Myocarditis, focal: mild
Intestine, duodenum	Degeneration/necrosis, mucosal: mild
Intestine, jejunum	Degeneration/necrosis, mucosal: moderate
Intestine, ileum (Peyer's patch)	Atrophy, Peyer's patch: mild Degeneration/necrosis, mucosal: minimal
Intestine, cecum	Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: minimal
Lymph node, mesenteric	Atrophy: minimal Activation, histiocyte, sinus: mild
Lymph node, submandibular	Atrophy: minimal
Spleen	Atrophy: mild
Stomach	Erosion, glandular stomach: mild Decrease, mucus, glandular stomach: mild, pyloric No finding correlating with distention in gross findings
Thymus	Atrophy: severe
Urinary bladder	Basophilic change, mucosal: minimal Vacuolation, umbrella cell: mild
Vagina	Cell infiltration, mucosal/submucosal: mild, neutrophilic
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Eye, Intestine, rectum
Kidney, Liver, Lung (bronchus), Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Spinal cord, thoracic, Trachea, Thyroid, Uterus

Appendix 9-98(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4104 Female 100 mg/kg Day 9 Found dead

Gross pathology:

General descriptions Undernourishment

Lung(bronchus) Focus,dark red: 2 present
5x4mm,5x4mm

Stomach Focus,white,forestomach: many
less than 1x1mm

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy,cortical cell: mild

Eye Dysplasia,retinal: minimal

Intestine,jejunum Sample autolysed

Intestine,ileum(Peyer's patch) Sample autolysed

Intestine,cecum Decrease,goblet cell: mild

Intestine,rectum Decrease,goblet cell: minimal

Lymph node,mesenteric Activation,histiocyte,sinus: mild

Liver Microgranuloma: minimal

Spleen Atrophy: minimal

Stomach Hyperplasia,squamous,forestomach: mild
Erosion/Ulcer,forestomach: mild
Decrease,mucus,glandular stomach: mild, pyloric

Thymus Atrophy: severe

Urinary bladder Dilatation,lumina: minimal

Uterus Atrophy: mild, bilateral

Vagina Atrophy,mucosal: mild
Cell infiltration,mucosal/submucosal: minimal, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Heart, Intestine,duodenum
Intestine,colon, Kidney, Lymph node,submandibular, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Spinal cord,thoracic, Trachea, Thyroid

Appendix 9-99(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4105 Female 100 mg/kg Day 8 Moribund sacrifice

Gross pathology:

General descriptions Smudge, fur:
perioral

Spleen Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Heart Myocarditis, focal: minimal

Lymph node, mesenteric Activation, histiocyte, sinus: mild

Liver Microgranuloma: minimal

Spleen Atrophy: mild

Stomach Decrease, mucus, glandular stomach: minimal, pyloric
Single cell necrosis, gastric gland: minimal

Thymus Atrophy: mild

Urinary bladder Basophilic change, mucosal: minimal

Cause of demise Test substance toxicity

Following tissues : Not remarkable

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, submandibular
Lung(bronchus), Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Spinal cord, thoracic, Trachea, Thyroid, Uterus, Vagina

Appendix 9-100(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4106 Female 100 mg/kg Day 9 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment

Spleen Small: mild

Stomach Distention
Focus, white, forestomach: many
less than 1x1mm

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Heart Myocarditis, focal: mild

Intestine, duodenum Degeneration/necrosis, mucosal: mild

Intestine, jejunum Degeneration/necrosis, mucosal: minimal

Intestine, ileum(Peyer's patch) Degeneration/necrosis, mucosal: mild

Intestine, cecum Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: minimal

Intestine, rectum Decrease, goblet cell: mild

Lymph node, mesenteric Activation, histiocyte, sinus: mild

Pancreas Decrease, zymogen granule: mild

Spleen Atrophy: minimal

Stomach Hyperplasia, squamous, forestomach: mild
No finding correlating with distention in gross
findings
Decrease, mucus, glandular stomach: minimal, pyloric

Thymus Atrophy: severe

Urinary bladder Basophilic change, mucosal: minimal

Vagina Cell infiltration, mucosal/submucosal: minimal, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Eye, Kidney
Lymph node, submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pituitary
Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Spinal cord, thoracic, Trachea, Thyroid, Uterus

Appendix 9-101(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4107 Female 100 mg/kg Day 12 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment

Other tissues Not remarkable

Histopathology:

Intestine, cecum Cell infiltration: mild, mucosal mononuclear
Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: minimal

Intestine, rectum Decrease, goblet cell: mild

Liver Microgranuloma: minimal

Stomach Hyperplasia, squamous, forestomach: minimal
Single cell necrosis, gastric gland: mild

Thymus Atrophy: mild

Urinary bladder Basophilic change, mucosal: minimal

Vagina Cell infiltration, mucosal/submucosal: minimal, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch), Kidney
Lymph node, mesenteric, Lymph node, submandibular, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular, Sciatic nerve
Spleen, Skeletal muscle, femoral, Spinal cord, thoracic, Trachea, Thyroid, Uterus

Appendix 9-102(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4108 Female 100 mg/kg Day 10 Moribund sacrifice

Gross pathology:

Spleen	Small: mild
Thymus	Small: mild
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Heart	Myocarditis, focal: minimal
Intestine, cecum	Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: minimal
Intestine, rectum	Decrease, goblet cell: minimal
Kidney	Regeneration, tubular: minimal
Spleen	Atrophy: minimal
Stomach	Decrease, mucus, glandular stomach: minimal, pyloric Single cell necrosis, gastric gland: minimal
Thymus	Atrophy: moderate
Urinary bladder	Basophilic change, mucosal: minimal
Vagina	Cell infiltration, mucosal/submucosal: minimal, neutrophilic
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Eye, Intestine, duodenum
Intestine, jejunum, Intestine, ileum(Peyer's patch), Lymph node, mesenteric
Lymph node, submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Spinal cord, thoracic, Trachea, Thyroid, Uterus

Appendix 9-103(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4109 Female 100 mg/kg Day 8 Found dead

Gross pathology:

General descriptions	Undernourishment Smudge, fur: perioral
Spleen	Small: mild
Stomach	Distention: moderate retention, liquid material
Thymus	Small: moderate
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Heart	Myocarditis, focal: minimal
Intestine, duodenum	Degeneration/necrosis, mucosal: minimal
Intestine, jejunum	Degeneration/necrosis, mucosal: minimal
Intestine, ileum(Peyer's patch)	Atrophy, Peyer's patch: moderate Degeneration/necrosis, mucosal: minimal
Intestine, cecum	Sample autolysed
Intestine, colon	Decrease, goblet cell: minimal
Intestine, rectum	Decrease, goblet cell: minimal
Lymph node, mesenteric	Atrophy: minimal Activation, histiocyte, sinus: mild
Lymph node, submandibular	Atrophy: mild
Spleen	Atrophy: mild
Stomach	Sample autolysed
Thymus	Atrophy: severe
Urinary bladder	Basophilic change, mucosal: minimal
Uterus	Atrophy: mild, bilateral
Vagina	Atrophy, mucosal: mild
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Eye, Kidney, Liver
Lung(bronchus), Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Spinal cord, thoracic, Trachea, Thyroid

Appendix 9-104(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4110 Female 100 mg/kg Day 6 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment

Stomach Focus, white, forestomach: many
less than 1x1mm

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Heart Myocarditis, focal: minimal

Intestine, cecum Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: minimal

Intestine, rectum Decrease, goblet cell: minimal

Spleen Atrophy: minimal

Stomach Hyperplasia, squamous, forestomach: mild
Erosion/Ulcer, forestomach: mild
Single cell necrosis, gastric gland: minimal

Thymus Atrophy: severe

Urinary bladder Basophilic change, mucosal: minimal

Vagina Atrophy, mucosal: mild
Cell infiltration, mucosal/submucosal: minimal, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Eye, Intestine, duodenum
Intestine, jejunum, Intestine, ileum(Peyer's patch), 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, Trachea, Thyroid, Uterus

Appendix 9-105(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4111 Female 100 mg/kg Day 10 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment

Spleen Small: mild

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy,cortical cell: mild

Heart Myocarditis,focal: minimal

Intestine,cecum Decrease,goblet cell: mild

Intestine,colon Decrease,goblet cell: minimal

Lymph node,mesenteric Activation,histiocyte,sinus: mild

Liver Microgranuloma: minimal

Spleen Atrophy: minimal

Thymus Atrophy: severe

Urinary bladder Basophilic change,mucosal: minimal

Vagina Cell infiltration,mucosal/submucosal: mild, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Intestine,duodenum
Intestine,jejunum, Intestine,ileum(Peyer's patch), Intestine,rectum, Kidney
Lymph node,submandibular, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Trachea, Thyroid, Uterus

Appendix 9-106(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4112 Female 100 mg/kg Day 7 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment
Smudge, fur:
lower abdominal, perioral

Stomach Distention: moderate
retention, liquid material

Thymus Small: moderate

Other tissues Not remarkable

Histopathology:

Adrenal Hemorrhage, focal: mild, cortical
Hypertrophy, cortical cell: mild

Heart Myocarditis, focal: mild

Intestine, duodenum Degeneration/necrosis, mucosal: minimal

Intestine, jejunum Degeneration/necrosis, mucosal: mild

Intestine, ileum (Peyer's patch) Atrophy, Peyer's patch: mild

Intestine, cecum Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: minimal

Intestine, rectum Decrease, goblet cell: mild

Liver Necrosis, focal: minimal
Microgranuloma: minimal

Stomach Hyperplasia, squamous, forestomach: minimal
No finding correlating with distention in gross findings
Erosion/Ulcer, forestomach: mild
Decrease, mucus, glandular stomach: mild, pyloric

Thymus Atrophy: severe

Urinary bladder Basophilic change, mucosal: minimal

Vagina Cell infiltration, mucosal/submucosal: mild, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Eye, Kidney
Lymph node, mesenteric, Lymph node, submandibular, Lung (bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular, Sciatic nerve
Spleen, Skeletal muscle, femoral, Spinal cord, thoracic, Trachea, Thyroid, Uterus

Appendix 9-107(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4113 Female 100 mg/kg Day 11 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Bone+Bone marrow, femoral Hypocellularity, bone marrow: mild

Intestine, cecum Decrease, goblet cell: mild

Thymus Atrophy: severe

Urinary bladder Basophilic change, mucosal: minimal

Vagina Atrophy, mucosal: mild

Cause of demise Test substance toxicity

Following tissues : Not remarkable

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
Spleen, Stomach, Skeletal muscle, femoral, Spinal cord, thoracic, Trachea, Thyroid
Uterus

Appendix 9-108(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4114 Female 100 mg/kg Day 8 Moribund sacrifice

Gross pathology:

Spleen	Small: mild
Stomach	Focus, white, forestomach: many fine
Thymus	Small: moderate
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Heart	Myocarditis, focal: minimal
Intestine, cecum	Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: mild
Intestine, rectum	Decrease, goblet cell: mild
Lymph node, mesenteric	Atrophy: minimal Activation, histiocyte, sinus: mild
Spleen	Atrophy: minimal
Stomach	Hyperplasia, squamous, forestomach: mild Erosion/Ulcer, forestomach: mild
Thymus	Atrophy: severe
Vagina	Atrophy, mucosal: mild Cell infiltration, mucosal/submucosal: mild, neutrophilic
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Eye, Intestine, duodenum
Intestine, jejunum, Intestine, ileum(Peyer's patch), Kidney
Lymph node, submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Spinal cord, thoracic, Trachea, Thyroid, Urinary bladder, Uterus

Appendix 9-109(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4115 Female 100 mg/kg Day 12 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment

Other tissues Not remarkable

Histopathology:

Intestine, cecum Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: mild

Intestine, rectum Decrease, goblet cell: minimal

Thymus Atrophy: moderate

Urinary bladder Basophilic change, mucosal: minimal

Vagina Cell infiltration, mucosal/submucosal: mild, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch), 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, Trachea, Thyroid
Uterus

Appendix 9-110(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4116 Female 100 mg/kg Day 11 Found dead

Gross pathology:

General descriptions	Undernourishment
Spleen	Small: mild
Stomach	Focus, white, forestomach: 2 present 1x1mm, 1x1mm
Thymus	Small: mild
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Heart	Myocarditis, focal: minimal
Intestine, duodenum	Degeneration/necrosis, mucosal: minimal
Intestine, jejunum	Degeneration/necrosis, mucosal: mild
Intestine, ileum (Peyer's patch)	Atrophy, Peyer's patch: moderate Degeneration/necrosis, mucosal: moderate
Intestine, rectum	Decrease, goblet cell: minimal
Lymph node, mesenteric	Atrophy: minimal Activation, histiocyte, sinus: mild
Spleen	Atrophy: mild
Stomach	Hyperplasia, squamous, forestomach: mild Decrease, mucus, glandular stomach: minimal, pyloric
Thymus	Atrophy: severe
Urinary bladder	Basophilic change, mucosal: minimal
Uterus	Atrophy: mild, bilateral
Vagina	Atrophy, mucosal: mild Cell infiltration, mucosal/submucosal: minimal, neutrophilic
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Eye, Intestine, cecum
Intestine, colon, Kidney, Lymph node, submandibular, Liver, Lung (bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular, Sciatic nerve
Skeletal muscle, femoral, Spinal cord, thoracic, Trachea, Thyroid

Appendix 9-111(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4117 Female 100 mg/kg Day 12 Moribund sacrifice

Gross pathology:

All tissues Not remarkable

Histopathology:

Bone+Bone marrow, femoral Hypocellularity, bone marrow: mild

Heart Myocarditis, focal: minimal

Intestine, colon Decrease, goblet cell: mild

Thymus Atrophy: severe

Urinary bladder Basophilic change, mucosal: minimal

Vagina Cell infiltration, mucosal/submucosal: mild, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Adrenal, Cerebellum(Pons), Cerebrum, Eye, Intestine, duodenum, Intestine, jejunum
Intestine, ileum(Peyer's patch), Intestine, cecum, 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, Trachea, Thyroid
Uterus

Appendix 9-112(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4118 Female 100 mg/kg Day 11 Moribund sacrifice

Gross pathology:

General descriptions	Undernourishment
Stomach	Focus, white, forestomach: many less than 1x1mm
Thymus	Small: mild
Other tissues	Not remarkable
Histopathology:	
Adrenal	Hypertrophy, cortical cell: mild
Bone+Bone marrow, femoral	Hypocellularity, bone marrow: minimal
Heart	Myocarditis, focal: minimal
Intestine, jejunum	Degeneration/necrosis, mucosal: minimal
Intestine, cecum	Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: minimal
Intestine, rectum	Decrease, goblet cell: mild
Lymph node, mesenteric	Atrophy: minimal Activation, histiocyte, sinus: mild
Spleen	Atrophy: minimal
Stomach	Hyperplasia, squamous, forestomach: mild Decrease, mucus, glandular stomach: minimal, pyloric
Thymus	Atrophy: moderate
Urinary bladder	Basophilic change, mucosal: minimal
Vagina	Cell infiltration, mucosal/submucosal: mild, neutrophilic
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Cerebellum(Pons), Cerebrum, Eye, Intestine, duodenum
Intestine, ileum(Peyer's patch), Kidney, Lymph node, submandibular, Liver
Lung(bronchus), Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Spinal cord, thoracic, Trachea, Thyroid, Uterus

Appendix 9-113(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4119 Female 100 mg/kg Day 10 Found dead

Gross pathology:

General descriptions	Undernourishment
Spleen	Small: mild
Stomach	Distention: retention, content
Thymus	Small: mild
Uterus	Small: mild
Other tissues	Not remarkable

Histopathology:

Adrenal	Hypertrophy, cortical cell: mild
Heart	Myocarditis, focal: mild
Intestine, duodenum	Sample autolysed
Intestine, jejunum	Sample autolysed
Intestine, ileum (Peyer's patch)	Sample autolysed
Intestine, cecum	Sample autolysed
Intestine, colon	Sample autolysed
Intestine, rectum	Decrease, goblet cell: minimal
Lymph node, mesenteric	Atrophy: minimal Activation, histiocyte, sinus: mild
Lymph node, submandibular	Atrophy: mild
Liver	Microgranuloma: minimal
Spleen	Atrophy: mild
Stomach	Sample autolysed
Thymus	Atrophy: severe
Urinary bladder	Basophilic change, mucosal: minimal
Uterus	Atrophy: mild, bilateral
Vagina	Atrophy, mucosal: mild Cell infiltration, mucosal/submucosal: minimal, neutrophilic
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Eye, Kidney
Lung (bronchus), Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland, submandibular, Sciatic nerve, Skeletal muscle, femoral
Spinal cord, thoracic, Trachea, Thyroid

Appendix 9-114(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4120 Female 100 mg/kg Day 9 Moribund sacrifice

Gross pathology:

General descriptions	Undernourishment Smudge, fur: perioral
Spleen	Small: mild
Thymus	Small: mild
Other tissues	Not remarkable
Histopathology:	
Adrenal	Hypertrophy, cortical cell: mild
Intestine, ileum (Peyer's patch)	Atrophy, Peyer's patch: mild
Intestine, cecum	Decrease, goblet cell: mild
Intestine, colon	Decrease, goblet cell: minimal
Lymph node, mesenteric	Activation, histiocyte, sinus: mild
Stomach	Decrease, mucus, glandular stomach: mild, pyloric Single cell necrosis, gastric gland: minimal
Thymus	Atrophy: moderate
Urinary bladder	Basophilic change, mucosal: minimal
Cause of demise	Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Eye, Heart
Intestine, duodenum, Intestine, jejunum, Intestine, rectum, Kidney
Lymph node, submandibular, Liver, Lung (bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland, submandibular, Sciatic nerve, Spleen
Skeletal muscle, femoral, Spinal cord, thoracic, Trachea, Thyroid, Uterus, Vagina

Appendix 9-115(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4121 Female 100 mg/kg Day 8 Found dead

Gross pathology:

General descriptions Undernourishment

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Adrenal Hypertrophy, cortical cell: mild

Intestine, duodenum Sample autolysed

Intestine, jejunum Sample autolysed

Intestine, ileum (Peyer's patch) Sample autolysed

Intestine, cecum Sample autolysed

Intestine, colon Sample autolysed

Intestine, rectum Sample autolysed

Lymph node, mesenteric Activation, histiocyte, sinus: mild

Liver Microgranuloma: minimal

Stomach Sample autolysed

Thymus Atrophy: severe

Urinary bladder Basophilic change, mucosal: minimal

Uterus Atrophy: mild, bilateral

Vagina Atrophy, mucosal: mild
Cell infiltration, mucosal/submucosal: minimal, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Bone+Bone marrow, femoral, Cerebellum (Pons), Cerebrum, Eye, Heart, Kidney
Lymph node, submandibular, Lung (bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland, submandibular, Sciatic nerve, Spleen
Skeletal muscle, femoral, Spinal cord, thoracic, Trachea, Thyroid

Appendix 9-116(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats

Individual gross and histopathological findings

Animal No. 4122 Female 100 mg/kg Day 12 Moribund sacrifice

Gross pathology:

General descriptions Undernourishment

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Bone+Bone marrow, femoral Hypocellularity, bone marrow: mild

Heart Myocarditis, focal: mild

Intestine, cecum Cell infiltration: mild, mucosal mononuclear
Decrease, goblet cell: mild

Intestine, colon Decrease, goblet cell: mild

Liver Microgranuloma: minimal

Thymus Atrophy: severe

Urinary bladder Basophilic change, mucosal: minimal

Uterus Atrophy: mild, bilateral

Vagina Atrophy, mucosal: mild
Cell infiltration, mucosal/submucosal: minimal, neutrophilic

Cause of demise Test substance toxicity

Following tissues : Not remarkable

Adrenal, Cerebellum(Pons), Cerebrum, Eye, Intestine, duodenum, Intestine, jejunum
Intestine, ileum(Peyer's patch), 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, Trachea, Thyroid

Appendix 10-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
1102	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
1103	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
1104	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
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	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
1108	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
1109	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
1110	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
1111	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
1112	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
Total (%)b)																		0/12 (0.0)
Mean																3.8	4.0	
S.D.																0.5	0.0	

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 10-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual estrous cycle in female rats during the pre-mating period (Main group)
 Dose (mg/kg): 10

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	D	P	E	M	D	D	P	E	M	D	D	P	E	M	D	3	5.0	
2102	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
2103	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
2104	D	P	E	M	D	P	E	M	D	D	P	E	M	D	D	3	4.5	
2105	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
2106	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
2107	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
2108	E	M	D	P	E	M	D	D	P	E	E	M	D	P	E	4	4.7	
2109	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
2110	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
2111	P	E	M	D	D	P	E	M	D	D	P	E	M	D	P	3	5.0	
2112	E	M	D	P	E	M	D	D	P	E	M	D	D	P	E	4	4.7	
Total (%)b)																		0/12 (0.0)
Mean																3.7	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
 didec-1-yl(methyl)amine by oral administration in rats
 Individual estrous cycle in female rats during the pre-mating period (Main group)
 Dose (mg/kg): 30

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	P	E	M	D	D	P	E	M	D	P	E	M	D	P	3	4.5	
3103	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
3104	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
3105	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
3106	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
3107	E	M	D	P	E	E	M	D	P	E	E	M	D	P	E	4	4.7	
3108	P	E	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.3	
3109	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
3110	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
3111	M	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)																		0/12 (0.0)
Mean																3.7	4.1	
S.D.																0.5	0.2	

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 10-4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Individual estrous cycle in female rats during the pre-mating period (Main group)
Dose (mg/kg): 100

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)	D	P	E	M	D	D	D	D	D	D								*
4102c)	M	D	P	E	M	D	D	D										*
4103d)	D	P	E	M	D	D	D	D										*
4104d)	P	E	M	D	D	D	D	D										*
4105c)	D	P	E	M	D	P	E	E										
4106c)	P	E	M	D	P	E	M	D	D									
4107c)	P	E	M	D	P	E	M	D	P	E	M	D						
4108c)	E	M	D	P	E	M	D	D	P	E								
4109d)	M	D	P	E	M	D	D											
4110c)	D	P	E	M	D	D												
4111c)	P	E	E	M	D	P	E	M	D	D								
4112c)	D	P	E	M	D	D	D											*
Total (%) b)																		5/12 (41.7)
Mean																		
S.D.																		

P: Proestrus E: Estrus M: Metestrus D: Diestrus

*: Abnormal estrous cycle

a): Day of sampling

b): (No. of animals with abnormal estrous cycle / No. of animals examined)×100

c): Sacrificed moribund

d): Dead

Appendix 11-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 0

Pairing number Male	Pairing number Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
1001	1101	C	1	P
1002	1102	C	10	P
1003	1103	C	4	P
1004	1104	C	4	P
1005	1105	C	2	P
1006	1106	C	1	P
1007	1107	C	2	P
1008	1108	C	2	P
1009	1109	C	3	P
1010	1110	C	3	P
1011	1111	C	2	P
1012	1112	C	1	P

C: Copulated P: Pregnant

Appendix 11-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 10

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
2001	2101	NC	-	-
2002	2102	C	3	P
2003	2103	C	1	P
2004	2104	C	6	P
2005	2105	C	2	P
2006	2106	C	3	P
2007	2107	C	3	P
2008	2108	C	4	P
2009	2109	C	3	P
2010	2110	C	3	P
2011	2111	C	1	P
2012	2112	C	1	P

C: Copulated NC: Not copulated P: Pregnant

Appendix 11-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 30

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
3001	3101	C	1	P
3002	3102	C	2	P
3003	3103	C	4	P
3004	3104	C	1	P
3005	3105	C	3	P
3006	3106	C	3	P
3007	3107	C	1	P
3008	3108	C	4	P
3009	3109	C	4	P
3010	3110	C	3	P
3011	3111	C	1	P
3012	3112	C	2	P

C: Copulated P: Pregnant

Appendix 12-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	10	4	40.0	100.0	0 (0.0)	4	0 (0.0)
1102	21	22	15	68.2	93.3	0 (0.0)	14	0 (0.0)
1103	22	21	21	100.0	90.5	0 (0.0)	19	0 (0.0)
1104	23	11	6	54.5	66.7	1 (25.0)	3	0 (0.0)
1105	22	15	15	100.0	93.3	0 (0.0)	14	0 (0.0)
1106	22	16	16	100.0	100.0	0 (0.0)	16	0 (0.0)
1107	22	17	16	94.1	93.8	1 (6.7)	14	0 (0.0)
1108	22	18	17	94.4	100.0	1 (5.9)	16	0 (0.0)
1109	22	16	16	100.0	93.8	0 (0.0)	15	0 (0.0)
1110	22	15	15	100.0	100.0	0 (0.0)	15	0 (0.0)
1111	22	12	11	91.7	81.8	0 (0.0)	9	0 (0.0)
1112	22	16	13	81.3	100.0	0 (0.0)	13	0 (0.0)
Total		189	165			3	152	0
Mean	22.0	15.8	13.8	85.4	92.8	(3.1)	12.7	(0.0)
S.D.	0.4	3.6	4.7	20.4	9.9	(7.3)	4.9	(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 12-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Delivery data on dams
 Dose (mg/kg): 10

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 abnormalities(%)e)
2101	Not copulated							
2102	22	16	15	93.8	100.0	0 (0.0)	15	0 (0.0)
2103	22	15	15	100.0	100.0	0 (0.0)	15	1 (6.7)g)
2104	21	20	17	85.0	100.0	0 (0.0)	17	0 (0.0)
2105	22	14	14	100.0	100.0	0 (0.0)	14	0 (0.0)
2106f)								
2107	22	16	14	87.5	100.0	0 (0.0)	14	0 (0.0)
2108	22	16	16	100.0	87.5	0 (0.0)	14	0 (0.0)
2109	22	15	14	93.3	85.7	0 (0.0)	12	0 (0.0)
2110	22	17	17	100.0	94.1	0 (0.0)	16	0 (0.0)
2111	22	18	17	94.4	88.2	0 (0.0)	15	0 (0.0)
2112	22	19	15	78.9	60.0	0 (0.0)	9	0 (0.0)
Total		166	154			0	141	1
Mean	21.9	16.6	15.4	93.3	91.6	(0.0)	14.1	(0.7)
S.D.	0.3	1.9	1.3	7.4	12.6	(0.0)	2.2	(2.1)

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 gestation day 22

g): Brachyury

Appendix 12-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Delivery data on dams
 Dose (mg/kg): 30

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	22	16	15	93.8	93.3	0 (0.0)	14	0 (0.0)
3102	22	14	14	100.0	92.9	0 (0.0)	13	0 (0.0)
3103	22	14	14	100.0	85.7	0 (0.0)	12	1 (8.3)f)
3104	22	14	13	92.9	100.0	0 (0.0)	13	0 (0.0)
3105	22	16	16	100.0	93.8	0 (0.0)	15	0 (0.0)
3106	22	17	17	100.0	100.0	0 (0.0)	17	0 (0.0)
3107	22	13	10	76.9	70.0	0 (0.0)	7	0 (0.0)
3108	22	14	14	100.0	85.7	0 (0.0)	12	0 (0.0)
3109	22	14	14	100.0	92.9	0 (0.0)	13	0 (0.0)
3110	22	12	11	91.7	90.9	0 (0.0)	10	0 (0.0)
3111	22	16	15	93.8	100.0	1 (6.7)	14	0 (0.0)
3112	22	15	15	100.0	73.3	0 (0.0)	11	0 (0.0)
Total		175	168			1	151	1
Mean	22.0	14.6	14.0	95.8	89.9	(0.6)	12.6	(0.7)
S.D.	0.0	1.4	2.0	6.8	9.8	(1.9)	2.5	(2.4)

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): Absent, left hind limb

Appendix 13-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	4	4	100.0	4	4	100.0
1102	14	14	100.0	14	14	100.0
1103	19	19	100.0	19	16	84.2
1104	3	4	75.0	3	3	100.0
1105	14	14	100.0	14	14	100.0
1106	16	16	100.0	16	15	93.8
1107	14	15	93.3	14	14	100.0
1108	16	17	94.1	16	16	100.0
1109	15	15	100.0	15	14	93.3
1110	15	15	100.0	15	14	93.3
1111	9	9	100.0	9	9	100.0
1112	13	13	100.0	13	13	100.0
Total	152	155		152	146	
Mean	12.7	12.9	96.9	12.7	12.2	97.1
S.D.	4.9	4.8	7.3	4.9	4.4	5.0

a): (No. of liveborns / No. of delivered pups)×100

b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 13-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual viability index of pups
 Dose (mg/kg): 10

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	Not copulated					
2102	15	15	100.0	15	15	100.0
2103	15	15	100.0	14d)	13	92.9
2104	17	17	100.0	17	16	94.1
2105	14	14	100.0	14	14	100.0
2106c)						
2107	14	14	100.0	14	13	92.9
2108	14	14	100.0	14	14	100.0
2109	12	12	100.0	12	12	100.0
2110	16	16	100.0	16	14	87.5
2111	15	15	100.0	15	15	100.0
2112	9	9	100.0	9	4	44.4
Total	141	141		140	130	
Mean	14.1	14.1	100.0	14.0	13.0	91.2
S.D.	2.2	2.2	0.0	2.2	3.4	17.0

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 gestation day 22

d): One pup with external abnormality was excluded.

Appendix 13-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual viability index of pups
 Dose (mg/kg): 30

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	14	14	100.0	14	14	100.0
3102	13	13	100.0	13	12	92.3
3103	12	12	100.0	11c)	11	100.0
3104	13	13	100.0	13	13	100.0
3105	15	15	100.0	15	15	100.0
3106	17	17	100.0	17	17	100.0
3107	7	7	100.0	7	7	100.0
3108	12	12	100.0	12	12	100.0
3109	13	13	100.0	13	13	100.0
3110	10	10	100.0	10	10	100.0
3111	14	15	93.3	14	14	100.0
3112	11	11	100.0	11	11	100.0
Total	151	152		150	149	
Mean	12.6	12.7	99.4	12.5	12.4	99.4
S.D.	2.5	2.6	1.9	2.6	2.6	2.2

a): (No. of liveborns / No. of delivered pups)×100

b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

c): One pup with external abnormality was excluded.

Appendix 14-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual sex ratio of pups
 Dose (mg/kg): 0

Dam number	Liveborns		Stillborns		Sex ratio of delivered pups	Sex ratio of liveborns	Postnatal day 4		Sex ratio of live pups on day 4
	No. of males	No. of females	No. of males	No. of females	a)	b)	No. of males	No. of females	c)
1101	1	3	0	0	0.25	0.25	1	3	0.25
1102	10	4	0	0	0.71	0.71	10	4	0.71
1103	8	11	0	0	0.42	0.42	6	10	0.38
1104	1	2	1	0	0.50	0.33	1	2	0.33
1105	3	11	0	0	0.21	0.21	3	11	0.21
1106	7	9	0	0	0.44	0.44	6	9	0.40
1107	6	8	0	1	0.40	0.43	6	8	0.43
1108	11	5	1	0	0.71	0.69	11	5	0.69
1109	8	7	0	0	0.53	0.53	8	6	0.57
1110	6	9	0	0	0.40	0.40	6	8	0.43
1111	6	3	0	0	0.67	0.67	6	3	0.67
1112	4	9	0	0	0.31	0.31	4	9	0.31
Total	71	81	2	1			68	78	
Mean	5.9	6.8	0.2	0.1	0.46	0.45	5.7	6.5	0.45
S.D.	3.2	3.2	0.4	0.3	0.17	0.17	3.1	3.1	0.17

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 14-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual sex ratio of pups
 Dose (mg/kg): 10

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	Not copulated								
2102	8	7	0	0	0.53	0.53	8	7	0.53
2103	6	9	0	0	0.40	0.40	5	8	0.38
2104	10	7	0	0	0.59	0.59	9	7	0.56
2105	10	4	0	0	0.71	0.71	10	4	0.71
2106d)									
2107	9	5	0	0	0.64	0.64	8	5	0.62
2108	6	8	0	0	0.43	0.43	6	8	0.43
2109	10	2	0	0	0.83	0.83	10	2	0.83
2110	8	8	0	0	0.50	0.50	7	7	0.50
2111	8	7	0	0	0.53	0.53	8	7	0.53
2112	5	4	0	0	0.56	0.56	1	3	0.25
Total	80	61	0	0			72	58	
Mean	8.0	6.1	0.0	0.0	0.57	0.57	7.2	5.8	0.53
S.D.	1.8	2.2	0.0	0.0	0.13	0.13	2.7	2.1	0.16

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 gestation day 22

Appendix 14-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual sex ratio of pups
 Dose (mg/kg): 30

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	4	10	0	0	0.29	0.29	4	10	0.29
3102	6	7	0	0	0.46	0.46	5	7	0.42
3103	7	5	0	0	0.58	0.58	7	4	0.64
3104	10	3	0	0	0.77	0.77	10	3	0.77
3105	8	7	0	0	0.53	0.53	8	7	0.53
3106	10	7	0	0	0.59	0.59	10	7	0.59
3107	3	4	0	0	0.43	0.43	3	4	0.43
3108	0	12	0	0	0.00	0.00	0	12	0.00
3109	6	7	0	0	0.46	0.46	6	7	0.46
3110	7	3	0	0	0.70	0.70	7	3	0.70
3111	7	7	0	1	0.47	0.50	7	7	0.50
3112	5	6	0	0	0.45	0.45	5	6	0.45
Total	73	78	0	1			72	77	
Mean	6.1	6.5	0.0	0.1	0.48	0.48	6.0	6.4	0.48
S.D.	2.8	2.6	0.0	0.3	0.20	0.20	2.9	2.7	0.20

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 15-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine 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	7.7	15.5	7.8	7.2	14.2	7.0
1102	6.4	9.5	3.1	6.0	8.7	2.7
1103	5.9	9.5	3.6	5.6	8.6	3.0
1104	6.6	9.5	2.9	7.3	10.5	3.2
1105	6.7	9.8	3.1	6.2	9.8	3.6
1106	6.7	10.5	3.8	6.7	11.1	4.4
1107	6.4	7.9	1.5	5.9	7.4	1.5
1108	6.4	10.3	3.9	6.1	9.8	3.7
1109	6.6	9.0	2.4	6.2	8.8	2.6
1110	6.6	10.0	3.4	5.9	9.7	3.8
1111	7.4	11.7	4.3	6.8	11.2	4.4
1112	6.9	11.7	4.8	6.6	11.3	4.7
Mean	6.7	10.4	3.7	6.4	10.1	3.7
S.D.	0.5	1.9	1.5	0.5	1.8	1.4

Unit: g

a): Postnatal day

Appendix 15-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of pups
 Dose (mg/kg): 10

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
2101	Not copulated					
2102	6.7	10.4	3.7	6.0	9.8	3.8
2103	5.9	9.3	3.4	5.7	8.9	3.2
2104	5.7	6.5	0.8	5.5	6.5	1.0
2105	6.2	10.1	3.9	5.8	8.8	3.0
2106b)						
2107	6.9	11.2	4.3	6.4	9.6	3.2
2108	6.4	10.1	3.7	6.0	9.6	3.6
2109	7.0	10.9	3.9	6.6	10.5	3.9
2110	6.3	8.8	2.5	6.1	8.4	2.3
2111	6.9	9.6	2.7	6.6	9.4	2.8
2112	6.5	11.5	5.0	7.0	11.1	4.1
Mean	6.5	9.8	3.4	6.2	9.3	3.1
S.D.	0.4	1.4	1.2	0.5	1.3	0.9

Unit: g

a): Postnatal day

b): Died on gestation day 22

Appendix 15-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual body weight of pups
 Dose (mg/kg): 30

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
3101	6.7	11.2	4.5	6.2	9.9	3.7
3102	6.0	9.5	3.5	5.9	9.3	3.4
3103	7.0	10.9	3.9	6.7	10.0	3.3
3104	6.4	10.4	4.0	5.6	9.5	3.9
3105	7.0	10.2	3.2	6.6	9.7	3.1
3106	6.5	9.6	3.1	5.9	9.1	3.2
3107	8.2	12.9	4.7	7.9	12.2	4.3
3108	b)			6.6	10.1	3.5
3109	6.9	11.4	4.5	6.5	10.5	4.0
3110	6.9	10.8	3.9	6.7	11.1	4.4
3111	6.9	10.0	3.1	6.5	9.7	3.2
3112	7.4	11.0	3.6	6.9	10.6	3.7
Mean	6.9	10.7	3.8	6.5	10.1	3.6
S.D.	0.6	1.0	0.6	0.6	0.9	0.4

Unit: g

a): Postnatal day

b): No male pups were born.

Appendix 16-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine 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	0	
1102	0	
1103	0	
1104	0	
1105	0	
1106	0	
1107	0	
1108	0	
1109	1 (0 + 1)	NAF
1110	0	
1111	0	
1112	0	

NAF: No abnormal findings

Appendix 16-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
 didec-1-yl(methyl)amine by oral administration in rats
 Individual externally for gross abnormalities in dead pups
 Dose (mg/kg): 10

Dam number	No. of pups examined Total (Male + Female)	Findings
2101	Not copulated	
2102	0	
2103	0	
2104	1 (1 + 0)	NAF
2105	0	
2106a)		
2107	1 (1 + 0)	NAF
2108	0	
2109	0	
2110	2 (1 + 1)	NAF
2111	0	
2112	3 (2 + 1)	NAF

NAF: No abnormal findings
 a): Died on gestation day 22

Appendix 16-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
didec-1-yl(methyl)amine by oral administration in rats
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 30

Dam number	No. of pups examined Total (Male + Female)	Findings
3101	0	
3102	1 (1 + 0)	NAF
3103	0	
3104	0	
3105	0	
3106	0	
3107	0	
3108	0	
3109	0	
3110	0	
3111	0	
3112	0	

NAF: No abnormal findings

Appendix 17-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine 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	4 (1 + 3)	NAF
1102	14 (10 + 4)	NAF
1103	16 (6 + 10)	NAF
1104	3 (1 + 2)	NAF
1105	14 (3 + 11)	NAF
1106	15 (6 + 9)	NAF
1107	14 (6 + 8)	NAF
1108	16 (11 + 5)	NAF
1109	14 (8 + 6)	NAF
1110	14 (6 + 8)	NAF
1111	9 (6 + 3)	NAF
1112	13 (4 + 9)	NAF

NAF: No abnormal findings

Appendix 17-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
 Individual externally for gross abnormalities in pups on postnatal day 4
 Dose (mg/kg): 10

Dam number	No. of pups examined Total (Male + Female)	Findings
2101	Not copulated	
2102	15 (8 + 7)	NAF
2103	13 (5 + 8)	NAF
2104	16 (9 + 7)	NAF
2105	14 (10 + 4)	NAF
2106a)		
2107	13 (8 + 5)	NAF
2108	14 (6 + 8)	NAF
2109	12 (10 + 2)	NAF
2110	14 (7 + 7)	NAF
2111	15 (8 + 7)	NAF
2112	4 (1 + 3)	NAF

NAF: No abnormal findings

a): Died on gestation day 22

Appendix 17-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of didec-1-yl(methyl)amine by oral administration in rats
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 30

Dam number	No. of pups examined Total (Male + Female)	Findings
3101	14 (4 + 10)	NAF
3102	12 (5 + 7)	NAF
3103	11 (7 + 4)	NAF
3104	13 (10 + 3)	NAF
3105	15 (8 + 7)	NAF
3106	17 (10 + 7)	NAF
3107	7 (3 + 4)	NAF
3108	12 (0 + 12)	NAF
3109	13 (6 + 7)	NAF
3110	10 (7 + 3)	NAF
3111	14 (7 + 7)	NAF
3112	11 (5 + 6)	NAF

NAF: No abnormal findings

R-1103

信頼性保証書 (1/3)

試験番号 : R-1103

試験表題 : ジデカー1-イル (メチル) アミンのラットを用いた
経口投与による反復投与毒性・生殖発生毒性併合試験

本試験は以下に示す基準を遵守して実施されたことを保証致します。

- 「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)

なお、調査は下記の通り実施致しました。

2013年3月28日

株式会社ボゾリサーチセンター
信頼性保証部門

試験における調査

項目	担当者	調査日	試験責任者及び 運営管理者への 報告日
試験計画書		2012年 9月 10日	2012年 9月 10日
作業予定表・ コンピュータプロトコール		2012年 9月 18日	2012年 9月 18日
調製・保存 (被験物質)		2012年 9月 27日	2012年 9月 28日
被験液の濃度確認		2012年 9月 27日	2012年 9月 28日
群分け		2012年 9月 30日	2012年 10月 1日
腫瘍検査・体重・摂餌量測定・ 投与・一般状態の観察		2012年 10月 1日	2012年 10月 1日
詳細な一般状態の観察		2012年 10月 4日	2012年 10月 5日

信頼性保証書 (2/3)

項目	担当者	調査日	試験責任者及び 運営管理者への 報告日
試験計画書変更書 (1)		2012年 10月 13日	2012年 10月 15日
交配		2012年 10月 16日	2012年 10月 16日
試験計画書変更書 (2)		2012年 11月 2日	2012年 11月 2日
尿検査 (尿量・色調・定性・沈渣)		2012年 11月 6日	2012年 11月 6日
摂水量測定		2012年 11月 7日	2012年 11月 7日
分娩・哺育観察・体重測定		2012年 11月 7日	2012年 11月 7日
機能検査・握力測定・ 自発運動量測定		2012年 11月 8日	2012年 11月 9日
採血・剖検		2012年 11月 12日	2012年 11月 12日
病理組織学検査 (切り出し)		2012年 11月 19日	2012年 11月 19日
被験物質の安定性		2012年 12月 5日	2012年 12月 5日
生データ (被験物質関係、被験液の濃度 確認、被験物質の安定性)		2013年 2月 4日	
改善確認		2013年 2月 5日	
測定レポート (被験液の濃度 確認、被験物質の安定性)		2013年 2月 6日	2013年 2月 6日
改善確認		2013年 2月 12日	2013年 2月 12日
測定レポート (被験液の濃度 確認、被験物質の安定性)		2013年 2月 6日	2013年 2月 6日
改善確認		2013年 2月 12日	2013年 2月 12日
測定レポート (被験液の濃度 確認、被験物質の安定性)		2013年 2月 12日	2013年 2月 12日
生データ (入荷～器官重量、飼育関係)		2013年 2月 12日	
		2013年 2月 14日	
		2013年 2月 15日	
		2013年 2月 16日	
	2013年 2月 18日		
	2013年 2月 20日	2013年 2月 20日	
改善確認	2013年 2月 21日	2013年 2月 22日	

信頼性保証書 (3/3)

項目	担当者	調査日	試験責任者及び 運営管理者への 報告日
最終報告書草案・図・表・付表		2013年 2月 14日	
		2013年 2月 15日	
		2013年 2月 16日	
		2013年 2月 18日	
		2013年 2月 19日	
		2013年 2月 20日	2013年 2月 20日
改善確認		2013年 2月 21日	2013年 2月 22日
生データ (血液学・血液化学検査、 剖検・病理)		2013年 2月 25日	
		2013年 2月 26日	
生データ (被験物質関係)		2013年 2月 27日	2013年 2月 27日
生データ (被験物質関係)		2013年 3月 25日	2013年 3月 25日
最終報告書		2013年 3月 28日	2013年 3月 28日

プロセス調査

項目	試験番号	担当者	調査日	試験責任者及び 運営管理者への 報告日
動物入荷	B-7293		2012年 8月 20日	2012年 8月 20日
検疫・馴化	B-7293		2012年 8月 20日	2012年 8月 20日
	B-7293		2012年 8月 25日	2012年 8月 27日
尿検査 (浸透圧・電解質)	R-1100		2012年 10月 31日	2012年 10月 31日
血液学検査・ 血液化学検査	B-7321		2012年 10月 4日	
			2012年 10月 5日	2012年 10月 5日
病理組織学検査 (包埋・薄切・染色)	B-7279		2012年 10月 10日	2012年 10月 10日
	B-7279		2012年 10月 12日	2012年 10月 12日
	B-7279		2012年 10月 22日	2012年 10月 22日