試験番号 R-12-004

最終報告書

N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミドのラットを用いる反復投与毒性・生殖発生毒性併合試験

厚生労働省医薬食品局審査管理課 化学物質安全対策室 委託

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試験番号	R-12-004
被験物質	N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミド
試験項目	反復投与毒性ならびに生殖発生毒性試験
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実験開始日	2012 年 11 月 12 日
実験終了日	2013 年 9 月 18 日
試験終了日	試験責任者の捺印日
試資料保管場所	秦野研究所資料保存室
被験物質保管場所	秦野研究所被験物質保存庫
保管期間	試験終了後 10 年間 その後の保管については試験委託者と協議する。
運営管理者	一般財団法人食品薬品安全センター 秦野研究所 所長[redacted]

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

2014 年 1 月 27 日　　試験責任者 [redacted]

試験従事者

試験責任者	[redacted]
試験担当主任者	[redacted]
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尿検査	
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血液生化学検査	
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信頼性保証書

要約

N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミドの反復投与毒性ならびに生殖発生毒性試験を化審法ガイドラインに従って実施した。被験物質を日局注射用水に懸濁して 0、15、50 ならびに 150 mg/kg の用量で、各群とも雌雄各 12 匹の Crl:CD(SD)ラットに強制経口投与した。雄は 42 日間投与した後に剖検し、雌は交配前 2 週間および妊娠期間を通して哺育 4 日までの 42～49 日間投与し、出生児は哺育 4 日、母動物は哺育 5 日に剖検した。また、0 および 150 mg/kg の用量では非交配雌(10 匹/群)を設け、42 日間投与した後に半数を剖検し、残りの半数と雄の 0 および 150 mg/kg 群の 5 例は、投与終了後に 14 日間飼育して剖検した。

1. 反復投与毒性および回復性

死亡は、150 mg/kg 群の非交配雌 2 例にみられた。生存例では、一過性の軟便が 150 mg/kg 群の雄、交配雌および非交配雌に散見された他、排便量の減少、自発運動の低下、体温下降、呼吸困難、呼吸不整、蒼白が 150 mg/kg 群の雄、分娩雌または非交配雌の 1～2 例で認められた。体重の増加抑制は 150 mg/kg 群の雄で、摂餌量の低下は 150 mg/kg 群の雄および交配雌でみられた。血液学検査では網状赤血球比率の低下が、血液生化学検査では総蛋白濃度とアルブミン濃度の低下がいずれも 150 mg/kg 群の雄でみられた。死亡例の病理組織学検査では、胸腺の萎縮、気管腔内の膿瘍、肺の水腫などが観察された。生存例の病理組織学検査では、150 mg/kg 群の雄で門脈周囲性の肝細胞の脂肪化が減少した。また、前胃では、粘膜下織の炎症性細胞浸潤、粘膜固有層および粘膜下織の水腫、びらん、扁平上皮の過形成が 150 mg/kg 群の雄、分娩雌および非交配雌で、腺胃では粘膜下織の水腫またはびらんが 150 mg/kg 群の雄および分娩雌で観察された。

回復期間中には、軟便を含む一般状態の異常は観察されず、150 mg/kg 群の雄の体重低下はすみやかに回復した。胃の病理組織学検査では、雌雄とも被験物質投与の影響は認められなかった。

2. 生殖発生毒性

性周期、交尾率、妊娠率、妊娠期間および出産率に被験物質投与の影響は認められなかった。また、分娩状態、哺育状態、黄体数、着床数および着床率にも被験物質投与の影響は認められなかった。

出生児の生存性および形態に被験物質投与の影響は認められなかったが、哺育 4 日の出生児体重が雌雄とも 150 mg/kg 群で低下した。

3. 無毒性量

150 mg/kg 群の雄では、軟便や排便量の減少などの一般状態の変化と体重低下、胃に炎症性変化が、同群の雌でも軟便や排便量の減少などの一般状態の変化と胃の炎症性変化が認められたことから雌雄動物の反復投与毒性に対する無毒性量(NOAEL)は 50 mg/kg/day と判断された。

150 mg/kg までの用量に親動物への生殖毒性を示唆する変化は認められなかったが、哺育 4 日の出生児体重が 150 mg/kg 群で低下したことから、生殖発生毒性に対する無毒性量は 50 mg/kg/day と判断された。

試験目的

雌雄ラットの交配前(2 週間)および交配期間中(最長 2 週間)、ならびに雄では交配期間終了後 2 週間、雌では妊娠期間を通して周産期(哺育 4 日まで)に N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミドを経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

試験ガイドラインと GLP

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

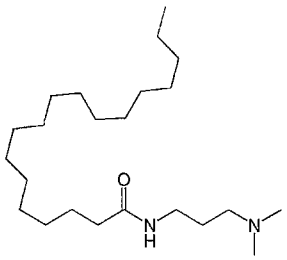
動物愛護

全ての実験操作は、「動物の愛護及び管理に関する法律」(昭和 48 年 10 月 1 日 法律第 105 号、平成 24 年 9 月 5 日 一部改正)、「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」(平成 18 年 4 月 28 日、環境省告示第 88 号)および「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」(平成 18 年 6 月 1 日、科発第 0601001 号)を遵守し、「財団法人食品薬品安全センター秦野研究所動物実験に関する指針」(平成 2 年 10 月 1 日、平成 22 年 10 月 1 日改正)に基づいて実施した。本試験における動物実験計画は、秦野研究所動物実験委員会の審査を受け、承認されている(動物実験承認番号:1120225A)。なお、承認された動物実験計画からの変更はなかった。

材料と方法

1. 被験物質

被験物質である N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミド(別名:N-[3-(ジメチルアミノ)プロピル]ステアラミド、CAS No. 7651-02-7、化学式:$C_{23}H_{48}N_2O$、分子量:368.64、性状:白色の結晶性粉末、ロット番号:TLH9065、含量:98.6%(毛管カラム GC)、Annex A、以下、N-DPS)は、[redacted]より購入し(被験物質入手:2012 年 10 月 1 日)、使用時まで室温(実測値 14.6～24.3℃)、密閉で保管した。N-DPS の構造式を次に示す。



被験物質の安定性については、実験開始前および実験終了後に秦野研究所にて赤外吸収スペクトルを測定し、それぞれの様相を比較した。その結果、得られた赤外吸収スペクトルの様相に変化がなかったことから本試験の実施期間中、被験物質は安定であったと判断した(Annex B-1、B-2)。測定法はAnnex C、第 1 項に従った。

2. 動物および飼育方法

日本チャールス・リバー厚木飼育センターより 8 週齢の Sprague-Dawley(SD)系〔Crl:CD(SD)、SPF〕ラット雄 55 匹、雌 83 匹を購入し、飼育室(7 号室)に収容した。入荷日も含めて 15 日間、検疫と飼育環境への馴化のため飼育した。その間毎日、動物の一般状態を観察し、入荷日(検疫 1 日)および検疫終了日に体重を測定した。検疫・馴化期間中は動物の尾に赤のフェルトペンで馴化番号を記し、飼育ケージに試験番号、性別および馴化番号を記入した動物カードを掛けて識別した。また、雌動物については、検疫 3 日から毎日、性周期を観察した。入荷動物の入荷時および検疫終了時の体重は下記の通りであった。

動物入荷日　:2012 年 10 月 29 日
入荷時体重　:雄 253.8～284.6 g、雌 182.6～209.7 g
検疫終了日　:2012 年 11 月 12 日
検疫終了時体重　:雄 335.7～427.7 g、雌 221.1～276.3 g

検疫・馴化期間中、一般状態、詳細な症状観察および体重推移に試験実施に影響を及ぼすと判断される異常は認められなかった。なお、雌動物では、規則的な性周期の回帰が認められない 12 匹を除外し、検疫終了時の体重に基づく体重別層化無作為抽出法により群分けを行った。群分けした動物には一連の動物番号を割り当て、フェルトペンで尾に動物番号を標識し、色彩の異なった動物カードに試験番号および動物番号を記入して飼育ケージに掛けた。群分けから棄却した雄動物 7 匹、雌動物 15 匹(性周期の結果により除外した例を含む)は全て余剰動物とし、他の目的に使用予定がなかったため、安楽死させた。

動物は許容温度 21.0～25.0℃、許容湿度 40.0～75.0%、換気設定約 15 回/時間、明暗サイクル 12 時間(7 時～19 時)点灯、12 時間(19 時～7 時)消灯に設定された飼育室内で、金属製金網床ケージ(220w×270d×190h mm)に 1 匹ずつ(交配時は 2 匹)収容し、固型飼料(CE-2、日本クレア)と水道水(秦野市水道局給水)を自由に摂取させて飼育した(剖検前の絶食に関しては剖検の項を参照)。雌動物は分娩例全例について、妊娠 18 日から哺育 4 日までラット用プラスチック製繁殖ケージ(350w×

400d×180h mm)に1匹ずつ収容し、床敷として紙パルプ製チップ(ペパークリーン、日本エスエルシー)を適宜供給した。飼育期間中の動物室の温度は 21.0～25.0℃、湿度は 44.5～70.0%であった。また、供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを確認した。

3. 投与検体

1)調製

被験物質を秤量し、媒体(日局注射用水、製造元:光製薬、製造番号:C23VS1)を加え懸濁させ、3 w/v%液を調製した。さらに 3 w/v%液を媒体によって希釈し、1 ならびに 0.3 w/v%液を段階的に調製した。調製した検体は冷蔵・遮光下(実測値 2～6℃)で保管し、安定性の保証期間内に使用した。

2)安定性試験

投与に先立ち、日局注射用水を媒体とした 0.1、1 および 60 mg/mL(0.01、0.1 および 6 w/v%)濃度の被験物質調製液について、冷蔵、遮光条件下における 8 日間の安定性を確認した。その結果、0.1 mg/mL 液では調製後 8 日の平均含量が調製指示濃度の 79.6%となり、規定範囲を下回ったが、1 および 60 mg/mL 液については、8 日間の安定性が確認された(Annex D)。調製検体中の被験物質濃度測定法は Annex C、第 2 項に従った。

3)含量および均一性試験

初回に調製した投与検体(0.3、1 および 3 w/v%)について、被験物質含量および均一性を測定した。その結果、平均含量は調製濃度の 93.6～99.0%であり、各測定値のばらつきはそれぞれ平均値の 98.8～101.0%で規定範囲内にあった(Annex E)。投与検体中の被験物質濃度測定法は Annex C、第 2 項に従った。

4. 投与量の設定および投与方法

本試験の投与量は、本被験物質を用いて行った「N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミドのラットを用いる反復投与毒性・生殖発生毒性併合試験(予備試験)」(試験番号:R-12-003)および「予備試験 2」(試験番号:S-12-034)の結果をもとに設定した。なお、使用した被験物質は予備試験(試験番号:R-12-003)では本試験と異なるロットを、予備試験 2(試験番号:S-12-034)では本試験と同一ロットを使用した。

予備試験(試験番号:R-12-003)では、0(媒体、注射用水)、100、300 および 1000 mg/kg の N-DPS を 8 週齢の雌雄各 3 匹の SD 系ラットに 14 日間、反復強制経口投与した結果、1000 mg/kg 群の動物は、投与 3～5 日の間に軟便を発症し、その後、自発運動の低下、下痢、泥状便、腹部または口周囲の汚れ、体表温の低下などを呈し、雌は投与 9 日までに、雄は投与 12 日までに全例が死亡した。また、300 mg/kg 群の雄においても、3 例中 2 例に死亡例と同様の重篤な症状がみられ、投与 5 日以降の体

重が初回体重を下回り、血液学検査では好中球の増加と網状赤血球比率の低下が、血液生化学検査では肝機能障害を示唆する変化が認められた。300 mg/kg 群の雌では、軟便および肝機能の低下を示唆する変化はみられたが、重篤な変化はなかった。100 mg/kg 群では、雌雄とも被験物質投与の影響を示唆する変化は観察されなかった。

予備試験 2(試験番号:S-12-034)では、0(媒体、注射用水)、100、200 および 300 mg/kg の N-DPS を 11～12 週齢の雌雄各 3 匹の SD 系ラットに反復強制経口投与した結果、軟便または下痢を発症し、死亡あるいは瀕死状態となった動物が 300 mg/kg の雌雄で各 1 例、200 mg/kg の雄で 1 例に観察された。100 mg/kg 群では、雌雄とも被験物質投与の影響を示唆する変化は観察されなかった。

以上の結果から、150 mg/kg を本試験の最高用量に設定し、中用量には 50 mg/kg を、最低用量には無毒性量(NOAEL)が得られると期待される 15 mg/kg を設定した。

本試験では、雄動物は交配前 2 週間、交配期間を通して剖検前日まで(総投与回数 42 回)、雌動物は交配前 2 週間、交配期間、妊娠期間を通して分娩後の哺育 4 日まで(総投与回数 42～49 回)、分娩しない雌は剖検前日(妊娠 25 日相当日)、非交配雌の反復毒性を評価するために設定したサテライト群は投与 42 日まで、1 日 1 回、1 週 7 回、毎日 9 時～13 時の間(9 時 00 分～11 時 57 分)に投与した。投与容量は 5 mL/kg とし、雌雄とも最新の測定日の体重を基に投与液量を算出した。なお、対照群には媒体である日局注射用水を同様に投与した。投与経路は化審法ガイドラインに拠り、ラット用胃管による強制経口投与とした。

本試験の群構成および動物番号を以下に示した。

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

*:雄の対照群および高用量群、雌の対照群(サテライト群)については動物番号の大きい各 5 例を、雌の高用量群(サテライト群)については動物番号の大きい 4 例を回復観察に供した。

5. 検査法

1)親動物(F_0)

①一般状態の観察

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

②回復および遅発毒性の観察

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

号の大きい 5 例(高用量群は 4 例)を最終投与翌日(回復 1 日)から 14 日間、毎日 1 回以上、一般状態を観察した。

③詳細な症状観察

全例について、検疫終了日、投与 8、15、24、30、36 および 42 日(分娩例は哺育 0 日から 4 日の間)、回復期間中は回復 7 および 14 日にスコアリング法による詳細な症状観察を行った。観察は、いずれも 13 時～17 時の間(13 時 06 分～15 時 21 分)に行った。

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

④機能検査

各群の動物番号の若い雄 5 例とサテライト群の動物番号の若い 5 例(高用量群は 3 例)については、投与 39 日に自発運動測定と握力測定を実施し、投与 42 日に詳細な症状観察に引き続いて刺激に対する感覚運動反応を検査した。分娩例については投与期間が近接し、出来るだけ分娩から日数が経過した各群の 5 例を選び、投与最終週に自発運動測定、握力測定および刺激に対する感覚運動反応を検査した。

(1) 自発運動測定

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

(2) 握力測定

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

(3) 刺激に対する感覚運動反応

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

⑤体重測定

雌動物のサテライト群と雄動物は、投与 1、4、7、14、21、28、35、42 日、回復 1、7、14 日および剖検日に測定した。雌動物は投与 1、4、7、14 日、妊娠 0(交尾確認日)、7、14、20 日、哺育 0、4 日および剖検日に測定した。

⑥摂餌量測定

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

⑦尿検査

雌動物のサテライト群と雄動物を検査対象とし、投与 37 日の検査では各群の動物番号が若い 5 例、

また、回復 13 日における検査では回復観察に供した全例を検査した。

投与 37 日の検査では当日の投与後に、回復 13 日の検査では一般状態の観察終了後に動物を代謝ケージに収容し、以下の項目について検査した。ただし、色調・濁度、試験紙による検査および尿沈渣は、採尿開始後約 4～8 時間の時点で採取した蓄尿で、その他の項目は約 24 時間の蓄尿で行った。

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

⑧性周期観察

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

⑨交配

投与 15 日の 15 時 04 分より同群内の雌雄を 1 対 1 で同居させた。翌朝より毎朝、腟栓を確認し、同居中の雌の腟スメア標本を作製して鏡検した。腟内に腟栓あるいは腟スメア標本中に精子が確認された動物を交尾成立動物とし、この日を妊娠 0 日と起算して個別飼育に戻した。交配結果および妊娠の成否により、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数、交尾率〔(交尾動物数/交配に用いた動物数)×100, %〕、妊娠率〔(妊娠動物数/交尾した雌動物数)×100, %〕を算出した。

⑩妊娠・分娩・哺育状態の観察

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

⑪採血

雄の投与終了時剖検では各群の動物番号が若い 5 例、回復 15 日における剖検では回復観察に供した全例について採血を行った。分娩雌の投与終了時剖検では、可能な限り分娩から日数が経過した

各群の 5 例について採血を行った。サテライト群の投与終了時剖検では各群の動物番号が若い 5 例(高用量群は 4 例)、回復 15 日における剖検では回復観察に供した全例について採血を行った。いずれも解剖前 18～24 時間絶食させた後、腹部後大静脈から以下の(1)、(2)、(3)の順に注射筒を換えて採血した。

(1) 血液学検査用:抗凝固剤 EDTA-2K

(2) 血液学検査用:抗凝固剤 クエン酸ナトリウム

(3) 血液生化学検査用:抗凝固剤 ヘパリン

⑫血液学検査

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

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

⑬血液生化学検査

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

項目	測定法	使用機器
総蛋白濃度(TP)	ﾋﾞｳﾚｯﾄ法	自動分析装置 JCA-BM6010(日本電子)
ｱﾙﾌﾞﾐﾝ濃度(rALB)	BCG 法	同上
ｸﾞﾙｺｰｽ濃度(Glc)	ﾍｷｿｷﾅｰｾﾞ・G-6-PDH 法	同上
総ｺﾚｽﾃﾛｰﾙ濃度(TC)	ｺﾚｽﾃﾛｰﾙｵｷｼﾀﾞｰｾﾞ・HMMPS 法	同上
ﾄﾘｸﾞﾘｾﾗｲﾄﾞ濃度(TG)	GPO・HMMPS 法、ｸﾞﾘｾﾘﾝ消去法	同上
ﾘﾝ脂質濃度(PL)	ｺﾘﾝｵｷｼﾀﾞｰｾﾞ・DAOS 法	同上

項目	測定法	使用機器
尿素窒素濃度(BUN)	ｳﾚｱｰｾﾞ・GℓDH法,ｳﾚｱｰｾﾞ律速系	自動分析装置 JCA-BM6010(日本電子)
ｸﾚｱﾁﾆﾝ濃度(cre)	Jaffé法	同上
γ-ｸﾞﾙﾀﾐﾙﾄﾗﾝｽﾍﾟﾌﾟﾁﾀﾞｰｾﾞ活性(γ-GTP)	IFCC法	同上
ｱﾙｶﾘﾌｫｽﾌｧﾀｰｾﾞ活性(ALP)	GSCC法	同上
ｱｽﾊﾟﾗｷﾞﾝ酸ｱﾐﾉﾄﾗﾝｽﾌｪﾗｰｾﾞ活性(AST)	IFCC法	同上
ｱﾗﾆﾝｱﾐﾉﾄﾗﾝｽﾌｪﾗｰｾﾞ活性(ALT)	IFCC法	同上
乳酸脱水素酵素活性(LDH)	JSCC標準化対応法	同上
ｶﾙｼｳﾑ濃度(Ca)	OCPC法	同上
総ﾋﾞﾘﾙﾋﾞﾝ濃度(tbil)	酵素法	同上
無機ﾘﾝ濃度(IP)	ﾓﾘﾌﾞﾃﾞﾝ酸直接法	同上
胆汁酸濃度(TBA)	酵素サイクリング法	同上
A/G比	計算(rALB/(TP- rALB))	同上
ﾅﾄﾘｳﾑｲｵﾝ濃度(Na)	ｲｵﾝ電極法	全自動電解質分析装置 EA05(ｴｲｱﾝﾄﾞﾃｨｰ)
ｶﾘｳﾑｲｵﾝ濃度(K)	同上	同上
塩素ｲｵﾝ濃度(Cl)	同上	同上

⑭剖検および器官重量

以下の時期に、採血対象動物はペントバルビタールナトリウム麻酔下で採血した後、これ以外の動物はペントバルビタールナトリウム麻酔下で放血致死させ、引き続き剖検した。

対象動物	解剖時期	屠殺前の絶食
雄		
投与終了時剖検例	投与 42 日の翌日	18～24 時間絶食(剖検例全例)
回復観察例	回復 15 日	18～24 時間絶食(剖検例全例)
雌		
分娩例	哺育 4 日の翌日	18～24 時間絶食(剖検例全例)
交尾したが分娩しなかった例(未分娩)	妊娠26日相当日	実施せず
サテライト群(投与終了時剖検例)	投与42日の翌日	18～24 時間絶食(剖検例全例)
サテライト群(回復観察例)	回復15日	18～24 時間絶食(剖検例全例)
死亡動物	死亡確認日	実施せず

全例について、脳、甲状腺および上皮小体、胸腺、心臓、肝臓、腎臓、脾臓、副腎、精巣、精巣上体、前立腺(腹側葉)および精嚢(凝固腺を含む)、卵巣、子宮の重量を測定した。また、全例の脳、脊髄、下垂体、眼球(ハーダー腺)、顎下腺および舌下腺、気管、甲状腺および上皮小体、胸腺、心臓、肺および気管支、肝臓、腎臓、脾臓、膵臓、副腎、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、下顎ﾘﾝﾊﾟ節、腸間膜ﾘﾝﾊﾟ節、精巣、精巣上体、前立腺、精嚢および凝固腺、卵巣、子宮、腟、膀胱、大腿骨および大腿骨骨髄、骨格筋、坐骨神経、乳腺、および病変部を採取し、保存した。死亡動物以外の肺／気管支は 15 cm 水柱以下の圧力で、気管内に 10%中性緩衝ホルマリン溶液 5 mL 以下を注入し固定してから摘出して同固定液に保存した。精巣および精巣上体はブアン液に固定(長期保存は 10%中性緩衝ホルマリン溶液)し、その他の器官・組織は 10%中性緩衝ホルマリン溶液に固定した。

なお、不妊例の器官重量値は評価対象から除外した。

⑮病理組織学検査

投与終了時に剖検した動物のうち、雄では動物番号が若い対照群ならびに高用量群の各 5 例、サテライト群では動物番号が若い対照群の 5 例ならびに高用量群の 4 例、分娩雌では採血を行った対照群ならびに高用量群の 5 例について、組織学検査対象器官(保存した器官・組織のうち乳腺は除く)のヘマトキシリン・エオジン(HE)標本を作製し、病理組織学検査を実施した。

死亡動物についても同様に、病理組織学検査を実施した。なお、投与期間終了時の剖検例で被験物質投与の影響が示唆された器官・組織については、中用量群の 5 例と回復期間終了時の剖検例についても病理組織学検査を実施した。また、剖検時に異常がみられた器官・組織に関しても同様に HE 標本を作製し、病理組織学検査を実施した。

2)出生児(F_1)

①出生児の観察

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

②剖検

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

6. データの解析法

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

その他のデータは、個体ごとに得られた値あるいは litter ごとの平均値を 1 標本とし、サテライト群内あるいはその他の群内で比較した。その際、解析の対象が 2 群の場合には、まず F 検定を行い、有意差が認められなければ Student's-t 検定を行った。F 検定において有意差が認められた場合は、Aspin-Welch 検定を行った。解析の対象が 3 群以上の場合は、先ず、Bartlett の方法により各群の分散の一様性について検定(有意水準:5%)を行った。分散が一様であった場合には、一元配置型の分散分析(有

意水準:5%)を行い、群間に有意性が認められた場合は、Dunnett 法により多重比較を行った(有意水準:5%)。一方、いずれかの群で分散が 0 となった場合および分散が一様でなかった場合には、Kruskal-Wallis の順位検定(有意水準:5%)を行い、群間に有意性が認められた場合には、Dunnett 型の検定法により多重比較を行った(有意水準:5%)。

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

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

試験成績

1. 親動物

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

雄では、死亡動物はみられなかった。150 mg/kg 群の雄 6 例に一過性の軟便が観察され、このうちの 2 例(動物番号:M04038、M04045)では排便量の減少も観察されたが、いずれも 1～3 日で回復した。投与 7 日に一過性の軟便が観察された 150 mg/kg 群の雄 1 例(動物番号:M04040)は、投与 42 日から自発運動の低下、翌日の剖検日には体温下降、呼吸困難および蒼白が観察された。回復期間中には、軟便を含む一般状態の異常は観察されなかった。

雌では、150 mg/kg 群の非交配雌 2 例が投与 7 日(動物番号:F06060)と投与 19 日(動物番号:F06062)に死亡した。死亡した非交配雌 1 例(動物番号:F06062)には、投与 3 日に軟便が観察されたが、それ以外に死亡動物の一般状態に異常は観察されなかった。雌の生存例では、150 mg/kg 群の非交配雌 1 例(動物番号:F06059)に投与 7 日から体温下降、呼吸困難、投与 8 日から排便量の減少が観察されたが、投与 11 日までに回復した。その他、150 mg/kg 群では、呼吸不整(ラッセル音)が交配雌 1 例(動物番号:F04048)に、軟便が交配雌 1 例(動物番号:F04042)および非交配雌 1 例(動物番号:F06061)に観察されたが、いずれも一過性であった。回復期間中には、一般状態の異常は観察されなかった。

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

詳細な症状観察では、一般状態の観察で異常がみられた 150 mg/kg 群の雄 1 例(動物番号:M04040)にうずくまりと自発運動の低下が、150 mg/kg 群の非交配雌 1 例(動物番号:F06059)に体温低下、呼吸困難がそれぞれ投与 42 日と投与 8 日に観察された。それ以外に、雌雄とも投与期間ならびに回復期間を通して、被験物質投与の影響を示唆する変化は認められなかった。

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

投与期間中の雄では、150 mg/kg 群に体重増加抑制がみられ、投与 4、21、28、35 および 42 日の体重が対照群と比較して有意に低下した。50 mg/kg 以下の群では、被験物質投与の影響を示唆する体重の変化は認められなかった。

回復期間中の雄では、150 mg/kg 群と対照群との間で有意差は認められなかった。

非交配雌を含む雌では、投与期間および回復期間を通して、被験物質投与の影響を示唆する体重の変化は認められなかった。

妊娠期間中および哺育期間中の体重推移には、被験物質の影響を示唆する変化は認められなかった。

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

投与期間中の雄では、150 mg/kg 群の投与 1 日(1～2 日)、14 日(14～15 日)および 41 日(41～42 日)の摂餌量が対照群と比較して有意に低下した。50 mg/kg 以下の群の摂餌量には、対照群と比較して有意差は認められなかった。

回復期間中の雄では、被験物質投与の影響を示唆する摂餌量の変化は認められなかった。

投与期間中の交配雌では、150 mg/kg 群の投与 1 日(1～2 日)の摂餌量が対照群と比較して有意に低下したが、非交配雌の摂餌量には、投与期間および回復期間を通して 150 mg/kg 群と対照群との間で有意差は認められなかった。

妊娠期間中および哺育期間中の摂餌量には、被験物質投与の影響を示唆する変化は認められなかった。

5)機能検査

①刺激に対する感覚運動反応（Table 15, Appendix 15）

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

②握力測定（Table 16～Table 18, Appendix 16～Appendix 18）

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

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

投与最終週に自発運動量測定装置を用いて計測した 20 分間の区画移動数および立ち上がり回数には、非交配雌を含む雌雄とも被験物質投与の影響を示唆する変化は観察されなかった。

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

投与期間中および回復期間中に実施した尿検査では、色調、濁度、pH、潜血、蛋白、糖、ケトン体、ウ

ロビリノーゲン、ビリルビン、沈渣、尿量、比重、ナトリウムイオン濃度、カリウムイオン濃度、塩素イオン濃度に、被験物質投与の影響は認められなかった。

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

①雄動物

投与期間終了時の雄では、150 mg/kg 群の網状赤血球比率(平均 2.34%)が有意に低下し、背景データの範囲(下表参照)を下回った。その他の項目に被験物質の影響を示唆する変化は認められなかった。

雄(投与終了時)	試験数*	サンプル数	平均	平均±2SD
網状赤血球比率	4	20	3.44	3.03-3.86

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

回復期間終了時の雄では、150 mg/kg 群の MCV (平均 51.9 fL)が対照群と比較して有意に増加し、MCHC(平均 34.8 g/dL)が有意に低下したが、いずれも背景データの範囲(下表参照)内であったことから、偶発的な変化と判断した。その他の項目に被験物質の影響を示唆する変化は認められなかった。

雄(回復終了時)	試験数*	サンプル数	平均	平均±2SD
MCV	4	20	50.9	47.9-53.8
MCHC	4	20	34.7	32.9-36.5

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

②雌動物

投与期間終了時の分娩雌では、150 mg/kg 群の網状赤血球比率(平均 6.18%)が対照群と比較して有意に低下したが、背景データの範囲(下表参照)内であった。

分娩雌(投与終了時)	試験数*	サンプル数	平均	平均±2SD
網状赤血球比率	4	20	8.65	4.83-12.47

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

投与期間終了時の非交配雌では、いずれの検査項目においても被験物質投与の影響を示唆する変化は認められなかった。

回復期間終了時の非交配雌では、いずれの検査項目についても被験物質の影響を示唆する変化は認められなかった。

8)血液生化学検査 (Table 26～Table 27, Appendix 26～Appendix 27)

①雄動物

投与期間終了時の雄では、150 mg/kg 群の総蛋白濃度(平均 5.0 g/dL)とアルブミン濃度(平均 3.3 g/dL)が対照群と比較して有意に低下した。

雄(投与終了時)	試験数*	サンプル数	平均	平均±2SD
総蛋白濃度	4	20	5.7	5.4-5.9
アルブミン濃度	4	20	3.6	3.6-3.6

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

回復期間終了時の雄では、150 mg/kg 群の胆汁酸濃度、尿素窒素濃度および ALP が対照群と比較して有意に増加した。

②雌動物

投与期間終了時の分娩雌では、50 mg/kg 群の尿素窒素濃度が対照群と比較して有意に低下したが、用量に依存した変化ではなかった。

投与期間終了時の非交配雌では、150 mg/kg 群の尿素窒素濃度(平均 21 mg/dL)と ALP(平均 137 U/L)が対照群と比較して有意に増加した。このうち、ALP は背景データの範囲(下表参照)内であったが、尿素窒素濃度は背景値をわずかに上回った。その他の検査項目に被験物質の影響を示唆する変化は認められなかった。

非交配雌(投与終了時)	試験数*	サンプル数	平均	平均±2SD
尿素窒素濃度	4	20	18	16-20
ALP	4	20	156	84-229

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

回復期間終了時の非交配雌では、150 mg/kg 群の総コレステロール濃度(平均 68 mg/dL)が対照群と比較して有意に増加したが、背景データの範囲(下表参照)内であった。その他の検査項目に被験物質投与の影響を示唆する変化は認められなかった。

非交配雌(回復終了時)	試験数*	サンプル数	平均	平均±2SD
総コレステロール濃度	4	20	63	53-73

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

9)器官重量 (Table 28～Table 29, Appendix 28～Appendix 29)

①雄動物

投与期間終了時の雄では、150 mg/kg 群において脳、心臓および肝臓の絶対重量が対照群と比較して有意に低下し、左側精巣上体の相対重量が有意に増加したが、いずれも解剖時体重の低下に伴う変化と推定された。その他、150 mg/kg 群の副腎の相対重量が対照群と比較して有意に増加した。

回復期間終了時の雄では、150 mg/kg 群の右副腎の絶対重量が対照群と比較して有意に低下したが、その他の測定器官に 150 mg/kg 群と対照群との間で有意差は認められなかった。

②雌動物

投与期間終了時の分娩雌では、50 mg/kg 群の右副腎の絶対重量が対照群と比較して有意に低下したが、用量に依存した変化ではなく、被験物質投与の影響を示唆する変化は認めれらなかった。

投与期間終了時の非交配雌では、被験物質投与の影響を示唆する変化は、いずれの器官重量にも認めれらなかった。

回復期間終了時の雌では脳、甲状腺および副腎の相対重量が対照群と比較して有意に低下したが、解剖時体重の差に伴う変化と推察された。

10)剖検所見 (Table 30～Table 31, Appendix 30～Appendix 31)

①雄の投与終了時剖検例

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

胸腺では、暗赤色化および小型化が 150 mg/kg の 1 例にみられた。

肝臓では、白色斑が 150 mg/kg 群の 1 例にみられた他、横隔膜との癒着および癒着部の結節が 50 mg/kg 群の 1 例に観察された。

胃では、前胃粘膜の水腫様変化が 150 mg/kg 群の 4 例にみられ、そのうちの 1 例(動物番号:M04040)には腺胃粘膜に暗色点散在とガスの貯留が観察された。

空腸では、粘膜の暗赤色域が 150 mg/kg 群の 1 例(動物番号:M04040)に観察され、同例の小腸にはガスの貯留が認められた。

回腸では、憩室が 15 mg/kg 群の 1 例にみられた。

精巣上体では、両側性の小型化が 150 mg/kg 群の 1 例(動物番号:M04039)に認められ、前立腺と精嚢の小型化も観察された。その他に、前立腺の小型化と精嚢の小型化が 150 mg/kg 群の各 1 例で観察された。

②雄の回復観察例

回復 15 日に剖検した雄動物、対照群 5 例および 150 mg/kg 群 5 例では、対照群の 1 例に精巣上体尾部の黄白色結節がみられたのみで、被験物質投与の影響を示唆する異常は観察されなかった。

③雌の死亡例

途中死亡した 150 mg/kg 群の非交配雌 2 例(動物番号:F06060、F06062)の剖検所見は以下の通り

である。

肺では、暗色斑散在および退縮不全が 1 例(動物番号:F06062)、暗赤色域が 1 例(動物番号:F06060)に認められた。

肝臓では、暗色化が 1 例(動物番号:F06062)、暗赤色化および白色域が 1 例(動物番号:F06060)に認められた。

胃および小腸ではガスの貯留が 2 例に観察された。

卵巣では、両側性の暗赤色化が 1 例(動物番号:F06060)に観察された。

④分娩雌の投与終了時剖検例

哺育 4 日の翌日に剖検した分娩雌、対照群 12 例、15 mg/kg 群 12 例、50 mg/kg 群 11 例および 150 mg/kg 群 12 例の剖検所見は以下の通りである。

胃では、腺胃粘膜に暗色点が 15 および 50 mg/kg 群の各 1 例、腺胃粘膜に暗赤色域が 150 mg/kg 群の 1 例に観察されたが、対照群の 1 例にも腺胃粘膜に陥凹部がみられた。

子宮では、頸部の結節が 50 mg/kg 群の 1 例にみられた。

⑤不妊例

妊娠 26 日相当日に剖検した 50 mg/kg 群の不妊例 1 例に、異常は認められなかった。

⑥サテライト群の投与終了時剖検例

投与 42 日の翌日に剖検した非交配雌、対照群 5 例および 150 mg/kg 群 4 例では、前胃粘膜の水腫様変化が 150 mg/kg 群の 1 例に認められたが、その他の動物に異常は認められなかった。

⑦サテライト群の回復観察例

回復 15 日に剖検した非交配雌、対照群 5 例および 150 mg/kg 群 4 例に異常は認められなかった。

11)病理組織学検査 (Table 32～Table 33, Appendix 32～Appendix 33)

①雄の投与終了時剖検例

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

胸腺では、萎縮が 150 mg/kg 群の 3 例に認められたが、対照群にも観察された変化であった。

気管では、粘膜下層に好中球浸潤が 150 mg/kg 群の 1 例に認められたが、ごく軽度な変化であった。

肺では、肺胞内泡沫細胞の集簇が 150 mg/kg 群の 2 例にみられ、うち 1 例には限局性の出血および肺胞内好中球浸潤がみられたが、いずれも対照群にみられた所見であり、ごく軽度な変化であった。

肝臓では、門脈周囲性の肝細胞の脂肪化が 150 mg/kg 群の 1 例にみられ、その頻度は対照群と比較して有意に減少した。また、肝臓の小肉芽腫が 150 mg/kg 群の 4 例に観察されたが、対照群と比較して頻度および程度に有意差はなかった。その他、限局性の壊死が 150 mg/kg 群の 1 例に認められたが軽度な変化であった。剖検時に肝臓に異常が認められた 50 mg/kg 群の 1 例では、周囲に線維化を

伴った限局性の壊死と小肉芽腫が確認されたが、いずれもごく軽度または軽度な変化であった。

前胃では、150 mg/kg 群において粘膜下織に軽度の炎症性細胞浸潤および粘膜固有層/粘膜下織に中等度の水腫が 3 例、軽度のびらんが 2 例、ごく軽度の扁平上皮過形成が 4 例に観察され、扁平上皮過形成の頻度は対照群と比較して有意に増加した。50 mg/kg 以下の群では、前胃の異常は観察されなかった。

腺胃では、150 mg/kg 群において粘膜下織の水腫とびらんが各 1 例に認められたが、いずれもごく軽度な変化であり、50 mg/kg 以下の群では、腺胃の異常は観察されなかった。

空腸では、剖検時に粘膜の暗赤色域が観察された 150 mg/kg 群の 1 例(動物番号:M04040)でごく軽度なびらんが観察された。

回腸では、剖検時に異常がみられた 15 mg/kg 群の 1 例で憩室が確認された。

脾臓では、対照群と 150 mg/kg 群の全例に髄外造血および褐色色素の沈着が観察されたが、150 mg/kg 群と対照群との間で程度の差はなかった。その他、白脾髄の萎縮が 150 mg/kg 群の 1 例に観察されたが、ごく軽度な変化であった。

腎臓では、150 mg/kg 群において皮質の好塩基性尿細管が 3 例、硝子円柱が 1 例、間質のリンパ球浸潤が 3 例、遠位尿細管の管腔拡張が 1 例、皮質の鉱質沈着が 2 例に認められたが、対照群と比較して頻度および程度の差はなかった。

副腎では、束状帯細胞の肥大が 150 mg/kg 群の 1 例にみられたが、ごく軽度な変化であった。

精巣では、両側性の精細管萎縮が 150 mg/kg 群の 1 例にみられ、精巣上体の萎縮を伴っていたが、いずれもごく軽度な変化であった。

前立腺では、150 mg/kg 群において萎縮が 2 例、間質のリンパ球浸潤が 1 例に観察されたが、対照群と比較して頻度および程度の差はなかった。

精嚢では、前立腺の萎縮がみられた 150 mg/kg 群の 2 例に軽度な萎縮が認められた。

凝固腺では、150 mg/kg 群の 1 例にごく軽度な萎縮がみられた。

②雄の回復観察例

回復 15 日に剖検した対照群および 150 mg/kg 群の 5 例については、投与終了時の剖検例で被験物質の影響が示唆された胃について病理組織学検査を実施した。その結果、異常は認められなかった。

③雌の死亡例

死亡した 150 mg/kg 群の非交配雌 2 例(動物番号:F06060、F06062)について病理組織学検査を実施した。病理組織所見は、以下の通りである。

下顎リンパ節では、中等度の可染体マクロファージが 2 例に観察された。

甲状腺では、鰓後体遺残が 1 例(動物番号:F06060)に観察された。

胸腺では、ごく軽度の萎縮と軽度または中等度の可染体マクロファージが 2 例に観察された。

気管では、管腔内に中等度の膿瘍が 2 例に観察された。

肺では、肺胞内にごく軽度または軽度の好中球浸潤が 2 例に、中等度の水腫が 1 例(動物番号:F06060)に観察された。

気管支では、ごく軽度の好中球浸潤が 1 例(動物番号:F06060)に観察された。

肝臓では、被膜下に中等度の限局性壊死が 1 例(動物番号:F06060)に観察された。

前胃では、粘膜下織に炎症性細胞浸潤、粘膜固有層/粘膜下織の水腫および扁平上皮の過形成が 1 例(動物番号:F06062)に観察されたが、いずれもごく軽度な変化であった。

脾臓では、軽度または中等度の白脾髄の萎縮が 2 例に観察された。その他、髄外造血が 2 例、褐色色素の沈着が 1 例(動物番号:F06062)に観察された。

腎臓では、遠位尿細管の管腔拡張が 2 例に観察されたが、ごく軽度な変化であった。

副腎では、束状帯細胞の肥大が 1 例(動物番号:F06062)にみられたが、ごく軽度な変化であった。

④分娩雌の投与終了時剖検例

哺育 4 日の翌日に剖検した分娩雌のうち、採血を行った対照群および 150 mg/kg 群の各 5 例について病理組織学検査を実施し、さらに被験物質の影響が示唆された胃については、15 および 50 mg/kg 群の 5 例についても病理組織学検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は以下の通りである。

甲状腺では、異所性の胸腺組織および鰓後体遺残が 150 mg/kg 群の 1 例に観察されたが、被験物質投与の影響を示唆する変化は認められなかった。

胸腺では、ごく軽度な萎縮が 150 mg/kg 群の 5 例(全例)に認められたが、対照群の全例にもみられた所見であった。

肺では、肺胞内に泡沫細胞の集簇が 150 mg/kg 群の 1 例に認められたが、対照群の 1 例にもみられたごく軽度な変化であった。

肝臓では、150 mg/kg 群において、門脈周囲性に肝細胞の脂肪化が 4 例、小肉芽腫が 3 例、限局性の壊死が 1 例にみられたが、いずれもごく軽度な変化であり、対照群と比較して頻度の差もなかった。

前胃では、剖検時に胃の異常がみられた 150 mg/kg 群の 1 例(動物番号:F04048)に粘膜下織の炎症性細胞浸潤、粘膜固有層/粘膜下織の水腫および扁平上皮の過形成が観察された。その他、15 mg/kg 群の 1 例(動物番号:F02024)にびらんが観察されたが、ごく軽度な変化であった。

腺胃では、剖検時に胃の異常がみられた 150 mg/kg 群の 1 例(動物番号:F04048)にごく軽度なびらんが観察された。

脾臓では、対照群と 150 mg/kg 群の全例に褐色色素沈着と髄外造血が観察されたが、その程度に両群間の差はなかった。

腎臓では、皮質の好塩基性尿細管および間質のリンパ球浸潤が 150 mg/kg 群の 1 例に認められたが、ごく軽度な変化であり、間質のリンパ球浸潤は対照群の 1 例にもみられた。

卵巣では、閉鎖卵胞の増加が 150 mg/kg 群の 1 例に認められたが、ごく軽度な変化であった。

子宮では、剖検時に頸部の結節が認められた 50 mg/kg 群の 1 例(動物番号:F03036)に嚢胞が確認されたのみで、150 mg/kg 群に異常は観察されなかった。

⑤サテライト群の投与終了時剖検例

投与終了時に剖検した非交配雌、対照群 5 例および 150 mg/kg 群 4 例の病理組織所見は以下の通

りである。

胸腺では、ごく軽度または軽度の萎縮が 150 mg/kg 群の 4 例(全例)に観察されたが、その頻度および程度に対照群との差はなかった。

肝臓では、150 mg/kg 群において、門脈周囲性に肝細胞の脂肪化が 3 例、小肉芽腫が 4 例観察されたが、いずれもごく軽度な変化であり、対照群と比較して程度および頻度の差はなかった。

前胃では、粘膜下織のごく軽度な炎症性細胞浸潤、粘膜固有層/粘膜下織の軽度または中等度な水腫および扁平上皮のごく軽度な過形成が 150 mg/kg 群の 2 例に観察された。

脾臓では、髄外造血と褐色色素の沈着が対照群と 150 mg/kg 群の全例にみられたが、両群間で程度の差はなかった。

腎臓では、皮質の好塩基性尿細管と間質のリンパ球浸潤が 150 mg/kg 群の 3 例に認められたが、いずれもごく軽度な変化であり、対照群と比較して頻度の差はなかった。その他、髄質の鉱質沈着が 150 mg/kg 群の 1 例に認められたが、ごく軽度な変化であった。

卵巣では、卵胞のう胞/黄体のう胞が 150 mg/kg 群の 1 例に認められた。

⑥サテライト群の回復観察例

回復 15 日に剖検した非交配雌、対照群の 5 例および 150 mg/kg 群の 4 例については、投与終了時の剖検例で被験物質の影響が示唆された胃について病理組織学検査を実施した。その結果、異常は認められなかった。

2. 生殖能力

1)性周期および交配成績 (Table 34～Table 35, Appendix 34～Appendix 35)

投与開始後に性周期の異常を示した動物は、いずれの投与群においても観察されなかった。投与期間中の平均発情回帰日数、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数に被験物質投与の影響を示唆する変化は認めらなかった。各群の交尾率はいずれも 100%であり、妊娠率は 50 mg/kg 群で不妊が 1 例認められたことから 91.7%であったが、それ以外は 100%であった。

2)出産率および妊娠期間 (Table 36, Appendix 36)

妊娠期間および出産率に被験物質投与の影響は認められなかった。

3)分娩および哺育状態 (Table 36, Appendix 36)

分娩状態と哺育状態は、いずれの動物も良好であった。

4)黄体数、着床数および着床率 (Table 36, Appendix 36)

黄体数、着床数および着床率に被験物質投与の影響は認められなかった。

3. 出生児

1)生存 (Table 36, Appendix 36)

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

2)体重 (Table 37, Appendix 37)

哺育 0 日では、15 mg/kg 群の出生児体重が低値を示し、雌児の体重が対照群と比較して有意に低下したが、用量に依存した変化ではなかった。

哺育 4 日では、雌雄とも 150 mg/kg 群の体重が対照群と比較して有意に低下した。その他、15 mg/kg 群の雌児の体重が対照群と比較して有意に低下したが、50 mg/kg 群の出生児体重には、対照群と比較して有意差はなかった。

3)出生児観察(Table 38～Table 39, Appendix 38)

出生児の一般状態に被験物質投与の影響を示唆する変化はみられなかった。また、死亡児および哺育 4 日の生存児の剖検では、異常は認められなかった。

考察

雌雄ラットの交配前(2 週間)および交配期間中、ならびに雄では交配期間終了後を通して計 42 日間、雌では妊娠期間を通して周産期(哺育 4 日まで)に N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミドを経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

1. 反復投与毒性

150 mg/kg 群の雄、交配雌および非交配雌に一過性の軟便が散見された他、排便量の減少、自発運動の低下、体温下降などが少数例で認められた。これらの症状は投与量設定のための予備試験(試験番号 R-12-003)においても観察されていることから、被験物質投与の影響と考えられる。

150 mg/kg 群では、非交配雌 2 例が途中死亡した。死亡例の病理組織学検査では、下顎リンパ節や胸腺に可染体マクロファージが、気管腔内に中等度の膿瘍が観察され、さらに 1 例の肺に水腫が認められたことから、投与過誤の可能性が考えられた。しかしながら、生存例においても、一過性の軟便や排便量の減少以外に、呼吸困難を示した動物も認められていることから、被験物質の影響により死亡した可能性は否定できなかった。

150 mg/kg 群の雄では、投与開始から体重増加抑制が認められ、150 mg/kg 群の雄および交配雌では、摂餌量の低下がみられた。しかし、150 mg/kg 群の交配雌および非交配雌では、体重推移に被験物

質投与の影響は認められなかったことから、被験物質に起因した体重増加抑制は、雌動物よりも雄動物に発現しやすいと推察された。

150 mg/kg 群の雄では、血液学検査において網状赤血球比率が背景データの範囲を下回ったことから、投与の影響は否定できないと考える。なお、同群の分娩雌にも網状赤血球比率の低下がみられたが、背景データの範囲内であることから被験物質の投与に起因した影響ではないと判断した。

150 mg/kg 群の雄では、血液生化学検査において総蛋白濃度とアルブミン濃度が低下し、肝臓の病理組織学検査では、門脈周囲性の肝細胞の脂肪化が減少した。これらのことから、150 mg/kg 群の雄では、体重増加抑制に反映される低栄養状態にあったことが推察された。

150 mg/kg 群の非交配雌では、血液生化学検査で尿素窒素濃度の増加がみられたが、尿検査および腎臓の病理組織学検査において被験物質の影響を示唆する変化は認められていないことから、被験物質の影響ではないと判断した。

胃の病理組織学検査において、前胃では粘膜下織の炎症性細胞浸潤、粘膜固有層および粘膜下織の水腫、びらんまたは扁平上皮の過形成が 150 mg/kg 群の雄、分娩雌および非交配雌に観察され、腺胃では、粘膜下織の水腫またはびらんが 150 mg/kg 群の雄および分娩雌に観察された。これらのことから、被験物質の 150 mg/kg は、胃に炎症性の変化を誘発すると考えられた。

2. 毒性の回復性

回復期間中には、軟便を含む一般状態の異常は観察されず、150 mg/kg 群の雄にみられた体重増加抑制と摂餌量の低下も認められなかったことから、これらの変化は回復性が早いと考えられる。また、回復期間終了時の病理組織学検査では、投与終了時にみられた胃の炎症性変化が認められなかったことから、胃の変化も投与終了後にすみやかに回復するものと推察された。

回復期間終了時の雄では、150 mg/kg 群の胆汁酸濃度(平均 21.7 μmol/L)、尿素窒素濃度(平均 18 mg/dL)および ALP(平均 334 U/L)が対照群と比較して有意に増加した。このうち、胆汁酸の値は、各個体ともすべて背景データの範囲にあった。尿素窒素は 4 例中 5 例が背景データからはずれていたが、その差はいずれもごくわずかであった。また、ALP は 5 例中 2 例が背景データからはずれており、その値に平均値が引きずられた結果と考えられる。以上のことから、回復終了時に雄の血液生化学的検査でみられたこれらの変化は、いずれも被験物質投与の影響ではないと判断した。

雄(回復終了時)	試験数*	サンプル数	平均	平均±2SD
胆汁酸濃度	4	20	18.6	5.4-31.8
尿素窒素濃度	4	20	15	14-16
ALP	4	20	270	172-368

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

3. 生殖発生毒性

投与開始後の性周期、交尾率、妊娠率に被験物質投与の影響は認められなかった。また、妊娠期間、出産率、分娩状態、哺育状態、黄体数、着床数および着床率にも被験物質投与の影響がみられなかったことから、150 mg/kg までの被験物質は、親動物の生殖能力に影響を及ぼさないと考えられる。

出生児の生存性および形態に被験物質投与の影響は認められなかったが、150 mg/kg 群の哺育 4 日の出生児体重が低値を示したことから、被験物質投与により次世代の発育に影響を及ぼす可能性が示唆された。

4. 無毒性量

150 mg/kg 群の雄では、軟便や排便量の減少などの一般状態の変化と体重低下、胃に炎症性変化が、同群の雌では、軟便や排便量の減少などの一般状態の変化と胃の炎症性変化が認められたことから、雌雄動物の反復投与毒性に対する無毒性量(NOAEL)は 50 mg/kg/day と判断された。

150 mg/kg までの用量に親動物への生殖毒性を示唆する変化は認められなかったが、哺育 4 日の出生児体重が 150 mg/kg 群で低下したことから、生殖発生毒性に対する無毒性量は 50 mg/kg/day と判断された。

Annex A

試験成績書

財団法人　食品薬品安全センター　御中

2012年9月24日
和光純薬工業株式会社

品　名　N-[3-(ジメチルアミノ)プロピル]ステアラミド

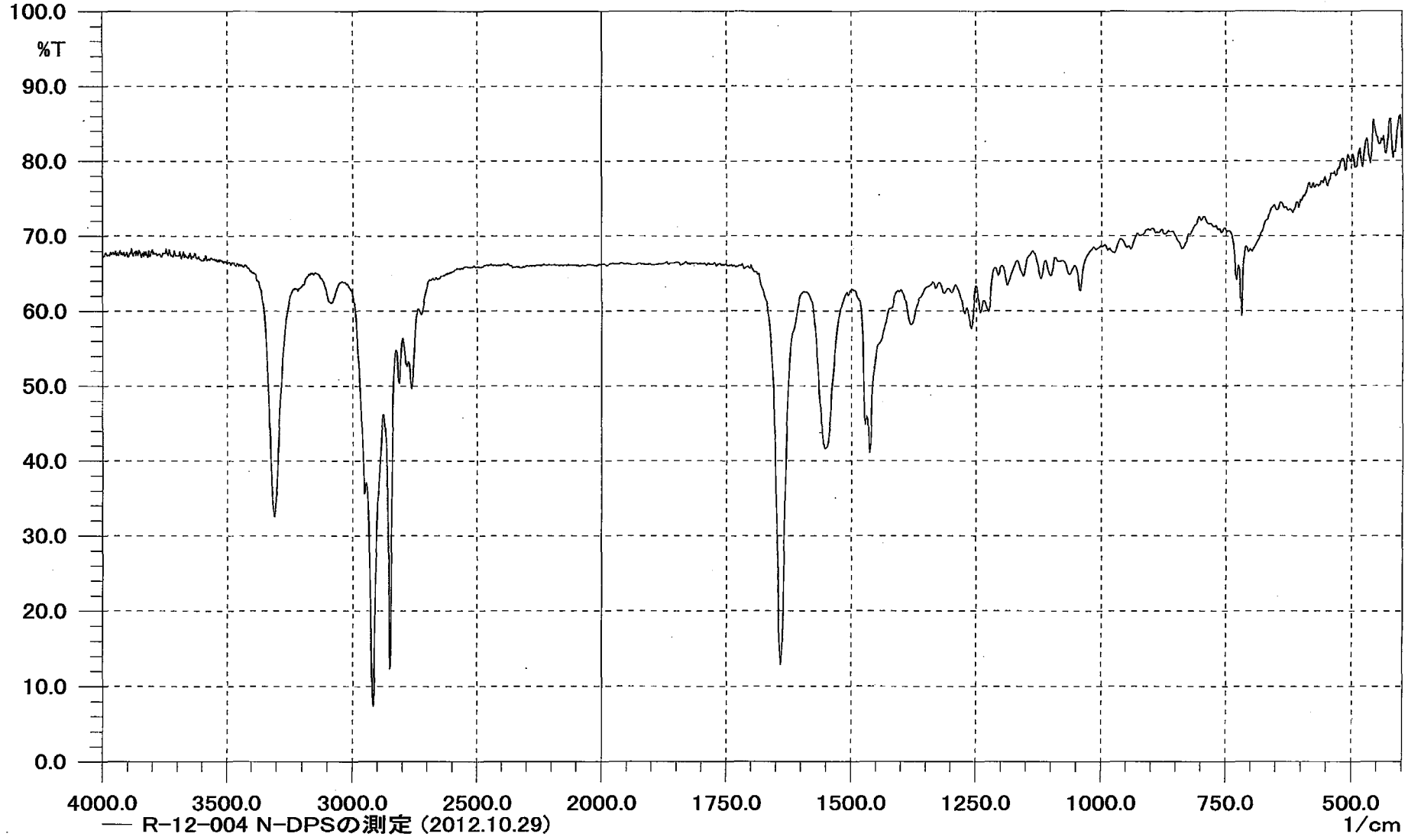
Code No.　287-15921
Lot No.　TLH9065
数　量　1kg

試験項目	測定値	品質目標
外観	白色の結晶性粉末	白色～うすい黄色、結晶性粉末～粉末
ジクロロメタン溶液	澄明	試験適合(ほとんど澄明以内)
水分	0.32%	実測値報告
含量(キャピラリーカラムGC)	98.6%	95.0%以上
定性(IR)	測定	試験適合
定性(^{1}H-NMR)	試験適合	試験適合
定性(LC/MS)	試験適合	試験適合
試験年月日	2012/09/24	

＊上記の通り御報告申し上げます。

試験責任者 [redacted]

Annex B-1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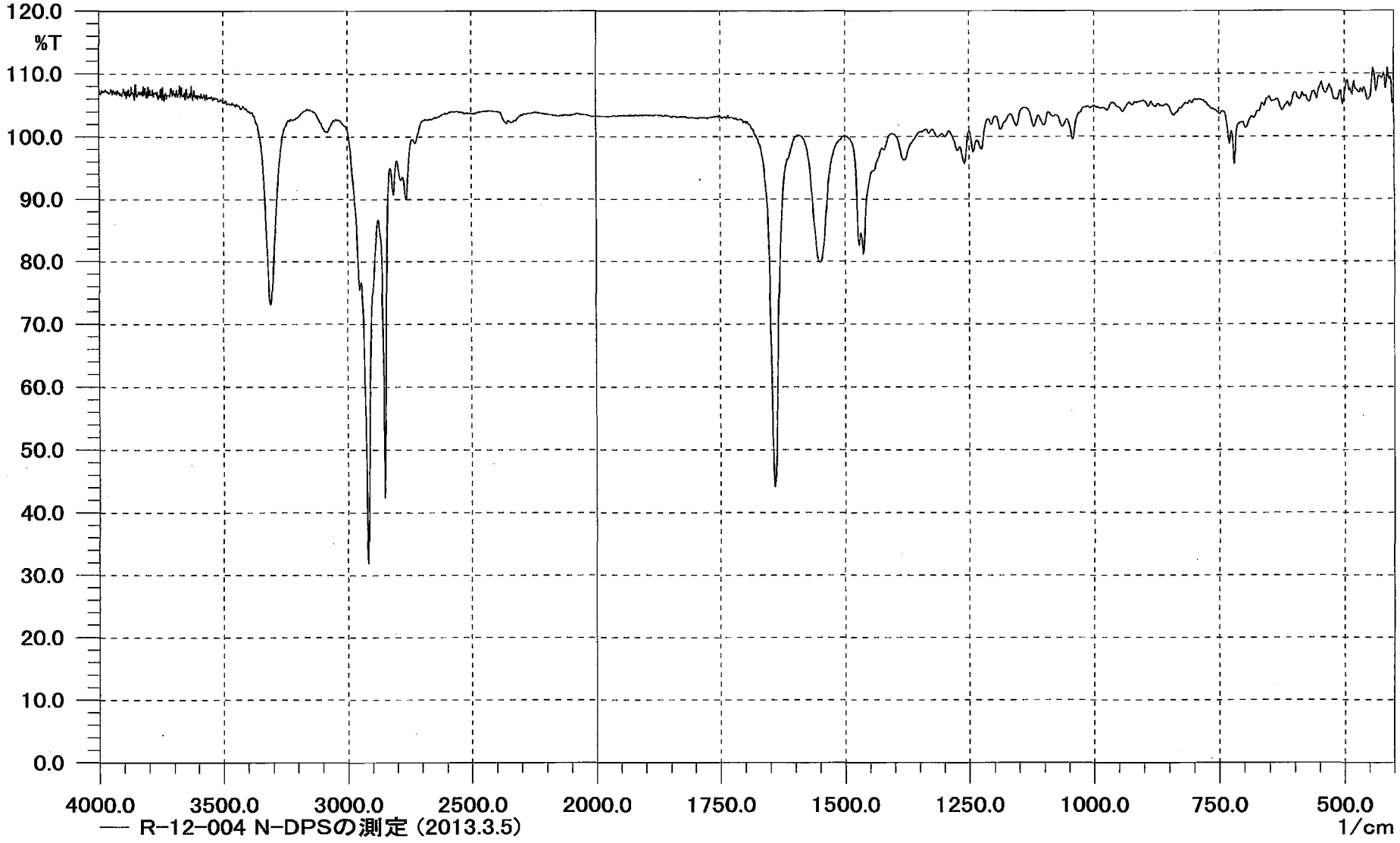
1/cm
— R-12-004 N-DPSの測定 (2012.10.29)

Annex B-2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500.0
1/cm
R-12-004 N-DPSの測定 (2013.3.5)

Annex C

1. 被験物質原体の安定性の測定方法

① 使用機器

フーリエ変換赤外分光光度計(FTIR-8300)	島津製作所
電子天秤(LA230S)	ザルトリウス

② 測定条件

測定方法	臭化カリウム錠剤法
波数範囲	4000～400 cm^{-1}

③ 測定方法

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

2. 投与検体中の被験物質濃度測定法

① 試薬

蒸留水(HPLC 用)	和光純薬工業
メタノール(HPLC 用)	和光純薬工業
アセトン(HPLC 用)	和光純薬工業
過塩素酸ナトリウム一水和物(試薬特級)	和光純薬工業
りん酸(試薬特級)	和光純薬工業
中性りん酸塩 pH 標準液第 2 種(pH 6.86、25°C)	和光純薬工業
フタル酸塩 pH 標準液第 2 種(pH 4.01、25°C)	和光純薬工業

② 試液の調製(代表例)

1) 移動相

過塩素酸ナトリウム一水和物 14 g に蒸留水を加えて 100 mL とする(1 mol/L 過塩素酸ナトリウム溶液)。1 mol/L 過塩素酸ナトリウム溶液及びメタノールを 1:9 (v/v)の割合で混合した後、りん酸を加えて pH 2.5 に調整する。

2) 希釈液

アセトン及びメタノールを 1:1 (v/v)の割合で混合する。

③ 使用機器

電子天秤(R200D)	ザルトリウス
カスタニーLAB pH メーター(F-22)	堀場製作所
高速液体クロマトグラフ(HPLC)システム	島津製作所

主要構成: LC-10AD VP(ポンプ)、SIL-10AD VP(オートインジェクタ)、CTO-10AC VP(カラムオーブン)、SPD-10A VP(検出器)、SCL-10A VP(システムコントローラ)、DGU-20A_3(デガッサ)、C-R7A または C-R7A plus(データ処理装置)

④ 標準溶液の調製

被験物質約 50 mg を精密に量り、希釈液に溶解して正確に 50 mL とする。この液 2 mL を正確にとり、希釈液を加えて正確に 20 mL として、標準原液(約 100 μg/mL)とする。この標準原液 1、2、3 および 4 mL を正確にとり、希釈液を加えてそれぞれ正確に 10 mL とし、標準溶液(約 10、20、30 および 40 μg/mL、各濃度 n=1)を調製する。

⑤ 試料溶液の調製

投与検体の 1 mL を正確にとり、希釈液で適宜希釈し、試料溶液(約 20 μg/mL)を調製する。試料溶液は、投与検体の採取から n=3 で調製する。

⑥ 検量線の作成および被験物質調製液中被験物質濃度の算出

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

Annex C (continued)

⑦ HPLC 測定条件

検出器	紫外分光光度計(測定波長 210 nm)
分析カラム	CAPCELL PAK C18 MG II (内径 4.6 mm、長さ 100 mm、粒子径 3 μm、資生堂)
移動相	1 mol/L 過塩素酸ナトリウム溶液/メタノール混液(1:9 v/v)、pH 2.5
流量	0.7 mL/min
カラム設定温度	50℃
試料設定温度	室温
試料注入量	20 μL
オートインジェクタ洗浄液	メタノール
システムの適合性	SOP/CHE/001 に従い、測定開始前および測定終了後に、標準溶液(約 20 μg/mL)を 1 回ずつ測定し、ピーク保持時間の変動が±3.0%以内、ピーク面積の変動が±5.0%以内であることを確認する。

⑧ 数値の取り扱い

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

Annex D

SOP/CHE/001
採用開始 2010年4月23日

試験番号	R - 12 - 004

安定性試験結果

被験(対照)物質：N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミド
ロット番号：TLH9065
媒体：日局注射用水

調製年月日　：2012年10月31日
測定年月日 A：2012年10月31日(調製後 0 日)
B：2012年11月8日(調製後 8 日)
保管条件：冷蔵、遮光

調製濃度	A				B				
(mg/mL)	試料番号	測定濃度 (mg/mL)	含量 a) (%)	ばらつき b) (%)	試料番号	測定濃度 (mg/mL)	含量 a) (%)	ばらつき b) (%)	残存率 c) (%)
0.100	1	0.09065	90.7	102.6	10	0.08117	81.2	101.9	91.9
	2	0.08694	86.9	98.4	11	0.08113	81.1	101.9	91.8
	3	0.08746	87.5	99.0	12	0.07660	76.6	96.2	86.7
	平均	0.08835	88.4		平均	0.07963	79.6		90.1
1.00	7	0.9116	91.2	96.8	16	0.8985	89.9	99.8	95.4
	8	0.9579	95.8	101.7	17	0.9086	90.9	100.7	96.4
	9	0.9571	95.7	101.6	18	0.9007	90.1	99.8	95.6
	平均	0.9422	94.2		平均	0.9026	90.3		95.8
60.0	4	59.93	99.9	101.3	13	61.54	102.6	103.5	104.1
	5	58.51	97.5	98.9	14	58.39	97.3	98.2	98.7
	6	58.99	98.3	99.7	15	58.45	97.4	98.3	98.8
	平均	59.14	98.6		平均	59.46	99.1		100.5

a)：各測定時の測定濃度／調製濃度×100　　b)：各測定時の測定濃度／各測定時の平均測定濃度×100
c)：各測定時の測定濃度／初回の平均測定濃度×100

安定性の判定基準(懸濁液検体)
各試料採取時点の平均含量がそれぞれ調製濃度の85.0～115.0%、また、各測定値のばらつきがそれぞれ平均値の90.0～110.0%以内であり、かつ、初回の測定平均値に対する各保管期間後の測定値の比(残存率)の平均値が90.0%以上を示す期間とする

Annex E

- 36
SOP/CHE/001
採用開始 2010年4月23日

試験番号	R - 12 - 004

含 量 ・ 均 一 性 試 験 結 果

被験(対照)物質： N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミド　　調製年月日：2012年11月12日

ロット番号： TLH9065　　測定年月日：2012年11月12日

媒体： 日局注射用水

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
19	3.00	2.827	2.808	94.2	93.6	100.7
20		2.822		94.1		100.5
21		2.775		92.5		98.8
22	10.0	10.00	9.897	100.0	99.0	101.0
23		9.838		98.4		99.4
24		9.854		98.5		99.6
25	30.0	29.84	29.56	99.5	98.5	100.9
26		29.55		98.5		100.0
27		29.29		97.6		99.1

含量の判定基準(懸濁液検体)

平均含量が調製濃度の85.0～115.0%、各測定値のばらつきが平均値の90.0～110.0%以内とする。

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 1-1. General conditions of male rats

Group	Number of males and general conditions	Days of administration																									
		1		2		3		4		5		6		7		8		9		10		11		12		13	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 15 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 50 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 150 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	11	12	11	12	12	12	12	12	10	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Loose stool	0	0	0	0	1	0	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0

Group	Number of males and general conditions	Days of administration																							
		14		15		16		17		18		19		20		21		22		23		24		25	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 15 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 50 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 150 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	12	12	12
	Excretion, Loose stool	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0

Pre: Before administration, Post: after administration.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 1-1(continued). General conditions of male rats

Group	Number of males and general conditions	Days of administration																																			
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Breathing, Dyspnea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 15 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Breathing, Dyspnea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 50 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Pale skin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Breathing, Dyspnea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 150 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	General appearance, No abnormality	9	12	10	12	10	12	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	6	
	Excretion, Decrease in amount of feces	2	0	2	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	2	0	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
	Skin, Pale skin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
	Breathing, Dyspnea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 1-2. General conditions of male rats at the recovery period

Group	Number of males and general conditions	Days of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: water for injection)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
N-DPS 150 mg/kg	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 2-1. General conditions of female rats

Group	Number of females and general conditions	Days of administration																																																			
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	7	2	2	2	2	0	0	0	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	7	2	2	2	2	0	0	0	0	0	0	0	0	0	0
	Breathing, Irregular respiration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Breathing, Rale	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 15 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	8	8	3	3	0	0	0	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	8	8	3	3	0	0	0	0	0	0	0	0	0	0
	Breathing, Irregular respiration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Breathing, Rale	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 50 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	8	8	4	4	1	1	0	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	8	8	4	4	1	1	0	0	0	0	0	0	0	0
	Breathing, Irregular respiration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Breathing, Rale	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 150 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	4	4	3	3	1	1	1	1	1	1	1	1	1	1
	General appearance, No abnormality	12	12	12	12	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	12	12	8	8	4	4	3	3	1	1	1	1	1	1	1	1	1	1
	Breathing, Irregular respiration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Breathing, Rale	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Number of females and general conditions	Days of administration																																																	
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Breathing, Dyspnea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N-DPS 150 mg/kg	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8
	General appearance, No abnormality	10	10	10	10	9	10	10	10	10	10	10	10	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	8	8	8	8	8	8	8	8	8	8	7	8	8	8
	Breathing, Dyspnea	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 2-2(continued). General conditions of female rats, satellite group

Group	Number of females and general conditions	Days of administration																																									
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
Control (vehicle: water for injection)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
N-DPS 150 mg/kg	Number of females	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	4
	General appearance, No abnormality	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	4

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 2-3. General conditions of female rats at the recovery period

Group	Number of females and general conditions	Days of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: water for injection)	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
N-DPS 150 mg/kg	Number of females	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	General appearance, No abnormality	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 3. General conditions in dams during pregnancy

Group	Number of dams and general conditions	Days of pregnancy																											
		0		1		2		3		4		5		6		7		8		9		10		11		12		13	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
N-DPS 15 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
N-DPS 50 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
N-DPS 150 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 3(continued). General conditions in dams during pregnancy

Group	Number of dams and general conditions	Days of pregnancy																								
		14		15		16		17		18		19		20		21		22		23		24		25		26
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5	0	0	0	0	0	0	0
N-DPS 15 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	0	0	0	0	0	0	0
N-DPS 50 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4	0	0	0	0	0	0	0
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4	0	0	0	0	0	0	0
N-DPS 150 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 4. General conditions in dams during lactation

Group	Number of dams and general conditions	Days of lactation										
		0		1		2		3		4		5
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of dams	7	7	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	7	7	12	12	12	12	12	12	12	12	12
N-DPS 15 mg/kg	Number of dams	8	8	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	8	8	12	12	12	12	12	12	12	12	12
N-DPS 50 mg/kg	Number of dams	7	7	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	7	7	11	11	11	11	11	11	11	11	11
N-DPS 150 mg/kg	Number of dams	7	7	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	7	7	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 5. Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of administration						Days of recovery [a]	
				8	15	24	30	36	42	7	14
[Posture in home-cage]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Crouching position	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	1	0	0
[Locomotor in home-cage]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Decrease in locomotor activity	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	1	0	0
[Hndling behavior]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
No resistance	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Heart beats]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
bradycardia	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Body temperature]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
hypothemia	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Fur]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Moist fur	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Skin color/Mucuous membranse]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Abnormal	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Lacrimation]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
observed	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Piloerection]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Slight	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Respiratory rate]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
Hypopnea	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0
[Stereotypy]	Control (vehicle: water for injection)	12	0 [b]	0	0	0	0	0	0	0	0
observed	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0

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

[b] Values represent number of animals with the findings.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 5(continued). Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery [a]	
				8	15	24	30	36	42	7	14
[Urination]	Control (vehicle: water for injection)	12	3 [b]	5	1	1	1	0	3	4	0
(frequency/30sec)	N-DPS (15 mg/kg)	12	0	4	4	1	3	0	3		
	N-DPS (50 mg/kg)	12	0	3	1	0	0	2	1		
	N-DPS (150 mg/kg)	12	0	2	0	0	0	2	1	3	0
[Defecation]	Control (vehicle: water for injection)	12	1 [b]	0	1	0	0	0	1	0	0
(frequency/30sec)	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0		
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0	0

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 6-1. Detailed clinical observations of female rats

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

[a] Values represent number of animals with the findings.
Figures in parenthese indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 6-1(continued). Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of administration						The lactation period
				8	15	24	30	36	42	
[Urination]	Control (vehicle: water for injection)	12	0 [a]	0	1	0	0	0	0	
(frequency/30sec)	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0	
	N-DPS (50 mg/kg)	12	1	0	0	2	0	0	3	0 (1)
	N-DPS (150 mg/kg)	12	2	1	1	0	0	0	0	0 (1)
[Defecation]	Control (vehicle: water for injection)	12	0 [a]	0	0	0	0	0	0	
(frequency/30sec)	N-DPS (15 mg/kg)	12	0	0	0	0	0	0	0	
	N-DPS (50 mg/kg)	12	0	0	0	0	0	0	0	0 (1)
	N-DPS (150 mg/kg)	12	0	0	0	0	0	0	0	0 (1)

[a] Values represent total score of each group.
Figures in parenthese indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Findings	Group	Initial number of animals	Pre-treatment	Days of administration 8	15	24	30	36	42	Days of recovery[a] 7	14
[Posture in home-cage] Crouching position	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	0 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Locomotor in home-cage] Decrease in locomotor activity	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	0 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Handling behavior] No resistance	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	0 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Heart beats] bradycardia	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	0 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Body temperature] hypothemia	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	1 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Fur] Moist fur	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	0 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Skin color/Mucuous membranse] Abnormal	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	0 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Lacrimation] observed	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	0 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Piloerection] Slight	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	0 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Respiratory rate] Hypopnea(dyspnea)	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	1 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)
[Stereotypy] observed	Control (vehicle: water for injection)	10	0[b]	0	0	0	0	0	0	0	0
	N-DPS (150 mg/kg)	10	0	0 (9)	0 (8)	0 (8)	0 (8)	0 (8)	0 (8)	0 (4)	0 (4)

[a] The recovery test was performed in 5 animals for the 0 mg/kg and 4 animals for the 150 mg/kg groups

[b] Values represent number of animals with the findings.

Figures in parenthese indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 6-2(continued). Detailed clinical observations of female rats, satellite group

Findings	Group	Initial number of animals	Pre-treatment	Days of administration												Days of recovery [a]			
				8		15		24		30		36		42		7		14	
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	10	1 [b]	0		0		4		0		0		2		0		0	
	N-DPS (150 mg/kg)	10	0	0		0		0		0		0		0		0	(4)	0	(4)
[Defecation] (frequency/30sec)	Control (vehicle: water for injection)	10	1 [b]	0		0		0		0		0		0		0		0	
	N-DPS (150 mg/kg)	10	0	0	(9)	0	(9)	0	(8)	0	(8)	0	(8)	0	(8)	0	(4)	0	(4)

[a] The recovery test was performed in 5 animals for the 0 mg/kg and 4 animals for the 150 mg/kg groups
[b] Values represent total score of each group.
Figures in parenthese indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 7-1. Body weights of male rats

Group	Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of males	12	12	12	12
Days of administration				
1	392.5 ± 13.5	392.4 ± 14.6	389.8 ± 17.0	388.3 ± 15.2
4	403.9 ± 12.7	402.0 ± 16.8	401.5 ± 21.8	383.0 ± 19.5 *
7	411.7 ± 15.0	410.1 ± 18.8	408.2 ± 26.2	391.1 ± 20.9
14	436.5 ± 19.7	437.1 ± 21.0	436.8 ± 25.7	412.6 ± 31.1
21	454.8 ± 21.4	453.3 ± 22.3	454.0 ± 21.4	431.3 ± 28.1 *
28	478.9 ± 24.8	472.7 ± 28.5	479.1 ± 25.9	435.9 ± 30.4 **
35	493.6 ± 28.9	489.8 ± 29.4	497.6 ± 27.6	452.7 ± 30.4 **
42	506.4 ± 36.0	503.8 ± 35.3	510.4 ± 30.8	449.2 ± 36.8 **

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)	N-DPS 150 mg/kg
Number of males	5	5
Days of recovery		
1	495.2 ± 37.5	475.0 ± 38.3
7	516.2 ± 37.1	499.2 ± 35.7
14	521.6 ± 38.4	512.2 ± 38.4

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 8-1. Body weights of female rats

Group	Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of females	12	12	12	12
Days of administration				
1	242.2 ± 11.2	246.4 ± 15.6	243.9 ± 12.4	242.6 ± 14.7
4	248.9 ± 16.0	251.3 ± 14.3	250.4 ± 12.0	248.5 ± 12.7
7	255.9 ± 16.4	257.2 ± 16.3	255.6 ± 11.7	254.6 ± 13.9
14	264.4 ± 18.4	266.6 ± 18.9	262.4 ± 13.8	265.3 ± 13.9

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)				N-DPS 150 mg/kg			
Number of females	10				10			
Days of administration								
1	239.9	±	14.2		245.2	±	11.6	
4	246.2	±	12.5		246.6	±	13.2	
7	255.2	±	11.9		254.4	±	13.6	(9)
14	265.4	±	13.3		270.8	±	17.9	(9)
21	278.0	±	17.7		276.5	±	19.0	(8)
28	288.5	±	18.9		283.7	±	18.9	(8)
35	296.6	±	19.7		288.0	±	19.9	(8)
42	297.6	±	20.7		289.1	±	20.8	(8)

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)	N-DPS 150 mg/kg
Number of females	5	4
Days of recovery		
1	292.1 ± 25.7	298.5 ± 17.2
7	304.4 ± 29.9	324.6 ± 10.7
14	307.3 ± 31.9	329.9 ± 11.8

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 9. Body weights of dams during pregnancy

Group	Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of dams	12	12	11	12
Days of pregnancy				
0	272.0 ± 18.5	277.6 ± 19.9	269.2 ± 12.6	270.4 ± 8.6
7	311.9 ± 22.3	313.8 ± 17.9	307.3 ± 14.8	308.0 ± 16.7
14	347.4 ± 21.2	352.3 ± 20.9	344.3 ± 16.8	348.9 ± 18.6
20	427.0 ± 26.7	437.0 ± 29.3	422.9 ± 22.8	438.0 ± 21.6

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 10. Body weights of dams during lactation

Group	Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of dams	12	12	11	12
Days of lactation				
0	336.2 ± 32.0	328.7 ± 26.0	329.5 ± 27.1	329.7 ± 21.8
4	340.6 ± 26.3	345.0 ± 21.3	337.4 ± 15.3	341.1 ± 21.6

Each value shows mean ± S.D. (g).
Figures in parentheses indicate number of dams.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 11-1. Food consumption of male rats

Group	Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of males	12	12	12	12
Days of administration				
1	30.7 ± 2.5	30.4 ± 1.4	30.2 ± 3.7	25.2 ± 4.9 *
7	30.1 ± 2.4	29.3 ± 1.9	28.6 ± 4.1	28.7 ± 4.0
14	30.4 ± 2.3	29.3 ± 3.3	29.2 ± 3.9	25.4 ± 4.4 **
29	31.6 ± 3.2	31.3 ± 3.8	30.1 ± 3.7	30.7 ± 4.8
35	29.6 ± 2.9	29.2 ± 3.1	27.9 ± 2.6	26.9 ± 5.0
41	30.4 ± 3.8	30.1 ± 2.8	29.7 ± 3.4	18.9 ± 7.3 **

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)	N-DPS 150 mg/kg
Number of males	5	5
Days of recovery		
6	32.0 ± 2.4	30.9 ± 2.5
12	32.2 ± 2.2	31.4 ± 4.5

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 12-1. Food consumption of female rats

Group	Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of females	12	12	12	12
Days of administration				
1	21.7 ± 2.2	19.5 ± 4.2	19.8 ± 2.8	18.2 ± 2.1 *
7	20.5 ± 4.1	20.7 ± 1.7	20.8 ± 2.5	19.7 ± 2.1
14	21.9 ± 2.8	20.5 ± 2.2	20.0 ± 3.6	19.5 ± 2.5

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)				N-DPS 150 mg/kg			
Number of females	10				10			
Days of administration								
1	21.2	±	2.6		19.2	±	3.2	
7	20.8	±	2.8		18.0	±	7.2	(9)
14	22.0	±	3.4		19.8	±	4.3	(9)
21	21.4	±	3.4		21.4	±	4.9	(8)
29	24.2	±	3.3		23.4	±	4.7	(8)
35	21.4	±	1.9		21.2	±	3.3	(8)
41	20.8	±	3.8		16.3	±	6.1	(8)

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)	N-DPS 150 mg/kg
Number of females	5	4
Days of recovery		
6	22.6 ± 4.6	26.3 ± 2.0
12	24.5 ± 4.6	25.5 ± 2.1

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 13. Food consumption in dams during pregnancy

Group	Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of dams	12	12	11	12
Days of pregnancy				
0	21.2 ± 2.5	23.9 ± 2.7	22.2 ± 3.3	19.9 ± 3.4
7	27.4 ± 2.5	29.9 ± 2.9	28.8 ± 3.5	28.5 ± 4.8
14	27.8 ± 3.4	30.6 ± 2.6	29.6 ± 3.1	28.3 ± 3.0
20	25.7 ± 3.4	25.9 ± 5.1	27.2 ± 3.2	29.0 ± 3.2

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 14. Food consumption in dams during lactation

Group	Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of dams	12	12	11	12
Days of lactation				
3	42.8 ± 5.4	46.5 ± 4.6	43.6 ± 7.0	45.6 ± 7.5

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Male, Administration period				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
Female, dam				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
Female, Administration period				
Number of animals	5			4
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Preyer's reaction	100			100
Withdrawal reflex	100			100
Eyelid reflex	100			100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 16. Assessment of grip strength of male rats at the last week of the dosing period

Group	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Number of males	5	5	5	5
Administration period				
Forelimb	1.063 ± 0.180	1.116 ± 0.108	1.164 ± 0.086	1.220 ± 0.032
Hindlimb	0.848 ± 0.100	0.867 ± 0.064	0.939 ± 0.094	0.956 ± 0.088

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Number of females	5	5	5	5
Administration period				
Forelimb	1.114 ± 0.046	1.127 ± 0.076	1.137 ± 0.080	1.089 ± 0.046
Hindlimb	0.507 ± 0.033	0.520 ± 0.029	0.484 ± 0.012	0.485 ± 0.024

Each value shows mean (kg) ±S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)			N-DPS (150 mg/kg)		
Number of females	5			4		
Administration period						
Forelimb	1.109	±	0.072	1.106	±	0.053
Hindlimb	0.488	±	0.042	0.511	±	0.060

Each value shows mean (kg) ±S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 19. Motor activity of male rats at the last week of the dosing period

Group	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Number of males	5	5	5	5
Administration period				
Ambulation (counts)				
5min	1008 ± 181	1185 ± 58	1343 ± 254 *	1223 ± 114
10min	1031 ± 104	1084 ± 204	1188 ± 345	1117 ± 105
15min	954 ± 98	1067 ± 75	1172 ± 215	1051 ± 345
20min	862 ± 145	1046 ± 64	1007 ± 202	1050 ± 214
Total	3856 ± 476	4382 ± 363	4710 ± 932	4441 ± 642
Rearing (counts)				
5min	28 ± 9	41 ± 6	36 ± 11	38 ± 11
10min	40 ± 10	35 ± 12	30 ± 4	31 ± 4
15min	28 ± 7	33 ± 13	29 ± 10	28 ± 16
20min	24 ± 11	27 ± 5	18 ± 7	24 ± 10
Total	120 ± 26	136 ± 30	113 ± 24	120 ± 36

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 20. Motor activity of female rats at the last week of the dosing period

Group	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Number of females	5	5	5	5
Administration period				
Ambulation (counts)				
5min	1118 ± 179	1090 ± 87	1358 ± 290	1187 ± 178
10min	829 ± 198	919 ± 143	974 ± 483	898 ± 166
15min	564 ± 69	749 ± 259	910 ± 353	755 ± 185
20min	406 ± 288	524 ± 166	695 ± 350	301 ± 491
Total	2917 ± 571	3283 ± 424	3937 ± 1223	3142 ± 826
Rearing (counts)				
5min	33 ± 8	30 ± 8	47 ± 14	25 ± 12
10min	17 ± 8	23 ± 10	27 ± 12	16 ± 8
15min	5 ± 8	15 ± 8	17 ± 5	9 ± 5
20min	5 ± 7	14 ± 8	7 ± 5	6 ± 13
Total	60 ± 26	82 ± 16	97 ± 20	56 ± 32

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)			N-DPS (150 mg/kg)		
Number of females	5			4		
Administration period						
Ambulation (counts)						
5min	1203	±	134	1196	±	102
10min	1122	±	207	1140	±	75
15min	1053	±	246	1177	±	173
20min	910	±	220	1092	±	102
Total	4288	±	753	4606	±	334
Rearing (counts)						
5min	42	±	11	39	±	9
10min	38	±	9	36	±	11
15min	27	±	11	45	±	13
20min	22	±	10	29	±	14
Total	129	±	38	149	±	43

Each value shows mean±S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 22-1. Urinalysis in male rats

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

Group	Number of males	Urinary sediments[a)]								Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals			Epithelial cells									
		-	-	-	-	±	+	-	±	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	0	5	0	4	1	19.3 ±4.4	1.055 ±0.014	99.4 ±33.7	185.1 ±33.0	114.0 ±39.2	1.81 ±0.20	3.51 ±0.65	2.08 ±0.29
N-DPS (15 mg/kg)	5	5	5	5	0	4	1	5	0	16.2 ±3.6	1.060 ±0.009	108.9 ±27.4	187.5 ±22.0	127.6 ±22.4	1.69 ±0.14	3.00 ±0.59	2.01 ±0.23
N-DPS (50 mg/kg)	5	5	5	5	1	4	0	5	0	19.4 ±4.2	1.057 ±0.010	120.9 ±42.7	182.7 ±43.2	137.6 ±37.2	2.26 ±0.48	3.45 ±0.50	2.61 ±0.51
N-DPS (150 mg/kg)	5	5	5	5	1	4	0	5	0	21.2 ±6.6	1.051 ±0.010	75.9 ±26.6	158.0 ±23.8	94.2 ±43.0	1.69 ±0.83	3.27 ±0.80	2.09 ±1.05

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 22-2. Urinalysis in male rats of the recovery period

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

Group	Number of males	Urinary sediments[a)]						Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells								
		-	-	-	-	±	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	1	4	5	26.1 ±12.4	1.049 ±0.016	98.0 ±28.7	166.1 ±36.8	112.8 ±29.9	2.29 ±0.24	4.00 ±0.76	2.65 ±0.20
N-DPS (150 mg/kg)	5	5	5	5	0	5	5	20.5 ±3.2	1.058 ±0.008	109.8 ±13.4	181.6 ±19.9	128.3 ±26.1	2.24 ±0.39	3.67 ±0.31	2.59 ±0.46

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL ; 3+: 300≦and<600 mg/dL ; 4+: 600 mg/dL <
Glucose, -: negative ; ±: 30≦and<70 mg/dL ; +: 70≦and<150 mg/dL ; 2+: 150≦and<300 mg/dL ; 3+: 300≦and<1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL ; 2+: 40≦and<80 mg/dL ; 3+: 80≦and<150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and<2.0 mg/dL ; 2+: 2.0≦and<6.0 mg/dL ; 3+: 6.0≦and<10.0 mg/dL ; 4+: 10.0 mg/dL <
Occult blood, -: negative ; ±: 0.03≦and<0.06 mg/dL ; +: 0.06≦and<020 mg/dL ; 2+: 0.20≦and<1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL ; 3+: 8.0≦and<12.0 mg/dL ; 4+: 12.0 mg/dL <
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 23-1. Urinalysis in female rats, satellite group

Group	Number of females	Quality[a)]														
		Color	Turbidity	pH			Protein			Glucose	Ketone		Bilirubin	Occult blood		Urobilinogen
		Light yellow	-	6.0	6.5	7.0	-	±	+	-	-	±	-	-	±	±
Control (vehicle: water for injection)	5	5	5	1	4	0	2	1	2	5	3	2	5	4	1	5
N-DPS (150 mg/kg)	5	5	5	1	3	1	2	3	0	5	5	0	5	5	0	5

Group	Number of females	Urinary sediments[a)]							Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells									
		-	-	-	-	±	-	±	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	3	2	5	0	11.6 ±7.4	1.059 ±0.018	88.9 ±35.0	147.6 ±41.5	86.4 ±33.5	0.94 ±0.42	1.64 ±0.86	0.98 ±0.63
N-DPS (150 mg/kg)	5	5	5	5	2	3	4	1	13.6 ±4.4	1.057 ±0.015	106.5 ±38.4	153.5 ±25.3	118.7 ±38.6	1.34 ±0.29	2.01 ±0.38	1.53 ±0.38

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL ; 3+: 300≦and<600 mg/dL ; 4+: 600 mg/dL <
Glucose, -: negative ; ±: 30≦and<70 mg/dL ; +: 70≦and<150 mg/dL ; 2+: 150≦and<300 mg/dL ; 3+: 300≦and<1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL ; 2+: 40≦and<80 mg/dL ; 3+: 80≦and<150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and<2.0 mg/dL ; 2+: 2.0≦and<6.0 mg/dL ; 3+: 6.0≦and<10.0 mg/dL ; 4+: 10.0 mg/dL <
Occult blood, -: negative ; ±: 0.03≦and<0.06 mg/dL ; +: 0.06≦and<020 mg/dL ; 2+: 0.20≦and<1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL ; 3+: 8.0≦and<12.0 mg/dL ; 4+: 12.0 mg/dL <
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 23-2. Urinalysis in female rats of the recovery period

Group	Number of females	Quality[a)]												
		Color	Turbidity	pH			Protein		Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen
		Light yellow	-	6.5	7.0	7.5	-	±	-	-	-	-	±
Control (vehicle: water for injection)	5	5	5	1	4	0	4	1	5	5	5	5	5
N-DPS (150 mg/kg)	4	4	4	1	0	3	4	0	4	4	4	4	4

Group	Number of females	Urinary sediments[a)]						Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells								
		-	-	-	-	±	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	3	2	5	18.6 ±1.6	1.045 ±0.006	83.2 ±18.5	158.9 ±9.4	100.6 ±19.2	1.53 ±0.32	2.95 ±0.23	1.85 ±0.25
N-DPS (150 mg/kg)	4	4	4	4	1	3	4	19.0 ±5.6	1.046 ±0.009	84.9 ±8.4	150.7 ±21.6	95.5 ±18.8	1.60 ±0.47	2.78 ±0.52	1.74 ±0.26

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and<30 mg/dL ; +: 30≦and<100 mg/dL ; 2+: 100≦and<300 mg/dL ; 3+: 300≦and<600 mg/dL ; 4+: 600 mg/dL <
Glucose, -: negative ; ±: 30≦and<70 mg/dL ; +: 70≦and<150 mg/dL ; 2+: 150≦and<300 mg/dL ; 3+: 300≦and<1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and<10 mg/dL ; +: 10≦and<40 mg/dL ; 2+: 40≦and<80 mg/dL ; 3+: 80≦and<150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and<2.0 mg/dL ; 2+: 2.0≦and<6.0 mg/dL ; 3+: 6.0≦and<10.0 mg/dL ; 4+: 10.0 mg/dL <
Occult blood, -: negative ; ±: 0.03≦and<0.06 mg/dL ; +: 0.06≦and<020 mg/dL ; 2+: 0.20≦and<1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and<4.0 mg/dL ; 2+: 4.0≦and<8.0 mg/dL ; 3+: 8.0≦and<12.0 mg/dL ; 4+: 12.0 mg/dL <
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 24-1. Hematological findings of male rats at the end of the dosing period

Group	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Number of males	5	5	5	5
RBC ($\times 10^4/\mu L$)	830 ± 32	855 ± 38	846 ± 51	902 ± 77
Hemoglobin (g/dL)	15.0 ± 0.5	14.9 ± 0.9	15.4 ± 0.3	16.0 ± 1.9
Hematocrit (%)	43.4 ± 1.2	42.4 ± 2.9	44.4 ± 1.4	46.1 ± 5.7
MCV (fL)	52.3 ± 2.0	49.6 ± 2.3	52.6 ± 4.7	51.0 ± 2.0
MCH (pg)	18.1 ± 0.3	17.4 ± 0.7	18.2 ± 1.1	17.7 ± 0.5
MCHC (g/dL)	34.6 ± 1.1	35.1 ± 0.5	34.7 ± 0.9	34.8 ± 0.7
Platelet ($\times 10^4/\mu L$)	109.7 ± 9.8	122.1 ± 15.7	112.7 ± 16.5	111.5 ± 22.4
PT (sec)	22.8 ± 3.6	19.6 ± 4.0	17.3 ± 2.3	23.2 ± 11.0
APTT (sec)	29.5 ± 3.5	28.3 ± 3.3	29.2 ± 1.5	34.6 ± 14.1
WBC ($\times 10^2/\mu L$)	80.3 ± 8.7	85.3 ± 25.3	81.8 ± 9.3	76.2 ± 13.5
Differental leukocyte count (%)				
Neutrophil	16.2 ± 5.6	15.8 ± 3.6	17.7 ± 6.2	24.9 ± 9.3
Eosinophil	2.0 ± 0.7	1.4 ± 0.4	1.8 ± 0.7	1.5 ± 1.1
Basophil	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
Monocyte	4.6 ± 0.7	3.9 ± 1.1	3.8 ± 1.5	4.1 ± 1.6
Lymphocyte	77.2 ± 5.5	78.9 ± 3.9	76.7 ± 7.0	69.4 ± 10.5
Reticulocyte count (%)	3.34 ± 0.54	3.36 ± 0.14	2.87 ± 0.76	2.34 ± 0.47 *

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 24-2. Hematological findings of male rats at the end of the recovery period

Group	Control (vehicle: water for injection)			N-DPS (150 mg/kg)			
Number of males	5			5			
RBC ($\times 10^4/\mu L$)	856	±	35	844	±	32	
Hemoglobin (g/dL)	15.2	±	0.6	15.2	±	0.8	
Hematocrit (%)	42.7	±	1.3	43.8	±	2.2	
MCV (fL)	49.9	±	1.3	51.9	±	1.0	*
MCH (pg)	17.8	±	0.5	18.0	±	0.3	
MCHC (g/dL)	35.7	±	0.5	34.8	±	0.4	*
Platelet ($\times 10^4/\mu L$)	101.5	±	7.3	113.6	±	12.6	
PT (sec)	17.9	±	2.6	18.5	±	4.0	
APTT (sec)	25.3	±	2.3	25.7	±	1.7	
WBC ($\times 10^2/\mu L$)	101.2	±	20.0	92.9	±	33.9	
Differental leukocyte count (%)							
Neutrophil	25.3	±	16.0	20.0	±	5.9	
Eosinophil	1.3	±	0.4	1.4	±	0.6	
Basophil	0.0	±	0.1	0.0	±	0.0	
Monocyte	4.1	±	0.5	3.1	±	0.8	
Lymphocyte	69.3	±	16.1	75.5	±	6.7	
Reticulocyte count (%)	3.48	±	0.34	3.97	±	0.58	

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 25-1. Hematological findings of female rats at the end of the dosing period

Group	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Number of females	5	5	5	5
RBC ($\times 10^4/\mu L$)	717 ± 36	699 ± 43	677 ± 41	733 ± 41
Hemoglobin (g/dL)	13.9 ± 0.4	13.7 ± 0.4	13.3 ± 0.8	14.3 ± 0.6
Hematocrit (%)	41.4 ± 0.9	40.7 ± 0.5	39.5 ± 2.2	42.1 ± 1.5
MCV (fL)	57.9 ± 2.1	58.5 ± 3.3	58.4 ± 0.6	57.5 ± 1.9
MCH (pg)	19.4 ± 0.6	19.6 ± 0.8	19.7 ± 0.3	19.6 ± 0.4
MCHC (g/dL)	33.5 ± 0.4	33.5 ± 0.6	33.7 ± 0.3	34.0 ± 0.5
Platelet ($\times 10^4/\mu L$)	136.9 ± 19.9	114.3 ± 13.5	112.8 ± 14.2	116.3 ± 12.7
PT (sec)	12.3 ± 0.3	12.7 ± 0.5	12.2 ± 0.9	12.9 ± 0.6
APTT (sec)	21.8 ± 1.8	21.2 ± 1.9	19.1 ± 1.6	20.8 ± 1.6
WBC ($\times 10^2/\mu L$)	59.3 ± 16.2	111.9 ± 43.5	95.6 ± 17.1	105.1 ± 32.2
Differental leukocyte count (%)				
Neutrophil	26.2 ± 6.2	33.2 ± 9.3	29.4 ± 8.0	25.6 ± 13.3
Eosinophil	1.1 ± 0.3	0.7 ± 0.4	1.2 ± 0.7	1.2 ± 0.4
Basophil	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
Monocyte	5.8 ± 1.4	4.4 ± 1.2	4.6 ± 0.9	4.6 ± 0.8
Lymphocyte	66.9 ± 5.4	61.6 ± 9.3	64.8 ± 6.7	68.6 ± 13.4
Reticulocyte count (%)	8.84 ± 1.65	8.20 ± 1.24	8.68 ± 1.18	6.18 ± 1.16 *

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 25-2. Hematological findings of female rats at the end of the dosing period, satellite group

Group	Control (vehicle: water for injection)			N-DPS (150 mg/kg)		
Number of females	5			4		
RBC ($\times 10^4/\mu L$)	776	±	50	802	±	25
Hemoglobin (g/dL)	14.6	±	0.7	14.8	±	0.2
Hematocrit (%)	42.1	±	2.5	41.8	±	0.3
MCV (fL)	54.2	±	3.1	52.2	±	1.3
MCH (pg)	18.9	±	0.6	18.5	±	0.3
MCHC (g/dL)	34.8	±	0.8	35.5	±	0.3
Platelet ($\times 10^4/\mu L$)	110.0	±	4.9	106.9	±	12.1
PT (sec)	12.2	±	0.5	12.1	±	0.6
APTT (sec)	21.3	±	1.8	19.7	±	2.3
WBC ($\times 10^2/\mu L$)	60.5	±	15.8	52.7	±	18.6
Differental leukocyte count (%)						
Neutrophil	14.2	±	4.5	13.6	±	4.8
Eosinophil	1.9	±	0.7	2.5	±	1.0
Basophil	0.0	±	0.0	0.0	±	0.0
Monocyte	2.5	±	0.9	3.3	±	1.4
Lymphocyte	81.4	±	5.2	80.6	±	5.8
Reticulocyte count (%)	3.41	±	0.43	2.65	±	0.53

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group	Control (vehicle: water for injection)			N-DPS (150 mg/kg)		
Number of females	5			5		
RBC ($\times 10^4/\mu L$)	790	±	26	794	±	14
Hemoglobin (g/dL)	14.8	±	0.4	14.7	±	0.6
Hematocrit (%)	42.3	±	0.9	41.8	±	0.6
MCV (fL)	53.6	±	1.4	52.7	±	0.7
MCH (pg)	18.8	±	0.5	18.6	±	0.6
MCHC (g/dL)	35.0	±	0.4	35.2	±	1.0
Platelet ($\times 10^4/\mu L$)	104.4	±	7.8	100.9	±	8.2
PT (sec)	12.0	±	0.6	11.9	±	0.5
APTT (sec)	21.5	±	2.7	19.2	±	2.1
WBC ($\times 10^2/\mu L$)	51.7	±	14.5	44.9	±	1.4
Differental leukocyte count (%)						
Neutrophil	16.7	±	5.2	17.7	±	1.8
Eosinophil	2.1	±	0.6	2.2	±	0.9
Basophil	0.0	±	0.0	0.0	±	0.0
Monocyte	4.3	±	1.7	5.2	±	2.0
Lymphocyte	76.8	±	6.5	74.9	±	3.8
Reticulocyte count (%)	3.45	±	1.02	3.53	±	0.50

Each value shows mean±S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 26-1. Biochemical findings of male rats at the end of the dosing period

Group		Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg	
Number of males		5	5	5	5	
Total protein	g/dL	5.6 ± 0.2	5.6 ± 0.2	5.6 ± 0.2	5.0 ± 0.2	**
Albumin	g/dL	3.6 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	3.3 ± 0.1	**
A/G		1.85 ± 0.16	1.76 ± 0.14	1.83 ± 0.17	2.00 ± 0.31	
Glucose	mg/dL	137 ± 5	136 ± 4	143 ± 11	122 ± 13	
Total cholesterol	mg/dL	40 ± 9	41 ± 7	44 ± 11	51 ± 13	
Triglyceride	mg/dL	27 ± 12	28 ± 20	37 ± 18	25 ± 6	
Phospholipid	mg/dL	72 ± 13	72 ± 8	77 ± 15	78 ± 16	
AST	U/L	75 ± 27	58 ± 6	78 ± 19	121 ± 99	
ALT	U/L	33 ± 6	31 ± 7	30 ± 4	57 ± 39	
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0	
LDH	U/L	77 ± 31	76 ± 21	134 ± 60	265 ± 239	
Bile acid	μmol/L	9.0 ± 4.0	11.2 ± 4.7	6.5 ± 1.9	8.9 ± 3.1	
BUN	mg/dL	14 ± 1	14 ± 2	14 ± 1	19 ± 9	
Creatinine	mg/dL	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0	0.5 ± 0.1	
Total bilirubin	mg/dL	0.05 ± 0.01	0.06 ± 0.01	0.04 ± 0.01	0.06 ± 0	
ALP	U/L	335 ± 50	288 ± 12	297 ± 57	263 ± 128	
Inorganic phosphorus	mg/dL	6.1 ± 0.6	6.2 ± 0.4	6.1 ± 0.6	7.1 ± 2.0	
Ca	mg/dL	9.2 ± 0.3	9.3 ± 0.1	9.5 ± 0.3	9.5 ± 0.7	
Na	mEq/L	144.3 ± 0.7	143.2 ± 0.7	144.1 ± 0.5	144.4 ± 2.0	
K	mEq/L	4.02 ± 0.11	4.03 ± 0.13	3.76 ± 0.18	3.91 ± 0.21	
Cl	mEq/L	105.5 ± 1.5	105.1 ± 0.3	104.8 ± 0.9	104 ± 4.1	

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 26-2. Biochemical findings of male rats at the end of the recovery period

Group		Control (vehicle: water for injection)	N-DPS 150 mg/kg	
Number of males		5	5	
Total protein	g/dL	5.7 ± 0.2	5.8 ± 0.2	
Albumin	g/dL	3.6 ± 0.1	3.7 ± 0.1	
A/G		1.73 ± 0.07	1.77 ± 0.17	
Glucose	mg/dL	143 ± 14	134 ± 7	
Total cholesterol	mg/dL	48 ± 7	47 ± 10	
Triglyceride	mg/dL	18 ± 9	20 ± 9	
Phospholipid	mg/dL	75 ± 9	78 ± 9	
AST	U/L	62 ± 16	65 ± 9	
ALT	U/L	28 ± 5	30 ± 6	
γ-GTP	U/L	0 ± 0	0 ± 0	
LDH	U/L	155 ± 50	242 ± 73	
Bile acid	μmol/L	15.4 ± 4.7	21.7 ± 3.2	*
BUN	mg/dL	15 ± 1	18 ± 2	*
Creatinine	mg/dL	0.5 ± 0	0.6 ± 0.1	
Total bilirubin	mg/dL	0.06 ± 0.01	0.06 ± 0.01	
ALP	U/L	231 ± 13	334 ± 63	*
Inorganic phosphorus	mg/dL	6.2 ± 0.6	6.4 ± 1.2	
Ca	mg/dL	9.1 ± 0.3	9.3 ± 0.2	
Na	mEq/L	143.7 ± 0.7	143.8 ± 0.5	
K	mEq/L	3.53 ± 0.17	3.70 ± 0.08	
Cl	mEq/L	106.3 ± 1.6	105.6 ± 1.3	

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group		Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg		N-DPS 150 mg/kg
Number of females		5	5	5		5
Total protein	g/dL	5.9 ± 0.2	5.9 ± 0.1	5.9 ± 0.4		5.7 ± 0.2
Albumin	g/dL	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.3		3.8 ± 0.2
A/G		2.10 ± 0.10	2.00 ± 0.08	2.07 ± 0.09		2.01 ± 0.19
Glucose	mg/dL	122 ± 13	120 ± 14	120 ± 7		119 ± 10
Total cholesterol	mg/dL	61 ± 19	48 ± 5	60 ± 11		53 ± 13
Triglyceride	mg/dL	23 ± 7	23 ± 13	25 ± 6		22 ± 6
Phospholipid	mg/dL	107 ± 23	100 ± 9	112 ± 12		102 ± 17
AST	U/L	97 ± 31	163 ± 68	98 ± 23		124 ± 47
ALT	U/L	47 ± 12	57 ± 19	44 ± 5		41 ± 8
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0		0 ± 0
LDH	U/L	71 ± 23	143 ± 126	123 ± 73		85 ± 59
Bile acid	μmol/L	11.8 ± 2.7	19.3 ± 7.3	19.8 ± 9.9		17.4 ± 6.8
BUN	mg/dL	19 ± 1	17 ± 3	16 ± 2	*	19 ± 2
Creatinine	mg/dL	0.5 ± 0	0.6 ± 0.1	0.5 ± 0		0.5 ± 0
Total bilirubin	mg/dL	0.06 ± 0.01	0.07 ± 0	0.07 ± 0.02		0.07 ± 0.01
ALP	U/L	153 ± 35	168 ± 40	162 ± 34		173 ± 52
Inorganic phosphorus	mg/dL	6.5 ± 0.4	6.9 ± 1.0	6.1 ± 0.5		6.4 ± 0.4
Ca	mg/dL	10.0 ± 0.1	10.0 ± 0.4	9.9 ± 0.3		9.6 ± 0.4
Na	mEq/L	142.2 ± 1.0	141.3 ± 0.9	140.8 ± 0.7		141.2 ± 0.3
K	mEq/L	3.77 ± 0.36	4.98 ± 2.43	3.72 ± 0.47		3.67 ± 0.09
Cl	mEq/L	107.0 ± 0.9	106.5 ± 1.6	106.1 ± 1.4		106.9 ± 0.8

Each value shows mean ± S.D.

Figures in parentheses indicate number of females.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group		Control (vehicle: water for injection)	N-DPS 150 mg/kg	
Number of females		5	4	
Total protein	g/dL	6.2 ± 0.3	6.0 ± 0.3	
Albumin	g/dL	4.3 ± 0.2	4.1 ± 0.2	
A/G		2.27 ± 0.11	2.24 ± 0.13	
Glucose	mg/dL	129 ± 22	114 ± 7	
Total cholesterol	mg/dL	70 ± 13	66 ± 5	
Triglyceride	mg/dL	23 ± 13	23 ± 13	
Phospholipid	mg/dL	129 ± 13	121 ± 8	
AST	U/L	61 ± 12	57 ± 8	
ALT	U/L	25 ± 8	24 ± 4	
γ-GTP	U/L	0 ± 0	0 ± 0	
LDH	U/L	95 ± 55	69 ± 32	
Bile acid	μmol/L	13.8 ± 4.5	15.5 ± 10.1	
BUN	mg/dL	18 ± 1	21 ± 3	*
Creatinine	mg/dL	0.7 ± 0.1	0.6 ± 0.1	
Total bilirubin	mg/dL	0.09 ± 0.02	0.07 ± 0.01	
ALP	U/L	110 ± 15	137 ± 18	*
Inorganic phosphorus	mg/dL	4.0 ± 0.2	4.7 ± 0.8	
Ca	mg/dL	9.5 ± 0.3	9.5 ± 0.2	
Na	mEq/L	143.2 ± 0.9	142.9 ± 1.0	
K	mEq/L	3.35 ± 0.12	3.37 ± 0.20	
Cl	mEq/L	107.6 ± 1.6	107.6 ± 1.5	

Each value shows mean ± S.D.

Figures in parentheses indicate number of females.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 27-3. Biochemical findings of female rats at the end of the recovery period

Group		Control (vehicle: water for injection)	N-DPS 150 mg/kg	
Number of females		5	4	
Total protein	g/dL	5.9 ± 0.3	5.8 ± 0.6	
Albumin	g/dL	4.0 ± 0.2	4.0 ± 0.5	
A/G		2.09 ± 0.08	2.24 ± 0.24	
Glucose	mg/dL	106 ± 10	111 ± 12	
Total cholesterol	mg/dL	58 ± 4	68 ± 6	*
Triglyceride	mg/dL	11 ± 4	12 ± 3	
Phospholipid	mg/dL	109 ± 12	124 ± 13	
AST	U/L	72 ± 10	89 ± 22	
ALT	U/L	27 ± 7	39 ± 24	
γ-GTP	U/L	0 ± 0	0 ± 0	
LDH	U/L	80 ± 20	87 ± 42	
Bile acid	μmol/L	12.0 ± 3.1	14.4 ± 8.9	
BUN	mg/dL	20 ± 3	17 ± 3	
Creatinine	mg/dL	0.6 ± 0	0.6 ± 0	
Total bilirubin	mg/dL	0.08 ± 0.01	0.10 ± 0.03	
ALP	U/L	194 ± 25	176 ± 61	
Inorganic phosphorus	mg/dL	4.4 ± 0.5	5.0 ± 0.6	
Ca	mg/dL	9.2 ± 0.4	9.5 ± 0.4	
Na	mEq/L	143.1 ± 1.1	142.7 ± 0.3	
K	mEq/L	3.48 ± 0.12	3.35 ± 0.17	
Cl	mEq/L	108.5 ± 1.9	106.9 ± 1.2	

Each value shows mean ± S.D.

Figures in parentheses indicate number of females.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 28-1. Organ weights of male rats at the end of the dosing period

Group		Control (vehicle: water for injection)			N-DPS 15 mg/kg			N-DPS 50 mg/kg			N-DPS 150 mg/kg			
Number of males		7			12			12			7			
Body weight	(g)	475.5	±	36.2	473.0	±	33.1	475.3	±	28.9	409.4	±	27.8	**
Brain	(mg)	2088.0	±	83.8	2033.0	±	64.7	1990.5	±	64.8	1938.3	±	145.2	**
	(mg/g)	4.411	±	0.355	4.316	±	0.305	4.202	±	0.294	4.737	±	0.234	
Thymus	(mg)	321.0	±	73.1	318.1	±	78.7	343.2	±	78.9	275.5	±	85.1	
	(mg/g)	0.674	±	0.144	0.669	±	0.146	0.725	±	0.174	0.672	±	0.212	
Heart	(mg)	1394.6	±	89.7	1466.1	±	83.0	1419.5	±	95.0	1263.8	±	51.5	*
	(mg/g)	2.937	±	0.116	3.116	±	0.311	2.988	±	0.137	3.099	±	0.239	
Liver	(mg)	12405.1	±	1512.4	12501.6	±	1322.0	12666.4	±	1292.0	10638.4	±	564.9	*
	(mg/g)	26.079	±	2.408	26.387	±	1.330	26.620	±	1.825	26.061	±	1.825	
Kidney (R)	(mg)	1568.0	±	146.9	1624.1	±	139.5	1587.0	±	131.5	1414.9	±	160.1	
	(mg/g)	3.300	±	0.220	3.437	±	0.217	3.336	±	0.132	3.457	±	0.340	
Kidney (L)	(mg)	1586.0	±	105.0	1640.2	±	176.6	1566.5	±	143.7	1419.1	±	178.4	
	(mg/g)	3.340	±	0.146	3.468	±	0.263	3.293	±	0.190	3.472	±	0.437	
Kidneys	(mg)	3154.1	±	247.9	3264.3	±	306.3	3153.4	±	270.7	2834.1	±	333.0	
	(mg/g)	6.640	±	0.351	6.905	±	0.449	6.629	±	0.307	6.929	±	0.766	
Spleen	(mg)	800.4	±	154.4	809.5	±	85.7	886.5	±	118.6	714.8	±	134.4	
	(mg/g)	1.673	±	0.221	1.716	±	0.189	1.862	±	0.198	1.746	±	0.322	
Testis (R)	(mg)	1699.6	±	138.9	1685.8	±	111.4	1612.6	±	170.4	1631.5	±	160.1	
	(mg/g)	3.589	±	0.369	3.582	±	0.358	3.401	±	0.384	3.983	±	0.237	
Testis (L)	(mg)	1715.5	±	151.4	1677.9	±	91.0	1603.2	±	152.5	1655.3	±	187.8	
	(mg/g)	3.616	±	0.313	3.565	±	0.326	3.381	±	0.351	4.038	±	0.291	
Testes	(mg)	3415.2	±	283.9	3363.7	±	198.7	3215.8	±	321.8	3286.8	±	347.2	
	(mg/g)	7.205	±	0.673	7.146	±	0.679	6.782	±	0.733	8.021	±	0.523	
Epididymis (R)	(mg)	609.7	±	39.5	634.0	±	39.2	597.5	±	61.3	581.7	±	67.5	
	(mg/g)	1.288	±	0.118	1.344	±	0.096	1.261	±	0.145	1.421	±	0.146	
Epididymis (L)	(mg)	591.1	±	37.3	631.7	±	42.5	586.8	±	52.0	585.2	±	81.3	
	(mg/g)	1.246	±	0.080	1.341	±	0.117	1.237	±	0.116	1.428	±	0.175	*
Epididymides	(mg)	1200.8	±	74.3	1265.7	±	78.2	1184.3	±	111.9	1166.8	±	148.2	
	(mg/g)	2.534	±	0.197	2.685	±	0.208	2.498	±	0.259	2.849	±	0.320	

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 28-1(continued). Organ weights of male rats at the end of the dosing period

Group		Control (vehicle: water for injection)			N-DPS 15 mg/kg			N-DPS 50 mg/kg			N-DPS 150 mg/kg			
Number of males		7			12			12			7			
Body weight	(g)	475.5	±	36.2	473.0	±	33.1	475.3	±	28.9	409.4	±	27.8	**
Prostate, ventral	(mg)	612.9	±	125.2	558.7	±	159.7	620.7	±	145.9	435.3	±	120.0	
	(mg/g)	1.293	±	0.269	1.177	±	0.322	1.309	±	0.317	1.059	±	0.274	
Seminal vesicles	(mg)	1564.5	±	325.8	1563.5	±	230.4	1610.4	±	263.3	1182.9	±	472.2	
	(mg/g)	3.315	±	0.783	3.321	±	0.529	3.394	±	0.568	2.871	±	1.119	
Thyroid gland	(mg)	20.4	±	3.7	21.6	±	5.0	18.6	±	3.4	16.4	±	2.6	
	(mg/g)	0.043	±	0.008	0.046	±	0.011	0.039	±	0.007	0.040	±	0.005	
Adrenal gland (R)	(mg)	23.4	±	2.5	24.6	±	2.6	27.3	±	6.1	28.3	±	5.5	
	(mg/g)	0.050	±	0.007	0.052	±	0.007	0.058	±	0.013	0.070	±	0.016	*
Adrenal gland (L)	(mg)	25.1	±	3.5	25.0	±	3.0	28.1	±	5.8	30.1	±	6.1	
	(mg/g)	0.053	±	0.009	0.053	±	0.008	0.059	±	0.013	0.074	±	0.018	**
Adrenal glands	(mg)	48.6	±	5.8	49.6	±	5.5	55.4	±	11.8	58.4	±	11.4	
	(mg/g)	0.103	±	0.015	0.105	±	0.015	0.117	±	0.026	0.144	±	0.033	**

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 28-2. Organ weights of male rats at the end of the recovery period

Group		Control (vehicle: water for injection)			N-DPS 150 mg/kg		
Number of males		5			5		
Body weight	(g)	495.0	±	36.8	485.5	±	32.7
Brain	(mg)	2062.0	±	68.9	2040.7	±	99.5
	(mg/g)	4.178	±	0.223	4.217	±	0.316
Thymus	(mg)	295.0	±	30.6	282.6	±	82.8
	(mg/g)	0.597	±	0.065	0.579	±	0.155
Heart	(mg)	1437.6	±	101.6	1428.8	±	100.0
	(mg/g)	2.912	±	0.236	2.948	±	0.195
Liver	(mg)	12520.6	±	1024.8	12612.9	±	866.1
	(mg/g)	25.304	±	1.174	25.985	±	0.771
Kidney (R)	(mg)	1709.2	±	183.3	1552.7	±	185.9
	(mg/g)	3.460	±	0.369	3.206	±	0.392
Kidney (L)	(mg)	1682.4	±	111.8	1548.3	±	183.2
	(mg/g)	3.411	±	0.292	3.195	±	0.369
Kidneys	(mg)	3391.6	±	288.7	3101.0	±	367.6
	(mg/g)	6.870	±	0.635	6.401	±	0.757
Spleen	(mg)	778.6	±	50.6	819.0	±	106.3
	(mg/g)	1.581	±	0.162	1.688	±	0.198
Testis (R)	(mg)	1608.0	±	90.8	1683.6	±	188.0
	(mg/g)	3.270	±	0.383	3.460	±	0.185
Testis (L)	(mg)	1578.9	±	142.5	1672.9	±	186.1
	(mg/g)	3.213	±	0.458	3.440	±	0.211
Testes	(mg)	3186.9	±	226.6	3356.5	±	372.5
	(mg/g)	6.483	±	0.832	6.900	±	0.391
Epididymis (R)	(mg)	667.5	±	56.4	664.4	±	95.1
	(mg/g)	1.355	±	0.154	1.365	±	0.132
Epididymis (L)	(mg)	609.3	±	71.7	638.8	±	72.8
	(mg/g)	1.237	±	0.182	1.314	±	0.084
Epididymides	(mg)	1276.8	±	122.9	1303.2	±	162.7
	(mg/g)	2.592	±	0.329	2.678	±	0.200

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 28-2(continued). Organ weights of male rats at the end of the recovery period

Group		Control (vehicle: water for injection)			N-DPS 150 mg/kg			
Number of males		5			5			
Body weight	(g)	495.0	±	36.8	485.5	±	32.7	
Prostate, ventral	(mg)	539.2	±	84.2	574.8	±	111.4	
	(mg/g)	1.088	±	0.143	1.183	±	0.204	
Seminal vesicles	(mg)	1788.6	±	496.4	1587.8	±	198.6	
	(mg/g)	3.592	±	0.832	3.283	±	0.476	
Thyroid gland	(mg)	17.9	±	4.5	14.7	±	4.6	
	(mg/g)	0.036	±	0.010	0.030	±	0.009	
Adrenal gland (R)	(mg)	27.4	±	4.8	21.6	±	1.8	*
	(mg/g)	0.056	±	0.011	0.045	±	0.007	
Adrenal gland (L)	(mg)	28.3	±	6.9	23.7	±	2.5	
	(mg/g)	0.057	±	0.015	0.049	±	0.006	
Adrenal glands	(mg)	55.6	±	11.6	45.3	±	3.7	
	(mg/g)	0.113	±	0.026	0.094	±	0.012	

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group		Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of females		12	12	11	12
Body weight	(g)	304.4 ± 22.1	308.1 ± 20.7	304.8 ± 16.4	305.2 ± 16.2
Brain	(mg)	1897.9 ± 53.5	1915.9 ± 86.1	1901.6 ± 84.8	1930.9 ± 112.9
	(mg/g)	6.263 ± 0.458	6.238 ± 0.398	6.253 ± 0.404	6.332 ± 0.313
Thymus	(mg)	207.0 ± 53.0	179.2 ± 43.9	216.0 ± 62.5	226.5 ± 59.4
	(mg/g)	0.678 ± 0.159	0.583 ± 0.142	0.708 ± 0.199	0.737 ± 0.168
Heart	(mg)	1030.8 ± 81.4	983.5 ± 71.1	1011.5 ± 45.3	992.6 ± 92.0
	(mg/g)	3.394 ± 0.261	3.197 ± 0.198	3.329 ± 0.249	3.249 ± 0.197
Liver	(mg)	10033.5 ± 983.7	10214.6 ± 835.0	9760.6 ± 618.9	10130.1 ± 935.1
	(mg/g)	32.989 ± 2.652	33.189 ± 2.198	32.051 ± 1.747	33.209 ± 2.762
Kidney (R)	(mg)	1050.4 ± 77.8	1050.1 ± 104.3	1026.5 ± 60.2	1070.0 ± 67.7
	(mg/g)	3.464 ± 0.329	3.410 ± 0.254	3.376 ± 0.257	3.510 ± 0.225
Kidney (L)	(mg)	1036.7 ± 73.0	1039.0 ± 112.7	1089.5 ± 284.1	1052.5 ± 72.0
	(mg/g)	3.419 ± 0.312	3.373 ± 0.283	3.576 ± 0.900	3.455 ± 0.274
Kidneys	(mg)	2087.1 ± 148.6	2089.1 ± 215.6	2116.1 ± 286.1	2122.6 ± 135.8
	(mg/g)	6.883 ± 0.636	6.783 ± 0.532	6.952 ± 0.925	6.966 ± 0.489
Spleen	(mg)	696.2 ± 139.4	760.1 ± 124.4	738.4 ± 97.4	784.3 ± 118.1
	(mg/g)	2.275 ± 0.347	2.471 ± 0.385	2.428 ± 0.341	2.571 ± 0.364
Ovary (R)	(mg)	52.7 ± 9.0	56.1 ± 9.0	50.9 ± 5.3	53.7 ± 7.9
	(mg/g)	0.175 ± 0.037	0.182 ± 0.023	0.168 ± 0.021	0.176 ± 0.022
Ovary (L)	(mg)	50.7 ± 6.3	52.6 ± 6.2	53.8 ± 7.6	53.4 ± 6.3
	(mg/g)	0.167 ± 0.023	0.172 ± 0.025	0.176 ± 0.022	0.175 ± 0.015
Ovaries	(mg)	103.5 ± 10.9	108.7 ± 10.7	104.7 ± 6.3	107.2 ± 12.0
	(mg/g)	0.342 ± 0.048	0.353 ± 0.031	0.344 ± 0.021	0.351 ± 0.027
Uterus	(mg)	631.3 ± 87.8	635.2 ± 92.0	634.1 ± 66.5	646.6 ± 61.5
	(mg/g)	2.080 ± 0.292	2.057 ± 0.225	2.087 ± 0.260	2.121 ± 0.203
Thyroid gland	(mg)	15.8 ± 2.7	14.4 ± 1.5	15.6 ± 3.0	16.4 ± 3.6
	(mg/g)	0.053 ± 0.010	0.047 ± 0.006	0.051 ± 0.010	0.054 ± 0.012
Adrenal gland (R)	(mg)	38.2 ± 6.1	38.4 ± 5.6	33.1 ± 2.9 *	38.9 ± 4.2
	(mg/g)	0.126 ± 0.023	0.125 ± 0.020	0.109 ± 0.012	0.128 ± 0.017
Adrenal gland (L)	(mg)	40.0 ± 5.6	39.9 ± 5.2	36.3 ± 2.7	42.5 ± 5.4
	(mg/g)	0.132 ± 0.020	0.130 ± 0.018	0.119 ± 0.011	0.140 ± 0.020
Adrenal glands	(mg)	78.1 ± 11.2	78.3 ± 10.3	69.4 ± 5.1	81.3 ± 9.3
	(mg/g)	0.258 ± 0.042	0.255 ± 0.036	0.229 ± 0.022	0.268 ± 0.037

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Group		Control (vehicle: water for injection)			N-DPS 150 mg/kg		
Number of females		5			4		
Body weight	(g)	284.3	±	16.4	263.9	±	17.8
Brain	(mg)	1896.1	±	37.5	1863.0	±	58.2
	(mg/g)	6.688	±	0.406	7.077	±	0.374
Thymus	(mg)	307.1	±	103.6	284.2	±	37.3
	(mg/g)	1.080	±	0.357	1.075	±	0.099
Heart	(mg)	909.1	±	58.3	884.1	±	88.5
	(mg/g)	3.207	±	0.271	3.345	±	0.138
Liver	(mg)	6874.6	±	557.3	6976.6	±	751.3
	(mg/g)	24.186	±	1.460	26.391	±	1.564
Kidney (R)	(mg)	914.8	±	53.8	910.1	±	96.2
	(mg/g)	3.221	±	0.157	3.441	±	0.149
Kidney (L)	(mg)	895.8	±	59.3	864.8	±	85.5
	(mg/g)	3.160	±	0.275	3.272	±	0.129
Kidneys	(mg)	1810.6	±	104.7	1774.9	±	181.3
	(mg/g)	6.381	±	0.422	6.713	±	0.275
Spleen	(mg)	584.6	±	42.2	538.6	±	38.4
	(mg/g)	2.060	±	0.157	2.041	±	0.047
Ovary (R)	(mg)	48.5	±	9.1	46.1	±	8.6
	(mg/g)	0.171	±	0.035	0.174	±	0.027
Ovary (L)	(mg)	42.7	±	1.1	39.1	±	13.0
	(mg/g)	0.151	±	0.009	0.148	±	0.047
Ovaries	(mg)	91.3	±	9.9	85.2	±	17.7
	(mg/g)	0.322	±	0.041	0.322	±	0.060
Uterus	(mg)	551.4	±	163.0	425.4	±	51.7
	(mg/g)	1.953	±	0.627	1.613	±	0.184
Thyroid gland	(mg)	15.2	±	3.1	13.6	±	2.9
	(mg/g)	0.054	±	0.012	0.051	±	0.009
Adrenal gland (R)	(mg)	32.3	±	4.6	32.5	±	3.2
	(mg/g)	0.114	±	0.016	0.124	±	0.018
Adrenal gland (L)	(mg)	33.9	±	3.9	34.7	±	3.9
	(mg/g)	0.120	±	0.014	0.133	±	0.020
Adrenal glands	(mg)	66.2	±	8.5	67.2	±	7.0
	(mg/g)	0.233	±	0.031	0.256	±	0.038

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 29-3. Organ weights of female rats at the end of the recovery period

Group		Control (vehicle: water for injection)			N-DPS 150 mg/kg			
Number of females		5			4			
Body weight	(g)	286.1	±	29.5	309.0	±	8.2	
Brain	(mg)	1908.5	±	159.0	1877.4	±	24.2	
	(mg/g)	6.699	±	0.518	6.078	±	0.124	*
Thymus	(mg)	225.2	±	58.4	246.5	±	42.5	
	(mg/g)	0.799	±	0.247	0.799	±	0.147	
Heart	(mg)	900.2	±	101.8	934.4	±	45.0	
	(mg/g)	3.146	±	0.155	3.023	±	0.093	
Liver	(mg)	7469.9	±	1012.8	7551.6	±	567.1	
	(mg/g)	26.048	±	1.525	24.422	±	1.385	
Kidney (R)	(mg)	912.1	±	97.3	954.8	±	53.8	
	(mg/g)	3.194	±	0.250	3.088	±	0.093	
Kidney (L)	(mg)	917.1	±	99.6	939.7	±	61.4	
	(mg/g)	3.214	±	0.281	3.039	±	0.119	
Kidneys	(mg)	1829.2	±	196.5	1894.5	±	115.2	
	(mg/g)	6.408	±	0.530	6.127	±	0.212	
Spleen	(mg)	554.6	±	79.6	540.7	±	28.2	
	(mg/g)	1.944	±	0.262	1.753	±	0.136	
Ovary (R)	(mg)	50.2	±	14.6	43.2	±	9.4	
	(mg/g)	0.173	±	0.038	0.139	±	0.027	
Ovary (L)	(mg)	47.7	±	10.1	43.9	±	7.7	
	(mg/g)	0.166	±	0.025	0.142	±	0.023	
Ovaries	(mg)	97.9	±	24.4	87.1	±	15.7	
	(mg/g)	0.339	±	0.061	0.281	±	0.047	
Uterus	(mg)	568.6	±	67.3	499.8	±	202.0	
	(mg/g)	2.002	±	0.304	1.617	±	0.660	
Thyroid gland	(mg)	14.8	±	0.6	13.6	±	1.5	
	(mg/g)	0.052	±	0.005	0.044	±	0.004	*
Adrenal gland (R)	(mg)	34.0	±	8.6	28.8	±	4.4	
	(mg/g)	0.118	±	0.023	0.093	±	0.014	
Adrenal gland (L)	(mg)	35.9	±	8.7	28.8	±	3.9	
	(mg/g)	0.124	±	0.020	0.093	±	0.010	*
Adrenal glands	(mg)	69.9	±	17.0	57.6	±	8.0	
	(mg/g)	0.242	±	0.041	0.186	±	0.023	*

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 30-1. Macroscopic findings of male rats at the end of the dosing period

Group	Control (Vehicle)		N-DPS 15 mg/kg		N-DPS 50 mg/kg		N-DPS 150 mg/kg	
Findings / Grade	-	P	-	P	-	P	-	P
Thymus								
Discoloration, dark reddish	7	0	12	0	12	0	6	1
Small	7	0	12	0	12	0	6	1
Liver								
Adhesion, with diaphragm	7	0	12	0	11	1	7	0
Nodule, site of adhesion	7	0	12	0	11	1	7	0
Whitish area	7	0	12	0	12	0	6	1
Stomach								
Dark colored spot, mucosa, scattered, glandular stomach	7	0	12	0	12	0	6	1
Edematous, mucosa, forestomach	7	0	12	0	12	0	3	4
Retention, gas	7	0	12	0	12	0	6	1
Jejunum								
Dark reddish area, mucosa	7	0	12	0	12	0	6	1
Ileum								
Diverticulum	7	0	11	1	12	0	7	0
Small intestine								
Retention, gas	7	0	12	0	12	0	6	1
Epididymis								
Small, bilateral	7	0	12	0	12	0	6	1
Prostate								
Small	7	0	12	0	12	0	5	2
Seminal vesicle								
Small	7	0	12	0	12	0	5	2

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 30-2. Macroscopic findings of male rats at the end of the recovery period

Group	Control (Vehicle)		N-DPS 150 mg/kg	
Findings / Grade	-	P	-	P
Epididymis				
Nodule, yellowish white, corpus, unilateral	4	1	5	0

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

Numerals represent the number of animals.

Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 31-1. Macroscopic findings of female rats at the end of the dosing period

Group	Control (Vehicle)		N-DPS 15 mg/kg		N-DPS 50 mg/kg		N-DPS 150 mg/kg	
Findings / Grade	-	P	-	P	-	P	-	P
Stomach								
Dark colored spot, mucosa, glandular stomach	12	0	11	1	10	1	12	0
Dark reddish area, mucosa, glandular stomach	12	0	12	0	11	0	11	1
Recessed area, mucosa, glandular stomach	11	1	12	0	11	0	12	0
Uterus								
Nodule, cervix	12	0	12	0	10	1	12	0

Notes) - : No abnormal changes P : Non-graded change
Numerals represent the number of animals.
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 31-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Group	Control (Vehicle)		N-DPS 150 mg/kg	
Findings / Grade	-	P	-	P
Stomach				
Edematous, mucosa, forestomach	5	0	3	1

Notes) - : No abnormal changes P : Non-graded change
Numerals represent the number of animals.
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 31-3. Macroscopic findings of female rats at the end of the recovery period

Group	Control (Vehicle)		N-DPS 150 mg/kg	
Findings / Grade	-	P	-	P
All organs and tissues				
	5		4	

Notes) - : No abnormal changes P : Non-graded change
Numerals represent the number of animals.
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 32-1. Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							N-DPS 15 mg/kg							N-DPS 50 mg/kg							N-DPS 150 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5						2	0						12	0						12	5						2
Spinal cord	5						2	0						12	0						12	5						2
Pituitary gland	5						2	0						12	0						12	5						2
Submandibular gland	5						2	0						12	0						12	5						2
Sublingual gland	5						2	0						12	0						12	5						2
Lymph node, submandibular	5						2	0						12	0						12	5						2
Thyroid gland	5						2	0						12	0						12	5						2
Parathyroid gland	5						2	0						12	0						12	5						2
Thymus																												
Atrophy	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	2	2	1	0	0		2
Heart	5						2	0						12	0						12	5						2
Trachea																												
Cellular infiltration, neutrophil, submucosa	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Lung																												
Accumulation, foam cell, alveolus	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	3	2	0	0	0		2
Cellular infiltration, neutrophil, alveolus, focal	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Hemorrhage, focal	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Mineralization, alveolus	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		2
Bronchus	5						2	0						12	0						12	5						2

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 32-1(continued). Histopathological findings of male rats at the end of the dosing period

Findings / Group	Control (Vehicle)							N-DPS 15 mg/kg							N-DPS 50 mg/kg							N-DPS 150 mg/kg						
Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver																												
Fatty change, hepatocyte, periportal	0	5	0	0	0		2	0	0	0	0	0		12	1	0	0	0	0		11	4	1	0	0	0		2 #
Fibrosis, around necrosis	5	0	0	0	0		2	0	0	0	0	0		12	0	0	1	0	0		11	5	0	0	0	0		2
Microgranuloma	0	5	0	0	0		2	0	0	0	0	0		12	0	1	0	0	0		11	1	4	0	0	0		2
Necrosis, focal	5	0	0	0	0		2	0	0	0	0	0		12	0	0	1	0	0		11	4	0	1	0	0		2
Pancreas	5						2	0						12	0						12	5						2
Stomach																												
Forestomach																												
Cellular infiltration, inflammatory, submucosa	5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	3	0	3	0	0		1
Edema, lamina propria/submucosa	5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	3	0	0	3	0		1
Erosion	5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	4	0	2	0	0		1
Hyperplasia, squamous cell	5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	2	4	0	0	0		1 #
Glandular stomach																												
Edema, submucosa	5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	5	1	0	0	0		1
Erosion	5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	5	1	0	0	0		1
Duodenum	5						2	0						12	0						12	5						2
Jejunum																												
Erosion	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Ileum																												
Diverticulum	5					0	2	0					1	11	0					0	12	5					0	2
Cecum	5						2	0						12	0						12	5						2
Colon	5						2	0						12	0						12	5						2
Rectum	5						2	0						12	0						12	5						2
Lymph node, mesenteric	5						2	0						12	0						12	5						2
Spleen																												
Atrophy, white pulp	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Deposit, pigment, brown	0	0	4	1	0		2	0	0	0	0	0		12	0	0	0	0	0		12	0	0	5	0	0		2
Hematopoiesis, extramedullary	0	0	4	1	0		2	0	0	0	0	0		12	0	0	0	0	0		12	0	1	4	0	0		2

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 32-1(continued). Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							N-DPS 15 mg/kg							N-DPS 50 mg/kg							N-DPS 150 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney																												
Basophilic tubule, cortex	0	5	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	2	3	0	0	0		2
Cast, hyalin	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Cellular infiltration, lymphocyte, interstitial	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	2	3	0	0	0		2
Dilatation, lumen, distal tubule	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Mineralization, cortex	3	2	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	3	2	0	0	0		2
Urinary bladder	5						2	0						12	0						12	5						2
Adrenal gland																												
Hypertrophy, zona facsiculata	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Testis																												
Atrophy, seminiferous tubule, bilateral	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Epididymis																												
Atrophy, bilateral	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Prostate																												
Atrophy	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	3	1	1	0	0		2
Cellular infiltration, lymphocyte, interstitial	2	3	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Seminal vesicle																												
Atrophy	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	3	0	2	0	0		2
Coagulating gland																												
Atrophy	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		2
Eyeball	5						2	0						12	0						12	5						2
Harderian gland	5						2	0						12	0						12	5						2
Sciatic nerve	5						2	0						12	0						12	5						2
Skeletal muscle	5						2	0						12	0						12	5						2
Femur	5						2	0						12	0						12	5						2
Marrow, femur	5						2	0						12	0						12	5						2

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
Not significantly different from control.
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 32-2. Histopathological findings of male rats at the end of the recovery period

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 32-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group / Grade	Control (Vehicle)							N-DPS 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver		0						5	0						5
Pancreas		0						5	0						5
Stomach															
Forestomach		5							5						
Glandular stomach		5							5						
Duodenum		0						5	0						5
Jejunum		0						5	0						5
Ileum		0						5	0						5
Cecum		0						5	0						5
Colon		0						5	0						5
Rectum		0						5	0						5
Lymph node, mesenteric		0						5	0						5
Spleen		0						5	0						5

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 32-2(continued). Histopathological findings of male rats at the end of the recovery period

Group	Control (Vehicle)							N-DPS 150 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney	0						5	0						5
Urinary bladder	0						5	0						5
Adrenal gland	0						5	0						5
Testis	0						5	0						5
Epididymis														
Granuloma, spermatic, corpus, unilateral	0					1	4	0					0	5
Prostate	0						5	0						5
Seminal vesicle	0						5	0						5
Coagulating gland	0						5	0						5
Eyeball	0						5	0						5
Harderian gland	0						5	0						5
Sciatic nerve	0						5	0						5
Skeletal muscle	0						5	0						5
Femur	0						5	0						5
Marrow, femur	0						5	0						5

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 33-1. Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)							N-DPS 15 mg/kg							N-DPS 50 mg/kg							N-DPS 150 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5						7	0						12	0						11	5						7
Spinal cord	5						7	0						12	0						11	5						7
Pituitary gland	5						7	0						12	0						11	5						7
Submandibular gland	5						7	0						12	0						11	5						7
Sublingual gland	5						7	0						12	0						11	5						7
Lymph node, submandibular	5						7	0						12	0						11	5						7
Thyroid gland																												
Ectopic thymic tissue	5					0	7	0					0	12	0					0	11	4					1	7
Ultimobranchial body	3					2	7	0					0	12	0					0	11	4					1	7
Parathyroid gland	5						7	0						12	0						11	5						7
Thymus																												
Atrophy	0	4	1	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	0	5	0	0	0		7
Heart	5						7	0						12	0						11	5						7
Trachea	5						7	0						12	0						11	5						7
Lung																												
Accumulation, foam cell, alveolus	4	1	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	4	1	0	0	0		7
Mineralization, alveolus	4	1	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	5	0	0	0	0		7
Bronchus	5						7	0						12	0						11	5						7

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 33-1(continued). Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)							N-DPS 15 mg/kg							N-DPS 50 mg/kg							N-DPS 150 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver																												
Fatty change, hepatocyte, periprtal	1	4	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	1	4	0	0	0		7
Microgranuloma	4	1	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	2	3	0	0	0		7
Necrosis, focal	4	1	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	4	1	0	0	0		7
Pancreas	5						7	0						12	0						11	5						7
Stomach																												
Forestomach																												
Cellular infiltration, inflammatory, submucosa	5	0	0	0	0		7	6	0	0	0	0		6	5	0	0	0	0		7	5	1	0	0	0		6
Edema, lamina propria/submucosa	5	0	0	0	0		7	6	0	0	0	0		6	5	0	0	0	0		7	5	1	0	0	0		6
Erosion	5	0	0	0	0		7	5	0	1	0	0		6	5	0	0	0	0		7	6	0	0	0	0		6
Hyperplasia, squamous cell	5	0	0	0	0		7	6	0	0	0	0		6	5	0	0	0	0		7	5	1	0	0	0		6
Glandular stomach																												
Erosion	5	0	0	0	0		7	6	0	0	0	0		6	5	0	0	0	0		7	5	1	0	0	0		6
Duodenum	5						7	0						12	0						11	5						7
Jejunum	5						7	0						12	0						11	5						7
Ileum	5						7	0						12	0						11	5						7
Cecum	5						7	0						12	0						11	5						7
Colon	5						7	0						12	0						11	5						7
Rectum	5						7	0						12	0						11	5						7
Lymph node, mesenteric	5						7	0						12	0						11	5						7
Spleen																												
Deposit, pigment, brown	0	1	4	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	0	3	2	0	0		7
Hematopoiesis, extramedullary	0	0	0	5	0		7	0	0	0	0	0		12	0	0	0	0	0		11	0	1	0	4	0		7

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 33-1(continued). Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)							N-DPS 15 mg/kg							N-DPS 50 mg/kg							N-DPS 150 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney																												
Basophilic tubule, cortex	5	0	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	4	1	0	0	0		7
Cellular infiltration, lymphocyte, interstitial	4	1	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	4	1	0	0	0		7
Urinary bladder	5						7	0						12	0						11	5						7
Adrenal gland	5						7	0						12	0						11	5						7
Ovary																												
Increase, atretic follicle	5	0	0	0	0		7	0	0	0	0	0		12	0	0	0	0	0		11	4	1	0	0	0		7
Uterus																												
Cyst, cervix	5					0	7	0					0	12	0					1	10	5					0	7
Vagina	5						7	0						12	0						11	5						7
Eyeball	5						7	0						12	0						11	5						7
Harderian gland	5						7	0						12	0						11	5						7
Sciatic nerve	5						7	0						12	0						11	5						7
Skeletal muscle	5						7	0						12	0						11	5						7
Femur	5						7	0						12	0						11	5						7
Marrow, femur	5						7	0						12	0						11	5						7

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 33-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Group	Control (Vehicle)							N-DPS 150 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5							4						
Spinal cord	5							4						
Pituitary gland	5							4						
Submandibular gland	5							4						
Sublingual gland	5							4						
Lymph node, submandibular	5							4						
Thyroid gland														
Ectopic thymic tissue	4					1		4					0	
Parathyroid gland	5							4						
Thymus														
Atrophy	1	2	2	0	0			0	3	1	0	0		
Heart	5							4						
Trachea	5							4						
Lung														
Accumulation, foam cell, alveolus	4	1	0	0	0			4	0	0	0	0		
Bronchus	5							4						

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 33-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Group	Control (Vehicle)							N-DPS 150 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver														
Fatty change, hepatocyte, periportal	1	4	0	0	0			1	3	0	0	0		
Microgranuloma	0	5	0	0	0			0	4	0	0	0		
Pancreas	5							4						
Stomach														
Forestomach														
Cellular infiltration, inflammatory, submucosa	5	0	0	0	0			2	2	0	0	0		
Edema, lamina propria/submucosa	5	0	0	0	0			2	0	1	1	0		
Hyperplasia, squamous cell	5	0	0	0	0			2	2	0	0	0		
Glandular stomach	5							4						
Duodenum	5							4						
Jejunum	5							4						
Ileum	5							4						
Cecum	5							4						
Colon	5							4						
Rectum	5							4						
Lymph node, mesenteric	5							4						
Spleen														
Deposit, pigment, brown	0	0	0	5	0			0	0	0	4	0		
Hematopoiesis, extramedullary	0	4	0	1	0			0	3	0	1	0		

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 33-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Group	Control (Vehicle)							N-DPS 150 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney														
Basophilic tubule, cortex	4	1	0	0	0			1	3	0	0	0		
Cellular infiltration, lymphocyte, interstitial	3	2	0	0	0			1	3	0	0	0		
Mineralization, medulla	5	0	0	0	0			3	1	0	0	0		
Urinary bladder	5							4						
Adrenal gland	5							4						
Ovary														
Cyst, follicular/luteinized	5	0	0	0	0			3	0	1	0	0		
Uterus	5							4						
Vagina	5							4						
Eyeball	5							4						
Harderian gland	5							4						
Sciatic nerve	5							4						
Skeletal muscle	5							4						
Femur	5							4						
Marrow, femur	5							4						

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 33-3. Histopathological findings of female rats at the end of the recovery period

Findings	Group / Grade	Control (Vehicle)							N-DPS 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		0						5	0						4
Spinal cord		0						5	0						4
Pituitary gland		0						5	0						4
Submandibular gland		0						5	0						4
Sublingual gland		0						5	0						4
Lymph node, submandibular		0						5	0						4
Thyroid gland		0						5	0						4
Parathyroid gland		0						5	0						4
Thymus		0						5	0						4
Heart		0						5	0						4
Trachea		0						5	0						4
Lung		0						5	0						4
Bronchus		0						5	0						4

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 33-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group / Grade	Control (Vehicle)							N-DPS 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver		0						5	0						4
Pancreas		0						5	0						4
Stomach															
Forestomach		5						0	4						0
Glandular stomach		5						0	4						0
Duodenum		0						5	0						4
Jejunum		0						5	0						4
Ileum		0						5	0						4
Cecum		0						5	0						4
Colon		0						5	0						4
Rectum		0						5	0						4
Lymph node, mesenteric		0						5	0						4
Spleen		0						5	0						4

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 33-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group / Grade	Control (Vehicle)							N-DPS 150 mg/kg						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney		0						5	0						4
Urinary bladder		0						5	0						4
Adrenal gland		0						5	0						4
Ovary		0						5	0						4
Uterus		0						5	0						4
Vagina		0						5	0						4
Eyeball		0						5	0						4
Harderian gland		0						5	0						4
Sciatic nerve		0						5	0						4
Skeletal muscle		0						5	0						4
Femur		0						5	0						4
Marrow, femur		0						5	0						4

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 34. Results of observations about estrous cycle

Dose	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Number of animals examined	12	12	12	12
Pre-treatment period				
Number of animals showing type of cycle				
4-day cycle	10	10	9	10
4/5-day cycle	2	0	1	1
5-day cycle	0	2	1	1
irregular	0	0	1	0
Mean length of estrous cycle in days; Mean±S.D. (N)	4.1 ± 0.2 (12)	4.2 ± 0.4 (12)	4.3 ± 0.5 (12)	4.1 ± 0.3 (12)
Treatment period				
Number of animals showing each type of cycle				
4-day cycle	9	11	11	8
4/5-day cycle	1	1	0	3
5-day cycle	2	0	1	1
Mean length of estrous cycle in days; Mean±S.D. (N)	4.2 ± 0.4 (12)	4.0 ± 0.1 (12)	4.1 ± 0.3 (12)	4.2 ± 0.3 (12)
Frequency of animals that show abnormal estrous cycles after the treatment	0 / 12	0 / 12	0 / 12	0 / 12
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.1 ± 0.3 (12)

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 35. Results of observations about reproductive performance

Dose	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Number of mated pares [A]	12	12	12	12
Number of copulated pares [B]	12	12	12	12
Copulation index [(B/A)×100, %]	100.0	100.0	100.0	100.0
Number of fertile males [C]	12	12	11	12
Fertility index [(C/B)×100, %]	100.0	100.0	91.7	100.0
Paring days until copulation ; Mean±S.D. (N)	1.9 ± 1.1 (12)	2.7 ± 1.2 (12)	3.0 ± 1.1 (12)	2.6 ± 2.0 (12)

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 36. Observation of offspring (F_1)

Group	Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of dams	12	12	11	12
Gestation length (days)				
Mean ± S.D. per dam	22.0 ± 0.0	21.9 ± 0.3	22.0 ± 0.0	21.9 ± 0.3
Number of corpora lutea				
Total	185	197	165	189
Mean ± S.D. per dam	15.4 ± 2.2	16.4 ± 2.0	15.0 ± 1.9	15.8 ± 1.5
Number of implantation scars				
Total	179	195	161	185
Mean ± S.D. per dam	14.9 ± 2.2	16.3 ± 2.0	14.6 ± 2.0	15.4 ± 1.6
Implantation index (%) [a]	96.6 ± 5.8	99.0 ± 3.4	97.7 ± 5.2	97.9 ± 4.2
Delivery index (dams,%) [b]	100.0	100.0	100.0	100.0
Number of offspring at birth				
Total	160	178	156	179
Mean ± S.D. per dam	13.3 ± 2.6	14.8 ± 2.5	14.2 ± 2.2	14.9 ± 1.4
Number of live offspring at birth				
Male	77	81	80	88
Female	83	94	73	91
Total	160	175	153	179
Mean ± S.D. per dam	13.3 ± 2.6	14.6 ± 2.1	13.9 ± 2.3	14.9 ± 1.4
Sex ratio [c]				
Mean ± S.D. per dam	0.48 ± 0.11	0.47 ± 0.12	0.52 ± 0.16	0.49 ± 0.10
Number of dead offspring				
Total	0	3	3	0
Mean ± S.D. per dam	0.0 ± 0.0	0.3 ± 0.6	0.3 ± 0.5	0.0 ± 0.0
Delivery index (offspring) [d]				
Mean% ± S.D. per dam	90.0 ± 14.0	91.1 ± 8.6	96.7 ± 4.9	97.0 ± 4.8
Birth index [e]				
Mean% ± S.D. per dam	90.0 ± 14.0	89.8 ± 7.7	94.8 ± 5.4	97.0 ± 4.8
Live birth index [f]				
Mean% ± S.D. per dam	100.0 ± 0.0	98.7 ± 3.2	98.0 ± 3.4	100.0 ± 0.0
Number of offspring on day 4				
Male	77	80	80	88
Female	83	94	72	89
Sex ratio [c]				
Mean ± S.D. per dam	0.48 ± 0.11	0.47 ± 0.12	0.53 ± 0.16	0.49 ± 0.11
Viability index [g]				
Mean% ± S.D. per dam	100.0 ± 0.0	99.4 ± 1.9	99.3 ± 2.3	99.0 ± 2.5
Number of external abnormalities [h]	0	0	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

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

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

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

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

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

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

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

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

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

Figures in parentheses indicate number of dams.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 37. Body weights of offspring (F_1) before weaning

Group		Control (vehicle: water for injection)	N-DPS 15 mg/kg	N-DPS 50 mg/kg	N-DPS 150 mg/kg
Number of dams		12	12	11	12
Male					
Days after birth					
	0	7.0 ± 0.4	6.6 ± 0.4	6.9 ± 0.4	6.9 ± 0.5
	4	11.5 ± 0.9	10.8 ± 0.7	10.9 ± 1.0	9.9 ± 1.2 **
Number of dams		12	12	11	12
Female					
Days after birth					
	0	6.7 ± 0.4	6.2 ± 0.3 **	6.4 ± 0.3	6.5 ± 0.4
	4	11.1 ± 1.1	10.0 ± 0.8 *	10.6 ± 0.8	9.4 ± 1.0 **

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

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Table 38. General conditions in offspring (F_1) before weaning

Group	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
Control (vehicle: water for injection)	Number of offspring	160	160	160	160	160
	General appearance, No abnormality	160	160	160	160	160
	General appearance, Death					
N-DPS 15 mg/kg	Number of offspring	175	175	174	174	174
	General appearance, No abnormality	175	174	174	174	174
	General appearance, Death		1			
N-DPS 50 mg/kg	Number of offspring	153	153	152	152	152
	General appearance, No abnormality	153	152	152	152	152
	General appearance, Death		1			
N-DPS 150 mg/kg	Number of offspring	179	179	177	177	177
	General appearance, No abnormality	179	177	177	177	177
	General appearance, Death		2			

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Table 39. Morphological observations of offspring (F_1)

Dose	Control (vehicle: water for injection)	N-DPS (15 mg/kg)	N-DPS (50 mg/kg)	N-DPS (150 mg/kg)
Dead offspring				
Number of dead offspring [a]	0	4	4	2
Number of missing offspring	0	1	1	1
Number of dead offspring examined	0 (0) [b]	3 (1) [b]	3 (0) [b]	1 (0) [b]
Number of dead offspring with external changes	0	0	0	0
Number of dead offspring with visceral changes	0	0	0	0
Live offspring				
Number of live offspring examined (postnatal day 0)	160	175	153	179
Number of live offsping with external changes	0	0	0	0
Number of live offspring examined (postnatal day 4)	160	174	152	177
Number of live offspring with external changes	0	0	0	0
Number of live offspring with visceral changes	0	0	0	0

Significantly different from the control group (*: $p<0.05$, **: $p<0.01$).
a) including missing offspring
b) Parenthesis indicates the number of offspring not examined bacause of their autolysis.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Control (vehicle: water for injection)

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Loose stool.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 1-1-1(continued). General conditions of male rats

Control (vehicle: water for injection)

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

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
b: Excretion, Decrease in amount of feces.
a: Excretion, Loose stool.
c: Behavior, Decrease in locomotor activity.
d: Body temperature, Hypothermia.
e: Skin, Pale skin.
f: Breathing, Dyspnea.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 1-1-2. General conditions of male rats

N-DPS 15 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Loose stool.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 1-1-2(continued). General conditions of male rats

N-DPS 15 mg/kg

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

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
b: Excretion, Decrease in amount of feces.
a: Excretion, Loose stool.
c: Behavior, Decrease in locomotor activity.
d: Body temperature, Hypothermia.
e: Skin, Pale skin.
f: Breathing, Dyspnea.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 1-1-3. General conditions of male rats

N-DPS 50 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Excretion, Loose stool.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 1-1-3(continued). General conditions of male rats

N-DPS 50 mg/kg

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

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
b: Excretion, Decrease in amount of feces.
a: Excretion, Loose stool.
c: Behavior, Decrease in locomotor activity.
d: Body temperature, Hypothermia.
e: Skin, Pale skin.
f: Breathing, Dyspnea.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 1-1-4. General conditions of male rats

N-DPS 150 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M04037	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04047	-	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	11	12	11	12	12	12	12	12	10	12	12	12	12	12	12	12	12	12	12	12	12	12	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	12	12	12
a	0	0	0	0	1	0	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Excretion, Loose stool.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 1-1-4(continued). General conditions of male rats

N-DPS 150 mg/kg

Male No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	b	-	b,a	-	b,a	-	b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	c	c	c,d,e,f
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04043	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04045	b,a	-	b,a	-	b,a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
-	9	12	10	12	10	12	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	6
b	2	0	2	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
a	2	0	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
b: Excretion, Decrease in amount of feces.
a: Excretion, Loose stool.
c: Behavior, Decrease in locomotor activity.
d: Body temperature, Hypothermia.
e: Skin, Pale skin.
f: Breathing, Dyspnea.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 1-2-1. General conditions of male rats at the recovery period

Control (vehicle: water for injection)

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

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 1-2-2. General conditions of male rats at the recovery period

N-DPS 150 mg/kg

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

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 2-1-1. General conditions of female rats

Control (vehicle: water for injection)

Female No.	Days of administration																																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	7	2	2	2	2	0	0	0	0	0	0	0	0
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	7	2	2	2	2	0	0	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
g: Breathing, Irregular respiration.
h: Breathing, Rale.
a: Excretion, Loose stool.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 2-1-2. General conditions of female rats

N-DPS 15 mg/kg

Female No.	Days of administration																																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	8	8	3	3	0	0	0	0	0	0	0	0
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	8	8	3	3	0	0	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
g: Breathing, Irregular respiration.
h: Breathing, Rale.
a: Excretion, Loose stool.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 2-1-3. General conditions of female rats

N-DPS 50 mg/kg

Female No.	Days of administration																																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-										
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	8	8	4	4	1	1	0	0	0	0	0	0
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	8	8	4	4	1	1	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
g: Breathing, Irregular respiration.
h: Breathing, Rale.
a: Excretion, Loose stool.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 2-1-4. General conditions of female rats

N-DPS 150 mg/kg

Female No.	Days of administration																																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-												
F04042	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	g,h	g,h	g,h	g	-	-	-	-	-	-										
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	4	4	3	3	1	1	1	1	1	1	1	1
-	12	12	12	12	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	12	12	8	8	4	4	3	3	1	1	1	1	1	1	1	1
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
a	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
g: Breathing, Irregular respiration.
h: Breathing, Rale.
a: Excretion, Loose stool.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F05049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

f: Breathing, Dyspnea.

d: Body temperature, Hypothermia.

i: General appearance, Death.

a: Excretion, Loose stool.

b: Excretion, Decrease in amount of feces.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 2-2-1(continued). General conditions of female rats, satellite group

Control (vehicle: water for injection)

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

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

N-DPS 150 mg/kg

Female No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F06059	-	-	-	-	-	-	-	-	-	-	-	-	f,d	f,d	f,d,b	f,d	f,d,b	f,d	f	f	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06060	-	-	-	-	-	-	-	-	-	-	-	-	i																																					
F06061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-
F06062	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	i													
F06063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8
-	10	10	10	10	9	10	10	10	10	10	10	10	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	8	8	8	8	8	8	8	8	8	8	7	8	8	8
f	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
a	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

f: Breathing, Dyspnea.

d: Body temperature, Hypothermia.

i: General appearance, Death.

a: Excretion, Loose stool.

b: Excretion, Decrease in amount of feces.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 2-2-2(continued). General conditions of female rats, satellite group

N-DPS 150 mg/kg

Female No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F06059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	4
-	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	4

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 2-3-1. General conditions of female rats at the recovery period

Control (vehicle: water for injection)

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

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 2-3-2. General conditions of female rats at the recovery period

N-DPS 150 mg/kg

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

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 3-1. General conditions in dams during pregnancy

Control (vehicle: water for injection)

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

>: Excluded from analysis (not pregnant)

(Continued)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 3-1(continued). General conditions in dams during pregnancy

Control (vehicle: water for injection)

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

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 3-2. General conditions in dams during pregnancy

N-DPS 15 mg/kg

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

>: Excluded from analysis (not pregnant)

(Continued)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 3-2(continued). General conditions in dams during pregnancy

N-DPS 15 mg/kg

Dam No.	Days of pregnancy																								
	14		15		16		17		18		19		20		21		22		23		24		25		26
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	0	0	0	0	0	0	0
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	0	0	0	0	0	0	0

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 3-3. General conditions in dams during pregnancy

N-DPS 50 mg/kg

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

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 3-3(continued). General conditions in dams during pregnancy

N-DPS 50 mg/kg

Dam No.	Days of pregnancy																								
	14		15		16		17		18		19		20		21		22		23		24		25		26
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F03029	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -	> -
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4	0	0	0	0	0	0	0
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4	0	0	0	0	0	0	0

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 3-4. General conditions in dams during pregnancy

N-DPS 150 mg/kg

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

>: Excluded from analysis (not pregnant)

(Continued)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 3-4(continued). General conditions in dams during pregnancy

N-DPS 150 mg/kg

Dam No.	Days of pregnancy																								
	14		15		16		17		18		19		20		21		22		23		24		25		26
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4	0	0	0	0	0	0	0
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	4	0	0	0	0	0	0	0

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 4-1. General conditions in dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F01001	-	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-
F01004	#	#	-	-	-	-	-	-	-	-	-
F01005	#	#	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-
F01007	#	#	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-
F01010	#	#	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-
F01012	#	#	-	-	-	-	-	-	-	-	-
Number of dams	7	7	12	12	12	12	12	12	12	12	12
-	7	7	12	12	12	12	12	12	12	12	12

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 4-2. General conditions in dams during lactation

N-DPS 15 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F02013	#	#	-	-	-	-	-	-	-	-	-
F02014	#	#	#	#	-	-	-	-	-	-	-
F02015	-	-	-	-	-	-	-	-	-	-	-
F02016	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-
F02020	#	#	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-
F02024	#	#	-	-	-	-	-	-	-	-	-
Number of dams	8	8	12	12	12	12	12	12	12	12	12
-	8	8	12	12	12	12	12	12	12	12	12

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 4-3. General conditions in dams during lactation

N-DPS 50 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F03025	#	#	-	-	-	-	-	-	-	-	-
F03026	-	-	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-
F03030	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-
F03032	#	#	-	-	-	-	-	-	-	-	-
F03033	#	#	-	-	-	-	-	-	-	-	-
F03034	#	#	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-
Number of dams	7	7	11	11	11	11	11	11	11	11	11
-	7	7	11	11	11	11	11	11	11	11	11

Pre: Before administration, Post: after administration.

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

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 4-4. General conditions in dams during lactation

N-DPS 150 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F04037	-	-	-	-	-	-	-	-	-	-	-
F04038	#	#	-	-	-	-	-	-	-	-	-
F04039	#	#	-	-	-	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-
F04042	#	#	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	-	-	-	-	-	-
F04044	#	#	-	-	-	-	-	-	-	-	-
F04045	-	-	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	-	-	-	-	-	-
F04048	#	#	-	-	-	-	-	-	-	-	-
Number of dams	7	7	12	12	12	12	12	12	12	12	12
-	7	7	12	12	12	12	12	12	12	12	12

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 5-1. Detailed clinical observations of male rats

Control (vehicle: water for injection)

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

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

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

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

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

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, hypothermia]

Fur [2, normal; 1, Moist fur]

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

Lacrimation [2, not observed; 1, observed]

Piloerection [2, normal; 3, slight]

respiratory rate[2, normal; 1, hypopnea]

stereotypy[2, not observed; 3, observed]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 5-1(continued). Detailed clinical observations of male rats

Control (vehicle: water for injection)

Male No.	Removing from cage / Observations made while handling b)																											Open-field observations c)																										
	Fur									Skin color / Mucuous membranes									Lacrimation									Piloerection									Respiratory rate									Stereotypy								
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	R7[c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M01001	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01002	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01003	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01004	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01005	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01006	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01007	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 5-1(continued). Detailed clinical observations of male rats

Control (vehicle: water for injection)

Male No.	Open-field observations [c)]																		
	Urination									Defecation									
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M01001	0	2	0	0	0	0	1			0	0	0	0	0	0	0		
M01002	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01003	0	2	0	0	1	0	1			0	0	0	0	0	0	0		
M01004	0	0	0	0	0	0	0			0	0	0	0	0	0	1		
M01005	1	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01006	1	1	0	1	0	0	0			0	0	0	0	0	0	0		
M01007	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01008	0	0	1	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0
M01009	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01010	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M01011	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01012	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0
Total	3	5	1	1	1	0	3	4	0	1	0	1	0	0	0	1	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 5-2. Detailed clinical observations of male rats

N-DPS (15 mg/kg)

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

[a] pre-treatment; [b] day 8 of treatment

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 5-2(continued). Detailed clinical observations of male rats

N-DPS (15 mg/kg)

Male No.	Removing from cage / Observations made while handling [b)]																					Open-field observations [c)]																				
	Fur							Skin color / Mucuous membranes							Lacrimation							Piloerection							Respiratory rate							Stereotypy						
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02014	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02015	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02016	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02017	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02018	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02019	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02020	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02021	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02022	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02023	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02024	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 8 of treatment

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 5-2(continued). Detailed clinical observations of male rats

N-DPS (15 mg/kg)

Male No.	Open-field observations [c]													
	Urination							Defecation						
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M02013	0	4	1	1	1	0	1	0	0	0	0	0	0	0
M02014	0	0	0	0	1	0	0	0	0	0	0	0	0	0
M02015	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02017	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02018	0	0	2	0	0	0	1	0	0	0	0	0	0	0
M02019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02020	0	0	0	0	1	0	1	0	0	0	0	0	0	0
M02021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02022	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02024	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Total score	0	4	4	1	3	0	3	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 8 of treatment

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 5-3. Detailed clinical observations of male rats

N-DPS (50 mg/kg)

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

[a] pre-treatment; [b] day 8 of treatment

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 5-3(continued). Detailed clinical observations of male rats

N-DPS (50 mg/kg)

Male No.	Removing from cage / Observations made while handling b)																					Open-field observations c)																				
	Fur							Skin color / Mucuous membranes							Lacrimation							Piloerection							Respiratory rate							Stereotypy						
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M03025	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03026	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03027	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03028	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03029	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03030	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03031	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03032	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03033	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03034	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03035	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03036	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 8 of treatment

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 5-3(continued). Detailed clinical observations of male rats

N-DPS (50 mg/kg)

Male No.	Open-field observations [c]													
	Urination							Defecation						
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M03025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03026	0	1	0	0	0	1	1	0	0	0	0	0	0	0
M03027	0	0	1	0	0	0	0	0	0	0	0	0	0	0
M03028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03030	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03032	0	2	0	0	0	1	0	0	0	0	0	0	0	0
M03033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03034	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03035	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03036	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	0	3	1	0	0	2	1	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 8 of treatment

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 5-4. Detailed clinical observations of male rats

N-DPS (150 mg/kg)

Male No.	Cage-side observations [a)]																	
	Posture in home-cage									Locomotor in home-cage								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M04037	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04038	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04039	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04040	2	2	2	2	2	2	1			2	2	2	2	2	2	1		
M04041	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04042	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04043	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04044	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04045	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04046	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04048	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:1	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:1	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

Male No.	Removing from cage / Observations made while handling [b)]																										
	Handling behavior									Heart beats									Body temperature								
	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M04037	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04038	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04039	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04040	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04041	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04042	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04043	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04044	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04045	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04046	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04048	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

N-DPS (150 mg/kg)

Male No.	Removing from cage / Observations made while handling [b]																										
	Fur									Skin color / Mucuous membranes									Lacrimation								
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	R7[c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M04037	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04038	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04039	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04040	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04041	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04042	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04043	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04044	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04045	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04046	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04048	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

Male No.	Open-field observations [c]																										
	Piloerection									Respiratory rate									Stereotypy								
	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M04037	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04038	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04039	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04040	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04041	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04042	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04043	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04044	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04045	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04046	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04048	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 5-4(continued). Detailed clinical observations of male rats

N-DPS (150 mg/kg)

Male No.	Open-field observations [c]																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M04037	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04038	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04039	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04040	0	1	0	0	0	0	0			0	0	0	0	0	0	0		
M04041	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04042	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04043	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04044	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04045	0	0	0	0	0	1	1	2	0	0	0	0	0	0	0	0	0	0
M04046	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04047	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M04048	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Total score	0	2	0	0	0	2	1	3	0	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-1. Detailed clinical observations of female rats

Control (vehicle: water for injection)

Female No.	Cage-side observations a)																Removing from cage / Observations made while handling b)																															
	Posture in home-cage								Locomotor in home-cage								Handling behavior								Heart beats								body temperature								Fur							
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	L[c]	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L
F01001	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01002	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01003	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01004	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01005	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01006	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01007	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01008	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01009	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01010	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01011	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01012	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-1(continued). Detailed clinical observations of female rats

Control (vehicle: water for injection)

Female No.	Removing from cage / Observations made while handling [b]																Open-field observations [c]																													
	Skin color / Mucuous membranes								Lacrimation								Piloerection								respiratory rate								Stereotypy							
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	L [c]	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L
F01001	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01002	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01003	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01004	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01005	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01006	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01007	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01008	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01009	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01010	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01011	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F01012	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-1(continued). Detailed clinical observations of female rats

Control (vehicle: water for injection)

Female No.	Open-field observations [c]															
	Urination								Defecation							
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	L [c]	Pre	T8	T15	T24	T30	T36	T42	L
F01001	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01002	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01003	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01004	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01005	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01006	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01007	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01008	0	0	1	0	0	0	0		0	0	0	0	0	0	0	
F01009	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01010	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01011	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F01012	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
Total score	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-2. Detailed clinical observations of female rats

N-DPS (15 mg/kg)

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

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-2(continued). Detailed clinical observations of female rats

N-DPS (15 mg/kg)

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

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-2(continued). Detailed clinical observations of female rats

N-DPS (15 mg/kg)

Female No.	Open-field observations [c]															
	Urination								Defecation							
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	L [c]	Pre	T8	T15	T24	T30	T36	T42	L
F02013	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02014	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02015	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02016	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02017	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02018	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02019	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02020	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02021	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02022	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02023	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02024	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
Total score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

N-DPS (50 mg/kg)

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

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-3(continued). Detailed clinical observations of female rats

N-DPS (50 mg/kg)

Female No.	Removing from cage / Observations made while handling [b]																Open-field observations [c]																									
	Skin color / Mucuous membranes								Lacrimation								Piloerection								respiratory rate								Stereotypy							
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	L [c]	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L
F03025	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03026	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03027	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03028	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03029	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03030	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03031	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03032	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03033	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03034	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03035	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F03036	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-3(continued). Detailed clinical observations of female rats
(continued). Detailed clinical observations of females

N-DPS (50 mg/kg)

Female No.	Open-field observations [c)]															
	Urination								Defecation							
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	L [c]	Pre	T8	T15	T24	T30	T36	T42	L
F03025	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F03026	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F03027	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F03028	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F03029	0	0	0	1	0	0	0		0	0	0	0	0	0	0	
F03030	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F03031	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F03032	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03033	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F03034	1	0	0	0	0	0	3		0	0	0	0	0	0	0	
F03035	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F03036	0	0	0	1	0	0	0		0	0	0	0	0	0	0	
Total score	1	0	0	2	0	0	3	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-4. Detailed clinical observations of female rats

N-DPS (150 mg/kg)

	Cage-side observations [a)]															
Female No.	Posture in home-cage								Locomotor in home-cage							
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	L[c]	Pre	T8	T15	T24	T30	T36	T42	L
F04037	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04038	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04039	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04040	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04041	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04042	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04043	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04044	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04045	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04046	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04048	2	2	2	2	2	2	2		2	2	2	2	2	2	2	
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)

	Removing from cage / Observations made while handling [b)]																															
Female No.	Handling behavior								Heart beats								body temperature								Fur							
	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L
F04037	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04038	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04039	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04040	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04041	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04042	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04043	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04044	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04045	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04046	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04048	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-4(continued). Detailed clinical observations of female rats

N-DPS (150 mg/kg)

Female No.	Removing from cage / Observations made while handling [b]																Open-field observations [c]																													
	Skin color / Mucuous membranes								Lacrimation								Piloerection								respiratory rate								Stereotypy							
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	L [c]	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L	Pre	T8	T15	T24	T30	T36	T42	L
F04037	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04038	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04039	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04040	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04041	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04042	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04043	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04044	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04045	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04046	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
F04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F04048	2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2		2	2	2	2	2	2	2	
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-1-4(continued). Detailed clinical observations of female rats

N-DPS (150 mg/kg)

Female No.	Open-field observations [c]															
	Urination								Defecation							
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	L [c]	Pre	T8	T15	T24	T30	T36	T42	L
F04037	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04038	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04039	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04040	1	1	1	0	0	0	0		0	0	0	0	0	0	0	
F04041	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04042	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04043	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04044	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04045	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04046	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04047	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04048	0	0	0	0	0	0	0		0	0	0	0	0	0	0	
Total score	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-2-1. Detailed clinical observations of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Cage-side observations a)																	
	Posture in home-cage									Locomotor in home-cage								
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	R7[c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F05049	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05050	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05051	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05052	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05053	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05054	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05055	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05056	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05057	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05058	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

Female No.	Removing from cage / Observations made while handling b)																	
	Handling behavior									Heart beats								
	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F05049	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05050	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05051	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05052	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05053	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05054	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05055	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05056	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05057	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05058	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

Female No.	Removing from cage / Observations made while handling b)																	
	body temperature									Fur								
	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F05049	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05050	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05051	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05052	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05053	2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05054	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05055	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05056	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05057	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05058	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

Control (vehicle: water for injection)

Female No.	Removing from cage / Observations made while handling [b]																																												
	Skin color / Mucuous membranes									Lacrimation									Piloerection									respiratory rate									Stereotypy								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F05049	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05050	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05051	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05052	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05053	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05054	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05055	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05056	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05057	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05058	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-2-1(continued). Detailed clinical observations of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Open-field observations [c)]																		
	Urination									Defecation									
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F05049	0	0	0	3	0	0	0			1	0	0	0	0	0	0		
F05050	0	0	0	0	0	0	2			0	0	0	0	0	0	0		
F05051	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05052	0	0	0	1	0	0	0			0	0	0	0	0	0	0		
F05053	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05054	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05055	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05056	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05057	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05058	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	1	0	0	4	0	0	2	0	0	1	0	0	0	0	0	0	0	0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-2-2. Detailed clinical observations of female rats, satellite group

N-DPS (150 mg/kg)

Female No.	Cage-side observations a)																		Removing from cage / Observations made while handling b)								
	Posture in home-cage									Locomotor in home-cage									Handling behavior								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F06059	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06060	2									2									2								
F06061	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06062	2	2	2							2	2	2							2	2	2						
F06063	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06064	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06065	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06066	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06067	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06068	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)

Female No.																											
	Heart beats									body temperature									Fur								
	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F06059	2	2	2	2	2	2	2			2	1	2	2	2	2	2			2	2	2	2	2	2	2		
F06060	2									2									2								
F06061	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06062	2	2	2							2	2	2							2	2	2						
F06063	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06064	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06065	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06066	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06067	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06068	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:1	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0
(N)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

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

N-DPS (150 mg/kg)

Female No.	Removing from cage / Observations made while handling [b]																																												
	Skin color / Mucuous membranes									Lacrimation									Piloerection									respiratory rate									Stereotypy								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F06059	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	1	2	2	2	2	2			2	2	2	2	2	2	2		
F06060	2									2									2									2									2								
F06061	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06062	2	2	2							2	2	2							2	2	2							2	2	2							2	2	2						
F06063	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06064	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06065	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06066	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06067	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06068	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1:0	1:1	1:0	1:0	1:0	1:0	1:0	1:0	1:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 6-2-2(continued). Detailed clinical observations of female rats, satellite group

N-DPS (150 mg/kg)

Female No.	Open-field observations [c]																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F06059	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F06060	0									0								
F06061	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F06062	0	0	0							0	0	0						
F06063	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F06064	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F06065	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F06066	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F06067	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F06068	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)	(10)	(9)	(9)	(8)	(8)	(8)	(8)	(4)	(4)

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

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 7-1-1. Body weights of male rats

Control (vehicle: water for injection)

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M01001	385.3	395.5	405.6	427.4	441.6	457.6	479.3	484.6
M01002	386.0	392.8	400.5	408.9	420.9	447.2	468.1	459.7
M01003	397.6	412.6	428.3	469.5	498.9	530.0	543.3	551.8
M01004	392.4	399.1	403.3	424.7	447.9	467.3	477.7	478.7
M01005	399.3	413.2	415.7	447.7	466.1	493.1	508.7	524.1
M01006	407.0	415.2	421.3	443.3	459.5	477.1	490.3	519.2
M01007	415.9	425.5	436.9	465.1	474.2	496.9	521.5	554.7
M01008	368.2	385.1	388.0	416.2	433.0	458.1	458.5	471.5
M01009	403.8	412.2	417.9	445.4	468.7	505.7	528.9	541.8
M01010	394.6	411.5	424.4	446.6	455.2	469.5	472.9	483.3
M01011	384.9	396.6	408.4	431.1	458.8	490.7	514.9	541.8
M01012	375.5	387.4	390.3	412.5	432.2	453.4	458.9	465.6
Number of males	12	12	12	12	12	12	12	12
Mean	392.5	403.9	411.7	436.5	454.8	478.9	493.6	506.4
S.D.	13.5	12.7	15.0	19.7	21.4	24.8	28.9	36.0

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 7-1-2. Body weights of male rats
N-DPS 15 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M02013	393.8	408.4	412.0	441.3	455.1	457.8	472.6	476.5
M02014	412.5	419.5	432.4	453.3	468.0	485.0	496.1	512.0
M02015	376.7	380.8	389.6	414.0	426.1	438.6	459.0	461.1
M02016	374.5	387.8	391.5	418.8	430.0	449.0	465.2	473.7
M02017	390.8	399.0	403.3	421.4	434.7	439.2	455.6	459.4
M02018	393.7	404.5	413.1	443.1	463.7	481.1	503.3	519.6
M02019	386.3	397.1	405.7	436.7	458.0	487.1	509.7	529.0
M02020	392.7	403.9	418.4	448.3	461.5	487.2	506.8	525.9
M02021	406.6	411.6	418.4	449.7	463.3	493.7	507.8	531.6
M02022	368.5	369.3	376.3	401.5	424.8	442.3	459.0	471.0
M02023	396.9	411.2	415.0	437.2	451.1	476.8	486.6	512.1
M02024	415.6	430.9	445.6	480.4	503.4	534.6	555.5	573.9
Number of males	12	12	12	12	12	12	12	12
Mean	392.4	402.0	410.1	437.1	453.3	472.7	489.8	503.8
S.D.	14.6	16.8	18.8	21.0	22.3	28.5	29.4	35.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	AN	DU	DU	DU	DU	DU

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 7-1-3. Body weights of male rats
N-DPS 50 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M03025	385.1	387.8	355.5	405.3	433.7	463.9	484.2	489.7
M03026	387.6	393.3	395.3	425.5	432.6	453.2	471.8	480.3
M03027	382.1	397.5	411.3	442.8	458.3	487.0	500.6	496.9
M03028	425.9	450.4	458.1	495.9	495.8	541.0	564.3	574.0
M03029	376.3	387.2	398.2	429.8	446.3	463.6	474.9	486.6
M03030	389.3	398.9	407.7	438.5	450.5	470.0	493.5	504.9
M03031	379.5	400.9	419.3	452.9	476.2	510.6	535.1	566.1
M03032	365.2	371.4	382.7	402.0	420.3	447.8	468.3	482.4
M03033	390.0	404.7	408.7	426.6	454.5	474.1	491.8	504.9
M03034	409.5	421.8	429.8	452.3	463.2	486.0	497.2	519.6
M03035	408.7	424.7	433.6	454.1	475.0	485.4	506.2	521.9
M03036	378.0	379.7	398.3	415.8	441.4	466.4	483.7	497.3
Number of males	12	12	12	12	12	12	12	12
Mean	389.8	401.5	408.2	436.8	454.0	479.1	497.6	510.4
S.D.	17.0	21.8	26.2	25.7	21.4	25.9	27.6	30.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	AN	DU	DU	DU	DU	DU

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 7-1-4. Body weights of male rats
N-DPS 150 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M04037	408.1	384.0	365.9	435.4	447.3	463.5	465.5	461.5
M04038	413.1	419.4	440.0	467.4	489.6	417.1	460.4	453.9
M04039	374.8	361.6	364.5	380.2	388.5	395.2	408.6	398.3
M04040	383.1	370.8	389.5	413.1	427.1	444.7	450.7	402.1
M04041	401.9	400.3	407.3	431.2	443.2	465.4	473.8	485.1
M04042	374.4	369.1	382.1	401.2	410.8	421.4	426.7	428.9
M04043	388.6	384.5	400.4	415.3	419.3	425.4	432.6	428.5
M04044	378.7	383.8	390.3	423.5	451.3	470.8	481.9	493.0
M04045	393.5	399.2	404.7	427.4	433.4	387.4	420.8	430.0
M04046	361.9	360.3	370.2	380.5	403.3	411.6	421.1	417.7
M04047	382.7	359.3	388.7	349.3	405.0	449.4	491.4	485.7
M04048	398.2	403.4	389.0	426.6	456.3	478.3	498.3	505.6
Number of males	12	12	12	12	12	12	12	12
Mean	388.3	383.0	391.1	412.6	431.3	435.9	452.7	449.2
S.D.	15.2	19.5	20.9	31.1	28.1	30.4	30.4	36.8
Significance	NS	*	NS	NS	*	**	**	**
Statistical method	AN	DU	AN	DU	DU	DU	DU	DU

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 7-2-1. Body weights of male rats at the recovery period

Control (vehicle: water for injection)

Male No.	Days of recovery		
	1	7	14
M01008	473.0	489.2	502.2
M01009	539.1	550.0	561.3
M01010	473.1	493.3	485.4
M01011	532.3	562.9	564.9
M01012	458.7	485.7	494.1
Number of males	5	5	5
Mean	495.2	516.2	521.6
S.D.	37.5	37.1	38.4

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 7-2-2. Body weights of male rats at the recovery period

N-DPS 150 mg/kg

Male No.	Days of recovery		
	1	7	14
M04044	493.6	513.5	527.3
M04045	436.4	460.9	473.7
M04046	430.8	460.8	468.4
M04047	504.2	529.6	544.8
M04048	509.8	531.1	546.9
Number of males	5	5	5
Mean	475.0	499.2	512.2
S.D.	38.3	35.7	38.4
Significance	NS	NS	NS
Statistical method	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 8-1-1. Body weights of female rats

Control (vehicle: water for injection)

Female No.	Days of administration				
	1	4	7	14	21
F01001	246.3	258.0	257.4	264.6	
F01002	225.6	218.4	225.5	223.9	
F01003	261.6	271.5	283.4	293.8	
F01004	250.4	264.2	273.3	276.0	
F01005	238.0	245.9	254.9	260.1	
F01006	220.4	224.9	230.7	241.8	
F01007	240.8	245.1	246.8	261.2	
F01008	245.5	247.2	256.7	264.9	
F01009	238.4	252.3	257.0	256.7	
F01010	239.9	240.9	251.7	270.9	
F01011	247.2	268.1	268.5	279.0	
F01012	251.8	249.8	265.4	279.8	
Number of females	12	12	12	12	
Mean	242.2	248.9	255.9	264.4	
S.D.	11.2	16.0	16.4	18.4	

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 8-1-2. Body weights of female rats

N-DPS 15 mg/kg

Female No.	Days of administration				
	1	4	7	14	21
F02013	243.1	243.5	244.3	244.4	
F02014	246.9	253.0	251.6	261.9	
F02015	235.4	240.7	245.6	256.7	
F02016	244.5	240.2	240.0	256.2	
F02017	228.2	245.1	248.8	258.9	
F02018	264.0	267.2	276.9	301.1	
F02019	243.6	254.9	262.4	260.8	
F02020	256.5	257.3	266.9	280.8	
F02021	217.1	223.5	231.3	235.8	
F02022	242.4	246.8	258.8	271.9	
F02023	267.5	271.9	280.4	289.1	
F02024	267.9	271.2	279.4	281.8	
Number of females	12	12	12	12	
Mean	246.4	251.3	257.2	266.6	
S.D.	15.6	14.3	16.3	18.9	
Significance	NS	NS	NS	NS	
Statistical method	AN	AN	AN	AN	

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 8-1-3. Body weights of female rats

N-DPS 50 mg/kg

Female No.	Days of administration				
	1	4	7	14	21
F03025	264.8	268.9	267.5	288.7	
F03026	244.6	242.1	233.1	249.0	
F03027	263.4	273.2	275.3	281.5	
F03028	223.5	236.1	243.0	247.8	
F03029	256.7	260.1	262.8	268.1	
F03030	237.0	241.5	245.8	249.5	
F03031	232.8	242.4	252.3	253.5	
F03032	234.3	242.8	251.6	252.8	
F03033	243.8	254.8	264.9	263.6	
F03034	245.1	256.0	260.5	268.8	
F03035	238.5	243.5	251.7	251.6	
F03036	242.1	243.4	258.4	273.5	
Number of females	12	12	12	12	
Mean	243.9	250.4	255.6	262.4	
S.D.	12.4	12.0	11.7	13.8	
Significance	NS	NS	NS	NS	
Statistical method	AN	AN	AN	AN	

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 8-1-4. Body weights of female rats

N-DPS 150 mg/kg

Female No.	Days of administration				
	1	4	7	14	21
F04037	227.9	242.2	245.2	250.5	
F04038	230.7	240.2	246.9	258.7	
F04039	235.9	243.2	254.1	262.0	
F04040	261.3	263.7	271.2	288.2	
F04041	223.1	240.1	242.9	250.6	
F04042	250.1	251.0	255.1	262.0	
F04043	261.2	268.2	278.2	283.9	
F04044	247.6	246.6	249.4	261.4	
F04045	266.3	270.0	268.4	281.9	
F04046	239.5	239.9	260.2	276.7	
F04047	241.2	248.3	255.7	260.3	277.3
F04048	226.6	228.8	227.3	247.3	
Number of females	12	12	12	12	
Mean	242.6	248.5	254.6	265.3	
S.D.	14.7	12.7	13.9	13.9	
Significance	NS	NS	NS	NS	
Statistical method	AN	AN	AN	AN	

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 8-2-1. Body weights of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F05049	263.6	267.4	273.0	278.0	294.5	307.4	314.9	314.9
F05050	236.5	245.7	255.1	258.7	260.0	272.8	283.2	278.9
F05051	240.7	240.5	253.6	266.8	278.2	313.3	321.0	298.2
F05052	241.0	251.0	258.7	276.3	289.8	300.7	320.3	320.5
F05053	241.3	252.3	260.6	267.9	284.7	289.3	288.0	299.7
F05054	213.4	220.4	226.7	236.0	243.0	252.5	258.8	255.5
F05055	231.0	238.8	247.7	256.8	274.0	272.9	284.9	283.0
F05056	248.9	241.9	260.2	263.2	284.9	288.6	302.4	318.4
F05057	254.8	257.6	259.0	283.2	303.4	305.4	304.8	313.7
F05058	227.9	246.5	257.6	266.7	267.4	282.4	288.0	293.6
Number of females	10	10	10	10	10	10	10	10
Mean	239.9	246.2	255.2	265.4	278.0	288.5	296.6	297.6
S.D.	14.2	12.5	11.9	13.3	17.7	18.9	19.7	20.7

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 8-2-2. Body weights of female rats, satellite group

N-DPS 150 mg/kg

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F06059	252.6	250.7	239.3	262.7	269.5	274.8	284.1	290.7
F06060	226.9	229.9						
F06061	243.1	241.9	245.0	263.8	275.9	275.0	275.4	280.9
F06062	243.9	249.4	254.5	264.9				
F06063	228.3	221.4	230.8	238.8	235.9	251.1	250.0	254.7
F06064	247.9	256.9	264.3	271.8	286.4	302.3	298.7	301.6
F06065	240.3	244.4	257.3	262.9	270.7	274.6	288.4	294.2
F06066	247.4	247.1	259.9	298.4	285.3	283.2	286.0	290.0
F06067	260.8	262.8	266.1	281.4	293.7	304.2	309.9	326.2
F06068	261.0	261.9	272.5	292.3	294.7	304.4	311.6	274.8
Number of females	10	10	9	9	8	8	8	8
Mean	245.2	246.6	254.4	270.8	276.5	283.7	288.0	289.1
S.D.	11.6	13.2	13.6	17.9	19.0	18.9	19.9	20.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 8-3-1. Body weights of female rats at the recovery period

Control (vehicle: water for injection)

Female No.	Days of recovery		
	1	7	14
F05054	254.0	260.2	258.0
F05055	280.5	300.7	299.0
F05056	319.2	337.3	338.4
F05057	309.4	326.3	331.9
F05058	297.6	297.3	309.1
Number of females	5	5	5
Mean	292.1	304.4	307.3
S.D.	25.7	29.9	31.9

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 8-3-2. Body weights of female rats at the recovery period

N-DPS 150 mg/kg

Female No.	Days of recovery		
	1	7	14
F06065	300.5	313.4	316.2
F06066	293.2	320.8	324.1
F06067	320.7	338.8	337.7
F06068	279.5	325.2	341.4
Number of females	4	4	4
Mean	298.5	324.6	329.9
S.D.	17.2	10.7	11.8
Significance	NS	NS	NS
Statistical method	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 9-1. Body weights of dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy				
	0	7	14	20	26
F01001	270.8	323.4	364.2	468.8	
F01002	236.9	269.2	307.8	381.3	
F01003	305.0	343.7	374.8	444.9	
F01004	280.8	324.3	362.3	425.5	
F01005	271.2	321.2	357.1	436.0	
F01006	249.5	278.4	314.3	385.5	
F01007	277.5	302.0	335.4	422.6	
F01008	264.5	304.3	332.6	394.8	
F01009	258.8	300.8	344.9	437.1	
F01010	273.0	310.4	348.9	440.7	
F01011	294.1	332.4	356.7	442.1	
F01012	281.8	332.5	369.3	444.5	
Number of dams	12	12	12	12	
Mean	272.0	311.9	347.4	427.0	
S.D.	18.5	22.3	21.2	26.7	

>: Excluded from analysis (not pregnant)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 9-2. Body weights of dams during pregnancy

N-DPS 15 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F02013	265.4	309.9	344.9	408.4	
F02014	271.3	303.9	339.7	414.6	
F02015	263.0	305.8	346.0	444.5	
F02016	273.3	310.6	356.7	450.5	
F02017	254.1	293.9	318.9	379.4	
F02018	296.2	332.9	372.7	471.4	
F02019	290.0	328.0	375.4	457.8	
F02020	304.6	335.6	367.9	449.3	
F02021	253.3	281.0	323.4	417.4	
F02022	257.6	300.7	332.8	417.2	
F02023	305.2	331.4	372.0	456.3	
F02024	297.5	331.9	377.6	477.5	
Number of dams	12	12	12	12	
Mean	277.6	313.8	352.3	437.0	
S.D.	19.9	17.9	20.9	29.3	
Significance	NS	NS	NS	NS	
Statistical method	KW	AN	AN	AN	

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 9-3. Body weights of dams during pregnancy

N-DPS 50 mg/kg

Dam No.	Days of pregnancy						
	0	7	14	20	26		
F03025	291.1	324.0	356.4	439.2			
F03026	269.4	310.6	349.2	428.1			
F03027	282.7	325.8	359.6	443.2			
F03028	251.3	288.3	330.3	433.8			
F03029	> 278.2 >	323.9 >	345.1 >	321.6 >	325.5 >	>	>
F03030	261.5	292.6	330.2	399.0			
F03031	262.1	285.9	322.2	402.5			
F03032	264.1	302.3	331.0	382.2			
F03033	275.6	308.0	349.3	418.2			
F03034	281.9	324.6	362.8	445.4			
F03035	253.1	299.6	326.5	407.0			
F03036	268.5	318.7	370.0	453.7			
Number of dams	11	11	11	11			
Mean	269.2	307.3	344.3	422.9			
S.D.	12.6	14.8	16.8	22.8			
Significance	NS	NS	NS	NS			
Statistical method	KW	AN	AN	AN			

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 9-4. Body weights of dams during pregnancy

N-DPS 150 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	26
F04037	259.9	293.9	331.5	423.7	
F04038	262.1	292.4	336.8	418.3	
F04039	264.8	296.6	330.2	426.4	
F04040	276.2	334.1	373.9	482.4	
F04041	258.5	282.7	322.9	403.4	
F04042	274.7	298.0	332.6	429.2	
F04043	280.7	326.2	373.9	457.6	
F04044	269.6	304.0	347.5	429.0	
F04045	278.8	332.3	374.9	461.4	
F04046	280.2	313.6	353.8	436.0	
F04047	277.7	317.8	359.2	449.4	
F04048	261.5	304.1	349.6	439.2	
Number of dams	12	12	12	12	
Mean	270.4	308.0	348.9	438.0	
S.D.	8.6	16.7	18.6	21.6	
Significance	NS	NS	NS	NS	
Statistical method	KW	AN	AN	AN	

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 10-1. Body weights of dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation	
	0	4
F01001	351.4	357.5
F01002	277.4	299.0
F01003	389.0	390.9
F01004	363.5	357.9
F01005	351.5	339.8
F01006	290.4	303.7
F01007	319.7	323.5
F01008	336.8	328.0
F01009	330.0	331.6
F01010	331.9	336.9
F01011	322.6	350.9
F01012	370.3	367.6
Number of dams	12	12
Mean	336.2	340.6
S.D.	32.0	26.3

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 10-2. Body weights of dams during lactation

N-DPS 15 mg/kg

Dam No.	Days of lactation	
	0	4
F02013	337.2	335.5
F02014	301.3	320.2
F02015	319.5	343.1
F02016	330.1	349.9
F02017	297.7	312.9
F02018	344.8	369.5
F02019	354.3	365.9
F02020	378.5	380.9
F02021	293.4	321.0
F02022	311.1	332.6
F02023	353.5	356.6
F02024	323.4	352.3
Number of dams	12	12
Mean	328.7	345.0
S.D.	26.0	21.3
Significance	NS	NS
Statistical method	AN	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 10-3. Body weights of dams during lactation

N-DPS 50 mg/kg

Dam No.	Days of lactation	
	0	4
F03025	339.1	348.5
F03026	313.2	325.0
F03027	355.4	343.2
F03028	299.2	340.4
F03030	311.8	320.3
F03031	289.5	304.0
F03032	331.3	339.1
F03033	340.1	341.1
F03034	362.1	345.8
F03035	309.7	343.7
F03036	373.3	359.8
Number of dams	11	11
Mean	329.5	337.4
S.D.	27.1	15.3
Significance	NS	NS
Statistical method	AN	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 10-4. Body weights of dams during lactation

N-DPS 150 mg/kg

Dam No.	Days of lactation	
	0	4
F04037	296.5	334.0
F04038	322.2	324.6
F04039	311.0	304.3
F04040	360.8	358.3
F04041	296.9	319.9
F04042	330.4	343.1
F04043	340.2	366.8
F04044	354.2	338.1
F04045	351.0	349.7
F04046	314.1	340.2
F04047	346.6	384.2
F04048	332.0	330.3
Number of dams	12	12
Mean	329.7	341.1
S.D.	21.8	21.6
Significance	NS	NS
Statistical method	AN	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 11-1-1. Food consumption of male rats

Control (vehicle: water for injection)

Male No.	Days of administration					
	1	7	14	29	35	41
M01001	31.4	30.6	32.3	31.1	30.3	34.0
M01002	27.9	29.4	26.0	29.4	29.6	26.0
M01003	31.3	27.7	33.4	36.4	32.1	29.0
M01004	28.3	27.9	28.8	31.5	26.8	25.9
M01005	31.0	30.9	31.5	33.3	30.7	33.7
M01006	29.9	30.7	28.1	31.4	28.3	30.2
M01007	35.7	31.2	33.0	32.8	33.3	34.5
M01008	32.1	36.1	32.9	29.9	31.3	28.4
M01009	27.4	30.0	29.9	36.5	30.8	33.1
M01010	33.8	31.2	30.3	27.4	30.7	30.3
M01011	30.8	29.2	30.1	33.9	29.5	35.9
M01012	28.7	26.7	28.0	26.1	22.3	24.2
Number of males	12	12	12	12	12	12
Mean	30.7	30.1	30.4	31.6	29.6	30.4
S.D.	2.5	2.4	2.3	3.2	2.9	3.8

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 11-1-2. Food consumption of male rats

N-DPS 15 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02013	29.7	28.3	25.5	26.0	24.9	26.9
M02014	31.1	27.6	27.6	26.9	26.6	29.3
M02015	28.6	26.7	25.1	29.9	25.8	26.4
M02016	28.9	28.8	30.1	34.4	29.3	30.1
M02017	29.0	26.7	25.7	30.3	27.5	27.6
M02018	31.1	28.7	27.2	29.3	26.8	31.6
M02019	29.8	29.5	31.0	33.8	30.7	30.3
M02020	31.5	31.3	33.6	33.5	31.7	32.9
M02021	29.9	32.7	32.0	29.7	31.3	33.0
M02022	29.9	28.9	31.1	33.0	29.6	28.8
M02023	32.5	30.4	27.7	29.3	29.6	28.1
M02024	32.7	31.5	34.8	39.9	36.2	35.9
Number of males	12	12	12	12	12	12
Mean	30.4	29.3	29.3	31.3	29.2	30.1
S.D.	1.4	1.9	3.3	3.8	3.1	2.8
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DT	KW	DU	AN	AN	DT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 11-1-3. Food consumption of male rats

N-DPS 50 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03025	27.1	24.3	29.8	29.0	27.4	29.6
M03026	26.8	24.6	23.7	31.7	26.8	29.8
M03027	30.8	28.5	27.9	26.2	27.7	24.4
M03028	33.8	35.6	34.2	39.8	31.3	37.2
M03029	28.8	33.3	30.2	31.3	30.0	30.7
M03030	29.9	27.1	24.1	27.5	24.3	25.6
M03031	32.8	28.5	30.6	29.9	30.4	34.0
M03032	24.9	21.2	23.1	27.4	23.5	30.5
M03033	36.1	32.8	34.4	28.7	26.2	28.0
M03034	31.3	30.3	32.7	29.3	31.5	29.7
M03035	35.1	27.5	30.4	26.9	28.4	27.8
M03036	25.5	29.5	29.6	33.7	26.7	29.2
Number of males	12	12	12	12	12	12
Mean	30.2	28.6	29.2	30.1	27.9	29.7
S.D.	3.7	4.1	3.9	3.7	2.6	3.4
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DT	KW	DU	AN	AN	DT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 11-1-4. Food consumption of male rats

N-DPS 150 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04037	32.1	37.8	32.8	29.5	31.2	20.8
M04038	32.9	30.5	25.4	32.4	15.1	16.9
M04039	20.2	26.7	20.8	25.0	19.5	14.7
M04040	23.7	34.2	27.3	31.0	28.8	7.6
M04041	25.4	28.9	27.7	32.6	30.8	32.8
M04042	22.5	24.7	24.8	26.4	26.0	8.4
M04043	28.7	28.7	26.5	43.0	28.2	27.0
M04044	25.4	23.2	26.5	32.2	28.2	26.3
M04045	23.6	28.2	26.4	33.3	28.4	16.5
M04046	24.8	26.4	26.1	26.3	25.3	20.5
M04047	14.9	25.9	14.4	29.4	32.1	16.1
M04048	27.8	28.8	25.5	27.6	29.4	19.6
Number of males	12	12	12	12	12	12
Mean	25.2	28.7	25.4	30.7	26.9	18.9
S.D.	4.9	4.0	4.4	4.8	5.0	7.3
Significance	*	NS	**	NS	NS	**
Statistical method	DT	KW	DU	AN	AN	DT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 11-2-1. Food consumption of male rats at the recovery period

Control (vehicle: water for injection)

Male No.	Days of recovery	
	6	12
M01008	30.0	32.2
M01009	29.6	29.8
M01010	31.4	30.2
M01011	34.1	34.7
M01012	35.0	34.2
Number of males	5	5
Mean	32.0	32.2
S.D.	2.4	2.2

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 11-2-2. Food consumption of male rats at the recovery period

N-DPS 150 mg/kg

Male No.	Days of recovery	
	6	12
M04044	30.1	32.3
M04045	27.6	25.3
M04046	29.8	28.4
M04047	33.6	35.6
M04048	33.3	35.6
Number of males	5	5
Mean	30.9	31.4
S.D.	2.5	4.5
Significance	NS	NS
Statistical method	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 12-1-1. Food consumption of female rats

Control (vehicle: water for injection)

Female No.	Days of administration		
	1	7	14
F01001	19.0	22.2	22.3
F01002	19.9	13.5	18.7
F01003	22.9	24.0	22.8
F01004	21.6	23.7	22.6
F01005	22.4	21.9	24.6
F01006	19.2	15.0	19.9
F01007	22.2	21.2	19.7
F01008	21.4	16.1	18.9
F01009	22.3	20.4	18.2
F01010	20.0	27.0	23.6
F01011	22.6	23.4	26.6
F01012	27.0	17.1	25.1
Number of females	12	12	12
Mean	21.7	20.5	21.9
S.D.	2.2	4.1	2.8

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 12-1-2. Food consumption of female rats

N-DPS 15 mg/kg

Female No.	Days of administration		
	1	7	14
F02013	14.0	23.5	21.1
F02014	19.9	22.5	17.2
F02015	16.9	21.1	20.8
F02016	23.1	20.0	17.1
F02017	24.7	21.0	21.6
F02018	24.4	19.6	24.2
F02019	13.3	21.5	24.0
F02020	20.7	22.3	18.5
F02021	15.3	17.8	20.0
F02022	25.5	18.6	20.8
F02023	17.8	19.6	19.7
F02024	18.7	20.6	20.6
Number of females	12	12	12
Mean	19.5	20.7	20.5
S.D.	4.2	1.7	2.2
Significance	NS	NS	NS
Statistical method	DU	KW	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 12-1-3. Food consumption of female rats

N-DPS 50 mg/kg

Female No.	Days of administration		
	1	7	14
F03025	21.5	21.8	14.1
F03026	21.1	19.9	13.5
F03027	15.4	24.4	24.8
F03028	20.3	21.2	21.0
F03029	18.0	21.7	22.5
F03030	14.9	22.2	17.2
F03031	20.6	18.3	20.3
F03032	19.1	21.9	18.2
F03033	18.1	23.1	22.1
F03034	23.9	21.3	22.7
F03035	22.7	18.9	19.6
F03036	22.0	14.7	23.8
Number of females	12	12	12
Mean	19.8	20.8	20.0
S.D.	2.8	2.5	3.6
Significance	NS	NS	NS
Statistical method	DU	KW	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 12-1-4. Food consumption of female rats

N-DPS 150 mg/kg

Female No.	Days of administration		
	1	7	14
F04037	16.5	17.5	19.1
F04038	21.6	18.6	23.0
F04039	16.7	21.7	20.2
F04040	21.1	20.1	20.6
F04041	16.8	20.6	17.3
F04042	19.6	20.6	14.5
F04043	16.5	20.9	20.2
F04044	19.7	18.2	15.6
F04045	16.0	23.3	19.1
F04046	20.2	20.1	21.0
F04047	17.5	15.2	22.0
F04048	16.0	19.3	21.1
Number of females	12	12	12
Mean	18.2	19.7	19.5
S.D.	2.1	2.1	2.5
Significance	*	NS	NS
Statistical method	DU	KW	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 12-2-1. Food consumption of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Days of administration						
	1	7	14	21	29	35	41
F05049	18.4	20.5	20.8	18.2	19.4	20.1	18.4
F05050	22.0	21.4	22.2	18.5	21.3	19.6	22.9
F05051	24.9	16.1	22.4	23.5	26.9	25.4	12.8
F05052	22.3	21.2	26.4	25.6	24.5	22.2	25.4
F05053	21.8	23.7	23.3	22.0	24.6	22.7	19.3
F05054	17.4	16.6	17.9	16.7	18.6	18.7	17.3
F05055	18.2	22.9	25.2	21.4	25.3	22.5	21.5
F05056	21.9	19.0	22.1	23.9	26.7	20.2	23.7
F05057	20.6	23.4	15.2	18.2	27.5	21.9	22.3
F05058	24.5	23.6	24.7	26.3	27.3	21.0	24.3
Number of females	10	10	10	10	10	10	10
Mean	21.2	20.8	22.0	21.4	24.2	21.4	20.8
S.D.	2.6	2.8	3.4	3.4	3.3	1.9	3.8

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 12-2-2. Food consumption of female rats, satellite group

N-DPS 150 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06059	23.9	0.0	20.1	22.0	22.9	21.0	19.4
F06060	18.7						
F06061	17.9	20.4	17.3	19.6	23.6	19.4	19.6
F06062	14.1	22.4	18.4				
F06063	18.9	19.4	12.3	20.5	17.6	17.9	15.7
F06064	16.0	20.3	24.7	22.1	26.8	25.4	17.6
F06065	21.2	14.7	18.8	25.3	26.1	17.6	13.4
F06066	19.3	18.7	27.0	11.1	16.1	19.3	17.5
F06067	24.3	22.2	18.2	28.0	30.5	26.4	24.1
F06068	18.1	23.9	21.5	22.4	23.8	22.6	3.4
Number of females	10	9	9	8	8	8	8
Mean	19.2	18.0	19.8	21.4	23.4	21.2	16.3
S.D.	3.2	7.2	4.3	4.9	4.7	3.3	6.1
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	AW	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 12-3-1. Food consumption of female rats at the recovery period

Control (vehicle: water for injection)

Female No.	Days of recovery	
	6	12
F05054	17.3	19.2
F05055	27.1	28.8
F05056	26.9	21.2
F05057	23.1	23.7
F05058	18.4	29.6
Number of females	5	5
Mean	22.6	24.5
S.D.	4.6	4.6

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 12-3-2. Food consumption of female rats at the recovery period

N-DPS 150 mg/kg

Female No.	Days of recovery	
	6	12
F06065	23.3	27.3
F06066	27.8	25.6
F06067	27.1	22.4
F06068	26.9	26.5
Number of females	4	4
Mean	26.3	25.5
S.D.	2.0	2.1
Significance	NS	NS
Statistical method	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 13-1. Food consumption in dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	24.0	27.4	28.6	26.5
F01002	19.5	26.9	25.9	17.4
F01003	18.8	29.8	32.7	30.7
F01004	20.7	28.6	30.5	28.2
F01005	20.1	29.5	34.6	25.4
F01006	19.6	24.8	24.4	26.6
F01007	23.4	23.8	26.2	24.6
F01008	17.5	25.2	25.6	26.7
F01009	21.8	27.1	27.8	29.6
F01010	21.4	31.6	23.2	25.2
F01011	21.3	24.4	26.2	23.3
F01012	26.4	30.0	28.4	23.9
Number of dams	12	12	12	12
Mean	21.2	27.4	27.8	25.7
S.D.	2.5	2.5	3.4	3.4

>: Excluded from analysis (not pregnant)

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 13-2. Food consumption in dams during pregnancy

N-DPS 15 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	25.0	29.4	29.9	21.1
F02014	20.4	30.0	29.3	18.2
F02015	22.3	27.4	28.4	27.4
F02016	26.1	32.7	31.4	34.0
F02017	25.9	28.8	27.0	22.6
F02018	19.3	26.5	30.3	30.8
F02019	26.9	37.0	32.5	32.7
F02020	27.4	29.6	27.5	27.6
F02021	25.4	30.0	31.0	24.8
F02022	20.8	28.9	35.3	25.7
F02023	23.4	27.0	29.7	26.8
F02024	23.9	31.8	35.1	18.7
Number of dams	12	12	12	12
Mean	23.9	29.9	30.6	25.9
S.D.	2.7	2.9	2.6	5.1
Significance	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 13-3. Food consumption in dams during pregnancy

N-DPS 50 mg/kg

Dam No.	Days of pregnancy							
	0	7	14	20				
F03025	16.2	27.6	27.4	23.8				
F03026	26.9	28.3	31.4	27.3				
F03027	26.1	31.9	32.6	30.9				
F03028	18.8	26.1	33.4	32.0				
F03029	> 25.1	> 35.4	> 32.6	> 19.3	>	>	>	>
F03030	22.1	28.2	25.9	24.4				
F03031	22.5	26.4	26.6	22.3				
F03032	24.2	29.2	31.3	24.6				
F03033	21.1	27.3	28.1	27.2				
F03034	20.1	31.5	31.9	27.9				
F03035	20.4	24.0	24.4	28.3				
F03036	25.7	36.7	32.2	30.5				
Number of dams	11	11	11	11				
Mean	22.2	28.8	29.6	27.2				
S.D.	3.3	3.5	3.1	3.2				
Significance	NS	NS	NS	NS				
Statistical method	DU	AN	AN	AN				

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 13-4. Food consumption in dams during pregnancy

N-DPS 150 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	15.5	22.6	23.9	28.3
F04038	17.7	26.5	27.3	27.5
F04039	20.9	26.0	25.0	26.3
F04040	21.2	28.4	30.2	31.9
F04041	17.2	30.5	23.9	26.8
F04042	14.6	22.1	27.8	26.8
F04043	25.2	33.2	27.7	29.5
F04044	21.9	25.2	28.6	35.5
F04045	18.8	28.3	30.4	32.6
F04046	25.0	39.3	30.0	31.2
F04047	21.4	27.7	33.0	27.4
F04048	19.3	32.2	32.2	24.5
Number of dams	12	12	12	12
Mean	19.9	28.5	28.3	29.0
S.D.	3.4	4.8	3.0	3.2
Significance	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 14-1. Food consumption in dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation
	3
F01001	48.9
F01002	39.2
F01003	39.5
F01004	43.7
F01005	34.3
F01006	40.4
F01007	39.5
F01008	41.5
F01009	40.7
F01010	42.7
F01011	50.5
F01012	53.1
Number of dams	12
Mean	42.8
S.D.	5.4

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 14-2. Food consumption in dams during lactation

N-DPS 15 mg/kg

Dam No.	Days of lactation
	3
F02013	37.7
F02014	49.3
F02015	46.9
F02016	47.1
F02017	41.5
F02018	47.0
F02019	48.1
F02020	55.7
F02021	41.7
F02022	47.2
F02023	46.4
F02024	49.0
Number of dams	12
Mean	46.5
S.D.	4.6
Significance	NS
Statistical method	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 14-3. Food consumption in dams during lactation

N-DPS 50 mg/kg

Dam No.	Days of lactation
	3
F03025	48.6
F03026	45.2
F03027	33.3
F03028	50.5
F03030	38.5
F03031	42.1
F03032	42.5
F03033	41.3
F03034	33.8
F03035	56.4
F03036	47.3
Number of dams	11
Mean	43.6
S.D.	7.0
Significance	NS
Statistical method	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 14-4. Food consumption in dams during lactation

N-DPS 150 mg/kg

Dam No.	Days of lactation
	3
F04037	47.5
F04038	43.5
F04039	32.9
F04040	35.2
F04041	42.0
F04042	51.9
F04043	47.2
F04044	43.5
F04045	40.6
F04046	50.3
F04047	57.3
F04048	55.8
Number of dams	12
Mean	45.6
S.D.	7.5
Significance	NS
Statistical method	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 15-1. Functional findings of male and female rats at the end of the dosing period

Control (vehicle: water for injection)

Male, Administration period

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

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F01006	2	2	2	2	+	+	+
F01008	2	2	2	2	+	+	+
F01009	2	2	2	2	+	+	+
F01010	2	2	2	2	+	+	+
F01012	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 15-2. Functional findings of male and female rats at the end of the dosing period

N-DPS (15 mg/kg)

Male, Administration period

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

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F02013	2	2	2	2	+	+	+
F02015	2	2	2	2	+	+	+
F02017	2	2	2	2	+	+	+
F02018	2	2	2	2	+	+	+
F02022	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 15-3. Functional findings of male and female rats at the end of the dosing period

N-DPS (50 mg/kg)

Male, Administration period

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

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F03027	2	2	2	2	+	+	+
F03028	2	2	2	2	+	+	+
F03031	2	2	2	2	+	+	+
F03034	2	2	2	2	+	+	+
F03036	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 15-4. Functional findings of male and female rats at the end of the dosing period

N-DPS (150 mg/kg)

Male, Administration period

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

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F04037	2	2	2	2	+	+	+
F04040	2	2	2	2	+	+	+
F04043	2	2	2	2	+	+	+
F04045	2	2	2	2	+	+	+
F04046	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 15-5. Functional findings of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female, Administration period

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

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 15-6 Functional findings of female rats at the end of the dosing period, satellite group
N-DPS (150 mg/kg)
Female, Administration period

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F06059	2	2	2	2	+	+	+
F06061	2	2	2	2	+	+	+
F06063	2	2	2	2	+	+	+
F06064	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 16-1. Assessment of grip strength of male rats

Control (vehicle: water for injection)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M01001	1.189	0.912
M01002	1.191	0.967
M01003	0.888	0.785
M01004	0.845	0.858
M01005	1.204	0.716
Number of males	5	5
Mean	1.063	0.848
S.D.	0.180	0.100

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 16-2. Assessment of grip strength of male rats

N-DPS (15 mg/kg)

Male No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
M02013	1.002	0.802
M02014	1.036	0.895
M02015	1.257	0.812
M02016	1.087	0.870
M02017	1.198	0.958
Number of males	5	5
Mean	1.116	0.867
S.D.	0.108	0.064

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 16-3. Assessment of grip strength of male rats

N-DPS (50 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M03025	1.030	0.878
M03026	1.261	0.991
M03027	1.144	0.831
M03028	1.202	1.070
M03029	1.185	0.924
Number of males	5	5
Mean	1.164	0.939
S.D.	0.086	0.094

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 16-4. Assessment of grip strength of male rats

N-DPS (150 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M04037	1.181	1.047
M04038	1.223	0.970
M04039	1.240	1.023
M04040	1.195	0.913
M04041	1.260	0.829
Number of males	5	5
Mean	1.220	0.956
S.D.	0.032	0.088

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 17-1. Assessment of grip strength of female rats

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F01006	1.135	0.553
F01008	1.146	0.519
F01009	1.152	0.497
F01010	1.096	0.463
F01012	1.041	0.504
Number of females	5	5
Mean	1.114	0.507
S.D.	0.046	0.033

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 17-2. Assessment of grip strength of female rats

N-DPS (15 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F02013	1.157	0.569
F02015	1.194	0.521
F02017	1.042	0.503
F02018	1.048	0.513
F02022	1.194	0.496
Number of females	5	5
Mean	1.127	0.520
S.D.	0.076	0.029

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 17-3. Assessment of grip strength of female rats

N-DPS (50 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F03027	1.155	0.493
F03028	1.039	0.488
F03031	1.127	0.495
F03034	1.257	0.472
F03036	1.106	0.470
Number of females	5	5
Mean	1.137	0.484
S.D.	0.080	0.012

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 17-4. Assessment of grip strength of female rats

N-DPS (150 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F04037	1.111	0.490
F04040	1.043	0.479
F04043	1.141	0.452
F04045	1.114	0.519
F04046	1.037	0.487
Number of females	5	5
Mean	1.089	0.485
S.D.	0.046	0.024

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 18-1. Assessment of grip strength of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F05049	1.097	0.504
F05050	1.140	0.519
F05051	0.993	0.416
F05052	1.132	0.513
F05053	1.185	0.488
Number of females	5	5
Mean	1.109	0.488
S.D.	0.072	0.042

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 18-2. Assessment of grip strength of female rats, satellite group

N-DPS (150 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F06059	1.160	0.586
F06061	1.035	0.453
F06063	1.127	0.531
F06064	1.100	0.472
Number of females	4	4
Mean	1.106	0.511
S.D.	0.053	0.060

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 19-1. Motor activity of male rats

Control (vehicle: water for injection)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	705	852	824	693	3074	19	32	33	22	106
M01002	1145	1051	1040	826	4062	23	45	31	12	111
M01003	1027	1051	1042	990	4110	38	55	36	38	167
M01004	1017	1090	881	769	3757	37	36	22	16	111
M01005	1147	1113	984	1033	4277	25	30	19	31	105
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1008	1031	954	862	3856	28	40	28	24	120
S.D.	181	104	98	145	476	9	10	7	11	26

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 19-2. Motor activity of male rats

N-DPS (15 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02013	1232	1336	1158	1106	4832	47	54	48	34	183
M02014	1108	1058	1041	1062	4269	32	22	29	20	103
M02015	1251	1248	1090	1100	4689	42	38	20	27	127
M02016	1174	902	1090	960	4126	41	31	44	29	145
M02017	1160	877	955	1000	3992	44	32	23	24	123
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1185	1084	1067	1046	4382	41	35	33	27	136
S.D.	58	204	75	64	363	6	12	13	5	30

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 19-3. Motor activity of male rats

N-DPS (50 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03025	1099	848	881	1013	3841	19	25	17	14	75
M03026	1442	1297	1130	830	4699	36	32	24	12	104
M03027	1177	1122	1176	1014	4489	35	29	41	28	133
M03028	1262	948	1187	846	4243	38	30	38	23	129
M03029	1737	1723	1485	1332	6277	51	35	23	15	124
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1343 *	1188	1172	1007	4710	36	30	29	18	113
S.D.	254	345	215	202	932	11	4	10	7	24

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 19-4. Motor activity of male rats

N-DPS (150 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04037	1051	973	1090	933	4047	27	24	22	17	90
M04038	1319	1150	1186	1329	4984	50	35	35	36	156
M04039	1195	1209	1180	892	4476	27	29	29	21	106
M04040	1336	1207	1343	1230	5116	47	34	48	32	161
M04041	1215	1044	456	866	3581	37	32	5	12	86
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1223	1117	1051	1050	4441	38	31	28	24	120
S.D.	114	105	345	214	642	11	4	16	10	36

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 20-1. Motor activity of female rats

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01006	1274	1119	587	863	3843	33	22	1	4	60
F01008	829	663	658	493	2643	35	27	20	18	100
F01009	1220	935	555	328	3038	44	12	3	3	62
F01010	1065	651	467	180	2363	22	6	1	0	29
F01012	1203	776	553	166	2698	32	17	0	0	49
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1118	829	564	406	2917	33	17	5	5	60
S.D.	179	198	69	288	571	8	8	8	7	26

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 20-2. Motor activity of female rats

N-DPS (15 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02013	1141	820	777	325	3063	21	12	21	7	61
F02015	1180	950	336	622	3088	40	28	3	13	84
F02017	1118	1097	1053	746	4014	32	28	16	22	98
F02018	1056	994	812	414	3276	34	35	21	5	95
F02022	957	736	766	513	2972	23	13	12	23	71
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1090	919	749	524	3283	30	23	15	14	82
S.D.	87	143	259	166	424	8	10	8	8	16

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 20-3. Motor activity of female rats

N-DPS (50 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03027	1150	1033	889	858	3930	40	18	18	6	82
F03028	1202	740	455	862	3259	47	29	7	12	95
F03031	1384	1038	905	888	4215	70	30	20	11	131
F03034	1203	372	857	72	2504	49	12	19	0	80
F03036	1851	1687	1446	794	5778	31	44	19	4	98
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1358	974	910	695	3937	47	27	17	7	97
S.D.	290	483	353	350	1223	14	12	5	5	20

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 20-4. Motor activity of female rats

N-DPS (150 mg/kg)

Female No.	Administration period									
	Ambulation					Rearing				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04037	994	780	557	195	2526	13	18	10	0	41
F04040	1381	1128	829	30	3368	22	20	9	0	51
F04043	1006	843	803	96	2748	15	8	3	0	26
F04045	1245	730	585	16	2576	39	7	7	0	53
F04046	1311	1009	1003	1170	4493	38	26	17	30	111
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1187	898	755	301	3142	25	16	9	6	56
S.D.	178	166	185	491	826	12	8	5	13	32

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 21-1. Motor activity of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05049	1041	837	682	636	3196	28	23	18	17	86
F05050	1415	1239	1259	1178	5091	58	40	32	34	164
F05051	1196	1015	1015	925	4151	39	37	16	15	107
F05052	1174	1375	1295	1058	4902	48	48	44	33	173
F05053	1190	1144	1013	753	4100	39	40	26	12	117
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1203	1122	1053	910	4288	42	38	27	22	129
S.D.	134	207	246	220	753	11	9	11	10	38

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 21-2. Motor activity of female rats, satellite group

N-DPS (150 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06059	1342	1210	1077	1151	4780	47	51	47	44	189
F06061	1175	1176	1325	1030	4706	33	29	48	26	136
F06063	1105	1036	985	984	4110	30	25	27	11	93
F06064	1163	1139	1322	1202	4826	45	37	58	36	176
Number of females	4	4	4	4	4	4	4	4	4	4
Mean	1196	1140	1177	1092	4606	39	36	45	29	149
S.D.	102	75	173	102	334	9	11	13	14	43

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 22-1-1. Urinalysis in male rats

Control (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
M01002	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M01003	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M01004	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
M01005	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	±

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)				Electrolyte, gross volume (mEq/24 hr)		
			Na	K		Cl	Na	K	Cl
M01001	23.4	1.046	77.3	187.9		96.2	1.81	4.40	2.25
M01002	14.3	1.067	129.6	179.8	§	146.6	1.85	2.57	2.10
M01003	21.7	1.044	78.3	160.6		82.0	1.70	3.49	1.78
M01004	22.4	1.045	69.9	157.6	§	80.2	1.57	3.53	1.80
M01005	14.9	1.073	142.0	239.6		164.9	2.12	3.57	2.46
Number of males	5	5	5	5		5	5	5	5
Mean	19.3	1.055	99.4	185.1		114.0	1.81	3.51	2.08
±S.D.	4.4	0.014	33.7	33.0		39.2	0.20	0.65	0.29

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 22-1-2. Urinalysis in male rats

N-DPS (15 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02013	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	+	-
M02014	Light yellow	-	8.0	+	-	-	-	-	±	-	-	-	±	-
M02015	Light yellow	-	8.0	+	-	±	-	+	±	-	-	-	±	-
M02016	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
M02017	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M02013	13.0	1.069	143.9	181.6 §	162.4	1.87	2.36	2.11
M02014	18.5	1.057	96.8	155.9 §	120.2	1.79	2.88	2.22
M02015	16.6	1.055	91.0	195.8	115.8	1.51	3.25	1.92
M02016	20.7	1.051	80.9	187.7	104.3	1.67	3.89	2.16
M02017	12.2	1.070	132.0	216.3	135.4	1.61	2.64	1.65
Number of males	5	5	5	5	5	5	5	5
Mean	16.2	1.060	108.9	187.5	127.6	1.69	3.00	2.01
±S.D.	3.6	0.009	27.4	22.0	22.4	0.14	0.59	0.23

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 22-1-3. Urinalysis in male rats

Urinalysis in male rats
N-DPS (50 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03025	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-
M03026	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M03027	Light yellow	-	6.5	+	-	-	-	-	±	-	-	-	±	-
M03028	Light yellow	-	6.5	+	-	±	-	+	±	-	-	-	-	-
M03029	Light yellow	-	7.0	+	-	-	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M03025	15.4	1.068	195.9	251.5	203.7	3.02	3.87	3.14
M03026	19.5	1.054	98.8	158.8	124.2	1.93	3.10	2.42
M03027	16.7	1.058	106.9	164.3	116.5	1.79	2.74	1.95
M03028	19.3	1.063	112.3	196.4 §	125.5	2.17	3.79	2.42
M03029	26.3	1.043	90.5	142.4	118.1	2.38	3.75	3.11
Number of males	5	5	5	5	5	5	5	5
Mean	19.4	1.057	120.9	182.7	137.6	2.26	3.45	2.61
±S.D.	4.2	0.010	42.7	43.2	37.2	0.48	0.50	0.51

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 22-1-4. Urinalysis in male rats
N-DPS (150 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04037	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	±	-
M04038	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-
M04039	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	-	-
M04040	Light yellow	-	7.0	+	-	+	-	-	±	-	-	-	±	-
M04041	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)				Electrolyte, gross volume (mEq/24 hr)		
			Na		K	Cl	Na	K	Cl
M04037	28.0	1.042	93.8		147.0 §	108.2	2.63	4.12	3.03
M04038	17.4	1.060	88.9		191.0	132.5	1.55	3.32	2.31
M04039	27.6	1.039	73.9		128.1	87.6	2.04	3.54	2.42
M04040	12.7	1.060	30.5 §		154.0 §	23.1	0.39	1.96	0.29
M04041	20.1	1.054	92.3		170.0 §	119.6	1.86	3.42	2.40
Number of males	5	5	5		5	5	5	5	5
Mean	21.2	1.051	75.9		158.0	94.2	1.69	3.27	2.09
±S.D.	6.6	0.010	26.6		23.8	43.0	0.83	0.80	1.05

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 22-2-1. Urinalysis in male rats of the recovery period

Control (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01008	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	-
M01009	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
M01010	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M01011	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	-	-
M01012	Light yellow	-	8.5	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)				Electrolyte, gross volume (mEq/24 hr)		
			Na	K		Cl	Na	K	Cl
M01008	48.0	1.022	53.8	109.2		62.3	2.58	5.24	2.99
M01009	20.7	1.061	105.0	187.2	§	127.8	2.17	3.88	2.65
M01010	21.0	1.051	116.6	152.5		124.6	2.45	3.20	2.62
M01011	22.5	1.049	87.5	177.9	§	111.1	1.97	4.00	2.50
M01012	18.1	1.063	127.1	203.5	§	138.4	2.30	3.68	2.51
Number of males	5	5	5	5		5	5	5	5
Mean	26.1	1.049	98.0	166.1		112.8	2.29	4.00	2.65
±S.D.	12.4	0.016	28.7	36.8		29.9	0.24	0.76	0.20

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 22-2-2. Urinalysis in male rats of the recovery period

N-DPS (150 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04044	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M04045	Light yellow	-	7.5	+	-	-	-	-	±	-	-	-	±	-
M04046	Light yellow	-	8.0	+	-	-	-	-	±	-	-	-	±	-
M04047	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M04048	Light yellow	-	8.0	+	-	-	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)				Electrolyte, gross volume (mEq/24 hr)		
			Na	K		Cl	Na	K	Cl
M04044	19.6	1.069	132.9	197.6	§	168.3	2.60	3.87	3.30
M04045	19.2	1.057	102.3	194.3	§	118.3	1.96	3.73	2.27
M04046	21.8	1.049	99.0	158.7		103.3	2.16	3.46	2.25
M04047	16.6	1.063	107.6	196.3		139.7	1.79	3.26	2.32
M04048	25.1	1.051	107.1	161.1		111.9	2.69	4.04	2.81
Number of males	5	5	5	5		5	5	5	5
Mean	20.5	1.058	109.8	181.6		128.3	2.24	3.67	2.59
±S.D.	3.2	0.008	13.4	19.9		26.1	0.39	0.31	0.46

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 23-1-1. Urinalysis in female rats, satellite group

Control (vehicle: water for injection)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05049	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	-	-
F05050	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	-	-
F05051	Light yellow	-	6.0	+	-	±	-	±	±	-	-	-	-	-
F05052	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	±	-
F05053	Light yellow	-	6.5	±	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)				Electrolyte, gross volume (mEq/24 hr)		
			Na	K		Cl	Na	K	Cl
F05049	8.3	1.073	131.4	177.5	§	120.9	1.09	1.47	1.00
F05050	8.1	1.046	47.4	86.1	§	32.4	0.38	0.70	0.26
F05051	7.8	1.073	114.0	172.0		102.2	0.89	1.34	0.80
F05052	24.8	1.034	61.7	123.1	§	80.4	1.53	3.05	1.99
F05053	9.1	1.070	90.1	179.4	§	96.0	0.82	1.63	0.87
Number of females	5	5	5	5		5	5	5	5
Mean	11.6	1.059	88.9	147.6		86.4	0.94	1.64	0.98
±S.D.	7.4	0.018	35.0	41.5		33.5	0.42	0.86	0.63

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 23-1-2. Urinalysis in female rats, satellite group

N-DPS (150 mg/kg)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06059	Light yellow	-	6.0	-	-	-	-	-	±	-	-	-	-	±
F06061	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F06063	Light yellow	-	6.5	±	-	-	-	-	±	-	-	-	-	-
F06064	Light yellow	-	6.5	±	-	-	-	-	±	-	-	-	±	-
F06065	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06059	19.3	1.038	59.5	121.4	76.5	1.15	2.34	1.48
F06061	10.0	1.077	158.1	191.0	173.7	1.58	1.91	1.74
F06063	11.7	1.060	130.6	157.7	139.7	1.53	1.85	1.63
F06064	9.8	1.062	95.2	154.2	93.2	0.93	1.51	0.91
F06065	17.1	1.046	88.9	143.2 §	110.2	1.52	2.45	1.88
Number of females	5	5	5	5	5	5	5	5
Mean	13.6	1.057	106.5	153.5	118.7	1.34	2.01	1.53
±S.D.	4.4	0.015	38.4	25.3	38.6	0.29	0.38	0.38

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 23-2-1. Urinalysis in female rats of the recovery period

Control (vehicle: water for injection)

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

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05054	19.6	1.039	70.0	148.4	94.3	1.37	2.91	1.85
F05055	19.9	1.043	99.7	166.3 §	100.2	1.98	3.31	1.99
F05056	19.8	1.040	57.8	150.3 §	72.3	1.14	2.98	1.43
F05057	16.7	1.047	90.9	160.1	114.2	1.52	2.67	1.91
F05058	17.0	1.054	97.8	169.6	121.9	1.66	2.88	2.07
Number of females	5	5	5	5	5	5	5	5
Mean	18.6	1.045	83.2	158.9	100.6	1.53	2.95	1.85
±S.D.	1.6	0.006	18.5	9.4	19.2	0.32	0.23	0.25

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 23-2-2. Urinalysis in female rats of the recovery period

N-DPS (150 mg/kg)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells[a)]	White blood cells[a)]	Casts[a)]	Crystals[b)]	Epithelial cells[b)]
F06065	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	±	-
F06066	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	±	-
F06067	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	-	-
F06068	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06065	19.4	1.042	81.6	149.3	89.7	1.58	2.90	1.74
F06066	21.4	1.041	74.6	138.4	86.4	1.60	2.96	1.85
F06067	11.2	1.060	92.9	181.5 §	123.3	1.04	2.03	1.38
F06068	24.1	1.041	90.3	133.5	82.6	2.18	3.22	1.99
Number of females	4	4	4	4	4	4	4	4
Mean	19.0	1.046	84.9	150.7	95.5	1.60	2.78	1.74
±S.D.	5.6	0.009	8.4	21.6	18.8	0.47	0.52	0.26

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative; +: slight; 2+: moderate
Protein, -: negative ; ±: 10≦and＜30 mg/dL ; +: 30≦and＜100 mg/dL ; 2+: 100≦and＜300 mg/dL ; 3+: 300≦and＜600 mg/dL ; 4+: 600 mg/dL ＜
Glucose, -: negative ; ±: 30≦and＜70 mg/dL ; +: 70≦and＜150 mg/dL ; 2+: 150≦and＜300 mg/dL ; 3+: 300≦and＜1000 mg/dL ; 4+: 1000 mg/dL ≦
Ketone, -: negative ; ±: 5≦and＜10 mg/dL ; +: 10≦and＜40 mg/dL ; 2+: 40≦and＜80 mg/dL ; 3+: 80≦and＜150 mg/dL ; 4+: 150 mg/dL ≦
Bilirubin, -: negative ; +: 0.5≦and＜2.0 mg/dL ; 2+: 2.0≦and＜6.0 mg/dL ; 3+: 6.0≦and＜10.0 mg/dL ; 4+: 10.0 mg/dL ＜
Occult blood, -: negative ; ±: 0.03≦and＜0.06 mg/dL ; +: 0.06≦and＜020 mg/dL ; 2+: 0.20≦and＜1.00 mg/dL ; 3+: 1.00 mg/dL ≦
Urobilinogen, ±: normal ; +: 2.0≦and＜4.0 mg/dL ; 2+: 4.0≦and＜8.0 mg/dL ; 3+: 8.0≦and＜12.0 mg/dL ; 4+: 12.0 mg/dL ＜
Red blood cells, -: not observed
White blood cells, -: not observed; ±: a few
Casts, -: not observed
Crystals, -: not observed; ±: a few; +: abundant
Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 24-1-1. Hematological findings of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times10^4/\mu L$)	(sec)	(sec)
M01001	867	15.4	42.4	48.9	17.8	36.3	102.3	20.8	26.9
M01002	792	14.7	42.4	53.5	18.6	34.7	99.9	17.6	25.2
M01003	833	15.1	44.7	53.7	18.1	33.8	109.5	25.7	30.2 §
M01004	855	15.5	44.7	52.3	18.1	34.7	124.7	23.6	31.1 ∮
M01005	805	14.4	42.9	53.3	17.9	33.6	111.9	26.1	34.2
Number of males	5	5	5	5	5	5	5	5	5
Mean	830	15.0	43.4	52.3	18.1	34.6	109.7	22.8	29.5
S.D.	32	0.5	1.2	2.0	0.3	1.1	9.8	3.6	3.5

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M01001	89.8	12.7	1.7	0.1	4.1	81.4	3.10
M01002	85.2	13.2	1.1	0.0	4.2	81.5	2.86
M01003	83.3	22.5	2.6	0.0	4.7	70.2	3.91
M01004	67.7	10.6	2.8	0.0	5.8	80.8	2.90
M01005	75.6	22.0	1.7	0.0	4.1	72.2	3.94
Number of males	5	5	5	5	5	5	5
Mean	80.3	16.2	2.0	0.0	4.6	77.2	3.34
S.D.	8.7	5.6	0.7	0.0	0.7	5.5	0.54

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

∮, The sharp variation of the light scattering was not detected in the reaction in the first measurement. The re-measurement was carried out and the sharp variation was observed in the reaction to give the acceptable value. The re-measured value was employed as the measured value for the specimen.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 24-1-2. Hematological findings of male rats at the end of the dosing period

N-DPS (15 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M02013	883	15.7	44.1	49.9	17.8	35.6	128.4	18.0	26.9
M02014	866	14.2	40.9	47.2	16.4	34.7	132.4	19.6	28.1
M02015	863	14.7	41.4	48.0	17.0	35.5	120.2	24.8	29.7
M02016	789	13.8	39.3	49.8	17.5	35.1	133.9	14.0	23.9
M02017	876	16.0	46.5	53.1	18.3	34.4	95.8	21.6	32.8
Number of males	5	5	5	5	5	5	5	5	5
Mean	855	14.9	42.4	49.6	17.4	35.1	122.1	19.6	28.3
S.D.	38	0.9	2.9	2.3	0.7	0.5	15.7	4.0	3.3

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M02013	104.5	15.6	1.1	0.1	3.2	80.0	3.18
M02014	70.1	16.6	1.1	0.0	5.0	77.3	3.51
M02015	80.7	17.9	1.9	0.0	5.2	75.0	3.47
M02016	116.8	19.0	1.1	0.1	2.8	77.0	3.41
M02017	54.6	9.7	1.8	0.0	3.3	85.2	3.25
Number of males	5	5	5	5	5	5	5
Mean	85.3	15.8	1.4	0.0	3.9	78.9	3.36
S.D.	25.3	3.6	0.4	0.1	1.1	3.9	0.14

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 24-1-3. Hematological findings of male rats at the end of the dosing period

N-DPS (50 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M03025	873	15.4	44.1	50.5	17.6	34.9	111.6	21.2	31.5
M03026	868	15.6	45.0	51.8	18.0	34.7	89.8	16.5	28.4
M03027	865	15.0	42.1	48.7	17.3	35.6	132.8	16.9	28.4
M03028	756	15.3	45.9	60.7	20.2	33.3	105.8	16.9	29.9
M03029	870	15.7	44.8	51.5	18.0	35.0	123.3	15.1	27.9
Number of males	5	5	5	5	5	5	5	5	5
Mean	846	15.4	44.4	52.6	18.2	34.7	112.7	17.3	29.2
S.D.	51	0.3	1.4	4.7	1.1	0.9	16.5	2.3	1.5

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M03025	80.4	13.5	2.2	0.1	5.7	78.5	3.34
M03026	67.2	15.0	1.8	0.0	4.3	78.9	2.89
M03027	87.0	19.1	0.9	0.0	3.2	76.8	2.15
M03028	82.8	27.8	2.7	0.0	4.3	65.2	2.11
M03029	91.8	12.9	1.2	0.0	1.6	84.3	3.86
Number of males	5	5	5	5	5	5	5
Mean	81.8	17.7	1.8	0.0	3.8	76.7	2.87
S.D.	9.3	6.2	0.7	0.0	1.5	7.0	0.76

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 24-1-4. Hematological findings of male rats at the end of the dosing period

N-DPS (150 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M04037	886	15.7	44.1	49.8	17.7	35.6	93.4	22.1	31.4
M04038	891	15.6	44.3	49.7	17.5	35.2	114.8	17.0	25.1
M04039	873	15.3	43.8	50.2	17.5	34.9	103.7	13.1	24.1
M04040	1032 #	19.2	56.1 #	54.4	18.6	34.2	148.9	41.6	58.7 §
M04041	829	14.3	42.2	50.9	17.2	33.9	96.8	22.1	33.8
Number of males	5	5	5	5	5	5	5	5	5
Mean	902	16.0	46.1	51.0	17.7	34.8	111.5	23.2	34.6
S.D.	77	1.9	5.7	2.0	0.5	0.7	22.4	11.0	14.1

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M04037	68.8	19.0	2.3	0.1	3.9	74.7	1.77
M04038	59.9	28.4	3.0	0.0	3.7	64.9	2.99
M04039	92.5	13.4	1.1	0.0	2.3	83.2	2.03
M04040	72.3	37.8	0.3	0.0	6.6	55.3	2.39
M04041	87.7	26.0	1.0	0.0	4.1	68.9	2.53
Number of males	5	5	5	5	5	5	5
Mean	76.2	24.9	1.5	0.0	4.1	69.4	2.34 *
S.D.	13.5	9.3	1.1	0.0	1.6	10.5	0.47

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

#, The first measured value was out of the control values stated in the standard operating procedures. One re-measurement was carried out, and the difference between the values in two measurements was not more than 10% of the lower value. The first measured value was employed as the measured value for the specimen.

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 24-2-1. Hematological findings of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M01008	880	15.8	43.8	49.8	18.0	36.1	106.2	14.0	23.8
M01009	831	15.0	42.4	51.0	18.1	35.4	106.2	20.2	25.7
M01010	832	14.3	40.8	49.0	17.2	35.0	89.7	20.2	29.1
M01011	831	15.3	42.7	51.4	18.4	35.8	99.0	17.1	24.4
M01012	907	15.8	43.9	48.4	17.4	36.0	106.4	18.2	23.4
Number of males	5	5	5	5	5	5	5	5	5
Mean	856	15.2	42.7	49.9	17.8	35.7	101.5	17.9	25.3
S.D.	35	0.6	1.3	1.3	0.5	0.5	7.3	2.6	2.3

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M01008	129.8	16.5	1.3	0.1	3.6	78.5	3.60
M01009	108.2	16.8	0.9	0.1	4.7	77.5	3.96
M01010	91.9	23.4	0.9	0.0	3.6	72.1	3.14
M01011	100.2	53.4	1.5	0.0	4.2	40.9	3.16
M01012	75.8	16.2	1.7	0.0	4.4	77.7	3.56
Number of males	5	5	5	5	5	5	5
Mean	101.2	25.3	1.3	0.0	4.1	69.3	3.48
S.D.	20.0	16.0	0.4	0.1	0.5	16.1	0.34

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 24-2-2. Hematological findings of male rats at the end of the recovery period

N-DPS (150 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M04044	831	15.2	43.3	52.1	18.3	35.1	106.9	15.7	24.4
M04045	838	14.8	42.8	51.1	17.7	34.6	120.8	24.2	27.3
M04046	801	14.2	40.9	51.1	17.7	34.7	128.6	14.5	23.3
M04047	862	15.8	46.2	53.6	18.3	34.2	115.8	20.9	26.4
M04048	886	16.1	45.7	51.6	18.2	35.2	96.1	17.1	26.9
Number of males	5	5	5	5	5	5	5	5	5
Mean	844	15.2	43.8	51.9 *	18.0	34.8 *	113.6	18.5	25.7
S.D.	32	0.8	2.2	1.0	0.3	0.4	12.6	4.0	1.7

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M04044	125.5	23.5	1.7	0.0	3.7	71.1	3.66
M04045	132.6	19.7	0.5	0.0	2.4	77.4	4.98
M04046	80.3	13.1	1.1	0.0	2.1	83.7	3.50
M04047	62.4	15.7	1.9	0.0	3.7	78.7	3.87
M04048	63.6	27.8	1.7	0.0	3.8	66.7	3.83
Number of males	5	5	5	5	5	5	5
Mean	92.9	20.0	1.4	0.0	3.1	75.5	3.97
S.D.	33.9	5.9	0.6	0.0	0.8	6.7	0.58

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 25-1-1. Hematological findings of female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F01006	700	13.7	40.7	58.1	19.6	33.7	129.4	11.8	22.4
F01008	762	14.0	41.5	54.5	18.4	33.7	113.9	12.6	20.7 §
F01009	696	13.8	41.5	59.6	19.8	33.3	127.9	12.3	19.5
F01010	679	13.4	40.6	59.8	19.7	33.0	148.5	12.6	22.1
F01012	746	14.5	42.8	57.4	19.4	33.9	164.8	12.1	24.2
Number of females	5	5	5	5	5	5	5	5	5
Mean	717	13.9	41.4	57.9	19.4	33.5	136.9	12.3	21.8
S.D.	36	0.4	0.9	2.1	0.6	0.4	19.9	0.3	1.8

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F01006	54.6	29.1	0.9	0.0	4.2	65.8	7.48
F01008	62.2	15.4	1.3	0.0	6.9	76.4	6.87
F01009	84.6	31.2	0.7	0.0	4.5	63.6	10.75
F01010	40.6	27.1	1.5	0.0	7.4	64.0	9.04
F01012	54.3	28.0	1.3	0.0	6.1	64.6	10.05
Number of females	5	5	5	5	5	5	5
Mean	59.3	26.2	1.1	0.0	5.8	66.9	8.84
S.D.	16.2	6.2	0.3	0.0	1.4	5.4	1.65

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 25-1-2. Hematological findings of female rats at the end of the dosing period

N-DPS (15 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F02013	709	13.7	40.8	57.5	19.3	33.6	124.3	12.4	22.2
F02015	625	13.0	40.0	64.0	20.8	32.5	128.0	13.6	22.9 §
F02017	735	13.8	40.7	55.4	18.8	33.9	112.7	12.4	18.6
F02018	722	13.9	41.0	56.8	19.3	33.9	112.9	12.3	22.6 §
F02022	702	13.9	41.2	58.7	19.8	33.7	93.5	12.8	19.7
Number of females	5	5	5	5	5	5	5	5	5
Mean	699	13.7	40.7	58.5	19.6	33.5	114.3	12.7	21.2
S.D.	43	0.4	0.5	3.3	0.8	0.6	13.5	0.5	1.9

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F02013	106.0	42.1	1.1	0.0	4.0	52.8	6.27
F02015	88.1	29.3	0.6	0.1	2.7	67.3	9.69
F02017	187.9 #	42.9	1.2	0.1	4.5	51.3	8.07
F02018	80.4	21.0	0.2	0.0	6.0	72.8	8.38
F02022	97.3	30.7	0.5	0.0	4.9	63.9	8.58
Number of females	5	5	5	5	5	5	5
Mean	111.9	33.2	0.7	0.0	4.4	61.6	8.20
S.D.	43.5	9.3	0.4	0.1	1.2	9.3	1.24

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

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

#, The first measured value was out of the control values stated in the standard operating procedures. One re-measurement was carried out, and the difference between the values in two measurements was not more than 10% of the lower value. The first measured value was employed as the measured value for the specimen.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 25-1-3. Hematological findings of female rats at the end of the dosing period

N-DPS (50 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F03027	703	13.8	41.2	58.6	19.6	33.5	128.2	12.2	18.1 §
F03028	726	14.3	42.0	57.9	19.7	34.0	102.8	13.6	21.4
F03031	661	12.7	38.1	57.6	19.2	33.3	96.5	12.4	17.8
F03034	619	12.3	36.6	59.1	19.9	33.6	109.6	11.0	18.3
F03036	677	13.5	39.8	58.8	19.9	33.9	126.8	11.9	20.1
Number of females	5	5	5	5	5	5	5	5	5
Mean	677	13.3	39.5	58.4	19.7	33.7	112.8	12.2	19.1
S.D.	41	0.8	2.2	0.6	0.3	0.3	14.2	0.9	1.6

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F03027	118.7	30.6	1.1	0.1	3.8	64.4	8.69
F03028	80.2	32.4	0.9	0.0	4.9	61.8	8.83
F03031	105.5	32.8	0.4	0.0	4.5	62.3	7.54
F03034	95.6	35.6	1.4	0.0	3.9	59.1	7.81
F03036	78.1	15.4	2.4	0.0	6.0	76.2	10.54
Number of females	5	5	5	5	5	5	5
Mean	95.6	29.4	1.2	0.0	4.6	64.8	8.68
S.D.	17.1	8.0	0.7	0.0	0.9	6.7	1.18

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

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 25-1-4. Hematological findings of female rats at the end of the dosing period

N-DPS (150 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F04037	740	14.5	43.3	58.5	19.6	33.5	95.8	13.8	22.2
F04040	791	15.2	43.9	55.5	19.2	34.6	128.3	12.9	21.4
F04043	685	13.5	40.2	58.7	19.7	33.6	124.1	12.8	21.8
F04045	706	14.2	42.0	59.5	20.1	33.8	119.6	12.1	18.2
F04046	744	14.3	41.3	55.5	19.2	34.6	113.5	13.0	20.4 §
Number of females	5	5	5	5	5	5	5	5	5
Mean	733	14.3	42.1	57.5	19.6	34.0	116.3	12.9	20.8
S.D.	41	0.6	1.5	1.9	0.4	0.5	12.7	0.6	1.6

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F04037	120.5	42.8	1.4	0.0	4.1	51.7	7.13
F04040	96.4	17.3	0.8	0.0	5.0	76.9	4.81
F04043	101.5	36.8	1.4	0.0	5.2	56.6	7.40
F04045	147.3	17.4	1.7	0.1	3.4	77.4	6.43
F04046	60.0	13.5	0.7	0.0	5.3	80.5	5.14
Number of females	5	5	5	5	5	5	5
Mean	105.1	25.6	1.2	0.0	4.6	68.6	6.18 *
S.D.	32.2	13.3	0.4	0.0	0.8	13.4	1.16

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

§, The sharp variation of the light scattering was not detected in the reaction in the first measurement. The re-measurement was carried out and the sharp variation was observed in the reaction to give the acceptable value. The re-measured value was employed as the measured value for the specimen.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 25-2-1. Hematological findings of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F05049	755	13.8	38.6	51.1	18.3	35.8	104.7	12.3	19.3 §
F05050	762	14.3	41.3	54.2	18.8	34.6	116.0	12.6	21.0
F05051	712	14.2	42.0	59.0	19.9	33.8	106.4	12.2	23.9
F05052	821	15.2	42.8	52.1	18.5	35.5	114.2	12.6	20.1
F05053	832	15.6	45.6	54.8	18.8	34.2	108.9	11.4	22.3 §
Number of females	5	5	5	5	5	5	5	5	5
Mean	776	14.6	42.1	54.2	18.9	34.8	110.0	12.2	21.3
S.D.	50	0.7	2.5	3.1	0.6	0.8	4.9	0.5	1.8

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F05049	75.4	12.0	1.7	0.0	2.5	83.8	3.49
F05050	66.1	8.4	1.4	0.0	1.8	88.4	3.27
F05051	61.3	19.6	1.1	0.0	3.9	75.4	3.09
F05052	66.0	17.9	2.4	0.0	2.6	77.1	3.06
F05053	33.8	13.3	2.7	0.0	1.8	82.2	4.12
Number of females	5	5	5	5	5	5	5
Mean	60.5	14.2	1.9	0.0	2.5	81.4	3.41
S.D.	15.8	4.5	0.7	0.0	0.9	5.2	0.43

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 25-2-2. Hematological findings of female rats at the end of the dosing period, satellite group

N-DPS (150 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F06059	805	14.9	41.9	52.0	18.5	35.6	92.8	11.4 §	16.5 §
F06061	791	14.7	41.8	52.8	18.6	35.2	122.3	12.6	21.7
F06063	776	14.6	41.5	53.5	18.8	35.2	105.5	12.6	19.6
F06064	834	15.1	42.1	50.5	18.1	35.9	106.8	11.7	20.9
Number of females	4	4	4	4	4	4	4	4	4
Mean	802	14.8	41.8	52.2	18.5	35.5	106.9	12.1	19.7
S.D.	25	0.2	0.3	1.3	0.3	0.3	12.1	0.6	2.3

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F06059	73.0	17.2	1.9	0.0	2.3	78.6	2.89
F06061	62.8	8.6	1.4	0.0	3.7	86.3	3.29
F06063	32.1	10.3	3.4	0.0	2.2	84.1	2.27
F06064	42.8	18.2	3.3	0.0	5.1	73.4	2.16
Number of females	4	4	4	4	4	4	4
Mean	52.7	13.6	2.5	0.0	3.3	80.6	2.65
S.D.	18.6	4.8	1.0	0.0	1.4	5.8	0.53

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

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 25-3-1. Hematological findings of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F05054	836	15.3	43.4	51.9	18.3	35.3	99.6	12.4	19.8
F05055	771	14.8	42.3	54.9	19.2	35.0	103.3	10.9	19.4
F05056	782	14.9	42.1	53.8	19.1	35.4	98.3	12.3	26.1
F05057	780	15.0	42.8	54.9	19.2	35.0	103.1	12.3	21.7
F05058	781	14.1	41.0	52.5	18.1	34.4	117.8	12.2	20.5
Number of females	5	5	5	5	5	5	5	5	5
Mean	790	14.8	42.3	53.6	18.8	35.0	104.4	12.0	21.5
S.D.	26	0.4	0.9	1.4	0.5	0.4	7.8	0.6	2.7

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F05054	57.1	11.5	2.3	0.0	3.2	83.0	2.68
F05055	69.7	16.6	1.4	0.0	3.7	78.3	2.98
F05056	38.0	25.3	1.8	0.0	7.1	65.8	2.99
F05057	58.3	16.6	1.9	0.0	2.9	78.6	3.40
F05058	35.6	13.7	3.1	0.0	4.8	78.4	5.22
Number of females	5	5	5	5	5	5	5
Mean	51.7	16.7	2.1	0.0	4.3	76.8	3.45
S.D.	14.5	5.2	0.6	0.0	1.7	6.5	1.02

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 25-3-2. Hematological findings of female rats at the end of the recovery period

N-DPS (150 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F06065	800	15.0	42.3	52.9	18.8	35.5	94.3	11.7	16.7
F06066	798	14.1	41.3	51.8	17.7	34.1	99.0	12.6	21.8
F06067	804	15.4	42.3	52.6	19.2	36.4	112.8	11.7	19.5
F06068	773	14.3	41.3	53.4	18.5	34.6	97.6	11.4	18.7
Number of females	4	4	4	4	4	4	4	4	4
Mean	794	14.7	41.8	52.7	18.6	35.2	100.9	11.9	19.2
S.D.	14	0.6	0.6	0.7	0.6	1.0	8.2	0.5	2.1

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F06065	46.4	16.6	3.0	0.0	5.6	74.8	3.38
F06066	43.9	16.0	1.1	0.0	2.7	80.2	3.26
F06067	45.9	20.1	1.7	0.0	5.0	73.2	3.19
F06068	43.5	18.1	2.8	0.0	7.6	71.5	4.27
Number of females	4	4	4	4	4	4	4
Mean	44.9	17.7	2.2	0.0	5.2	74.9	3.53
S.D.	1.4	1.8	0.9	0.0	2.0	3.8	0.50

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 26-1-1. Biochemical findings of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01001	5.6	3.5	1.67	130	26	19	53	73	35	0	100	5.8	14	0.5	0.05	381	6.1	8.9	144.1	4.05	107.2
M01002	5.5	3.5	1.75	133	47	40	84	122	42	0	64	8.5	14	0.5	0.07	325	5.5	9.0	144.3	3.93	105.6
M01003	5.5	3.7	2.06	139	49	39	83	58	31	0	45	7.0	13	0.4	0.05	328	6.3	9.5	143.9	4.18	106.3
M01004	5.6	3.7	1.95	138	36	19	64	62	27	0	56	7.7	13	0.4	0.06	260	5.6	9.3	145.4	3.90	105.2
M01005	5.9	3.8	1.81	143	42	16	77	62	30	0	119	15.9	14	0.4	0.04	381	7.0	9.4	143.7	4.04	103.1
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.6	1.85	137	40	27	72	75	33	0	77	9.0	14	0.4	0.05	335	6.1	9.2	144.3	4.02	105.5
S.D.	0.2	0.1	0.16	5	9	12	13	27	6	0	31	4.0	1	0.1	0.01	50	0.6	0.3	0.7	0.11	1.5

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 26-1-2. Biochemical findings of male rats at the end of the dosing period

N-DPS 15 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M02013	5.9	3.7	1.68	137	42	15	74	56	35	0	87	14.4	17	0.5	0.05	281	5.6	9.2	142.5	4.14	104.7
M02014	5.8	3.6	1.64	140	38	24	62	53	26	0	79	11.1	15	0.5	0.06	300	6.6	9.4	143.3	4.12	104.9
M02015	5.5	3.6	1.89	138	32	61	69	67	40	0	57	5.3	13	0.4	0.05	272	6.0	9.3	142.7	4.06	105.5
M02016	5.6	3.5	1.67	134	44	30	73	59	31	0	104	8.2	13	0.4	0.06	289	6.6	9.3	144.4	3.82	105.3
M02017	5.3	3.5	1.94	131	50	12	84	53	23	0	54	17.2	11	0.4	0.06	300	6.0	9.2	143.0	4.02	105.0
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.6	1.76	136	41	28	72	58	31	0	76	11.2	14	0.4	0.06	288	6.2	9.3	143.2	4.03	105.1
S.D.	0.2	0.1	0.14	4	7	20	8	6	7	0	21	4.7	2	0.1	0.01	12	0.4	0.1	0.7	0.13	0.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	AN	DU	AN	AN	AN	DT	KW	AN	KW	AN	KW	AN	AN	KW	KW	KW	KW	AN	KW

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 26-1-3. Biochemical findings of male rats at the end of the dosing period

N-DPS 50 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M03025	5.7	3.6	1.71	127	33	35	65	63	28	0	110	7.6	15	0.4	0.05	377	5.7	9.4	144.7	3.86	105.3
M03026	5.3	3.6	2.12	144	39	33	77	88	34	0	127	4.8	16	0.5	0.05	292	6.9	9.4	143.9	3.93	105.9
M03027	5.8	3.7	1.76	157	48	46	86	72	24	0	215	8.3	14	0.4	0.04	325	5.3	9.7	144.4	3.54	105.1
M03028	5.7	3.6	1.71	142	61	59	97	106	34	0	163	4.1	14	0.4	0.03	226	6.3	9.9	144.3	3.60	103.5
M03029	5.4	3.5	1.84	146	37	11	62	60	30	0	55	7.9	13	0.4	0.05	266	6.5	9.2	143.3	3.87	104.3
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.6	1.83	143	44	37	77	78	30	0	134	6.5	14	0.4	0.04	297	6.1	9.5	144.1	3.76	104.8
S.D.	0.2	0.1	0.17	11	11	18	15	19	4	0	60	1.9	1	0	0.01	57	0.6	0.3	0.5	0.18	0.9
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	AN	DU	AN	AN	AN	DT	KW	AN	KW	AN	KW	AN	AN	KW	KW	KW	KW	AN	KW

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 26-1-4. Biochemical findings of male rats at the end of the dosing period

N-DPS 150 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04037	5.0	3.3	1.94	121	44	27	73	69	48	0	223	6.2	17	0.4	0.06	174	5.2	8.9	143.2	4.16	105.4
M04038	5.1	3.4	2.00	107	52	16	75	84	48	0	226	7.3	19	0.5	0.05	288	6.8	9.3	144.8	4.08	109.0
M04039	4.8	3.4	2.43	142	72	29	107	68	26	0	163	6.7	15	0.4	0.06	162	6.1	9.4	143.7	3.63	103.6
M04040	5.4	3.3	1.57	113	50	23	71	297	125	0	670	13.3	34	0.6	0.06	474	10.5	10.8	147.6	3.89	97.7
M04041	4.9	3.3	2.06	126	38	31	66	85	37	0	41	10.9	12	0.4	0.06	216	6.9	9.2	142.6	3.80	104.5
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.0	3.3	2.00	122	51	25	78	121	57	0	265	8.9	19	0.5	0.06	263	7.1	9.5	144.4	3.91	104.0
S.D.	0.2	0.1	0.31	13	13	6	16	99	39	0	239	3.1	9	0.1	0	128	2.0	0.7	2.0	0.21	4.1
Significance	**	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	AN	DU	AN	AN	AN	DT	KW	AN	KW	AN	KW	AN	AN	KW	KW	KW	KW	AN	KW

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 26-2-1. Biochemical findings of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01008	5.6	3.5	1.67	156	41	24	74	51	26	0	109	16.1	14	0.5	0.07	221	6.8	9.1	143.7	3.69 §	105.8
M01009	6.0	3.8	1.73	156	58	30	90	51	26	0	209	12.4	15	0.6	0.06	245	6.5	9.5	142.6	3.72 §	104.3
M01010	5.5	3.5	1.75	146	48	15	69	60	25	0	133	13.5	13	0.5	0.06	233	6.3	9.0	143.9	3.53	106.1
M01011	5.6	3.5	1.67	126	51	8	73	90	36	0	209	11.7	16	0.5	0.04	213	5.8	8.8	144.0	3.34	106.6
M01012	5.7	3.7	1.85	132	44	11	70	57	25	0	113	23.3	15	0.5	0.05	241	5.4	9.1	144.5	3.39	108.6
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.6	1.73	143	48	18	75	62	28	0	155	15.4	15	0.5	0.06	231	6.2	9.1	143.7	3.53	106.3
S.D.	0.2	0.1	0.07	14	7	9	9	16	5	0	50	4.7	1	0	0.01	13	0.6	0.3	0.7	0.17	1.6

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 26-2-2. Biochemical findings of male rats at the end of the recovery period

N-DPS 150 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04044	5.8	3.8	1.90	130	38	10	66	73	36	0	225	23.7	21	0.6	0.06	247	7.3	9.4	143.3	3.69	104.4
M04045	5.9	3.8	1.81	141	38	30	74	76	36	0	223	16.7	20	0.8	0.07	391	7.9	9.4	144.4	3.81	104.0
M04046	5.7	3.5	1.59	132	51	12	78	56	26	0	139	22.5	15	0.5	0.06	302	5.2	9.0	144.0	3.63	106.8
M04047	5.6	3.7	1.95	126	62	20	92	64	22	0	325	20.7	17	0.6	0.07	397	6.2	9.2	143.7	3.76	106.6
M04048	6.2	3.8	1.58	141	46	27	78	58	28	0	298	24.9	18	0.5	0.05	331	5.2	9.6	143.4	3.61	106.0
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.7	1.77	134	47	20	78	65	30	0	242	21.7	18	0.6	0.06	334	6.4	9.3	143.8	3.70	105.6
S.D.	0.2	0.1	0.17	7	10	9	9	9	6	0	73	3.2	2	0.1	0.01	63	1.2	0.2	0.5	0.08	1.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	*	NS	NS	*	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 27-1-1. Biochemical findings of female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F01006	5.7	3.9	2.17	115	46	20	92	88	48	0	98	8.8	20	0.6	0.05	167	6.7	9.8	143.7	3.60	107.8
F01008	6.1	4.2	2.21	139	61	31	110	66	33	0	51	15.4	19	0.5	0.08	133	6.3	10.1	141.0	3.83	106.4
F01009	5.7	3.8	2.00	104	53	20	93	91	51	0	85	12.4	18	0.5	0.05	209	6.7	10.0	141.9	4.04	107.6
F01010	6.0	4.0	2.00	124	51	14	94	150	64	0	43	9.4	18	0.5	0.06	136	6.9	10.1	142.0	4.13	105.6
F01012	5.9	4.0	2.11	128	94	28	145	92	40	0	78	12.9	20	0.5	0.06	122	5.9	9.9	142.6	3.25	107.4
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.0	2.10	122	61	23	107	97	47	0	71	11.8	19	0.5	0.06	153	6.5	10.0	142.2	3.77	107.0
S.D.	0.2	0.1	0.10	13	19	7	23	31	12	0	23	2.7	1	0	0.01	35	0.4	0.1	1.0	0.36	0.9

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 27-1-2. Biochemical findings of female rats at the end of the dosing period

N-DPS 15 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F02013	6.0	4.0	2.00	127	47	14	95	82	40	0	82	17.9	14	0.6	0.06	166	5.8	9.5	141.2	3.78	106.0
F02015	5.8	3.8	1.90	95	43	19	93	270	79	0	173	30.7	16	0.5	0.07	148	8.5	10.2	140.1	9.32 §	107.2
F02017	5.9	3.9	1.95	129	48	27	95	169	49	0	50	13.0	20	0.6	0.07	212	6.5	9.9	142.7	3.86	108.9
F02018	6.1	4.1	2.05	129	56	44	114	139	42	0	351	13.5	17	0.5	0.07	113	7.1	10.5	141.0	4.16	105.8
F02022	5.9	4.0	2.11	122	47	13	103	154	75	0	57	21.5	20	0.6	0.07	202	6.7	9.7	141.4	3.79	104.8
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.0	2.00	120	48	23	100	163	57	0	143	19.3	17	0.6	0.07	168	6.9	10.0	141.3	4.98	106.5
S.D.	0.1	0.1	0.08	14	5	13	9	68	19	0	126	7.3	3	0.1	0	40	1.0	0.4	0.9	2.43	1.6
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	DU	AN	AN	AN	AN	AN	AN	KW	AN

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

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 27-1-3. Biochemical findings of female rats at the end of the dosing period

N-DPS 50 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F03027	6.3	4.2	2.00	128	60	21	112	97	39	0	219	18.0	15	0.6	0.08	147	5.7	10.2	141.8	3.65	107.6
F03028	5.9	3.9	1.95	117	55	34	112	90	43	0	72	36.3	17	0.5	0.10	187	6.4	9.6	140.3	4.41 §	104.0
F03031	5.3	3.6	2.12	110	44	19	92	72	47	0	46	11.1	16	0.5	0.07	135	6.2	9.7	140.2	3.92	107.2
F03034	5.7	3.9	2.17	124	66	23	119	97	40	0	102	19.9	13	0.5	0.06	210	5.5	9.7	141.1	3.17	105.8
F03036	6.2	4.2	2.1	122	74	26	124	134	52	0	177	13.5	17	0.5	0.05	133	6.8	10.1	140.4	3.45	106.0
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.0	2.07	120	60	25	112	98	44	0	123	19.8	16	0.5	0.07	162	6.1	9.9	140.8	3.72	106.1
S.D.	0.4	0.3	0.09	7	11	6	12	23	5	0	73	9.9	2	0	0.02	34	0.5	0.3	0.7	0.47	1.4
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	DU	AN	AN	AN	AN	AN	AN	KW	AN

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

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.

NS: Not significantly different from the control group.

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

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

DU: Analysis by Dunnett's test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 27-1-4. Biochemical findings of female rats at the end of the dosing period

N-DPS 150 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F04037	5.5	3.7	2.06	124	46	31	102	122	47	0	66	28.3	17	0.5	0.08	176	6.3	9.1	141.1	3.78	106.9
F04040	5.9	3.7	1.68	120	51	20	91	86	28	0	190	15.4	20	0.5	0.06	255	6.2	9.8	141.7	3.65	107.2
F04043	5.6	3.8	2.11	123	38	24	86	95	41	0	50	14.0	18	0.5	0.07	179	5.8	9.4	140.9	3.58	108
F04045	6.0	4.1	2.16	125	73	21	130	113	42	0	51	18.7	21	0.6	0.06	132	6.8	9.8	141.1	3.75	106.6
F04046	5.5	3.7	2.06	102	56	16	100	204	48	0	69	10.4	18	0.5	0.06	124	6.7	10.1	141.1	3.60	105.8
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.8	2.01	119	53	22	102	124	41	0	85	17.4	19	0.5	0.07	173	6.4	9.6	141.2	3.67	106.9
S.D.	0.2	0.2	0.19	10	13	6	17	47	8	0	59	6.8	2	0	0.01	52	0.4	0.4	0.3	0.09	0.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	AN	DU	AN	AN	AN	AN	AN	AN	KW	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 27-2-1. Biochemical findings of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05054	5.7	4.0	2.35	140	71	13	122	52	24	0	48	20.6	19	0.6	0.1	120	4.1	9.2	142.7	3.53	107.3
F05055	6.2	4.2	2.10	139	84	17	139	57	20	0	59	9.6	16	0.7	0.08	107	4	9.3	142.7	3.30	106.4
F05056	6.5	4.5	2.25	154	80	24	145	52	27	0	156	15.7	18	0.7	0.07	99	3.8	9.6	142.6	3.36	105.7
F05057	6.5	4.5	2.25	110	54	44	117	80	38	0	58	10.1	17	0.6	0.10	92	3.8	9.9	143.4	3.35	109.0
F05058	6.1	4.3	2.39	103	61	16	120	65	18	0	153	12.8	18	0.7	0.11	130	4.1	9.6	144.7	3.21	109.4
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.2	4.3	2.27	129	70	23	129	61	25	0	95	13.8	18	0.7	0.09	110	4	9.5	143.2	3.35	107.6
S.D.	0.3	0.2	0.11	22	13	13	13	12	8	0	55	4.5	1	0.1	0.02	15	0.2	0.3	0.9	0.12	1.6

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 27-2-2. Biochemical findings of female rats at the end of the dosing period, satellite group

N-DPS 150 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06065	5.6	3.9	2.29	107	73	18	123	54	19	0	50	12.1	22	0.6	0.07	158	5.1	9.2	142.0	3.54	107.0
F06066	6.2	4.2	2.10	121	65	42	131	48	24	0	85	30.6	21	0.6	0.06	139	4.0	9.5	144.4	3.45	109.8
F06067	6.1	4.3	2.39	110	64	11	120	63	26	0	36	9.6	17	0.6	0.09	113	4.0	9.6	142.5	3.09	107.1
F06068	6.0	4.1	2.16	119	62	20	111	64	27	0	105	9.8	24	0.7	0.07	138	5.5	9.7	142.8	3.40	106.3
Number of females	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	6.0	4.1	2.24	114	66	23	121	57	24	0	69	15.5	21	0.6	0.07	137	4.7	9.5	142.9	3.37	107.6
S.D.	0.3	0.2	0.13	7	5	13	8	8	4	0	32	10.1	3	0.1	0.01	18	0.8	0.2	1.0	0.20	1.5
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	*	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 27-3-1. Biochemical findings of female rats at the end of the recovery period

Control (vehicle; water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05049	5.8	3.9	2.05	99	61	7	104	76	38	0	100	16.7	23	0.6	0.10	218	5.2	9.0	142.1	3.40	106.3
F05050	6.3	4.2	2.00	101	60	9	116	70	19	0	90	12.2	18	0.6	0.08	193	4.1	9.5	143.1	3.56	108.8
F05051	5.8	3.9	2.05	105	52	9	92	86	30	0	53	11.8	18	0.6	0.08	153	4.5	9.3	142.1	3.41	107.3
F05052	5.4	3.7	2.18	102	59	14	108	72	26	0	66	11.3	23	0.6	0.07	202	4.1	8.6	144.6	3.37	111.3
F05053	6.0	4.1	2.16	124	60	17	123	58	23	0	91	8.1	17	0.6	0.08	205	3.9	9.4	143.8	3.65	108.7
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.0	2.09	106	58	11	109	72	27	0	80	12.0	20	0.6	0.08	194	4.4	9.2	143.1	3.48	108.5
S.D.	0.3	0.2	0.08	10	4	4	12	10	7	0	20	3.1	3	0	0.01	25	0.5	0.4	1.1	0.12	1.9

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 27-3-2. Biochemical findings of female rats at the end of the recovery period

N-DPS 150 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06059	6.4	4.4	2.20	111	75	8	137	97	43	0	131	27.6	20	0.6	0.14	251	5.8	9.9	142.5	3.61	105.2
F06061	6.0	4.3	2.53	128	62	14	123	88	19	0	114	11.4	14	0.5	0.10	144	4.7	9.6	143.1	3.24	107.7
F06063	5.0	3.3	1.94	105	64	15	106	59	22	0	46	8.0	16	0.6	0.07	195	5.0	9.0	142.7	3.29	107.2
F06064	5.6	3.9	2.29	100	72	12	128	112	71	0	58	10.6	19	0.6	0.07	112	4.4	9.3	142.5	3.27	107.5
Number of ffemales	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	5.8	4	2.24	111	68	12	124	89	39	0	87	14.4	17	0.6	0.10	176	5.0	9.5	142.7	3.35	106.9
S.D.	0.6	0.5	0.24	12	6	3	13	22	24	0	42	8.9	3	0	0.03	61	0.6	0.4	0.3	0.17	1.2
Significance	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-1. Organ weights of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	444.6	2082.4	4.684	203.0	0.457	1258.1	2.830	10755.2	24.191	1465.5	3.296	1484.0	3.338	2949.5	6.634	719.1	1.617
M01002	432.5	2055.1	4.752	341.1	0.789	1331.9	3.080	11318.0	26.169	1367.9	3.163	1463.7	3.384	2831.6	6.547	578.5	1.338
M01003	522.0	2192.5	4.200	371.3	0.711	1542.4	2.955	13598.9	26.052	1734.1	3.322	1678.3	3.215	3412.4	6.537	1051.8	2.015
M01004	447.5	2135.2	4.771	361.0	0.807	1361.1	3.042	10908.4	24.376	1478.0	3.303	1498.2	3.348	2976.2	6.651	723.7	1.617
M01005	482.1	1947.5	4.040	347.4	0.721	1431.3	2.969	14771.1	30.639	1625.9	3.373	1605.8	3.331	3231.7	6.703	912.0	1.892
M01006	479.3	2164.1	4.515	231.9	0.484	1408.9	2.939	13148.1	27.432	1765.8	3.684	1731.5	3.613	3497.3	7.297	756.4	1.578
M01007	520.6	2039.1	3.917	391.3	0.752	1428.8	2.745	12335.8	23.695	1539.0	2.956	1640.8	3.152	3179.8	6.108	861.1	1.654
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	475.5	2088.0	4.411	321.0	0.674	1394.6	2.937	12405.1	26.079	1568.0	3.300	1586.0	3.340	3154.1	6.640	800.4	1.673
S.D.	36.2	83.8	0.355	73.1	0.144	89.7	0.116	1512.4	2.408	146.9	0.220	105.0	0.146	247.9	0.351	154.4	0.221

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-1(continued). Organ weights of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	1703.4	3.831	1662.3	3.739	3365.7	7.570	667.8	1.502	616.6	1.387	1284.4	2.889
M01002	1479.4	3.421	1478.7	3.419	2958.1	6.840	556.4	1.286	540.5	1.250	1096.9	2.536
M01003	1754.0	3.360	1896.3	3.633	3650.3	6.993	653.4	1.252	652.9	1.251	1306.3	2.502
M01004	1822.1	4.072	1794.9	4.011	3617.0	8.083	616.9	1.379	581.6	1.300	1198.5	2.678
M01005	1685.1	3.495	1674.7	3.474	3359.8	6.969	594.8	1.234	585.7	1.215	1180.5	2.449
M01006	1881.0	3.924	1884.0	3.931	3765.0	7.855	581.3	1.213	558.2	1.165	1139.5	2.377
M01007	1572.5	3.021	1617.7	3.107	3190.2	6.128	597.1	1.147	602.4	1.157	1199.5	2.304
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1699.6	3.589	1715.5	3.616	3415.2	7.205	609.7	1.288	591.1	1.246	1200.8	2.534
S.D.	138.9	0.369	151.4	0.313	283.9	0.673	39.5	0.118	37.3	0.080	74.3	0.197

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-1(continued). Organ weights of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	653.1	1.469	2073.6	4.664	18.5	0.042	26.6	0.060	28.8	0.065	55.4	0.125
M01002	671.1	1.552	1549.0	3.582	21.0	0.049	25.2	0.058	27.4	0.063	52.6	0.122
M01003	743.9	1.425	1735.8	3.325	21.8	0.042	25.0	0.048	29.8	0.057	54.8	0.105
M01004	401.0	0.896	1171.5	2.618	22.3	0.050	19.2	0.043	20.7	0.046	39.9	0.089
M01005	735.6	1.526	1591.1	3.300	12.9	0.027	23.4	0.049	22.7	0.047	46.1	0.096
M01006	575.1	1.200	1687.5	3.521	22.7	0.047	21.1	0.044	23.0	0.048	44.1	0.092
M01007	510.4	0.980	1142.9	2.195	23.7	0.046	23.5	0.045	23.6	0.045	47.1	0.090
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	612.9	1.293	1564.5	3.315	20.4	0.043	23.4	0.050	25.1	0.053	48.6	0.103
S.D.	125.2	0.269	325.8	0.783	3.7	0.008	2.5	0.007	3.5	0.009	5.8	0.015

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-2. Organ weights of male rats at the end of the dosing period

N-DPS 15 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	453.9	2033.5	4.480	286.5	0.631	1543.8	3.401	12547.5	27.644	1587.6	3.498	1551.0	3.417	3138.6	6.915	853.2	1.880
M02014	477.9	2132.5	4.462	440.9	0.923	1514.1	3.168	11820.6	24.734	1512.3	3.164	1458.8	3.053	2971.1	6.217	845.9	1.770
M02015	437.2	1988.9	4.549	233.7	0.535	1574.3	3.601	11235.0	25.698	1617.7	3.700	1579.4	3.613	3197.1	7.313	757.3	1.732
M02016	444.3	2067.4	4.653	324.0	0.729	1474.2	3.318	11313.0	25.463	1487.4	3.348	1462.9	3.293	2950.3	6.640	846.7	1.906
M02017	433.1	2034.6	4.698	191.9	0.443	1359.9	3.140	10599.5	24.474	1574.4	3.635	1613.4	3.725	3187.8	7.360	667.5	1.541
M02018	485.6	1917.6	3.949	293.4	0.604	1430.5	2.946	13093.9	26.964	1612.5	3.321	1580.9	3.256	3193.4	6.576	1013.8	2.088
M02019	498.2	2028.7	4.072	328.6	0.660	1523.7	3.058	14446.4	28.997	1644.7	3.301	1611.3	3.234	3256.0	6.536	762.1	1.530
M02020	505.0	2130.1	4.218	362.6	0.718	1527.1	3.024	13401.2	26.537	1920.8	3.804	1904.0	3.770	3824.8	7.574	826.9	1.637
M02021	492.0	1949.1	3.962	466.0	0.947	1373.8	2.792	13608.2	27.659	1565.0	3.181	1552.8	3.156	3117.8	6.337	736.8	1.498
M02022	433.2	1993.5	4.602	273.9	0.632	1539.4	3.554	11181.9	25.812	1552.3	3.583	1571.6	3.628	3123.9	7.211	812.0	1.874
M02023	477.7	2068.3	4.330	274.1	0.574	1331.8	2.788	12234.4	25.611	1522.7	3.188	1744.7	3.652	3267.4	6.840	755.5	1.582
M02024	537.5	2051.7	3.817	341.5	0.635	1401.1	2.607	14537.1	27.046	1891.5	3.519	2051.5	3.817	3943.0	7.336	836.2	1.556
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	473.0	2033.0	4.316	318.1	0.669	1466.1	3.116	12501.6	26.387	1624.1	3.437	1640.2	3.468	3264.3	6.905	809.5	1.716
S.D.	33.1	64.7	0.305	78.7	0.146	83.0	0.311	1322.0	1.330	139.5	0.217	176.6	0.263	306.3	0.449	85.7	0.189
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	AN	AN	DU	KW	DU	AN	DU	AN	DU	KW	DU	AN	DU	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-2(continued). Organ weights of male rats at the end of the dosing period

N-DPS 15 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	453.9	2033.5	4.480	286.5	0.631	1543.8	3.401	12547.5	27.644	1587.6	3.498	1551.0	3.417	3138.6	6.915	853.2	1.880
M02014	477.9	2132.5	4.462	440.9	0.923	1514.1	3.168	11820.6	24.734	1512.3	3.164	1458.8	3.053	2971.1	6.217	845.9	1.770
M02015	437.2	1988.9	4.549	233.7	0.535	1574.3	3.601	11235.0	25.698	1617.7	3.700	1579.4	3.613	3197.1	7.313	757.3	1.732
M02016	444.3	2067.4	4.653	324.0	0.729	1474.2	3.318	11313.0	25.463	1487.4	3.348	1462.9	3.293	2950.3	6.640	846.7	1.906
M02017	433.1	2034.6	4.698	191.9	0.443	1359.9	3.140	10599.5	24.474	1574.4	3.635	1613.4	3.725	3187.8	7.360	667.5	1.541
M02018	485.6	1917.6	3.949	293.4	0.604	1430.5	2.946	13093.9	26.964	1612.5	3.321	1580.9	3.256	3193.4	6.576	1013.8	2.088
M02019	498.2	2028.7	4.072	328.6	0.660	1523.7	3.058	14446.4	28.997	1644.7	3.301	1611.3	3.234	3256.0	6.536	762.1	1.530
M02020	505.0	2130.1	4.218	362.6	0.718	1527.1	3.024	13401.2	26.537	1920.8	3.804	1904.0	3.770	3824.8	7.574	826.9	1.637
M02021	492.0	1949.1	3.962	466.0	0.947	1373.8	2.792	13608.2	27.659	1565.0	3.181	1552.8	3.156	3117.8	6.337	736.8	1.498
M02022	433.2	1993.5	4.602	273.9	0.632	1539.4	3.554	11181.9	25.812	1552.3	3.583	1571.6	3.628	3123.9	7.211	812.0	1.874
M02023	477.7	2068.3	4.330	274.1	0.574	1331.8	2.788	12234.4	25.611	1522.7	3.188	1744.7	3.652	3267.4	6.840	755.5	1.582
M02024	537.5	2051.7	3.817	341.5	0.635	1401.1	2.607	14537.1	27.046	1891.5	3.519	2051.5	3.817	3943.0	7.336	836.2	1.556
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	473.0	2033.0	4.316	318.1	0.669	1466.1	3.116	12501.6	26.387	1624.1	3.437	1640.2	3.468	3264.3	6.905	809.5	1.716
S.D.	33.1	64.7	0.305	78.7	0.146	83.0	0.311	1322.0	1.330	139.5	0.217	176.6	0.263	306.3	0.449	85.7	0.189
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	AN	AN	DU	KW	DU	AN	DU	AN	DU	KW	DU	AN	DU	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-2(continued). Organ weights of male rats at the end of the dosing period

N-DPS 15 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	593.7	1.308	1287.9	2.837	35.7	0.079	25.6	0.056	24.1	0.053	49.7	0.109
M02014	694.6	1.453	1436.8	3.006	22.2	0.046	21.6	0.045	22.0	0.046	43.6	0.091
M02015	351.3	0.804	1373.8	3.142	23.1	0.053	23.0	0.053	22.1	0.051	45.1	0.103
M02016	743.6	1.674	1730.6	3.895	21.6	0.049	23.0	0.052	22.7	0.051	45.7	0.103
M02017	268.4	0.620	1757.5	4.058	17.8	0.041	25.8	0.060	28.7	0.066	54.5	0.126
M02018	761.5	1.568	1608.0	3.311	19.5	0.040	28.0	0.058	27.6	0.057	55.6	0.114
M02019	527.5	1.059	1390.1	2.790	21.4	0.043	20.8	0.042	20.2	0.041	41.0	0.082
M02020	394.5	0.781	2065.5	4.090	21.8	0.043	28.7	0.057	28.1	0.056	56.8	0.112
M02021	606.4	1.233	1758.4	3.574	17.7	0.036	23.8	0.048	24.2	0.049	48.0	0.098
M02022	475.8	1.098	1576.7	3.640	16.7	0.039	28.2	0.065	28.8	0.066	57.0	0.132
M02023	585.3	1.225	1446.8	3.029	18.1	0.038	24.1	0.050	27.5	0.058	51.6	0.108
M02024	701.8	1.306	1330.2	2.475	23.9	0.044	23.1	0.043	23.5	0.044	46.6	0.087
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	558.7	1.177	1563.5	3.321	21.6	0.046	24.6	0.052	25.0	0.053	49.6	0.105
S.D.	159.7	0.322	230.4	0.529	5.0	0.011	2.6	0.007	3.0	0.008	5.5	0.015
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	AN	DU	AN	KW	DT	AN	DU	KW	DU

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-3. Organ weights of male rats at the end of the dosing period

N-DPS 50 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	455.3	2043.5	4.488	283.9	0.624	1310.7	2.879	12722.8	27.944	1488.0	3.268	1518.3	3.335	3006.3	6.603	841.5	1.848
M03026	445.0	1882.2	4.230	369.0	0.829	1371.8	3.083	11256.6	25.296	1340.3	3.012	1350.4	3.035	2690.7	6.047	655.9	1.474
M03027	465.3	1993.2	4.284	255.2	0.548	1354.3	2.911	13819.8	29.701	1606.1	3.452	1567.6	3.369	3173.7	6.821	869.9	1.870
M03028	534.8	1900.7	3.554	296.2	0.554	1618.0	3.025	15127.5	28.286	1778.8	3.326	1751.3	3.275	3530.1	6.601	934.7	1.748
M03029	457.3	1964.5	4.296	250.6	0.548	1434.8	3.138	12134.7	26.536	1533.9	3.354	1496.1	3.272	3030.0	6.626	783.9	1.714
M03030	469.8	2086.2	4.441	415.4	0.884	1262.7	2.688	11963.5	25.465	1599.0	3.404	1605.6	3.418	3204.6	6.821	1054.9	2.245
M03031	524.2	1985.1	3.787	400.9	0.765	1513.6	2.887	13598.4	25.941	1789.7	3.414	1759.9	3.357	3549.6	6.771	1045.8	1.995
M03032	443.3	2058.6	4.644	413.9	0.934	1381.5	3.116	10073.0	22.723	1418.1	3.199	1321.9	2.982	2740.0	6.181	836.0	1.886
M03033	475.1	1957.9	4.121	315.7	0.664	1397.2	2.941	12909.0	27.171	1584.0	3.334	1475.8	3.106	3059.8	6.440	838.4	1.765
M03034	476.7	1996.8	4.189	494.0	1.036	1448.9	3.039	13374.9	28.057	1597.5	3.351	1569.7	3.293	3167.2	6.644	895.5	1.879
M03035	492.9	2069.3	4.198	253.6	0.515	1468.7	2.980	12534.4	25.430	1673.0	3.394	1665.5	3.379	3338.5	6.773	1045.3	2.121
M03036	464.2	1947.7	4.196	369.7	0.796	1471.3	3.170	12481.6	26.888	1635.3	3.523	1715.4	3.695	3350.7	7.218	836.4	1.802
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	475.3	1990.5	4.202	343.2	0.725	1419.5	2.988	12666.4	26.620	1587.0	3.336	1566.5	3.293	3153.4	6.629	886.5	1.862
S.D.	28.9	64.8	0.294	78.9	0.174	95.0	0.137	1292.0	1.825	131.5	0.132	143.7	0.190	270.7	0.307	118.6	0.198
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	AN	AN	DU	KW	DU	AN	DU	AN	DU	KW	DU	AN	DU	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-3(continued). Organ weights of male rats at the end of the dosing period

N-DPS 50 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	1610.2	3.537	1554.5	3.414	3164.7	6.951	688.7	1.513	641.4	1.409	1330.1	2.921
M03026	1668.0	3.748	1623.7	3.649	3291.7	7.397	634.4	1.426	604.8	1.359	1239.2	2.785
M03027	1637.5	3.519	1641.0	3.527	3278.5	7.046	587.3	1.262	589.5	1.267	1176.8	2.529
M03028	1672.8	3.128	1619.5	3.028	3292.3	6.156	606.6	1.134	622.4	1.164	1229.0	2.298
M03029	1587.5	3.471	1580.9	3.457	3168.4	6.928	575.6	1.259	567.8	1.242	1143.4	2.500
M03030	1333.6	2.839	1368.6	2.913	2702.2	5.752	507.3	1.080	529.8	1.128	1037.1	2.208
M03031	1754.6	3.347	1732.7	3.305	3487.3	6.653	663.5	1.266	652.5	1.245	1316.0	2.510
M03032	1631.5	3.680	1637.3	3.693	3268.8	7.374	581.5	1.312	579.1	1.306	1160.6	2.618
M03033	1501.1	3.160	1502.0	3.161	3003.1	6.321	581.4	1.224	560.5	1.180	1141.9	2.403
M03034	1294.8	2.716	1335.9	2.802	2630.7	5.519	475.7	0.998	464.6	0.975	940.3	1.973
M03035	1777.4	3.606	1794.4	3.640	3571.8	7.247	620.1	1.258	612.0	1.242	1232.1	2.500
M03036	1882.2	4.055	1847.6	3.980	3729.8	8.035	648.2	1.396	616.7	1.329	1264.9	2.725
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1612.6	3.401	1603.2	3.381	3215.8	6.782	597.5	1.261	586.8	1.237	1184.3	2.498
S.D.	170.4	0.384	152.5	0.351	321.8	0.733	61.3	0.145	52.0	0.116	111.9	0.259
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	AN	DU	AN	DU	AN	AN	AN	DU	AN	DU

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-3(continued). Organ weights of male rats at the end of the dosing period

N-DPS 50 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	428.8	0.942	1803.4	3.961	26.6	0.058	36.4	0.080	34.9	0.077	71.3	0.157
M03026	710.8	1.597	1715.5	3.855	18.5	0.042	35.1	0.079	34.7	0.078	69.8	0.157
M03027	870.7	1.871	1935.7	4.160	16.1	0.035	23.0	0.049	23.6	0.051	46.6	0.100
M03028	643.0	1.202	1631.8	3.051	20.2	0.038	33.2	0.062	36.0	0.067	69.2	0.129
M03029	403.5	0.882	1527.7	3.341	16.0	0.035	24.4	0.053	26.2	0.057	50.6	0.111
M03030	554.6	1.181	1306.9	2.782	15.8	0.034	21.0	0.045	21.1	0.045	42.1	0.090
M03031	535.7	1.022	1745.9	3.331	21.5	0.041	22.5	0.043	24.1	0.046	46.6	0.089
M03032	599.6	1.353	1159.4	2.615	18.3	0.041	20.9	0.047	22.3	0.050	43.2	0.097
M03033	587.9	1.237	1234.9	2.599	15.1	0.032	19.4	0.041	20.6	0.043	40.0	0.084
M03034	869.2	1.823	1976.9	4.147	19.3	0.040	31.5	0.066	32.1	0.067	63.6	0.133
M03035	668.2	1.356	1573.9	3.193	20.9	0.042	28.7	0.058	29.0	0.059	57.7	0.117
M03036	576.3	1.241	1712.3	3.689	14.7	0.032	31.3	0.067	32.8	0.071	64.1	0.138
Number of males	12	12	12	12	12	12	12	12	12	12	12	12
Mean	620.7	1.309	1610.4	3.394	18.6	0.039	27.3	0.058	28.1	0.059	55.4	0.117
S.D.	145.9	0.317	263.3	0.568	3.4	0.007	6.1	0.013	5.8	0.013	11.8	0.026
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	AN	DU	AN	KW	DT	AN	DU	KW	DU

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-4. Organ weights of male rats at the end of the dosing period

N-DPS 150 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	435.7	2037.9	4.677	285.2	0.655	1206.3	2.769	10330.2	23.709	1433.9	3.291	1408.9	3.234	2842.8	6.525	781.8	1.794
M04038	430.1	2097.6	4.877	221.2	0.514	1344.8	3.127	11185.3	26.006	1632.3	3.795	1658.9	3.857	3291.2	7.652	853.6	1.985
M04039	374.9	1718.1	4.583	368.9	0.984	1267.6	3.381	10220.0	27.261	1132.8	3.022	1195.0	3.188	2327.8	6.209	832.6	2.221
M04040	376.2	1956.9	5.202	121.0	0.322	1233.2	3.278	10526.4	27.981	1489.6	3.960	1574.5	4.185	3064.1	8.145	453.9	1.207
M04041	442.9	2079.9	4.696	363.0	0.820	1257.4	2.839	11147.9	25.170	1489.8	3.364	1478.5	3.338	2968.3	6.702	682.6	1.541
M04042	398.9	1803.9	4.522	281.7	0.706	1318.6	3.306	11254.2	28.213	1434.1	3.595	1434.0	3.595	2868.1	7.190	675.1	1.692
M04043	407.1	1873.5	4.602	287.5	0.706	1218.6	2.993	9805.1	24.085	1292.1	3.174	1184.2	2.909	2476.3	6.083	724.1	1.779
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	409.4	1938.3	4.737	275.5	0.672	1263.8	3.099	10638.4	26.061	1414.9	3.457	1419.1	3.472	2834.1	6.929	714.8	1.746
S.D.	27.8	145.2	0.234	85.1	0.212	51.5	0.239	564.9	1.825	160.1	0.340	178.4	0.437	333.0	0.766	134.4	0.322
Significance	**	**	NS	NS	NS	*	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	AN	AN	DU	KW	DU	AN	DU	AN	DU	KW	DU	AN	DU	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-4(continued). Organ weights of male rats at the end of the dosing period

N-DPS 150 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	1856.8	4.262	1932.8	4.436	3789.6	8.698	603.0	1.384	607.7	1.395	1210.7	2.779
M04038	1799.8	4.185	1851.3	4.304	3651.1	8.489	664.1	1.544	676.3	1.572	1340.4	3.116
M04039	1411.5	3.765	1400.2	3.735	2811.7	7.500	443.0	1.182	418.2	1.115	861.2	2.297
M04040	1533.7	4.077	1573.7	4.183	3107.4	8.260	610.6	1.623	628.8	1.671	1239.4	3.295
M04041	1659.4	3.747	1692.4	3.821	3351.8	7.568	581.6	1.313	612.2	1.382	1193.8	2.695
M04042	1652.5	4.143	1631.7	4.090	3284.2	8.233	587.1	1.472	586.5	1.470	1173.6	2.942
M04043	1506.8	3.701	1505.3	3.698	3012.1	7.399	582.2	1.430	566.4	1.391	1148.6	2.821
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1631.5	3.983	1655.3	4.038	3286.8	8.021	581.7	1.421	585.2	1.428	1166.8	2.849
S.D.	160.1	0.237	187.8	0.291	347.2	0.523	67.5	0.146	81.3	0.175	148.2	0.320
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS
Statistical method	AN	DU	AN	DU	AN	DU	AN	AN	AN	DU	AN	DU

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-1-4(continued). Organ weights of male rats at the end of the dosing period

N-DPS 150 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	438.2	1.006	790.6	1.815	18.7	0.043	22.0	0.050	24.5	0.056	46.5	0.107
M04038	381.3	0.887	1642.9	3.820	18.8	0.044	25.4	0.059	28.0	0.065	53.4	0.124
M04039	236.0	0.630	302.4	0.807	15.4	0.041	23.3	0.062	25.2	0.067	48.5	0.129
M04040	428.8	1.140	1320.0	3.509	15.7	0.042	37.9	0.101	40.4	0.107	78.3	0.208
M04041	580.4	1.310	1530.1	3.455	19.0	0.043	31.6	0.071	33.0	0.075	64.6	0.146
M04042	581.8	1.459	1391.3	3.488	15.0	0.038	30.6	0.077	34.6	0.087	65.2	0.163
M04043	400.5	0.984	1303.0	3.201	12.1	0.030	27.1	0.067	25.0	0.061	52.1	0.128
Number of males	7	7	7	7	7	7	7	7	7	7	7	7
Mean	435.3	1.059	1182.9	2.871	16.4	0.040	28.3	0.070	30.1	0.074	58.4	0.144
S.D.	120.0	0.274	472.2	1.119	2.6	0.005	5.5	0.016	6.1	0.018	11.4	0.033
Significance	NS	NS	NS	NS	NS	NS	NS	*	NS	**	NS	**
Statistical method	AN	AN	DU	AN	DU	AN	KW	DT	AN	DU	KW	DU

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-2-1. Organ weights of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M01008	478.2	2010.3	4.204	243.1	0.508	1560.5	3.263	12455.6	26.047	1930.2	4.036	1775.8	3.714	3706.0	7.750	803.1	1.679
M01009	524.1	2070.4	3.950	324.9	0.620	1463.1	2.792	13992.2	26.698	1602.3	3.057	1558.1	2.973	3160.4	6.030	843.0	1.608
M01010	466.1	1987.6	4.264	303.5	0.651	1418.4	3.043	11892.7	25.515	1640.3	3.519	1692.5	3.631	3332.8	7.150	769.8	1.652
M01011	544.1	2164.3	3.978	299.7	0.551	1464.6	2.692	12947.9	23.797	1871.5	3.440	1805.6	3.319	3677.1	6.758	705.3	1.296
M01012	462.5	2077.6	4.492	303.7	0.657	1281.4	2.771	11314.8	24.464	1501.6	3.247	1579.9	3.416	3081.5	6.663	771.7	1.669
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	495.0	2062.0	4.178	295.0	0.597	1437.6	2.912	12520.6	25.304	1709.2	3.460	1682.4	3.411	3391.6	6.870	778.6	1.581
S.D.	36.8	68.9	0.223	30.6	0.065	101.6	0.236	1024.8	1.174	183.3	0.369	111.8	0.292	288.7	0.635	50.6	0.162

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-2-1(continued). Organ weights of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	1740.7	3.640	1743.6	3.646	3484.3	7.286	763.5	1.597	715.6	1.496	1479.1	3.093
M01009	1517.6	2.896	1357.3	2.590	2874.9	5.485	656.8	1.253	531.5	1.014	1188.3	2.267
M01010	1646.4	3.532	1647.8	3.535	3294.2	7.068	650.8	1.396	616.0	1.322	1266.8	2.718
M01011	1532.8	2.817	1563.8	2.874	3096.6	5.691	652.8	1.200	627.3	1.153	1280.1	2.353
M01012	1602.3	3.464	1582.0	3.421	3184.3	6.885	613.6	1.327	555.9	1.202	1169.5	2.529
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1608.0	3.270	1578.9	3.213	3186.9	6.483	667.5	1.355	609.3	1.237	1276.8	2.592
S.D.	90.8	0.383	142.5	0.458	226.6	0.832	56.4	0.154	71.7	0.182	122.9	0.329

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-2-1(continued). Organ weights of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	600.5	1.256	1968.8	4.117	25.4	0.053	22.3	0.047	22.2	0.046	44.5	0.093
M01009	523.0	0.998	1510.2	2.882	18.4	0.035	22.5	0.043	20.5	0.039	43.0	0.082
M01010	416.1	0.893	1686.1	3.617	15.5	0.033	32.6	0.070	36.2	0.078	68.8	0.148
M01011	633.5	1.164	2539.0	4.666	15.8	0.029	30.8	0.057	33.9	0.062	64.7	0.119
M01012	523.1	1.131	1238.9	2.679	14.3	0.031	28.7	0.062	28.5	0.062	57.2	0.124
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	539.2	1.088	1788.6	3.592	17.9	0.036	27.4	0.056	28.3	0.057	55.6	0.113
S.D.	84.2	0.143	496.4	0.832	4.5	0.010	4.8	0.011	6.9	0.015	11.6	0.026

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-2-2. Organ weights of male rats at the end of the recovery period

N-DPS 150 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	501.4	2113.7	4.216	266.6	0.532	1395.9	2.784	13077.6	26.082	1859.9	3.709	1832.4	3.655	3692.3	7.364	985.4	1.965
M04045	448.4	2053.8	4.580	173.7	0.387	1455.3	3.246	11554.8	25.769	1433.0	3.196	1385.6	3.090	2818.6	6.286	691.1	1.541
M04046	451.8	1976.9	4.376	307.2	0.680	1283.8	2.842	11995.5	26.550	1550.5	3.432	1556.9	3.446	3107.4	6.878	827.4	1.831
M04047	512.1	1907.5	3.725	402.2	0.785	1558.2	3.043	12693.3	24.787	1539.1	3.005	1579.6	3.085	3118.7	6.090	793.5	1.550
M04048	514.0	2151.5	4.186	263.3	0.512	1450.8	2.823	13743.2	26.738	1381.2	2.687	1387.0	2.698	2768.2	5.386	797.8	1.552
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	485.5	2040.7	4.217	282.6	0.579	1428.8	2.948	12612.9	25.985	1552.7	3.206	1548.3	3.195	3101.0	6.401	819.0	1.688
S.D.	32.7	99.5	0.316	82.8	0.155	100.0	0.195	866.1	0.771	185.9	0.392	183.2	0.369	367.6	0.757	106.3	0.198
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-2-2(continued). Organ weights of male rats at the end of the recovery period

N-DPS 150 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	1820.5	3.631	1822.3	3.634	3642.8	7.265	729.4	1.455	725.1	1.446	1454.5	2.901
M04045	1463.8	3.264	1439.6	3.211	2903.4	6.475	619.6	1.382	562.1	1.254	1181.7	2.635
M04046	1514.5	3.352	1547.7	3.426	3062.2	6.778	535.7	1.186	569.5	1.261	1105.2	2.446
M04047	1726.3	3.371	1667.3	3.256	3393.6	6.627	657.5	1.284	643.7	1.257	1301.2	2.541
M04048	1893.0	3.683	1887.4	3.672	3780.4	7.355	779.8	1.517	693.8	1.350	1473.6	2.867
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1683.6	3.460	1672.9	3.440	3356.5	6.900	664.4	1.365	638.8	1.314	1303.2	2.678
S.D.	188.0	0.185	186.1	0.211	372.5	0.391	95.1	0.132	72.8	0.084	162.7	0.200
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 28-2-2(continued). Organ weights of male rats at the end of the recovery period

N-DPS 150 mg/kg

Male No.	Prostate, ventral		Seminal vesicles		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	742.9	1.482	1811.8	3.613	8.2	0.016	20.3	0.040	25.0	0.050	45.3	0.090
M04045	468.5	1.045	1404.4	3.132	12.8	0.029	21.8	0.049	20.1	0.045	41.9	0.093
M04046	554.3	1.227	1759.6	3.895	15.1	0.033	24.7	0.055	26.9	0.060	51.6	0.114
M04047	620.7	1.212	1586.5	3.098	20.8	0.041	20.6	0.040	23.3	0.045	43.9	0.086
M04048	487.8	0.949	1376.9	2.679	16.5	0.032	20.5	0.040	23.4	0.046	43.9	0.085
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	574.8	1.183	1587.8	3.283	14.7	0.030	21.6	0.045	23.7	0.049	45.3	0.094
S.D.	111.4	0.204	198.6	0.476	4.6	0.009	1.8	0.007	2.5	0.006	3.7	0.012
Significance	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-1-1. Organ weights of female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	316.0	1942.5	6.147	161.0	0.509	1079.6	3.416	11227.5	35.530	1101.4	3.485	1082.1	3.424	2183.5	6.910	805.9	2.550
F01002	263.9	1843.1	6.984	129.5	0.491	947.8	3.592	8659.2	32.812	1030.3	3.904	1017.4	3.855	2047.7	7.759	529.3	2.006
F01003	350.0	1842.4	5.264	223.2	0.638	1098.3	3.138	10143.3	28.981	1066.0	3.046	1058.9	3.025	2124.9	6.071	939.9	2.685
F01004	311.5	1827.5	5.867	319.9	1.027	1100.8	3.534	11503.1	36.928	1030.6	3.309	1009.4	3.240	2040.0	6.549	757.7	2.432
F01005	310.3	1972.1	6.355	155.6	0.501	970.1	3.126	9357.1	30.155	1040.8	3.354	977.1	3.149	2017.9	6.503	567.7	1.830
F01006	273.1	1882.5	6.893	172.3	0.631	958.9	3.511	8644.7	31.654	952.6	3.488	946.5	3.466	1899.1	6.954	577.4	2.114
F01007	301.4	1817.8	6.031	221.3	0.734	876.8	2.909	9010.9	29.897	891.4	2.958	898.7	2.982	1790.1	5.939	590.5	1.959
F01008	293.7	1937.2	6.596	179.4	0.611	1031.2	3.511	10203.3	34.741	1156.9	3.939	1153.6	3.928	2310.5	7.867	600.6	2.045
F01009	307.7	1914.0	6.220	185.5	0.603	1036.9	3.370	11281.1	36.663	1097.8	3.568	1051.1	3.416	2148.9	6.984	932.0	3.029
F01010	297.4	1907.3	6.413	249.7	0.840	1167.7	3.926	10203.8	34.310	1166.7	3.923	1134.6	3.815	2301.3	7.738	638.0	2.145
F01011	307.9	1936.5	6.289	238.7	0.775	1019.6	3.311	9852.2	31.998	1049.5	3.409	1053.0	3.420	2102.5	6.829	725.1	2.355
F01012	320.4	1952.4	6.094	248.4	0.775	1082.2	3.378	10315.2	32.195	1021.0	3.187	1058.0	3.302	2079.0	6.489	690.4	2.155
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	304.4	1897.9	6.263	207.0	0.678	1030.8	3.394	10033.5	32.989	1050.4	3.464	1036.7	3.419	2087.1	6.883	696.2	2.275
S.D.	22.1	53.5	0.458	53.0	0.159	81.4	0.261	983.7	2.652	77.8	0.329	73.0	0.312	148.6	0.636	139.4	0.347

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-1-1(continued). Organ weights of female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	52.6	0.166	54.5	0.172	107.1	0.339	532.0	1.684	15.3	0.048	50.6	0.160	47.3	0.150	97.9	0.310
F01002	46.3	0.175	42.1	0.160	88.4	0.335	549.1	2.081	18.1	0.069	41.0	0.155	39.9	0.151	80.9	0.307
F01003	43.2	0.123	49.4	0.141	92.6	0.265	563.3	1.609	10.6	0.030	29.6	0.085	31.3	0.089	60.9	0.174
F01004	51.4	0.165	45.0	0.144	96.4	0.309	635.8	2.041	15.8	0.051	37.0	0.119	40.8	0.131	77.8	0.250
F01005	48.4	0.156	56.5	0.182	104.9	0.338	677.6	2.184	13.9	0.045	44.5	0.143	44.0	0.142	88.5	0.285
F01006	67.7	0.248	52.3	0.192	120.0	0.439	624.1	2.285	13.3	0.049	34.1	0.125	31.9	0.117	66.0	0.242
F01007	40.6	0.135	50.7	0.168	91.3	0.303	591.2	1.962	15.7	0.052	32.7	0.108	34.8	0.115	67.5	0.224
F01008	63.4	0.216	53.6	0.182	117.0	0.398	591.0	2.012	14.7	0.050	39.5	0.134	38.6	0.131	78.1	0.266
F01009	51.2	0.166	44.4	0.144	95.6	0.311	673.2	2.188	17.7	0.058	35.9	0.117	42.8	0.139	78.7	0.256
F01010	64.4	0.217	53.4	0.180	117.8	0.396	724.6	2.436	17.2	0.058	41.5	0.140	45.9	0.154	87.4	0.294
F01011	44.4	0.144	63.7	0.207	108.1	0.351	571.9	1.857	16.4	0.053	40.9	0.133	46.4	0.151	87.3	0.284
F01012	59.3	0.185	43.3	0.135	102.6	0.320	841.5	2.626	21.4	0.067	30.7	0.096	35.7	0.111	66.4	0.207
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	52.7	0.175	50.7	0.167	103.5	0.342	631.3	2.080	15.8	0.053	38.2	0.126	40.0	0.132	78.1	0.258
S.D.	9.0	0.037	6.3	0.023	10.9	0.048	87.8	0.292	2.7	0.010	6.1	0.023	5.6	0.020	11.2	0.042

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-1-2. Organ weights of female rats at the end of the dosing period

N-DPS 15 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	303.2	1917.0	6.323	217.7	0.718	916.0	3.021	9791.8	32.295	1039.3	3.428	1046.4	3.451	2085.7	6.879	551.5	1.819
F02014	292.7	1898.4	6.486	112.3	0.384	976.7	3.337	9347.6	31.936	968.7	3.310	961.8	3.286	1930.5	6.595	845.1	2.887
F02015	315.2	2093.5	6.642	193.0	0.612	980.2	3.110	11857.2	37.618	1071.1	3.398	1073.4	3.405	2144.5	6.804	934.6	2.965
F02016	302.9	1887.7	6.232	216.9	0.716	931.9	3.077	10230.9	33.776	999.3	3.299	934.7	3.086	1934.0	6.385	708.9	2.340
F02017	278.2	1833.0	6.589	211.1	0.759	939.2	3.376	9164.3	32.941	902.1	3.243	870.2	3.128	1772.3	6.371	743.6	2.673
F02018	336.0	1969.5	5.862	236.8	0.705	1103.2	3.283	10718.4	31.900	1064.8	3.169	1071.7	3.190	2136.5	6.359	651.8	1.940
F02019	322.6	1860.3	5.767	215.0	0.666	1056.6	3.275	10922.4	33.857	1082.4	3.355	1038.0	3.218	2120.4	6.573	835.5	2.590
F02020	342.0	1949.5	5.700	169.1	0.494	1036.3	3.030	10402.5	30.417	1306.8	3.821	1296.5	3.791	2603.3	7.612	802.0	2.345
F02021	287.8	1875.7	6.517	171.7	0.597	945.9	3.287	9608.5	33.386	1017.0	3.534	1035.1	3.597	2052.1	7.130	759.8	2.640
F02022	284.4	1819.8	6.399	162.0	0.570	894.6	3.146	9371.5	32.952	1029.4	3.620	1003.1	3.527	2032.5	7.147	667.0	2.345
F02023	327.3	1836.9	5.612	146.0	0.446	929.9	2.841	9946.3	30.389	962.7	2.941	962.2	2.940	1924.9	5.881	973.8	2.975
F02024	304.7	2049.7	6.727	98.7	0.324	1091.7	3.583	11213.2	36.801	1157.8	3.800	1174.9	3.856	2332.7	7.656	648.1	2.127
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	308.1	1915.9	6.238	179.2	0.583	983.5	3.197	10214.6	33.189	1050.1	3.410	1039.0	3.373	2089.1	6.783	760.1	2.471
S.D.	20.7	86.1	0.398	43.9	0.142	71.1	0.198	835.0	2.198	104.3	0.254	112.7	0.283	215.6	0.532	124.4	0.385
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	KW	AN	AN	AN	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-1-2(continued). Organ weights of female rats at the end of the dosing period

N-DPS 15 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	61.1	0.202	44.1	0.145	105.2	0.347	592.6	1.954	11.6	0.038	38.8	0.128	40.5	0.134	79.3	0.262
F02014	58.5	0.200	59.8	0.204	118.3	0.404	711.0	2.429	15.6	0.053	32.5	0.111	39.2	0.134	71.7	0.245
F02015	62.5	0.198	63.1	0.200	125.6	0.398	647.1	2.053	13.4	0.043	40.6	0.129	39.7	0.126	80.3	0.255
F02016	57.6	0.190	50.8	0.168	108.4	0.358	610.0	2.014	14.7	0.049	35.6	0.118	35.5	0.117	71.1	0.235
F02017	39.8	0.143	49.2	0.177	89.0	0.320	469.5	1.688	15.0	0.054	31.7	0.114	34.6	0.124	66.3	0.238
F02018	52.2	0.155	54.1	0.161	106.3	0.316	766.9	2.282	16.6	0.049	35.4	0.105	35.9	0.107	71.3	0.212
F02019	68.5	0.212	52.9	0.164	121.4	0.376	700.9	2.173	13.6	0.042	38.2	0.118	38.5	0.119	76.7	0.238
F02020	69.0	0.202	47.5	0.139	116.5	0.341	744.6	2.177	11.9	0.035	46.3	0.135	48.0	0.140	94.3	0.276
F02021	45.8	0.159	54.4	0.189	100.2	0.348	662.1	2.301	14.8	0.051	47.5	0.165	43.4	0.151	90.9	0.316
F02022	45.3	0.159	55.3	0.194	100.6	0.354	507.4	1.784	15.8	0.056	40.5	0.142	38.1	0.134	78.6	0.276
F02023	57.3	0.175	42.1	0.129	99.4	0.304	654.5	2.000	15.5	0.047	30.2	0.092	34.1	0.104	64.3	0.196
F02024	55.8	0.183	58.0	0.190	113.8	0.373	556.1	1.825	14.8	0.049	43.7	0.143	50.7	0.166	94.4	0.310
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	56.1	0.182	52.6	0.172	108.7	0.353	635.2	2.057	14.4	0.047	38.4	0.125	39.9	0.130	78.3	0.255
S.D.	9.0	0.023	6.2	0.025	10.7	0.031	92.0	0.225	1.5	0.006	5.6	0.020	5.2	0.018	10.3	0.036
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	DU	AN	DU	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-1-3. Organ weights of female rats at the end of the dosing period

N-DPS 50 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03025	312.7	1810.6	5.790	275.1	0.880	1054.9	3.374	10746.3	34.366	1058.5	3.385	977.9	3.127	2036.4	6.512	922.2	2.949
F03026	292.5	1944.9	6.649	153.1	0.523	947.9	3.241	9071.8	31.015	1037.1	3.546	1052.6	3.599	2089.7	7.144	797.2	2.725
F03027	311.4	1943.7	6.242	162.9	0.523	1073.9	3.449	9734.9	31.262	983.4	3.158	1930.2	6.198	2913.6	9.356	606.1	1.946
F03028	300.7	2055.7	6.836	200.2	0.666	1035.9	3.445	9867.7	32.816	1119.2	3.722	1080.2	3.592	2199.4	7.314	653.0	2.172
F03030	294.1	1861.5	6.329	165.5	0.563	1046.1	3.557	9968.1	33.894	969.1	3.295	959.4	3.262	1928.5	6.557	755.0	2.567
F03031	274.6	1910.0	6.956	176.8	0.644	1022.7	3.724	9237.1	33.638	1025.7	3.735	995.2	3.624	2020.9	7.359	778.7	2.836
F03032	297.0	1800.0	6.061	331.4	1.116	1013.5	3.412	9611.6	32.362	987.8	3.326	933.4	3.143	1921.2	6.469	583.6	1.965
F03033	318.5	1933.1	6.069	210.8	0.662	1023.1	3.212	9946.4	31.229	1149.0	3.608	1107.1	3.476	2256.1	7.084	705.0	2.214
F03034	326.0	1990.9	6.107	305.6	0.937	922.1	2.829	9278.7	28.462	974.7	2.990	959.9	2.944	1934.6	5.934	809.7	2.484
F03035	296.1	1778.5	6.006	231.7	0.783	995.6	3.362	9031.8	30.503	990.2	3.344	973.6	3.288	1963.8	6.632	766.5	2.589
F03036	329.3	1888.4	5.735	163.3	0.496	990.9	3.009	10872.0	33.015	997.0	3.028	1015.5	3.084	2012.5	6.111	745.4	2.264
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	304.8	1901.6	6.253	216.0	0.708	1011.5	3.329	9760.6	32.051	1026.5	3.376	1089.5	3.576	2116.1	6.952	738.4	2.428
S.D.	16.4	84.8	0.404	62.5	0.199	45.3	0.249	618.9	1.747	60.2	0.257	284.1	0.900	286.1	0.925	97.4	0.341
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	KW	AN	AN	AN	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-1-3(continued). Organ weights of female rats at the end of the dosing period

N-DPS 50 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03025	42.7	0.137	66.5	0.213	109.2	0.349	607.5	1.943	14.2	0.045	33.4	0.107	32.0	0.102	65.4	0.209
F03026	52.5	0.179	43.6	0.149	96.1	0.329	598.0	2.044	12.7	0.043	35.7	0.122	37.4	0.128	73.1	0.250
F03027	50.1	0.161	59.8	0.192	109.9	0.353	509.7	1.637	21.5	0.069	34.3	0.110	38.0	0.122	72.3	0.232
F03028	47.6	0.158	53.0	0.176	100.6	0.335	653.3	2.173	18.7	0.062	36.0	0.120	37.9	0.126	73.9	0.246
F03030	57.5	0.196	46.8	0.159	104.3	0.355	716.5	2.436	13.4	0.046	34.6	0.118	37.8	0.129	72.4	0.246
F03031	49.2	0.179	50.7	0.185	99.9	0.364	617.5	2.249	14.2	0.052	31.2	0.114	34.3	0.125	65.5	0.239
F03032	59.9	0.202	50.9	0.171	110.8	0.373	591.1	1.990	19.4	0.065	33.9	0.114	35.4	0.119	69.3	0.233
F03033	45.1	0.142	51.6	0.162	96.7	0.304	628.0	1.972	11.9	0.037	28.5	0.089	32.6	0.102	61.1	0.192
F03034	49.6	0.152	66.4	0.204	116.0	0.356	628.5	1.928	15.2	0.047	35.7	0.110	41.2	0.126	76.9	0.236
F03035	49.3	0.166	55.1	0.186	104.4	0.353	763.1	2.577	14.4	0.049	33.9	0.114	37.7	0.127	71.6	0.242
F03036	56.3	0.171	47.3	0.144	103.6	0.315	662.2	2.011	15.9	0.048	27.4	0.083	34.9	0.106	62.3	0.189
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	50.9	0.168	53.8	0.176	104.7	0.344	634.1	2.087	15.6	0.051	33.1	0.109	36.3	0.119	69.4	0.229
S.D.	5.3	0.021	7.6	0.022	6.3	0.021	66.5	0.260	3.0	0.010	2.9	0.012	2.7	0.011	5.1	0.022
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	DU	AN	DU	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-1-4. Organ weights of female rats at the end of the dosing period

N-DPS 150 mg/kg

Female No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
F04037	293.1	1917.2	6.541	219.2	0.748	959.6	3.274	9776.9	33.357	1065.8	3.636	1043.5	3.560	2109.3	7.197	757.7	2.585
F04038	298.7	1757.5	5.884	156.7	0.525	926.4	3.101	9109.8	30.498	989.3	3.312	923.1	3.090	1912.4	6.402	775.3	2.596
F04039	280.3	1970.4	7.030	143.9	0.513	889.8	3.174	8995.3	32.092	1095.4	3.908	1117.4	3.986	2212.8	7.894	932.1	3.325
F04040	317.0	2054.6	6.481	250.9	0.791	1046.3	3.301	9987.1	31.505	1027.5	3.241	1016.8	3.208	2044.3	6.449	693.9	2.189
F04041	289.9	1824.1	6.292	224.7	0.775	875.8	3.021	11198.7	38.630	1096.7	3.783	1096.0	3.781	2192.7	7.564	713.4	2.461
F04042	298.8	1919.7	6.425	194.2	0.650	978.2	3.274	9766.6	32.686	990.2	3.314	1037.9	3.474	2028.1	6.787	696.8	2.332
F04043	331.2	2167.1	6.543	244.0	0.737	1156.7	3.492	10779.8	32.548	1119.9	3.381	1116.4	3.371	2236.3	6.752	1034.9	3.125
F04044	308.2	1826.7	5.927	306.5	0.994	943.5	3.061	9312.7	30.216	1021.8	3.315	972.5	3.155	1994.3	6.471	759.6	2.465
F04045	316.6	1959.0	6.188	275.7	0.871	1158.1	3.658	10819.6	34.174	1182.9	3.736	1154.9	3.648	2337.8	7.384	773.3	2.443
F04046	311.6	1958.2	6.284	229.4	0.736	1039.2	3.335	9305.6	29.864	1033.1	3.315	986.3	3.165	2019.4	6.481	639.8	2.053
F04047	328.6	1987.1	6.047	326.4	0.993	981.0	2.985	11994.8	36.503	1187.9	3.615	1134.9	3.454	2322.8	7.069	925.3	2.816
F04048	288.6	1829.2	6.338	146.9	0.509	956.4	3.314	10514.3	36.432	1030.0	3.569	1030.6	3.571	2060.6	7.140	709.7	2.459
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	305.2	1930.9	6.332	226.5	0.737	992.6	3.249	10130.1	33.209	1070.0	3.510	1052.5	3.455	2122.6	6.966	784.3	2.571
S.D.	16.2	112.9	0.313	59.4	0.168	92.0	0.197	935.1	2.762	67.7	0.225	72.0	0.274	135.8	0.489	118.1	0.364
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	KW	AN	AN	AN	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-1-4(continued). Organ weights of female rats at the end of the dosing period

N-DPS 150 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04037	47.8	0.163	57.0	0.194	104.8	0.358	636.1	2.170	14.3	0.049	41.6	0.142	48.5	0.165	90.1	0.307
F04038	44.7	0.150	50.3	0.168	95.0	0.318	530.3	1.775	24.0	0.080	40.5	0.136	41.2	0.138	81.7	0.274
F04039	56.5	0.202	47.6	0.170	104.1	0.371	596.2	2.127	15.7	0.056	37.3	0.133	37.8	0.135	75.1	0.268
F04040	44.8	0.141	55.8	0.176	100.6	0.317	617.5	1.948	17.2	0.054	38.4	0.121	42.3	0.133	80.7	0.255
F04041	54.6	0.188	46.7	0.161	101.3	0.349	634.3	2.188	21.2	0.073	44.8	0.155	51.4	0.177	96.2	0.332
F04042	49.6	0.166	47.0	0.157	96.6	0.323	594.5	1.990	11.9	0.040	36.9	0.123	37.8	0.127	74.7	0.250
F04043	72.5	0.219	57.6	0.174	130.1	0.393	654.8	1.977	14.5	0.044	43.4	0.131	49.3	0.149	92.7	0.280
F04044	49.5	0.161	50.8	0.165	100.3	0.325	682.6	2.215	15.4	0.050	41.4	0.134	40.6	0.132	82.0	0.266
F04045	57.7	0.182	55.1	0.174	112.8	0.356	729.9	2.305	11.7	0.037	30.1	0.095	36.3	0.115	66.4	0.210
F04046	55.6	0.178	55.4	0.178	111.0	0.356	745.7	2.393	16.9	0.054	34.6	0.111	36.7	0.118	71.3	0.229
F04047	61.4	0.187	68.9	0.210	130.3	0.397	633.1	1.927	19.4	0.059	35.4	0.108	39.4	0.120	74.8	0.228
F04048	50.1	0.174	48.9	0.169	99.0	0.343	704.5	2.441	14.4	0.050	41.9	0.145	48.2	0.167	90.1	0.312
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	53.7	0.176	53.4	0.175	107.2	0.351	646.6	2.121	16.4	0.054	38.9	0.128	42.5	0.140	81.3	0.268
S.D.	7.9	0.022	6.3	0.015	12.0	0.027	61.5	0.203	3.6	0.012	4.2	0.017	5.4	0.020	9.3	0.037
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	DU	AN	DU	AN

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	301.3	1924.0	6.386	396.0	1.314	838.0	2.781	6757.3	22.427	968.4	3.214	938.7	3.115	1907.1	6.330	547.7	1.818
F05050	262.0	1867.2	7.127	202.8	0.774	920.8	3.515	6025.6	22.998	836.4	3.192	870.9	3.324	1707.3	6.516	562.8	2.148
F05051	286.3	1904.0	6.650	340.7	1.190	936.7	3.272	7442.0	25.994	955.5	3.337	944.4	3.299	1899.9	6.636	640.0	2.235
F05052	297.7	1848.5	6.209	191.0	0.642	984.8	3.308	7304.5	24.536	887.0	2.980	803.3	2.698	1690.3	5.678	619.3	2.080
F05053	274.0	1937.0	7.069	404.9	1.478	865.2	3.158	6843.8	24.977	926.5	3.381	921.8	3.364	1848.3	6.746	553.0	2.018
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	284.3	1896.1	6.688	307.1	1.080	909.1	3.207	6874.6	24.186	914.8	3.221	895.8	3.160	1810.6	6.381	584.6	2.060
S.D.	16.4	37.5	0.406	103.6	0.357	58.3	0.271	557.3	1.460	53.8	0.157	59.3	0.275	104.7	0.422	42.2	0.157

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-2-1(continued). Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	45.9	0.152	43.6	0.145	89.5	0.297	556.6	1.847	17.0	0.056	27.6	0.092	29.1	0.097	56.7	0.188
F05050	55.9	0.213	43.6	0.166	99.5	0.380	525.5	2.006	17.4	0.066	27.2	0.104	30.3	0.116	57.5	0.219
F05051	55.1	0.192	42.5	0.148	97.6	0.341	361.9	1.264	17.9	0.063	37.5	0.131	37.9	0.132	75.4	0.263
F05052	51.9	0.174	43.0	0.144	94.9	0.319	502.4	1.688	11.2	0.038	34.6	0.116	35.9	0.121	70.5	0.237
F05053	33.9	0.124	41.0	0.150	74.9	0.273	810.7	2.959	12.5	0.046	34.5	0.126	36.2	0.132	70.7	0.258
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	48.5	0.171	42.7	0.151	91.3	0.322	551.4	1.953	15.2	0.054	32.3	0.114	33.9	0.120	66.2	0.233
S.D.	9.1	0.035	1.1	0.009	9.9	0.041	163.0	0.627	3.1	0.012	4.6	0.016	3.9	0.014	8.5	0.031

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-2-2. Organ weights of female rats at the end of the dosing period, satellite group

N-DPS 150 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	274.7	1841.2	6.703	302.9	1.103	899.5	3.274	7373.7	26.843	956.9	3.483	917.4	3.340	1874.3	6.823	545.5	1.986
F06061	261.0	1912.8	7.329	310.9	1.191	889.1	3.407	7343.1	28.134	918.9	3.521	878.8	3.367	1797.7	6.888	546.8	2.095
F06063	240.0	1790.6	7.461	229.3	0.955	766.6	3.194	5849.9	24.375	772.8	3.220	740.0	3.083	1512.8	6.303	485.2	2.022
F06064	280.0	1907.5	6.813	293.6	1.049	981.2	3.504	7339.7	26.213	991.6	3.541	923.0	3.296	1914.6	6.838	576.7	2.060
Number of females	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	263.9	1863.0	7.077	284.2	1.075	884.1	3.345	6976.6	26.391	910.1	3.441	864.8	3.272	1774.9	6.713	538.6	2.041
S.D.	17.8	58.2	0.374	37.3	0.099	88.5	0.138	751.3	1.564	96.2	0.149	85.5	0.129	181.3	0.275	38.4	0.047
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-2-2(continued). Organ weights of female rats at the end of the dosing period, satellite group

N-DPS 150 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	50.1	0.182	56.8	0.207	106.9	0.389	434.7	1.582	13.6	0.050	33.2	0.121	37.5	0.137	70.7	0.257
F06061	54.0	0.207	38.1	0.146	92.1	0.353	490.4	1.879	16.2	0.062	35.1	0.134	37.0	0.142	72.1	0.276
F06063	34.1	0.142	35.6	0.148	69.7	0.290	366.7	1.528	9.6	0.040	33.7	0.140	35.4	0.148	69.1	0.288
F06064	46.1	0.165	25.8	0.092	71.9	0.257	409.7	1.463	14.9	0.053	27.8	0.099	29.0	0.104	56.8	0.203
Number of females	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	46.1	0.174	39.1	0.148	85.2	0.322	425.4	1.613	13.6	0.051	32.5	0.124	34.7	0.133	67.2	0.256
S.D.	8.6	0.027	13.0	0.047	17.7	0.060	51.7	0.184	2.9	0.009	3.2	0.018	3.9	0.020	7.0	0.038
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	AW	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-3-1. Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	243.1	1701.0	6.997	279.5	1.150	727.0	2.991	5780.4	23.778	759.6	3.125	766.5	3.153	1526.1	6.278	459.3	1.889
F05055	274.1	1903.0	6.943	203.7	0.743	896.9	3.272	7682.8	28.029	900.2	3.284	909.4	3.318	1809.6	6.602	542.3	1.978
F05056	314.5	2096.3	6.666	181.9	0.578	983.6	3.128	8235.6	26.186	932.6	2.965	941.2	2.993	1873.8	5.958	544.8	1.732
F05057	312.2	1815.0	5.814	294.8	0.944	937.7	3.004	8252.1	26.432	941.1	3.014	923.5	2.958	1864.6	5.972	545.5	1.747
F05058	286.6	2027.0	7.073	166.1	0.580	955.8	3.335	7398.8	25.816	1027.1	3.584	1045.0	3.646	2072.1	7.230	680.9	2.376
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	286.1	1908.5	6.699	225.2	0.799	900.2	3.146	7469.9	26.048	912.1	3.194	917.1	3.214	1829.2	6.408	554.6	1.944
S.D.	29.5	159.0	0.518	58.4	0.247	101.8	0.155	1012.8	1.525	97.3	0.250	99.6	0.281	196.5	0.530	79.6	0.262

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-3-1(continued). Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	36.5	0.150	35.9	0.148	72.4	0.298	593.2	2.440	14.7	0.060	21.7	0.089	22.3	0.092	44.0	0.181
F05055	33.2	0.121	38.9	0.142	72.1	0.263	449.6	1.640	14.2	0.052	31.9	0.116	33.8	0.123	65.7	0.240
F05056	66.7	0.212	57.6	0.183	124.3	0.395	587.5	1.868	14.4	0.046	43.9	0.140	45.5	0.145	89.4	0.284
F05057	56.0	0.179	48.7	0.156	104.7	0.335	597.4	1.914	15.8	0.051	32.1	0.103	39.5	0.127	71.6	0.229
F05058	58.8	0.205	57.2	0.200	116.0	0.405	615.2	2.147	14.8	0.052	40.4	0.141	38.5	0.134	78.9	0.275
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	50.2	0.173	47.7	0.166	97.9	0.339	568.6	2.002	14.8	0.052	34.0	0.118	35.9	0.124	69.9	0.242
S.D.	14.6	0.038	10.1	0.025	24.4	0.061	67.3	0.304	0.6	0.005	8.6	0.023	8.7	0.020	17.0	0.041

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-3-2. Organ weights of female rats at the end of the recovery period

N-DPS 150 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06065	299.4	1843.4	6.157	266.5	0.890	869.6	2.904	6762.2	22.586	899.8	3.005	878.3	2.934	1778.1	5.939	582.3	1.945
F06066	305.4	1888.0	6.182	275.2	0.901	942.7	3.087	7609.7	24.917	920.6	3.014	899.0	2.944	1819.6	5.958	532.9	1.745
F06067	318.0	1878.8	5.908	261.0	0.821	952.3	2.995	7728.7	24.304	1015.4	3.193	1008.9	3.173	2024.3	6.366	520.6	1.637
F06068	313.2	1899.5	6.065	183.3	0.585	972.9	3.106	8105.6	25.880	983.3	3.140	972.7	3.106	1956.0	6.245	527.1	1.683
Number of females	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	309.0	1877.4	6.078	246.5	0.799	934.4	3.023	7551.6	24.422	954.8	3.088	939.7	3.039	1894.5	6.127	540.7	1.753
S.D.	8.2	24.2	0.124	42.5	0.147	45.0	0.093	567.1	1.385	53.8	0.093	61.4	0.119	115.2	0.212	28.2	0.136
Significance	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	AW	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 29-3-2(continued). Organ weights of female rats at the end of the recovery period

N-DPS 150 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06065	31.0	0.104	33.1	0.111	64.1	0.214	319.8	1.068	13.7	0.046	30.6	0.102	27.6	0.092	58.2	0.194
F06066	42.9	0.140	51.3	0.168	94.2	0.308	775.1	2.538	11.5	0.038	23.8	0.078	26.0	0.085	49.8	0.163
F06067	45.2	0.142	45.7	0.144	90.9	0.286	521.7	1.641	14.3	0.045	33.9	0.107	34.5	0.108	68.4	0.215
F06068	53.7	0.171	45.6	0.146	99.3	0.317	382.4	1.221	14.9	0.048	26.9	0.086	27.1	0.087	54.0	0.172
Number of females	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	43.2	0.139	43.9	0.142	87.1	0.281	499.8	1.617	13.6	0.044	28.8	0.093	28.8	0.093	57.6	0.186
S.D.	9.4	0.027	7.7	0.023	15.7	0.047	202.0	0.660	1.5	0.004	4.4	0.014	3.9	0.010	8.0	0.023
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	*	NS	*
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 30-1. Macroscopic findings of male rats at the end of the dosing period

Findings	Group	Control (Vehicle)							N-DPS 15 mg/kg												N-DPS 50 mg/kg												N-DPS 150 mg/kg						
	Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043
Thymus																																							
Discoloration, dark reddish		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-
Small		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-
Liver																																							
Adhesion, with diaphragm		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nodule, site of adhesion		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Whitish area		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-
Stomach																																							
Dark colored spot, mucosa, scattered, glandular stomach		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-
Edematous, mucosa, forestomach		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	-	P	-
Retention, gas		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-
Jejunum																																							
Dark reddish area, mucosa		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-
Ileum																																							
Diverticulum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Small intestine																																							
Retention, gas		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-
Epididymis																																							
Small, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-
Prostate																																							
Small		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	-	-	-
Seminal vesicle																																							
Small		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	P	-	-	-	-

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

Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 30-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
Epididymis											
Nodule, yellowish white, corpus, unilateral		-	-	-	-	P	-	-	-	-	-

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

Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 31-1. Macroscopic findings of female rats at the end of the dosing period

Findings	Group	Control (Vehicle)												N-DPS 15 mg/kg												N-DPS 50 mg/kg												N-DPS 150 mg/kg											
	Animal No.	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04
		001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048
	Fate																													NP																			
Stomach																																																	
Dark colored spot, mucosa, glandular stomach		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-
Dark reddish area, mucosa, glandular stomach		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Recessed area, mucosa, glandular stomach		-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Uterus																																																	
Nodule, cervix		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-

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

Vehicle: water for injection

Fate : blanks, Subjected to autopsy on day 5 of lactation; NP, Not pregnant.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 31-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg					
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063	F06 064
	Fate							D		D		
Lung												
Dark colored area, scattered		-	-	-	-	-	-	-	-	P	-	-
Dark reddish area		-	-	-	-	-	-	P	-	-	-	-
Incomplete retention		-	-	-	-	-	-	-	-	P	-	-
Liver												
Discoloration, dark colored		-	-	-	-	-	-	-	-	P	-	-
Discoloration, dark reddish		-	-	-	-	-	-	P	-	-	-	-
Whitish area		-	-	-	-	-	-	P	-	-	-	-
Stomach												
Edematous, mucosa, forestomach		-	-	-	-	-	-	-	P	-	-	-
Retention, gas		-	-	-	-	-	-	P	-	P	-	-
Small intestine												
Retention, gas		-	-	-	-	-	-	P	-	P	-	-
Ovary												
Discoloration, dark reddish, bilateral		-	-	-	-	-	-	P	-	-	-	-

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

Vehicle: water for injection

Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 31-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg			
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 065	F06 066	F06 067	F06 068
All organs										
		-	-	-	-	-	-	-	-	-

Notes) - : No abnormal changes P : Non-graded change
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 32-1. Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							N-DPS 15 mg/kg												N-DPS 50 mg/kg												N-DPS 150 mg/kg						
Animal No.	M01	M01	M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M04	M04	M04	M04	M04	M04	M04
Findings	001	002	003	004	005	006	007	013	014	015	016	017	018	019	020	021	022	023	024	025	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043
Brain						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		
Spinal cord						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		
Pituitary gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		
Submandibular gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		
Sublingual gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		
Lymph node, submandibular						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		
Thyroid gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		
Parathyroid gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		
Thymus						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Atrophy	±	-	-	-	-																											±	±	-	+	-		
Heart						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		
Trachea						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Cellular infiltration, neutrophil, submucosa	-	-	-	-	-																											-	-	-	±	-		
Lung						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Accumulation, foam cell, alveolus	±	-	-	-	-																											-	±	-	±	-		
Cellular infiltration, neutrophil, alveolus, focal	-	-	-	-	±																											-	-	-	±	-		
Hemorrhage, focal	-	-	-	-	±																											-	-	-	±	-		
Mineralization, alveolus	±	-	-	-	-																											-	-	-	-	-		
Bronchus						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
	-	-	-	-	-																											-	-	-	-	-		

Notes) - : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 32-1(continued). Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							N-DPS 15 mg/kg											
Findings / Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024
Liver						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Fatty change, hepatocyte, periportal	±	±	±	±	±														
Fibrosis, around necrosis	-	-	-	-	-														
Microgranuloma	±	±	±	±	±														
Necrosis, focal	-	-	-	-	-														
Pancreas						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Stomach																			
Forestomach						NE	NE						NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, inflammatory, submucosa	-	-	-	-	-			-	-	-	-	-							
Edema, lamina propria/submucosa	-	-	-	-	-			-	-	-	-	-							
Erosion	-	-	-	-	-			-	-	-	-	-							
Hyperplasia, squamous cell	-	-	-	-	-			-	-	-	-	-							
Glandular stomach						NE	NE						NE	NE	NE	NE	NE	NE	NE
Edema, submucosa	-	-	-	-	-			-	-	-	-	-							
Erosion	-	-	-	-	-			-	-	-	-	-							
Duodenum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Jejunum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Erosion	-	-	-	-	-														
Ileum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	
Diverticulum	-	-	-	-	-														P
Cecum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Colon						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Rectum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Lymph node, mesenteric						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Spleen						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy, white pulp	-	-	-	-	-														
Deposit, pigment, brown	+	2+	+	+	+														
Hematopoiesis, extramedullary	+	+	2+	+	+														

Group	N-DPS 50 mg/kg												N-DPS 150 mg/kg						
Findings / Animal No.	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043
Liver		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Fatty change, hepatocyte, periportal	-												-	-	±	-	-		
Fibrosis, around necrosis	+												-	-	-	-	-		
Microgranuloma	±												±	±	±	-	±		
Necrosis, focal	+												-	+	-	-	-		
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Stomach																			
Forestomach						NE	NE	NE	NE	NE	NE	NE							NE
Cellular infiltration, inflammatory, submucosa	-	-	-	-	-								-	+	+	-	-	+	
Edema, lamina propria/submucosa	-	-	-	-	-								-	2+	2+	-	-	2+	
Erosion	-	-	-	-	-								-	+	+	-	-	-	
Hyperplasia, squamous cell	-	-	-	-	-								-	±	±	±	-	±	
Glandular stomach						NE	NE	NE	NE	NE	NE	NE							NE
Edema, submucosa	-	-	-	-	-								-	±	-	-	-	-	
Erosion	-	-	-	-	-								-	-	-	±	-	-	
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Erosion													-	-	-	±	-		
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Diverticulum													-	-	-	-	-		
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Atrophy, white pulp													-	-	-	±	-		
Deposit, pigment, brown													+	+	+	+	+		
Hematopoiesis, extramedullary													±	+	+	+	+		

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 32-1(continued). Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							N-DPS 15 mg/kg											
Findings / Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024
Kidney						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex	±	±	±	±	±														
Cast, hyalin	-	-	-	-	-														
Cellular infiltration, lymphocyte, interstitial	-	-	±	-	-														
Dilatation, lumen, distal tubule	-	-	-	-	-														
Mineralization, cortex	±	±	-	-	-														
Urinary bladder						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Adrenal gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona facsiculata	-	-	-	-	-														
Testis						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy, seminiferous tubule, bilateral	-	-	-	-	-														
Epididymis						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy, bilateral	-	-	-	-	-														
Prostate						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy	-	-	-	-	-														
Cellular infiltration, lymphocyte, interstitial	±	-	-	±	±														
Seminal vesicle						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy	-	-	-	-	-														
Coagulating gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy	-	-	-	-	-														
Eyeball						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Harderian gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Sciatic nerve						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Skeletal muscle						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Femur						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														
Marrow, femur						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
	-	-	-	-	-														

Group	N-DPS 50 mg/kg												N-DPS 150 mg/kg						
Findings / Animal No.	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043
Kidney	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Basophilic tubule, cortex													±	±	-	-	±		
Cast, hyalin													-	-	-	±	-		
Cellular infiltration, lymphocyte, interstitial													±	±	±	-	-		
Dilatation, lumen, distal tubule													-	-	-	±	-		
Mineralization, cortex													±	±	-	-	-		
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Hypertrophy, zona facsiculata													-	-	-	±	-		
Testis	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Atrophy, seminiferous tubule, bilateral													-	-	±	-	-		
Epididymis	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Atrophy, bilateral													-	-	±	-	-		
Prostate	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Atrophy													±	-	+	-	-		
Cellular infiltration, lymphocyte, interstitial													-	-	-	±	-		
Seminal vesicle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Atrophy													+	-	+	-	-		
Coagulating gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
Atrophy													-	-	±	-	-		
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE
													-	-	-	-	-		

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 32-2. Histopathological findings of male rats at the end of the recovery period

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
Brain		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 32-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
Liver		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pancreas		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach											
Forestomach		-	-	-	-	-	-	-	-	-	-
Glandular stomach		-	-	-	-	-	-	-	-	-	-
Duodenum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 32-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 044	M04 045	M04 046	M04 047	M04 048
Kidney		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Testis		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Epididymis		NE	NE	NE	NE		NE	NE	NE	NE	NE
Granuloma, spermatic, corpus, unilateral						P					
Prostate		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Seminal vesicle		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Coagulating gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 33-1. Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)											
Animal No.	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01
Findings / Fate	001	002	003	004	005	006	007	008	009	010	011	012
Brain	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Spinal cord	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Pituitary gland	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Submandibular gland	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Sublingual gland	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Lymph node, submandibular	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Thyroid gland	NE	NE	NE	NE	NE		NE				NE	
Ectopic thymic tissue						-		-	-	-		-
Ultimobranchial body						P		P	-	-		-
Parathyroid gland	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Thymus	NE	NE	NE	NE	NE		NE				NE	
Atrophy						±		+	±	±		±
Heart	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Trachea	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Lung	NE	NE	NE	NE	NE		NE				NE	
Accumulation, foam cell, alveolus						±		-	-	-		-
Mineralization, alveolus						±		-	-	-		-
Bronchus	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-

Group	N-DPS 15 mg/kg											
Animal No.	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02
Findings / Fate	013	014	015	016	017	018	019	020	021	022	023	024
Brain	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Parathyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	N-DPS 50 mg/kg											
Animal No.	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03
Findings / Fate	025	026	027	028	029	030	031	032	033	034	035	036
					NP							
Brain	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Parathyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	N-DPS 150 mg/kg											
Animal No.	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04
Findings / Fate	037	038	039	040	041	042	043	044	045	046	047	048
Brain		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Spinal cord		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Pituitary gland		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Submandibular gland		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Sublingual gland		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Lymph node, submandibular		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Thyroid gland		NE	NE		NE	NE		NE			NE	NE
Ectopic thymic tissue	-			-			P		-	-		
Ultimobranchial body	-			-			P		-	-		
Parathyroid gland		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Thymus		NE	NE		NE	NE		NE			NE	NE
Atrophy	±			±			±		±	±		
Heart		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Trachea		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Lung		NE	NE		NE	NE		NE			NE	NE
Accumulation, foam cell, alveolus	-			-			±		-	-		
Mineralization, alveolus	-			-			-		-	-		
Bronchus		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy on day 5 of lactation; NP, Not pregnant.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 33-1(continued). Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)											
Animal No.	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01
Findings / Fate	001	002	003	004	005	006	007	008	009	010	011	012
Liver	NE	NE	NE	NE	NE		NE				NE	
Fatty change, hepatocyte, periprtal						-		±	±	±		±
Microgranuloma						-		-	±	-		-
Necrosis, focal						-		-	-	±		-
Pancreas	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Stomach												
Forestomach	NE	NE	NE	NE	NE		NE				NE	
Cellular infiltration, inflammatory, submucosa						-		-	-	-		-
Edema, lamina propria/submucosa						-		-	-	-		-
Erosion						-		-	-	-		-
Hyperplasia, squamous cell						-		-	-	-		-
Glandular stomach	NE	NE	NE	NE	NE		NE				NE	
Erosion						-		-	-	-		-
Duodenum	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Jejunum	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Ileum	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Cecum	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Colon	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Rectum	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Lymph node, mesenteric	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Spleen	NE	NE	NE	NE	NE		NE				NE	
Deposit, pigment, brown						+		+	+	±		+
Hematopoiesis, extramedullary						2+		2+	2+	2+		2+

Group	N-DPS 15 mg/kg											
Animal No.	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02
Findings / Fate	013	014	015	016	017	018	019	020	021	022	023	024
Liver	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Fatty change, hepatocyte, periprtal												
Microgranuloma												
Necrosis, focal												
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach												
Forestomach		NE		NE			NE	NE	NE		NE	
Cellular infiltration, inflammatory, submucosa	-		-		-	-				-		-
Edema, lamina propria/submucosa	-		-		-	-				-		-
Erosion	-		-		-	-				-		+
Hyperplasia, squamous cell	-		-		-	-				-		-
Glandular stomach		NE		NE			NE	NE	NE		NE	
Erosion	-		-		-	-				-		-
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Deposit, pigment, brown												
Hematopoiesis, extramedullary												

Group	N-DPS 50 mg/kg											
Animal No.	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03
Findings / Fate	025	026	027	028	029	030	031	032	033	034	035	036
					NP							
Liver	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Fatty change, hepatocyte, periprtal												
Microgranuloma												
Necrosis, focal												
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach												
Forestomach	NE	NE			NE	NE		NE	NE		NE	
Cellular infiltration, inflammatory, submucosa			-	-			-			-		-
Edema, lamina propria/submucosa			-	-			-			-		-
Erosion			-	-			-			-		-
Hyperplasia, squamous cell			-	-			-			-		-
Glandular stomach	NE	NE			NE	NE		NE	NE		NE	
Erosion			-	-			-			-		-
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Deposit, pigment, brown												
Hematopoiesis, extramedullary												

Group	N-DPS 150 mg/kg											
Animal No.	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04
Findings / Fate	037	038	039	040	041	042	043	044	045	046	047	048
Liver		NE	NE		NE	NE		NE			NE	NE
Fatty change, hepatocyte, periprtal	±			-			±		±	±		
Microgranuloma	±			±			-		-	±		
Necrosis, focal	-			-			±		-	-		
Pancreas		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Stomach												
Forestomach		NE	NE		NE	NE		NE			NE	
Cellular infiltration, inflammatory, submucosa	-			-			-		-	-		±
Edema, lamina propria/submucosa	-			-			-		-	-		±
Erosion	-			-			-		-	-		-
Hyperplasia, squamous cell	-			-			-		-	-		±
Glandular stomach		NE	NE		NE	NE		NE			NE	
Erosion	-			-			-		-	-		±
Duodenum		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Jejunum		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Ileum		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Cecum		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Colon		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Rectum		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Lymph node, mesenteric		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Spleen		NE	NE		NE	NE		NE			NE	NE
Deposit, pigment, brown	±			+			±		±	+		
Hematopoiesis, extramedullary	2+			±			2+		2+	2+		

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy on day 5 of lactation; NP, Not pregnant.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 33-1(continued). Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)											
Animal No.	F01 001	F01 002	F01 003	F01 004	F01 005	F01 006	F01 007	F01 008	F01 009	F01 010	F01 011	F01 012
Findings / Fate												
Kidney	NE	NE	NE	NE	NE		NE				NE	
Basophilic tubule, cortex						-		-	-	-		-
Cellular infiltration, lymphocyte, interstitial						-		-	±	-		-
Urinary bladder	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Adrenal gland	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Ovary	NE	NE	NE	NE	NE		NE				NE	
Increase, atretic follicle						-		-	-	-		-
Uterus	NE	NE	NE	NE	NE		NE				NE	
Cyst, cervix						-		-	-	-		-
Vagina	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Eyeball	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Harderian gland	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Sciatic nerve	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Skeletal muscle	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Femur	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-
Marrow, femur	NE	NE	NE	NE	NE		NE				NE	
						-		-	-	-		-

Group	N-DPS 15 mg/kg											
Animal No.	F02 013	F02 014	F02 015	F02 016	F02 017	F02 018	F02 019	F02 020	F02 021	F02 022	F02 023	F02 024
Findings / Fate												
Kidney	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex												
Cellular infiltration, lymphocyte, interstitial												
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ovary	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Increase, atretic follicle												
Uterus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cyst, cervix												
Vagina	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	N-DPS 50 mg/kg											
Animal No.	F03 025	F03 026	F03 027	F03 028	F03 029	F03 030	F03 031	F03 032	F03 033	F03 034	F03 035	F03 036
Findings / Fate					NP							
Kidney	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex												
Cellular infiltration, lymphocyte, interstitial												
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ovary	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Increase, atretic follicle												
Uterus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	
Cyst, cervix												P
Vagina	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	N-DPS 150 mg/kg											
Animal No.	F04 037	F04 038	F04 039	F04 040	F04 041	F04 042	F04 043	F04 044	F04 045	F04 046	F04 047	F04 048
Findings / Fate												
Kidney		NE	NE		NE	NE		NE			NE	NE
Basophilic tubule, cortex	-			-			-		-	±		
Cellular infiltration, lymphocyte, interstitial	-			-			-		-	±		
Urinary bladder		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Adrenal gland		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Ovary		NE	NE		NE	NE		NE			NE	NE
Increase, atretic follicle	-			-			-		-	±		
Uterus		NE	NE		NE	NE		NE			NE	NE
Cyst, cervix	-			-			-		-	-		
Vagina		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Eyeball		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Harderian gland		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Sciatic nerve		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Skeletal muscle		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Femur		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		
Marrow, femur		NE	NE		NE	NE		NE			NE	NE
	-			-			-		-	-		

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy on day 5 of lactation; NP, Not pregnant.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 33-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg					
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063	F06 064
	Fate							D		D		
Brain		-	-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular												
Tingible body macrophage		-	-	-	-	-	-	2+	-	2+	-	-
Thyroid gland												
Ectopic thymic tissue		-	P	-	-	-	-	-	-	-	-	-
Ultimobranchial body		-	-	-	-	-	-	P	-	-	-	-
Parathyroid gland		-	-	-	-	-	-	-	-	-	-	-
Thymus												
Atrophy		±	+	±	+	-	±	±	±	±	+	±
Tingible body macrophage		-	-	-	-	-	-	2+	-	+	-	-
Heart		-	-	-	-	-	-	-	-	-	-	-
Trachea												
Abscess, lumen		-	-	-	-	-	-	2+	-	2+	-	-
Lung												
Accumulation, foam cell, alveolus		±	-	-	-	-	-	-	-	-	-	-
Cellular infiltration, neutrophil, alveolus		-	-	-	-	-	-	+	-	±	-	-
Edema		-	-	-	-	-	-	2+	-	-	-	-
Bronchus												
Cellular infiltration, neutrophil		-	-	-	-	-	-	±	-	-	-	-

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 33-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg					
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063	F06 064
	Fate							D		D		
Liver												
Fatty change, hepatocyte, periportal		±	-	±	±	±	±	-	±	-	-	±
Microgranuloma		±	±	±	±	±	±	-	±	-	±	±
Necrosis, focal, subcapsule		-	-	-	-	-	-	2+	-	-	-	-
Pancreas												
		-	-	-	-	-	-	-	-	-	-	-
Stomach												
Forestomach												
Cellular infiltration, inflammatory, submucosa		-	-	-	-	-	-	-	±	±	±	-
Edema, lamina propria/submucosa		-	-	-	-	-	-	-	2+	±	+	-
Hyperplasia, squamous cell		-	-	-	-	-	-	-	±	±	±	-
Glandular stomach												
		-	-	-	-	-	-	-	-	-	-	-
Duodenum												
		-	-	-	-	-	-	-	-	-	-	-
Jejunum												
		-	-	-	-	-	-	-	-	-	-	-
Ileum												
		-	-	-	-	-	-	-	-	-	-	-
Cecum												
		-	-	-	-	-	-	-	-	-	-	-
Colon												
		-	-	-	-	-	-	-	-	-	-	-
Rectum												
		-	-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric												
		-	-	-	-	-	-	-	-	-	-	-
Spleen												
Atrophy, white pulp		-	-	-	-	-	-	+	-	2+	-	-
Deposit, pigment, brown		2+	2+	2+	2+	2+	2+	-	2+	+	2+	2+
Hematopoiesis, extramedullary		±	±	±	2+	±	2+	+	±	±	±	±

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 33-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg					
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063	F06 064
	Fate							D		D		
Kidney												
Basophilic tubule, cortex		-	-	±	-	-	±	-	±	-	-	±
Cellular infiltration, lymphocyte, interstitial		-	-	±	±	-	±	-	±	-	-	±
Dilatation, lumen, distal tubule		-	-	-	-	-	-	±	-	±	-	-
Mineralization, medulla		-	-	-	-	-	±	-	-	-	-	-
Urinary bladder		-	-	-	-	-	-	-	-	-	-	-
Adrenal gland												
Hypertrophy, zona facsiculata		-	-	-	-	-	-	-	-	±	-	-
Ovary												
Cyst, follicular/luteinized		-	-	-	-	-	+	-	-	-	-	-
Uterus		-	-	-	-	-	-	-	-	-	-	-
Vagina		-	-	-	-	-	-	-	-	-	-	-
Eyeball		-	-	-	-	-	-	-	-	-	-	-
Harderian gland		-	-	-	-	-	-	-	-	-	-	-
Sciatic nerve		-	-	-	-	-	-	-	-	-	-	-
Skeletal muscle		-	-	-	-	-	-	-	-	-	-	-
Femur		-	-	-	-	-	-	-	-	-	-	-
Marrow, femur		-	-	-	-	-	-	-	-	-	-	-

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 33-3. Histopathological findings of female rats at the end of the recovery period

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg			
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 065	F06 066	F06 067	F06 068
Brain		NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus		NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart		NE	NE	NE	NE	NE	NE	NE	NE	NE
Trachea		NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung		NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 33-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg			
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 065	F06 066	F06 067	F06 068
Liver		NE	NE	NE	NE	NE	NE	NE	NE	NE
Pancreas		NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach										
Forestomach		-	-	-	-	-	-	-	-	-
Glandular stomach		-	-	-	-	-	-	-	-	-
Duodenum		NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum		NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum		NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum		NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon		NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum		NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric		NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen		NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 33-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group	Control (Vehicle)					N-DPS 150 mg/kg			
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 065	F06 066	F06 067	F06 068
Kidney		NE	NE	NE	NE	NE	NE	NE	NE	NE
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland		NE	NE	NE	NE	NE	NE	NE	NE	NE
Ovary		NE	NE	NE	NE	NE	NE	NE	NE	NE
Uterus		NE	NE	NE	NE	NE	NE	NE	NE	NE
Vagina		NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball		NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland		NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve		NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle		NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur		NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur		NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 34-1. Results of observations about estrous cycle

Control (vehicle: water for injection)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F01001	E D D D E E D D P E D D P E	4/5-day	4.3	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F01002	D D D E D D P E D D P E D D	4-day	4.0	D P E D D P E D D P E E D D	4/5-day	4.5	P PL	1
F01003	E D D P E D D P E D D P E D	4-day	4.0	D P E D D D P E D D D P E D	5-day	5.0	D P E PL	1
F01004	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F01005	D D D E E D D D E E D D D E	4/5-day	4.5	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F01006	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F01007	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F01008	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F01009	D E D D D E D D P E D D P E	4-day	4.0	D D P E E D D P E E D D P P	5-day	5.0	PL	1
F01010	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F01011	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F01012	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
Mean			4.1			4.2		1.0
S.D.			0.2			0.4		0.0
(N)			(12)			(12)		(12)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 34-2. Results of observations about estrous cycle

N-DPS (15 mg/kg)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F02013	D D E D D D E D D D E D D D	4-day	4.0	E D D D E D D D E D D P E D	4-day	4.0	D P PL	1
F02014	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F02015	D P E D D P E D D D E D D P	4-day	4.0	E D D D E D D P E D D D D P	4-day	4.0	PL	1
F02016	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F02017	D P E E D D P E E D D P E E	5-day	5.0	D D D P E D D D D E D D P E	4/5-day	4.5	PL	1
F02018	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F02019	E D D D P E D D D E E D D P	5-day	5.0	E D D D E D D D E D D P E D	4-day	4.0	D D PL	1
F02020	D D D E D D P E D D P E D D	4-day	4.0	P E D D P E D D D E D D P E	4-day	4.0	D D D PL	1
F02021	D D E D D P E D D D E D D P	4-day	4.0	E D D D E D D D E D D P E D	4-day	4.0	D P PL	1
F02022	D D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D D	4-day	4.0	P PL	1
F02023	D P E D D P E D D P E D D P	4-day	4.0	E D D D E D D P E D D P E D	4-day	4.0	D P PL	1
F02024	D D E D D D E D D P E D D D	4-day	4.0	E D D D E D D D E D D P E D	4-day	4.0	D P PL	1
Mean			4.2			4.0		1.0
S.D.			0.4			0.1		0.0
(N)			(12)			(12)		(12)

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

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 34-3. Results of observations about estrous cycle

N-DPS (50 mg/kg)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F03025	D D P E D D D E D D D E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F03026	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F03027	D D E D D D E D D D E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D D PL	1
F03028	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03029	P E D D D P E D D P E D D P	4/5-day	4.5	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F03030	D D E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F03031	D E D D P E D D P E D D D E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03032	E D D D E E D D D E E D D D	5-day	5.0	E D D P E D D D E D D P E D	4-day	4.0	D D D E PL	1
F03033	D P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F03034	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D D E D D P E D D	4-day	4.0	P PL	1
F03035	D E D D D P E E D D P E E D	irregular	5.5	D P E D D D P E D D P E E D	5-day	5.0	D P E PL	1
F03036	E D D P E D D P E D D D E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
Mean			4.3			4.1		1.0
S.D.			0.5			0.3		0.0
(N)			(12)			(12)		(12)

Significantly different from the control group (*: p<0.05, **: p<0.01).
D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 34-4. Results of observations about estrous cycle

N-DPS (150 mg/kg)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F04037	P E D D D E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F04038	E D D D P E D D P E D D P E	4/5-day	4.3	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F04039	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F04040	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F04041	P E D D P E D D P E D D P E	4-day	4.0	D D D E D D D E D D P E D D	4-day	4.0	D PL	1
F04042	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F04043	D D E D D D E D D P E D D P	4-day	4.0	E D D P E D D P E E D D P E	4/5-day	4.3	PL	1
F04044	D D D E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F04045	D D E D D P E D D D E D D P	4-day	4.0	E D D P E D D P E D D D P E	4/5-day	4.3	PL	1
F04046	E D D P E D D P E D D D E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F04047	E D D D P E D D D E E D D D	5-day	5.0	P E D D D P E D D P E E D D	5-day	5.0	D E E D D D P PL	2
F04048	P E D D P E D D P E D D P E	4-day	4.0	D D D E D D D P E D D P E D	4/5-day	4.5	D P PL	1
Mean			4.1			4.2		1.1
S.D.			0.3			0.3		0.3
(N)			(12)			(12)		(12)

Significantly different from the control group (*: p<0.05, **: p<0.01).
D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 35-1. Results of observations about reproductive performance

Control (vehicle: water for injection)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M01001	F01001	+	+	2
M01002	F01002	+	+	2
M01003	F01003	+	+	4
M01004	F01004	+	+	2
M01005	F01005	+	+	2
M01006	F01006	+	+	1
M01007	F01007	+	+	4
M01008	F01008	+	+	1
M01009	F01009	+	+	1
M01010	F01010	+	+	1
M01011	F01011	+	+	2
M01012	F01012	+	+	1
Total		+: 12, -: 0	+: 12, -: 0	
Mean				1.9
S.D.				1.1
(N)				(12)

+, confirmed
-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 35-2. Results of observations about reproductive performance

N-DPS (15 mg/kg)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M02013	F02013	+	+	3
M02014	F02014	+	+	4
M02015	F02015	+	+	1
M02016	F02016	+	+	4
M02017	F02017	+	+	1
M02018	F02018	+	+	1
M02019	F02019	+	+	3
M02020	F02020	+	+	4
M02021	F02021	+	+	3
M02022	F02022	+	+	2
M02023	F02023	+	+	3
M02024	F02024	+	+	3
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.7
S.D.				1.2
(N)				(12)

+, confirmed
-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 35-3. Results of observations about reproductive performance

N-DPS (50 mg/kg)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M03025	F03025	+	+	4
M03026	F03026	+	+	4
M03027	F03027	+	+	3
M03028	F03028	+	+	2
M03029	F03029	+	-	3
M03030	F03030	+	+	3
M03031	F03031	+	+	2
M03032	F03032	+	+	5
M03033	F03033	+	+	3
M03034	F03034	+	+	2
M03035	F03035	+	+	4
M03036	F03036	+	+	1
Total		+: 12, -: 0	+: 11, -: 1	
Mean				3.0
S.D.				1.1
(N)				(12)

+, confirmed
-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 35-4. Results of observations about reproductive performance

N-DPS (150 mg/kg)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M04037	F04037	+	+	2
M04038	F04038	+	+	2
M04039	F04039	+	+	2
M04040	F04040	+	+	1
M04041	F04041	+	+	2
M04042	F04042	+	+	4
M04043	F04043	+	+	1
M04044	F04044	+	+	4
M04045	F04045	+	+	1
M04046	F04046	+	+	1
M04047	F04047	+	+	8
M04048	F04048	+	+	3
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.6
S.D.				2.0
(N)				(12)

+, confirmed
-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 36-1. Observation of offspring (F_1)

Control (vehicle: water for injection)

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities [b] (Number)	(%)
F01001	22	18	17	94.4	+	17	11	6	17	0.65	0	100.0	100.0	100.0	11	6	0.65	100.0	0	0.0
F01002	22	15	15	100.0	+	14	10	4	14	0.71	0	93.3	93.3	100.0	10	4	0.71	100.0	0	0.0
F01003	22	11	9	81.8	+	9	3	6	9	0.33	0	100.0	100.0	100.0	3	6	0.33	100.0	0	0.0
F01004	22	19	17	89.5	+	9	4	5	9	0.44	0	52.9	52.9	100.0	4	5	0.44	100.0	0	0.0
F01005	22	15	15	100.0	+	15	6	9	15	0.40	0	100.0	100.0	100.0	6	9	0.40	100.0	0	0.0
F01006	22	16	15	93.8	+	14	7	7	14	0.50	0	93.3	93.3	100.0	7	7	0.50	100.0	0	0.0
F01007	22	14	14	100.0	+	14	6	8	14	0.43	0	100.0	100.0	100.0	6	8	0.43	100.0	0	0.0
F01008	22	13	13	100.0	+	10	5	5	10	0.50	0	76.9	76.9	100.0	5	5	0.50	100.0	0	0.0
F01009	22	16	16	100.0	+	16	6	10	16	0.38	0	100.0	100.0	100.0	6	10	0.38	100.0	0	0.0
F01010	22	16	16	100.0	+	14	6	8	14	0.43	0	87.5	87.5	100.0	6	8	0.43	100.0	0	0.0
F01011	22	17	17	100.0	+	14	7	7	14	0.50	0	82.4	82.4	100.0	7	7	0.50	100.0	0	0.0
F01012	22	15	15	100.0	+	14	6	8	14	0.43	0	93.3	93.3	100.0	6	8	0.43	100.0	0	0.0
Number of dams	12	12	12	12	12 [a]	12			12	12	12	12	12	12			12	12	12	12
Total		185	179			160	77	83	160		0				77	83			0	
Mean	22.0	15.4	14.9	96.6		13.3	6.4	6.9	13.3	0.48	0.0	90.0	90.0	100.0	6.4	6.9	0.48	100.0		0.0
S.D.	0.0	2.2	2.2	5.8		2.6	2.2	1.8	2.6	0.11	0.0	14.0	14.0	0.0	2.2	1.8	0.11	0.0		0.0
%					100.0															

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 36-2. Observation of offspring (F_1)

N-DPS 15 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan-tation scars	Implan-tation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities b) (Number)	(%)
F02013	21	13	13	100.0	+	12	4	8	12	0.33	0	92.3	92.3	100.0	4	8	0.33	100.0	0	0.0
F02014	22	17	17	100.0	+	14	6	8	14	0.43	0	82.4	82.4	100.0	6	8	0.43	100.0	0	0.0
F02015	22	17	17	100.0	+	15	8	7	15	0.53	0	88.2	88.2	100.0	7	7	0.50	93.3	0	0.0
F02016	22	17	17	100.0	+	17	6	10	16	0.38	1	100.0	94.1	94.1	6	10	0.38	100.0	0	0.0
F02017	22	13	13	100.0	+	11	7	4	11	0.64	0	84.6	84.6	100.0	7	4	0.64	100.0	0	0.0
F02018	22	18	18	100.0	+	17	6	11	17	0.35	0	94.4	94.4	100.0	6	11	0.35	100.0	0	0.0
F02019	22	15	15	100.0	+	15	9	6	15	0.60	0	100.0	100.0	100.0	9	6	0.60	100.0	0	0.0
F02020	22	17	15	88.2	+	14	4	10	14	0.29	0	93.3	93.3	100.0	4	10	0.29	100.0	0	0.0
F02021	22	17	17	100.0	+	16	7	9	16	0.44	0	94.1	94.1	100.0	7	9	0.44	100.0	0	0.0
F02022	22	17	17	100.0	+	12	8	4	12	0.67	0	70.6	70.6	100.0	8	4	0.67	100.0	0	0.0
F02023	22	16	16	100.0	+	15	8	7	15	0.53	0	93.8	93.8	100.0	8	7	0.53	100.0	0	0.0
F02024	22	20	20	100.0	+	20	8	10	18	0.44	2	100.0	90.0	90.0	8	10	0.44	100.0	0	0.0
Number of dams	12	12	12	12	12 a)	12			12	12	12	12	12	12			12	12	12	12
Total		197	195			178	81	94	175		3				80	94			0	
Mean	21.9	16.4	16.3	99.0		14.8	6.8	7.8	14.6	0.47	0.3	91.1	89.8	98.7	6.7	7.8	0.47	99.4		0.0
S.D.	0.3	2.0	2.0	3.4		2.5	1.6	2.3	2.1	0.12	0.6	8.6	7.7	3.2	1.6	2.3	0.12	1.9		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	KW	KW	AN	AN	AN	AN		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
+: Dams with live offspring, -: dams without live offspring.
a): Number of dams with live offspring.
b): Number of external abnormalities in live offspring at birth.
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 36-3. Observation of offspring (F_1)

N-DPS 50 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities b) (Number)	(%)
F03025	22	16	16	100.0	+	15	8	6	14	0.57	1	93.8	87.5	93.3	8	6	0.57	100.0	0	0.0
F03026	22	15	15	100.0	+	15	11	4	15	0.73	0	100.0	100.0	100.0	11	4	0.73	100.0	0	0.0
F03027	22	16	14	87.5	+	14	7	6	13	0.54	1	100.0	92.9	92.9	7	5	0.58	92.3	0	0.0
F03028	22	17	17	100.0	+	17	8	9	17	0.47	0	100.0	100.0	100.0	8	9	0.47	100.0	0	0.0
F03029	Not pregnant																			
F03030	22	15	15	100.0	+	13	3	10	13	0.23	0	86.7	86.7	100.0	3	10	0.23	100.0	0	0.0
F03031	22	15	15	100.0	+	14	7	7	14	0.50	0	93.3	93.3	100.0	7	7	0.50	100.0	0	0.0
F03032	22	10	10	100.0	+	9	4	5	9	0.44	0	90.0	90.0	100.0	4	5	0.44	100.0	0	0.0
F03033	22	15	13	86.7	+	13	9	3	12	0.75	1	100.0	92.3	92.3	9	3	0.75	100.0	0	0.0
F03034	22	14	14	100.0	+	14	7	7	14	0.50	0	100.0	100.0	100.0	7	7	0.50	100.0	0	0.0
F03035	22	17	17	100.0	+	17	6	11	17	0.35	0	100.0	100.0	100.0	6	11	0.35	100.0	0	0.0
F03036	22	15	15	100.0	+	15	10	5	15	0.67	0	100.0	100.0	100.0	10	5	0.67	100.0	0	0.0
Number of dams	11	11	11	11	11 a)	11			11	11	11	11	11	11			11	11	11	11
Total		165	161			156	80	73	153		3				80	72			0	
Mean	22.0	15.0	14.6	97.7		14.2	7.3	6.6	13.9	0.52	0.3	96.7	94.8	98.0	7.3	6.5	0.53	99.3		0.0
S.D.	0.0	1.9	2.0	5.2		2.2	2.4	2.5	2.3	0.16	0.5	4.9	5.4	3.4	2.4	2.5	0.16	2.3		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	KW	KW	AN	AN	AN	AN		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
+: Dams with live offspring, -: dams without live offspring.
a): Number of dams with live offspring.
b): Number of external abnormalities in live offspring at birth.
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 36-4. Observation of offspring (F_1)

N-DPS 150 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities b) (Number)	(%)
F04037	22	14	14	100.0	+	14	8	6	14	0.57	0	100.0	100.0	100.0	8	6	0.57	100.0	0	0.0
F04038	22	15	13	86.7	+	13	5	8	13	0.38	0	100.0	100.0	100.0	5	8	0.38	100.0	0	0.0
F04039	22	17	17	100.0	+	17	10	7	17	0.59	0	100.0	100.0	100.0	10	6	0.63	94.1	0	0.0
F04040	22	17	17	100.0	+	17	9	8	17	0.53	0	100.0	100.0	100.0	9	8	0.53	100.0	0	0.0
F04041	22	13	13	100.0	+	13	6	7	13	0.46	0	100.0	100.0	100.0	6	7	0.46	100.0	0	0.0
F04042	22	17	16	94.1	+	16	8	8	16	0.50	0	100.0	100.0	100.0	8	8	0.50	100.0	0	0.0
F04043	22	17	16	94.1	+	14	9	5	14	0.64	0	87.5	87.5	100.0	9	5	0.64	100.0	0	0.0
F04044	21	15	15	100.0	+	14	6	8	14	0.43	0	93.3	93.3	100.0	6	8	0.43	100.0	0	0.0
F04045	22	16	16	100.0	+	15	4	11	15	0.27	0	93.8	93.8	100.0	4	11	0.27	100.0	0	0.0
F04046	22	18	18	100.0	+	16	9	7	16	0.56	0	88.9	88.9	100.0	9	7	0.56	100.0	0	0.0
F04047	22	15	15	100.0	+	15	8	7	15	0.53	0	100.0	100.0	100.0	8	7	0.53	100.0	0	0.0
F04048	22	15	15	100.0	+	15	6	9	15	0.40	0	100.0	100.0	100.0	6	8	0.43	93.3	0	0.0
Number of dams	12	12	12	12	12 a)	12			12	12	12	12	12	12			12	12	12	12
Total		189	185			179	88	91	179		0				88	89			0	
Mean	21.9	15.8	15.4	97.9		14.9	7.3	7.6	14.9	0.49	0.0	97.0	97.0	100.0	7.3	7.4	0.49	99.0		0.0
S.D.	0.3	1.5	1.6	4.2		1.4	1.9	1.5	1.4	0.10	0.0	4.8	4.8	0.0	1.9	1.5	0.11	2.5		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	KW	KW	AN	AN	AN	AN		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
+: Dams with live offspring, -: dams without live offspring.
a): Number of dams with live offspring.
b): Number of external abnormalities in live offspring at birth.
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats

Appendix 37-1. Body weights of offspring (F_1) before weaning

Control (vehicle: water for injection)

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F01001	6.9	(11)	11.6	(11)	6.6	(6)	10.7	(6)
F01002	6.5	(10)	10.2	(10)	5.9	(4)	10.3	(4)
F01003	7.4	(3)	12.5	(3)	7.1	(6)	12.2	(6)
F01004	7.9	(4)	13.5	(4)	7.2	(5)	13.0	(5)
F01005	6.6	(6)	10.2	(6)	6.2	(9)	8.8	(9)
F01006	7.1	(7)	11.0	(7)	6.5	(7)	10.7	(7)
F01007	7.3	(6)	11.0	(6)	7.1	(8)	10.7	(8)
F01008	6.8	(5)	11.7	(5)	6.6	(5)	12.1	(5)
F01009	6.6	(6)	11.4	(6)	6.5	(10)	11.1	(10)
F01010	7.4	(6)	11.2	(6)	7.3	(8)	11.1	(8)
F01011	6.5	(7)	11.7	(7)	6.4	(7)	11.1	(7)
F01012	6.9	(6)	11.7	(6)	6.5	(8)	11.1	(8)
Number of dams	12		12		12		12	
Mean	7.0		11.5		6.7		11.1	
S.D.	0.4		0.9		0.4		1.1	

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 37-2. Body weights of offspring (F_1) before weaning

N-DPS 15 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F02013	5.8	(4)	10.4	(4)	5.5	(8)	9.8	(8)
F02014	6.8	(6)	10.7	(6)	6.3	(8)	10.1	(8)
F02015	6.6	(8)	10.7	(7)	6.1	(7)	9.9	(7)
F02016	6.5	(6)	10.7	(6)	5.8	(10)	9.9	(10)
F02017	6.9	(7)	11.4	(7)	6.6	(4)	11.1	(4)
F02018	6.2	(6)	11.2	(6)	5.8	(11)	9.0	(11)
F02019	6.8	(9)	11.5	(9)	6.3	(6)	10.6	(6)
F02020	7.2	(4)	11.3	(4)	6.6	(10)	10.7	(10)
F02021	6.4	(7)	9.3	(7)	6.1	(9)	8.9	(9)
F02022	6.7	(8)	11.3	(8)	6.2	(4)	11.0	(4)
F02023	6.8	(8)	11.1	(8)	6.4	(7)	10.5	(7)
F02024	6.4	(8)	9.4	(8)	6.1	(10)	8.7	(10)
Number of dams	12		12		12		12	
Mean	6.6		10.8		6.2		10.0	
S.D.	0.4		0.7		0.3		0.8	
Significance	NS		NS		**		*	
Statistical method	AN		DU		DU		DU	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 37-3. Body weights of offspring (F_1) before weaning

N-DPS 50 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F03025	6.6	(8)	10.6	(8)	6.3	(6)	10.6	(6)
F03026	6.5	(11)	9.9	(11)	5.9	(4)	10.2	(4)
F03027	7.0	(7)	11.8	(7)	6.3	(6)	11.0	(5)
F03028	6.9	(8)	10.1	(8)	6.6	(9)	9.6	(9)
F03029	Not pregnant							
F03030	7.2	(3)	11.7	(3)	6.6	(10)	11.1	(10)
F03031	6.7	(7)	10.5	(7)	6.4	(7)	10.3	(7)
F03032	7.2	(4)	11.9	(4)	6.4	(5)	11.6	(5)
F03033	7.2	(9)	12.0	(9)	6.7	(3)	11.4	(3)
F03034	7.4	(7)	11.2	(7)	6.9	(7)	10.4	(7)
F03035	6.0	(6)	9.0	(6)	6.0	(11)	9.0	(11)
F03036	6.8	(10)	11.3	(10)	6.3	(5)	11.2	(5)
Number of dams	11		11		11		11	
Mean	6.9		10.9		6.4		10.6	
S.D.	0.4		1.0		0.3		0.8	
Significance	NS		NS		NS		NS	
Statistical method	AN		DU		DU		DU	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino)propyl]stearamide by oral administration in rats
Appendix 37-4. Body weights of offspring (F_1) before weaning

N-DPS 150 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F04037	7.2	(8)	11.5	(8)	6.8	(6)	10.9	(6)
F04038	7.6	(5)	10.4	(5)	6.9	(8)	10.0	(8)
F04039	6.5	(10)	8.8	(10)	6.1	(7)	8.6	(6)
F04040	6.5	(9)	9.3	(9)	6.1	(8)	8.6	(8)
F04041	6.6	(6)	9.2	(6)	6.4	(7)	9.3	(7)
F04042	6.8	(8)	9.7	(8)	6.5	(8)	8.7	(8)
F04043	7.3	(9)	11.2	(9)	6.5	(5)	10.4	(5)
F04044	6.0	(6)	8.8	(6)	5.8	(8)	8.5	(8)
F04045	6.9	(4)	11.2	(4)	6.7	(11)	10.4	(11)
F04046	6.6	(9)	10.4	(9)	6.4	(7)	10.1	(7)
F04047	6.8	(8)	7.6	(8)	6.3	(7)	7.5	(7)
F04048	7.5	(6)	10.5	(6)	7.0	(9)	9.9	(8)
Number of dams	12		12		12		12	
Mean	6.9		9.9		6.5		9.4	
S.D.	0.5		1.2		0.4		1.0	
Significance	NS		**		NS		**	
Statistical method	AN		DU		DU		DU	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.
NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino) propyl]stearamide by oral administration in rats

Appendix 38-1. General conditions in offspring (F_1) before weaning

Control (vehicle: water for injection)

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F01001	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F01002	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01003	Number of offspring	9	9	9	9	9
	General appearance, No abnormality	9	9	9	9	9
F01004	Number of offspring	9	9	9	9	9
	General appearance, No abnormality	9	9	9	9	9
F01005	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01006	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01007	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01008	Number of offspring	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10
F01009	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01010	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01011	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01012	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
	Number of offspring	160	160	160	160	160
	General appearance, No abnormality	160	160	160	160	160
	General appearance, Death					

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino) propyl]stearamide by oral administration in rats

Appendix 38-2. General conditions in offspring (F_1) before weaning

N-DPS 15 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth 0	1	2	3	4
F02013	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02014	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02015	Number of offspring	15	15	14	14	14
	General appearance, No abnormality	15	14	14	14	14
	General appearance, Death	0	1	0	0	0
F02016	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02017	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F02018	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F02019	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02020	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02021	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02022	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02023	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02024	Number of offspring	18	18	18	18	18
	General appearance, No abnormality	18	18	18	18	18
	Number of offspring	175	175	174	174	174
	General appearance, No abnormality	175	174	174	174	174
	General appearance, Death		1			

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino) propyl]stearamide by oral administration in rats

Appendix 38-3. General conditions in offspring (F_1) before weaning

N-DPS 50 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth 0	1	2	3	4
F03025	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03026	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03027	Number of offspring	13	13	12	12	12
	General appearance, No abnormality	13	12	12	12	12
	General appearance, Death	0	1	0	0	0
F03028	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F03029	Not pregnant					
F03030	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03031	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03032	Number of offspring	9	9	9	9	9
	General appearance, No abnormality	9	9	9	9	9
F03033	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F03034	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03035	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F03036	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
	Number of offspring	153	153	152	152	152
	General appearance, No abnormality	153	152	152	152	152
	General appearance, Death		1			

Combined repeat dose and reproductive/developmental toxicity screening test of N-[3-(Dimethylamino) propyl]stearamide by oral administration in rats
Appendix 38-4. General conditions in offspring (F_1) before weaning

N-DPS 150 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth 0	1	2	3	4
F04037	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04038	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F04039	Number of offspring	17	17	16	16	16
	General appearance, No abnormality	17	16	16	16	16
	General appearance, Death	0	1	0	0	0
F04040	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F04041	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F04042	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F04043	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04044	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04045	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04046	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F04047	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04048	Number of offspring	15	15	14	14	14
	General appearance, No abnormality	15	14	14	14	14
	General appearance, Death	0	1	0	0	0
	Number of offspring	179	179	177	177	177
	General appearance, No abnormality	179	177	177	177	177
	General appearance, Death		2			

信頼性保証書

表題　N-[3-(N,N-ジメチルアミノ)プロパン-1-イル]ステアルアミドのラットを用いる反復投与毒性・生殖発生毒性併合試験

試験番号　R-12-004

この試験に関する信頼性保証部門による査察および監査状況等は下記のとおりであった。

査察・監査項目	査察・監査年月日	運営管理者および試験責任者への報告年月日
試験計画書	2012年10月25日	2012年10月25日
試験計画書変更書		
R-12-004-No.1	2012年11月 1日	2012年11月 1日
R-12-004-No.2	2012年12月20日	2012年12月20日
R-12-004-No.3	2013年 1月 9日	2013年 1月 9日
R-12-004-No.4	2013年 3月21日	2013年 3月21日
R-12-004-No.5	2013年 4月 1日	2013年 4月 1日
動物の受入れおよび検疫	2012年10月29日	2012年10月29日
原体の安定性(実験開始前)	2012年10月29日	2012年10月30日
媒体中の安定性(安定性試験開始日)	2012年10月31日	2012年11月 1日
群分け、検体調製、含量・均一性試験	2012年11月12日	2012年11月12日
体重測定、給餌量測定、投与および一般状態の観察	2012年11月13日	2012年11月13日
性周期観察	2012年11月14日	2012年11月14日
詳細な症状観察	2012年11月20日	2012年11月20日
交尾確認	2012年11月28日	2012年11月28日
尿検査	2012年12月19、20日	2012年12月20日
分娩状態および出生児の観察	2012年12月20日	2012年12月20日
機能検査	2012年12月21、24日	2012年12月24日
出生児剖検、血液学検査、血液生化学検査、雄動物剖検、器官重量測定および固定	2012年12月25日	2012年12月25日
病理組織学検査(標本作製:切り出し)	2013年 2月 8日	2013年 2月 8日
報告書草案および生データ	2013年 4月4、5、9～12日	2013年 4月12日
最終報告書	2014年 1月27日	2014年 1月27日

試験は、「新規化学物質等に係る試験を実施する試験施設に関する基準について」(平成23年3月31日、薬食発0331第8号、平成23・03・29製局第6号、環保企発第110331010号)を遵守して実施され、また、この報告書は試験に使用された方法および手順を正確に記載し、記載された結果は試験の生データを正確に反映していることを保証する。

2014年1月27日

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信頼性保証部門責任者 [redacted]