



最 終 報 告 書

クロトン酸のラットを用いた
経口投与による反復投与毒性・生殖発生毒性併合試験

試験番号：R-1169

試験期間：2015年9月17日-2016年3月28日

試験施設

株式会社ボゾリサーチセンター 御殿場研究所
〒412-0039 静岡県御殿場市かまど 1284

試験委託者

厚生労働省 医薬食品局 審査管理課 化学物質安全対策室
〒100-8916 東京都千代田区霞が関 1-2-2

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

R-1169

1. GLP 陳述書

試験番号 : R-1169

試験表題 : クロトン酸のラットを用いた
経口投与による反復投与毒性・生殖発生毒性併合試験

本試験は以下に示す基準を遵守して実施したものであります。

- 「新規化学物質等に係る試験を実施する試験施設に関する基準」
(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、
環境企発第 110331010 号)

試験責任者

株式会社ボゾリサーチセンター 御殿場研究所

2016 年 3 月 28 日

2. 目次

1.	GLP 陳述書	2
2.	目次	3
3.	試験実施概要	8
3.1	試験番号	8
3.2	試験表題	8
3.3	試験目的	8
3.4	試験委託者	8
3.5	試験受託者	8
3.6	試験実施施設	8
3.7	被験物質	8
3.8	試験日程	9
3.9	試験責任者	9
3.10	試験担当者	9
3.11	試験成績の信頼性に影響を及ぼしたと思われる環境要因	9
3.12	予見することができなかった試験の信頼性に影響を及ぼす疑いの ある事態及び試験計画書に従わなかったこと	9
3.13	資料保存	10
3.14	試験責任者の記名・押印	11
4.	要約	12
4.1	反復投与毒性	12
4.2	生殖発生毒性	12
5.	緒言	13
5.1	GLP	13
5.2	毒性試験ガイドライン	13
5.3	動物の福祉	13
6.	試験材料及び方法	14
6.1	被験物質及び媒体	14
6.1.1	被験物質	14
6.1.2	媒体	15
6.2	投与液の調製及び保存方法	15
6.2.1	対照群投与液の採取	15
6.2.2	被験液の調製	15
6.2.3	投与液の保存	16
6.2.4	被験液の安定性	16
6.2.5	被験液の濃度及び均一性確認	16
6.3	試験動物種及び系統の選択理由	17

6.4	試験動物.....	18
6.5	飼育条件.....	18
6.6	動物の識別	19
6.7	投与経路、投与期間及び投与回数並びに回復期間 とそれらの 選択理由	19
6.8	投与方法.....	19
6.9	投与量及び群構成	20
6.10	投与量の設定根拠	20
6.11	観察及び検査の方法.....	21
6.11.1	一般状態の観察	21
6.11.2	詳細な一般状態の観察、機能検査、握力及び自発運動量の測定.....	21
6.11.3	体重測定	22
6.11.4	摂餌量測定	22
6.11.5	膣垢検査	22
6.11.6	交配方法	23
6.11.7	分娩及び哺育観察.....	23
6.11.8	尿検査及び摂水量測定	24
6.11.9	血液学検査	25
6.11.10	血液化学検査.....	26
6.11.11	血中ホルモン測定.....	26
6.11.12	病理学検査	27
6.12	統計解析.....	28
6.12.1	パラメータの算出.....	28
6.12.2	検定	28
7.	試験結果	30
7.1	一般状態 (Table 1-1~1-11、Appendix 1-1~1-34)	30
7.2	詳細な一般状態の観察、機能検査、握力測定及び自発運動量の測定 (Fig. 1~5、Table 2-1~2-171、Appendix 2-1~2-344)	30
7.2.1	ホームケージ内観察 (Table 2-1~2-23、Appendix 2-1~2-72)	30
7.2.2	手に持った観察 (Table 2-24~2-82、Appendix 2-73~2-144)	30
7.2.3	オープンフィールド内観察 (Table 2-83~2-151、 Appendix 2-145~2-288)	30
7.2.4	機能検査 (Table 2-152~2-161、Appendix 2-289~2-316)	31
7.2.5	握力 (Table 2-162~2-166、Appendix 2-317~2-330)	31
7.2.6	自発運動量 (Fig. 1~5、Table 2-167~2-171、 Appendix 2-331~2-344)	31
7.3	体重 (Fig. 6~12、Table 3-1~3-7、Appendix 3-1~3-22)	32
7.4	摂餌量 (Fig. 13~19、Table 4-1~4-7、Appendix 4-1~4-22)	32

7.5	尿検査（摂水量測定を含む）（Table 5-1~5-24、Appendix 5-1~5-30）	32
7.6	血液学検査（Table 6-1~6-7、Appendix 6-1~6-16）	33
7.7	血液化学検査（Table 7-1~7-7、Appendix 7-1~7-16）	33
7.8	器官重量（Table 8-1~8-7、Appendix 8-1~8-32）	33
7.9	剖検所見（Table 9-1~9-6、Appendix 9-1~9-116）	34
7.10	病理組織学検査（Table 10-1~10-14、Appendix 9-1~9-116）	34
7.11	性周期（Table 11、Appendix 10-1~10-8）	34
7.12	交配成績（Table 12-1 及び 12-2、Appendix 11-1~11-8）	35
7.13	分娩成績（Table 13、14-1、Appendix 12-1~12-4、13-1~13-4）並びに 分娩及び哺育状態（Table 1-5 及び 1-6、Appendix 1-17~1-24）	35
7.14	出生児の生存性及び性比（Table 15、Appendix 14-1~14-4）	35
7.15	出生児の体重（Table 16-1 及び 16-2、Appendix 15-1~15-8）	35
7.16	死亡児の肉眼観察所見（Table 17、Appendix 16-1~16-4）	35
7.17	出生児の生後 4 日肉眼観察所見（Table 14-2、Appendix 13-5~13-8）	35
8.	考察	36
8.1	反復投与毒性	36
8.2	生殖発生毒性	37
9.	文献	38

添付資料

Attached Data 1	試験成績書（被験物質の特性）	39
Attached Data 2	試験成績書（被験物質の安定性）	40
Attached Data 3	試験成績書（被験液中クロトン酸の安定性）	42
Attached Data 4	被験液中の被験物質濃度分析結果（初回投与）	44
Attached Data 5	被験液中の被験物質濃度分析結果（投与 6 週）	45
Attached Data 6	クロトン酸のラットを用いた 14 日間反復経口投与 毒性試験（投与量設定試験）における所見	46

図

Fig. 1~5	自発運動量	47
Fig. 6~12	体重	52
Fig. 13~19	摂餌量	59

表

Table 1-1~1-11	一般状態	66
Table 2-1~2-23	ホームケージ内観察	77

Table 2-24~2-82	手に持つての観察.....	100
Table 2-83~2-151	オープンフィールド内観察.....	159
Table 2-152~2-161	機能検査.....	228
Table 2-162~2-166	握力.....	238
Table 2-167~2-171	自発運動量.....	243
Table 3-1~3-7	体重.....	248
Table 4-1~4-7	摂餌量.....	255
Table 5-1~5-24	尿検査（含、摂水量）.....	262
Table 6-1~6-7	血液学検査.....	286
Table 7-1~7-7	血液化学検査.....	293
Table 8-1~8-7	器官重量.....	300
Table 9-1~9-6	剖検所見.....	307
Table 10-1~10-14	病理組織学検査.....	313
Table 11	性周期.....	327
Table 12-1、12-2	交配成績.....	328
Table 13	分娩成績.....	330
Table 14-1、14-2	出生児の外表観察.....	331
Table 15	出生児の生存性及び性比（生後4日）.....	333
Table 16-1、16-2	出生児の体重.....	334
Table 17	死亡児の外表観察.....	336

個体別表

Appendix 1-1~1-34	一般状態.....	337
Appendix 2-1~2-72	ホームケージ内観察.....	371
Appendix 2-73~2-144	手に持つての観察.....	443
Appendix 2-145~2-288	オープンフィールド内観察.....	515
Appendix 2-289~2-316	機能検査.....	659
Appendix 2-317~2-330	握力.....	687
Appendix 2-331~2-344	自発運動量.....	701
Appendix 3-1~3-22	体重.....	715
Appendix 4-1~4-22	摂餌量.....	737
Appendix 5-1~5-30	尿検査（含、摂水量）.....	759
Appendix 6-1~6-16	血液学検査.....	789
Appendix 7-1~7-16	血液化学検査.....	805
Appendix 8-1~8-32	器官重量.....	821
Appendix 9-1~9-116	剖検所見及び病理組織学検査.....	853
Appendix 10-1~10-8	性周期.....	969
Appendix 11-1~11-8	交配成績.....	977

R-1169

Appendix 12-1~12-4	分娩成績	985
Appendix 13-1~13-8	出生児の外表観察.....	989
Appendix 14-1~14-4	出生児の生存性及び性比（生後 4 日）	997
Appendix 15-1~15-8	出生児の体重	1001
Appendix 16-1~16-4	死亡児の外表観察.....	1009
信頼性保証書		1013

R-1169

3. 試験実施概要

3.1 試験番号

R-1169

3.2 試験表題

クロトン酸のラットを用いた経口投与による反復投与毒性・生殖発生毒性併合試験
(Combined repeated dose toxicity study with the reproduction / developmental toxicity screening test of crotonic acid by oral administration in rats)

3.3 試験目的

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

3.4 試験委託者

厚生労働省 医薬食品局 審査管理課 化学物質安全対策室
〒100-8916 東京都千代田区霞が関 1-2-2

3.5 試験受託者

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

3.6 試験実施施設

株式会社ボゾリサーチセンター 御殿場研究所
〒412-0039 静岡県御殿場市かまど 1284

3.7 被験物質

製造者	:	
名称	:	クロトン酸
CAS 番号	:	107-93-7
官報公示整理番号	:	(2)-963 (化審法)
入手日	:	2015 年 6 月 26 日

3.8 試験日程

試験開始日 : 2015 年 9 月 17 日
被験物質出庫日 : 2015 年 10 月 7 日
動物入荷日 : 2015 年 9 月 25 日
実験開始日（投与開始日）
: 2015 年 10 月 13 日
交配開始日 : 2015 年 10 月 27 日
分娩開始日 : 2015 年 11 月 18 日
母動物剖検開始日 : 2015 年 11 月 23 日
投与終了剖検日 : 2015 年 11 月 24 日（雄及び非交配群）
回復開始日 : 2015 年 11 月 24 日
回復終了剖検日 : 2015 年 12 月 8 日
動物試験終了日 : 2015 年 12 月 8 日
実験終了日（病理組織学検査終了日）
: 2016 年 2 月 8 日
試験終了日 : 2016 年 3 月 28 日

3.9 試験責任者

株式会社ボゾリサーチセンター 御殿場研究所 研究部

3.10 試験担当者

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

3.11 試験成績の信頼性に影響を及ぼしたと思われる環境要因

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

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

動物番号 1008、4110、5106 及び 6102 の上皮小体（両側）が標本上欠落していた。しかし、両側検索できなかった例は各群とも 1 例にとどまり、各群 80%以上の動物で片側の上皮小体の鏡検が可能であったことから、病理組織学的評価は可能と判断されたため、試験成績へ及ぼす影響はなかった。

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

3.13 資料保存

株式会社ボゾリサーチセンターの保存方法に従い、試験計画書原本、記録文書、生データ、報告書類（最終報告書は原本）及び標本（被験物質保存サンプルを含む）は株式会社ボゾリサーチセンター御殿場研究所の資料保存施設に最終報告書提出後 10 年間保存する。期間終了後の保存については、厚生労働省医薬食品局審査管理課化学物質安全対策室と株式会社ボゾリサーチセンター間で協議し、その処置を決定する。ただし、長期保存に耐えられない生体試料（尿、血漿、血清）及び腔垢標本については、試験終了までに廃棄した。また、死産児、死亡児及び生後 4 日生存児については、出生率及び生後 4 日生存率に被験物質投与の影響が認められなかったため試験終了までに廃棄した。

R-1169

3.14 試験責任者の記名・押印

____  2016 年 3 月 28 日 

4. 要約

クロトン酸をコーン油で懸濁し、50、150及び500 mg/kgの投与量でSprague-Dawley系 SPF ラット（交配群として雌雄各 12 匹/群、雌には非交配群として対照群及び500 mg/kg 投与群に各 10 匹を追加）の雄には交配前 14 日間に加え交配期間を通して剖検前日まで（42 日間）、雌には交配前 14 日間に加え交配期間及び妊娠期間を通して授乳 4 日まで（41~48 日間）、非交配群雌には 42 日間強制経口投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0 及び 500 mg/kg 投与群の一部の動物（交配群雄 5 匹と非交配群雌 5 匹）については、雄及び非交配群雌ともに 42 日間投与した後 14 日間の回復期間を設け、毒性変化の可逆性を検討した。なお、対照群には媒体であるコーン油を投与した。

4.1 反復投与毒性

いずれの投与群においても死亡動物はみられなかった。

500 mg/kg 群では、雄で投与期間中に体重増加抑制、総タンパク質及びアルブミンの低値、交配群雌で妊娠及び授乳期間中に摂餌量の低下を伴った体重増加抑制、クレアチニンの低値、非交配群雌で赤血球数の高値、平均赤血球血色素量及び平均赤血球血色素濃度の低値、血小板数の高値、総コレステロールの低値がみられた。更に雄及び交配群雌で前胃の壁肥厚、交配群雌で前胃の隆起巣、雄、交配群雌及び非交配群雌で胃の扁平上皮細胞の過形成がみられた。

150 mg/kg 群では、雄で胃の扁平上皮細胞の過形成がみられた。

50 mg/kg 群では、いずれの検査においても、被験物質投与による影響は認められなかった。

14 日間の回復期間により上記変化は消失するか、あるいは発現頻度及び程度の減弱がみられ、回復性が認められた。

4.2 生殖発生毒性

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

これらの結果から、本試験条件下において、本被験物質の反復投与毒性に対する雄での無影響量及び無毒性量は 50 mg/kg であり、雌ではいずれも 150 mg/kg と判断した。生殖発生毒性に対する無影響量及び無毒性量は雄親動物、母動物及び児動物でいずれも 500 mg/kg と判断した。

5. 緒言

厚生労働省医薬食品局審査管理課化学物質安全対策室の委託により、クロトン酸のラットを用いた経口投与による反復投与毒性・生殖発生毒性併合試験を実施したので、その成績を報告する。

なお、本試験は以下の基準を遵守し、ガイドライン等に準拠して、株式会社ボゾリサーチセンターで実施した。また、本試験は試験実施施設の動物実験委員会の承認（承認番号：G150295）を受けて実施した。

5.1 GLP

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

5.2 毒性試験ガイドライン

- 「新規化学物質等に係る試験の方法について」
（平成 23 年 3 月 31 日：薬食発 0331 第 7 号、平成 23・03・29 製局第 5 号、
環境企発第 110331009 号）

5.3 動物の福祉

- 「動物の愛護及び管理に関する法律」
（昭和 48 年 10 月 1 日法律第 105 号）
- 「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」
（平成 18 年 4 月 28 日環境省告示第 88 号）
- 「動物実験の適正な実施に向けたガイドライン」
（日本学術会議 平成 18 年 6 月 1 日）
- 「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の一部改正について」（平成 27 年 2 月 20 日科発 0220 第 1 号）

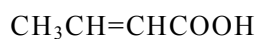
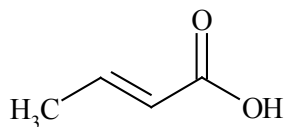
6. 試験材料及び方法

6.1 被験物質及び媒体

6.1.1 被験物質

クロトン酸は東京化成工業株式会社から以下の情報とともに購入した。また、試験開始前に赤外吸収スペクトルの測定により特性が確認されている（試験番号：A-2765、Attached Data 1）。

製造者	:	
名称	:	クロトン酸
英語名称	:	Crotonic Acid
CAS 番号	:	107-93-7
官報公示整理番号	:	(2)-963（化審法）
構造式又は示性式	:	



分子式	:	$\text{C}_4\text{H}_6\text{O}_2$
分子量	:	86.09
常温における性状*	:	白色~ごくうすい黄色の結晶性粉末
沸点/沸騰範囲*	:	185°C
蒸気圧*	:	25Pa/20°C
蒸気密度*	:	2.97
溶解度*	:	水；可溶（76g/L、20°C） その他溶剤；易溶（エーテル、アルコール、アセトン） ；可溶（トルエン）
自然発火温度*	:	396°C
ロット番号	:	MXJGG
純度（GC）	:	100.0%
純度（中和滴定）	:	99.9%
不純物	:	不明
融点	:	72.6°C
メタノール溶状	:	澄明
保存条件	:	密栓、冷暗所
保存方法	:	気密容器に入れ冷蔵庫内（許容値：1~10°C、実測値：4~8°C）に保存した。

保存場所	:	御殿場研究所被験物質保存室、第2研究棟4階被験物質調製室及び分析研究部標準物質保存場所
取扱い上の注意	:	作業場の換気を十分に行い、マスク、保護眼鏡、保護手袋等の適切な保護具を着用し、直接の接触を防いだ。取り扱い後は、手、顔等を良く洗い、うがいをした。
安定性	:	投与期間終了後に株式会社ボゾリサーチセンター御殿場研究所において、残余被験物質の赤外吸収スペクトルを確認した結果、実験実施前に確認した参照スペクトルとほぼ同様であり安定性に問題はなかった（Attached Data 2）。
被験物質残余の処理	:	被験物質 5 g を保存試料として御殿場研究所の資料保存施設に保存した。動物試験及び分析終了後の残量は全て焼却処分した。

*：製造元の東京化成工業株式会社発行の製品安全データシートに基づく

6.1.2 媒体

名称	:	コーン油
規格	:	生化学用
製造者	:	和光純薬工業株式会社
ロット番号（有効期限）	:	CTF5121（2020年8月3日、2020年10月5日）
保存方法	:	室温
保存場所	:	御殿場研究所第2研究棟4階被験物質調製室

なお、媒体については、本試験に先立って実施した被験液中濃度測定法バリデーション及び安定性・均一性試験（試験番号：A-2765）[1]において、コーン油中での被験物質の安定性に良好な結果が得られていることから、コーン油を選択した。

6.2 投与液の調製及び保存方法

6.2.1 対照群投与液の採取

対照群投与液として、被験液調製当日の被験物質を取り扱う前に必要量のコーン油を1日使用分ずつ、褐色ガラス瓶に貼付したラベルを確認しながら分注した。

6.2.2 被験液の調製

濃度ごとに必要量の被験物質を正確に秤取し、乳鉢に移した。乳棒を用いて十分に磨砕した後、媒体を徐々に加え、懸濁させた。調製液をメスシリンダーに移すとともに、乳鉢及び乳棒を少量の媒体で数回洗い、その液もメスシリンダーに加えた。更に媒体をメスシリンダーに加えて規定量にメスアップし、10、30及び100 mg/mL液（低、中及び高用量群投与液）を調製した。調製は7日に1回以上の頻度で最大7日分を一

括して行った。残液はポリ瓶に回収又はペーパータオル等に吸着させて焼却処分した。

6.2.3 投与液の保存

対照群投与液及び被験液は褐色ガラス瓶に入れ、冷所（冷蔵庫内、許容値：1~10℃、実測値：3~5℃）に保存し、安定性の確認された範囲内で投与に使用した。

6.2.4 被験液の安定性

本被験物質の 1 及び 200 mg/mL 濃度の被験液（媒体：コーン油）は、褐色ガラス瓶に入れ冷所（冷蔵庫内、許容値：1~10℃）で 8 日間保存後、更に室温下（許容値：1~30℃）で 24 時間保存（冷所 8 日間 + 室温 24 時間）したときに安定であることが試験施設で確認されている（試験番号：A-2765、Attached Data 3）[1]。

6.2.5 被験液の濃度及び均一性確認

初回投与及び投与 6 週の投与に使用する各濃度の被験液（上層、中層、下層から各 10 mL 採取）について、株式会社ボゾリサーチセンター御殿場研究所で GC により濃度及び均一性確認を実施した。なお、初回投与に使用する被験液については、投与開始前に確認を行った。その結果、各濃度液における表示値に対する被験物質の割合は 95.9~101.0%、変動係数（CV）は 1.6%以下であり（Attached Data 4、5）、いずれも許容範囲内（濃度：表示値に対する割合；100.0±10.0%、均一性：CV が 10%以下）であったことから、被験液の調製に問題はなかったと考えられた。なお、GC を用いた被験液中濃度測定法バリデーションは株式会社ボゾリサーチセンター御殿場研究所（試験番号：A-2765）[1]で実施された。分析法の概略を以下に示した。

[標準物質]

被験物質から一部分配したものをを用いた。

名称	:	クロトン酸
ロット番号	:	MXJGG
保存条件	:	密栓、冷暗所
保存方法	:	気密容器に入れ冷蔵庫内（許容値：1~10℃、実測値：4~8℃）に保存した。
保存場所	:	御殿場研究所 被験物質保存室及び分析研究部標準物質保存場所

[測定実測試料の調製]

各測定試料をスターラーで攪拌しながら n=1 で採取し、以下の表に示すように、アセトンで希釈した測定実測試料を用時調製した。

R-1169

測定試料濃度 (mg/mL)	1 次希釈		2 次希釈		希釈率
	採取量 (mL)	定容量 (mL)	1 次希釈液 採取量 (mL)	定容量 (mL)	
10	1	20	1	10	200
30	1	50	2.5	30	600
100	1	100	1	20	2000

溶媒：アセトン

[GC システム]

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

[GC 測定条件]

カラム	:	DB-WAX (0.25 mm I.D.×30 m、膜厚 0.25 μm、 Agilent Technologies Inc.)
キャリアガス	:	He
流量モード	:	コンスタントフローモード
流量	:	1.0 mL/min
注入口	:	スプリット注入口
スプリット比	:	2:1
注入口温度	:	250°C
検出器	:	Flame ionization detector (FID)
検出器温度	:	250°C
H ₂ 流量	:	45 mL/min
Air 流量	:	450 mL/min
メイクアップガス (N ₂) 流量	:	30 mL/min
オーブン温度	:	100°C (Hold 0 分) →180°C (10°C/min、Hold 0 分) →250°C (40°C/min、Hold 3.25 分)
注入量	:	1 μL

6.3 試験動物種及び系統の選択理由

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

6.4 試験動物

Sprague-Dawley 系 SPF ラット [Crl:CD(SD)、日本チャールス・リバー株式会社、厚木飼育センター] の雄 62 匹及び雌 83 匹をそれぞれ 8 週齢で入手^{注)} し、入荷日を馴化 1 日と起算して、3 日間の検疫期間を含む 18 日間の馴化飼育を行った。その間、一般状態の観察 (1 回/日)、体重測定 (馴化 1、3、6、13 及び 18 日の 5 回)、詳細な一般状態の観察 (1 回、雄：群分け 4 日前、雌：群分け 3 日前) を実施した。更に、雄について馴化終了日に陰嚢内の精巣の触診及び陰茎亀頭の観察を実施し、雌については膣垢を検疫期間終了後群分け日まで採取して性周期 (検疫期間終了後 14 日間) を調べた。その結果、精巣の小型化が 1 例 (耳標番号：509) に、外傷が雄 1 例 (耳標番号：508) に、性周期の異常が 2 例 (耳標番号：556、607) にみられた。それらの異常例を除き、検疫・馴化期間中の一般状態、詳細な一般状態、体重推移、精巣の触診結果及び性周期に異常がなく、性成熟に達した陰茎亀頭であり、健康と思われる雄 60 匹中 48 匹及び雌 81 匹中 68 匹を選択し、10 週齢で投与を開始した。投与開始時の体重の変動範囲は雄で 383~444 g (平均体重：410 g)、雌は 232~271 g (平均体重：253 g) であり、雌雄それぞれ平均体重の $\pm 20\%$ 以内であった。

なお、動物は検疫・馴化期間中の体重増加量 (入荷日~群分け時) により選別後、群分け当日 (投与開始の前日) の体重に基づいて、非交配群も含め各群の平均体重ができるだけ均等となるよう各群に割付けた。個体の割付けはコンピュータを用いたブロック配置法及び無作為抽出法の組み合わせ (ブロック配置法で必要な群を構成し、試験群及び群内の個体番号を無作為に割当てた) により行った。供試個体の選択条件を満たして余剰となった雌は交配予備動物 (無処置動物) として継続飼育したが、使用しなかったため、交配予備動物は全て交配終了後に試験から除外した。その他の雌雄残余動物は群分け当日に試験から除外した。なお、試験から除外された動物は、動物管部門に移管した (移管日：2015 年 10 月 12 日及び 11 月 10 日)。

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

6.5 飼育条件

動物は温度 $23\pm 3^{\circ}\text{C}$ (実測値：23~24 $^{\circ}\text{C}$)、相対湿度 $50\pm 20\%$ (実測値：44~53%)、換気回数 10~15 回/h、照明 12 時間/日 (07:00~19:00) の動物飼育室 (飼育室番号：906 号室) で飼育した。動物は床敷 (ALPHA-dri、Shepherd Specialty Papers Inc.、ロット番号：05115) を入れたプラスチックケージ (W440×D275×H180 mm：株式会社羽生精密) に、検疫・馴化期間中は同性 2 匹ずつ (なお、雌については入荷匹数が奇数であったため、最後のケージは 3 匹で飼育)、群構成以降は仕切り板を入れて 2 区分とし、それぞれの区画で個別収容した。ただし、交尾成立雌は床敷 (ALPHA-dri、Shepherd Specialty Papers Inc.、ロット番号：05115) を入れたプラスチック製エコネケージ (W340×D400×H185 mm：日本クレア株式会社) に 1 腹単位で収容した。また、動物試験期間中毎週 1 回、エンリッチメントとして、7979C.CS certified/ irradiated

Diamond Twists (Halan Laboratories, Inc.、ロット番号：7979C-040715P)を与えた。

飼料は NMF 固形(放射線滅菌、オリエンタル酵母工業株式会社、ロット番号：150622、150707、150824) をステンレス製給餌器により自由に摂取させた。

飲料水は御殿場市営水道水を自動給水装置（プラスチックケージでの飼育時）又は給水瓶（プラスチック製エコンケージでの飼育時）により自由に摂取させた。

飼料及び床敷中の混入物質の分析に関しては、使用したロットについて Eurofins Food and Product Testing 及び N・P Analytical Laboratories で実施した分析結果を入手した。飲料水については、水道法に準拠した施設全体の水質の分析を定期的（年 4 回）に芝浦セムテック株式会社に依頼して得られたデータを入手した。また、使用したロットについて Diamond Twists の汚染物質に関する分析書を入手した。これらのデータにより飼料、床敷及び飲料水並びにエンリッチメント中の混入物質が試験成績に影響を与える可能性のないことを確認し、分析報告書の写しを保存した。

6.6 動物の識別

動物は番号（雄：493~554、雌：555~637）が刻印された耳標を入荷時に装着し、個体識別を行った。また、検疫・馴化期間中に耳標番号の若い動物の尾に油性インクによる記号を記入し、補助識別とした。群分け後は、1000 の位は群（対照群、低、中及び高用量の順）、100 の位は性別（0 番を雄、1 番を雌）、10 と 1 の位は個体番号を示す 4 桁の動物番号を設定した。各飼育ケージに投与量（群）ごとに色分けしたケージラベルをつけ、試験番号、投与経路、投与量、性別、動物番号、耳標番号、剖検予定日（雄及び非交配群の雌）、交尾成立日（交配群の雌雄）及び分娩日（交配群の雌）を明記した。

6.7 投与経路、投与期間及び投与回数並びに回復期間とそれらの選択理由

投与経路は毒性試験法ガイドラインに準じ、経口投与を選択した。投与期間は、投与日数として、交配群雌雄ともに交配前 14 日、更に、雄については交配開始後 28 日（計 42 日）、雌については交配期間及び妊娠期間を通して授乳 4 日まで（計 41~48 日）とした。非交配群の雌については 42 日とした。回復動物については、42 日の投与期間が終了した後、被験物質投与に起因した変化の可逆性、持続性並びに遅発性毒性等について観察するため、14 日間の回復期間を設けた。投与回数は反復投与試験で一般的に行われている 1 日 1 回とした。

6.8 投与方法

投与方法は、げっ歯類の経口投与に際して一般的な強制経口投与とした。投与容量は 5.0 mL/kg 体重とし、胃ゾンデを用いて投与液を 08:32~11:46 の間に投与した。ただし、投与時に分娩途中であった動物は分娩終了を待って、13:48~14:32 の間に投与した。対照群には媒体のみを同様に投与した。個体ごとの投与液量は、直近の体重を

基準に算出した。

6.9 投与量及び群構成

投与量は 50、150 及び 500 mg/kg の 3 用量とし、試験群はこれらの用量群に媒体を投与する対照群を加え 4 群構成とした。1 群当たりの動物数は交配を行う交配群として各群で雌雄各 12 匹、交配しない非交配群として対照群及び高用量群で雌各 10 匹とした。なお、対照群及び高用量群における雄の群内番号 8 番以降、非交配群雌の群内番号 6 番以降の各 5 匹は、最終投与終了日以降、回復動物とした。群構成を表 1-1. 及び 1-2. に示した。

表 1-1. 群構成（雄）

試験群	投与量 (mg/kg)	被験液 濃度 (mg/mL)	投与 容量 (mL/kg)	交配群			
				投与終了時剖検群		回復終了時剖検群	
				動物数	動物番号	動物数	動物番号
対照群	0	0	5.0	7	1001-1007	5	1008-1012
低用量群	50	10	5.0	12	2001-2012		
中用量群	150	30	5.0	12	3001-3012		
高用量群	500	100	5.0	7	4001-4007	5	4008-4012

表 1-2. 群構成（雌）

試験群	投与量 (mg/kg)	被験液 濃度 (mg/mL)	投与 容量 (mL/kg)	交配群		非交配群			
				投与終了時剖検群		投与終了時剖検群		回復終了時剖検群	
				動物数	動物番号	動物数	動物番号	動物数	動物番号
対照群	0	0	5.0	12	1101-1112	5	5101-5105	5	5106-5110
低用量群	50	10	5.0	12	2101-2112				
中用量群	150	30	5.0	12	3101-3112				
高用量群	500	100	5.0	12	4101-4112	5	6101-6105	5	6106-6110

6.10 投与量の設定根拠

本試験の投与量は、先に実施した「クロトン酸のラットを用いた 14 日間反復経口投与毒性試験（投与量設定試験）、株式会社ボゾリサーチセンター、試験番号：N-R051、投与量：250、500 及び 1000 mg/kg/day」[2]の結果（Attached Data 6）を参考に設定した。投与量設定試験では、いずれの群においても被験物質投与に起因した死亡例はみられなかったが、250 mg/kg の雄で前胃の隆起巣及び腺胃の赤色巣、500 mg/kg の雌雄で血小板数の高値、総タンパク質の低値、前胃の隆起巣及び腺胃の赤色巣、雄で体重増加抑制、雌で白血球数の高値、食道の壁肥厚及び肺の暗赤色巣、1000 mg/kg の雌雄で投与後一過性に腹臥/横臥の症状、体重増加抑制、摂餌量の低値、貧血、網赤血球数、血小板数及び白血球数の高値、総タンパク質の低値、前胃の隆起巣、食道の壁肥厚、胸腺の小型化（雄では胸腺重量の低値）、雄で副腎重量の高値及び腺胃の赤色巣、雌で尿素窒素の低値がみられた。したがって、本試験では投与期間を考慮し、明らかな毒性兆候が予想される 500 mg/kg を高用量とし、以下公比約 3 で除して 150 及

び 50 mg/kg をそれぞれ中及び低用量に設定した。

6.11 観察及び検査の方法

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

6.11.1 一般状態の観察

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

6.11.2 詳細な一般状態の観察、機能検査、握力及び自発運動量の測定

詳細な一般状態の観察は全個体について行った。雄及び非交配群は投与期間中及び回復期間中毎週 1 回、交配群雌は交配前投与期間中毎週 1 回、交配期間中、妊娠期間中及び授乳期間中は指定された日（交尾動物は妊娠 1、7、14 及び 20 日、未交尾動物は交配開始後 6 及び 13 日、分娩動物は授乳 4 日）にそれぞれ行った。

機能検査、握力測定及び自発運動量測定は、各群の 5 匹（雄の群内番号 8~12 番、交配群雌の各群の分娩順で動物番号が若い順^注、非交配群の群内番号 6~10 番）について行った。投与期間中は交配群の雌で授乳 4 日（投与 41~44 日）に、その他は投与期間終了週（投与 6 週、雄：投与 38 日、雌：投与 39 日）に、回復期間中は対照群及び高用量群の雌雄で回復期間終了週（回復 2 週、雄：回復 10 日、雌：回復 11 日）に行った。

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

注：交配群雌の検査対象動物を以下に示した。

試験群	動物番号
対 照 群	1101、1104、1105、1107、1108
低用量群	2101、2102、2103、2107、2109
中用量群	3101、3103、3105、3107、3112
高用量群	4104、4105、4106、4109、4110

1) 詳細な一般状態の観察

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

2) 機能検査

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

3) 握力測定

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

4) 自発運動量の測定

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

6.11.3 体重測定

全個体について、交配群の雄及び非交配群の雌は投与 1、8、15、22、29、36、42 日及び剖検日に、回復動物は更に回復 1、8、14 日及び剖検日に、交配群の雌は投与 1、8、15 及び 22 日、妊娠 0、7、14 及び 20 日、授乳 0 及び 4 日並びに剖検日に体重を測定した。なお、投与後に分娩が終了した母動物の授乳 0 日の体重測定（13:39~17:04 の間）を除き、体重測定は測定日の 07:13~10:21 の間（投与期間中は投与前）に行った。剖検日には、前日から約 16 時間絶食させた後、相対器官重量算出に備えて体重を 07:20~08:23 の間に測定した。また、交尾不成立雌動物については、搬出前に体重を測定したが統計解析からは除外した。

6.11.4 摂餌量測定

全個体について、交配群の雄及び非交配群の雌は投与 2、8、15、30、36 及び 42 日に、回復動物は更に回復 2、8 及び 14 日に、交配群の雌は投与 2、8 及び 15 日、妊娠 1、7、14 及び 20 日並びに授乳 2 及び 4 日に残餌量を測定し、前日の給餌量との差から 1 匹当たりの 1 日摂餌量を算出した。給餌量及び残餌量の測定は測定日の 07:18~10:42 の間（投与期間中は投与前）に行った。

6.11.5 膣垢検査

投与期間中は交配群の雌の全個体について、投与開始日から交尾成立まで毎日（午前）膣垢を採取し、交配前投与期間中の標本について多数の角化上皮細胞から成る膣垢像を発情の指標とし、発情回数及び発情期から次の発情期までの日数（性周期）、

観察雌個体数に対する性周期異常を示した個体数の割合を調べた。交配期間中は腔垢内の精子の有無を調べるのに加え腔垢像を発情前期(P)、発情期(E)、発情後期(M)及び発情休止期(D)に分類したが、データは参考とした。

なお、P→E→M→D (→P) の順序で周期的変化を示し、4 又は 5 日の周期を繰り返す個体を正常、それ以外を性周期異常とした。

6.11.6 交配方法

交配前投与期間終了後、交配群の同投与群内の雌雄を 1:1 で終夜同居させ、翌朝、腔栓形成あるいは腔垢中に精子を確認したものを交尾成立とみなした。交配期間中、交配に際しては雄を金網ケージに移し、同居は雌を雄のケージへ移すことにより行った。交配開始日を 0 日と起算して交尾までに要した日数を求めた。同一雌雄による同居期間は最長 14 日間であった。14 日間の交配で交尾が成立しなかった雌（動物番号 2105、2108、3109）は交配期間終了日を妊娠 0 日と仮定して一般状態の観察、体重及び摂餌量測定並びに投与を継続し、25 日後にイソフルラン麻酔下で採血後、腹大動脈切断により放血致死させ、病理学検査に供した。交尾不成立雌動物については、仮定した妊娠日に基づくデータは統計解析より除外した。

6.11.7 分娩及び哺育観察

1) 母動物の観察

交尾成立雌動物は、妊娠 21 日から妊娠 23 日の午前まで 1 日 2 回（午前・午後、妊娠 23 日は午前に 1 回）、分娩の有無並びにその終了を確認するとともに分娩状態（胎盤の処理及び出産児の状態）を観察した。交尾成立から分娩終了までを妊娠期間とし、妊娠期間を 0.5 日単位で求めた。なお、分娩終了の確認は 17:00 までとした。

分娩が終了した母動物は授乳 4 日まで出生児を哺育させ、児集め、営巣及び授乳を指標として哺育状態を観察し、授乳 5 日に病理学検査に供した。

2) 出生児の観察

生後 0 日に出生児数及び死産児数を数え、合わせて出産児数とした。出産児は口腔内を含む外表異常^{注)}の有無を肉眼的に観察して性別を確認した。出生児は体重を個体別に測定した後、母動物に哺育させた。死産児はブアン液で固定して保存した。

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

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

6.11.8 尿検査及び摂水量測定

投与期間終了週（投与 6 週、投与 36~37 日）及び回復期間終了週（回復 2 週、回復 8~9 日）に検査を実施した。投与期間中は検査当日の投与後に各群の 5 匹（雄の群内番号 8~12 番、非交配群の群内番号 6~10 番）について、回復期間中は回復動物の全個体について、それぞれ採尿器をセットしたケージに収容し、絶食・自由摂水下で 4 時間尿を、次いで自由摂食・自由摂水下でその後の 20 時間尿を採取した。検査項目を表 2 に示した。採取した最初の 4 時間尿について pH 以下沈渣までの検査と尿量を、その後に得られた 20 時間尿について浸透圧、電解質（ナトリウム、カリウム及び塩素）及び尿量の測定を行った。尿量は 4 時間の尿量と 20 時間の尿量を合計して 1 日量を算出した。電解質は 20 時間尿について濃度を測定し、測定濃度と 24 時間の尿量から 1 日当たりの排泄量を算出した。

また、尿検査時には、前日からの 1 日当たりの摂水量を、給水瓶を用いて重量法（1 g = 1 mL とみなした）で測定した。

動物番号 4008 の回復 2 週検査において、初回測定時、ナトリウム及び塩素が測定下限を下回った。測定不良の可能性が考えられたため、同試料（2 倍希釈試料）を用いてナトリウム、カリウム及び塩素の再測定を実施した。その結果、初回値と再現性が認められたため、ナトリウム及び塩素の低値は試料の性質と判断した。標準操作手順書に従い測定下限を下回ったナトリウム及び塩素について原尿による再測定を実施し、再測定値（原尿）を採用した。なお、カリウムは初回測定値を採用した。

表 2.尿検査の項目、測定法及び使用機器など

検査項目	測定方法
pH	マルティスティックス試験紙 [シーメンスヘルスケア・タ [®] イアク [®] ノスティクス株式会社] a)
たん白質	マルティスティックス試験紙 [シーメンスヘルスケア・タ [®] イアク [®] ノスティクス株式会社] a)
ケトン体	マルティスティックス試験紙 [シーメンスヘルスケア・タ [®] イアク [®] ノスティクス株式会社] a)
グルコース	マルティスティックス試験紙 [シーメンスヘルスケア・タ [®] イアク [®] ノスティクス株式会社] a)
潜血	マルティスティックス試験紙 [シーメンスヘルスケア・タ [®] イアク [®] ノスティクス株式会社] a)
ビリルビン	マルティスティックス試験紙 [シーメンスヘルスケア・タ [®] イアク [®] ノスティクス株式会社] a)
ウロビリノーゲン	マルティスティックス試験紙 [シーメンスヘルスケア・タ [®] イアク [®] ノスティクス株式会社] a)
色調	肉眼観察
沈渣	鏡検法
尿量（4 時間量）	目盛付スピッツ管を用いた容量測定（単位：mL）
浸透圧	氷点降下法 ^{b)} （単位：mOsm/kg）
ナトリウム	イオン選択電極法 ^{c)} （単位：mmol/24h）
カリウム	イオン選択電極法 ^{c)} （単位：mmol/24h）
塩素	イオン選択電極法 ^{c)} （単位：mmol/24h）
尿量（20 時間量）	メスシリンダーを用いた容量測定（単位：mL）
摂水量（24 時間量）	重量測定（単位：mL/24h）
使用測定機器	
a)：尿自動分析装置 クリニテック 500 (Siemens Healthcare Diagnostics Inc., Illinois, USA)	
b)：自動浸透圧測定装置 オートアンドスタット OM-6060 (アークレイ株式会社)	
c)：臨床化学自動分析装置 TBA-120FR 形 (東芝メディカルシステムズ株式会社)	

6.11.9 血液学検査

全例について、剖検前日（最終投与日あるいは回復 14 日）から一夜（16~19 時間）絶食させた。そのうちの各群雌雄各 5 匹（動物番号が若い順、ただし、交配群雌は分娩順の 5 匹^注）について、イソフルラン麻酔下に開腹し、腹大動脈から EDTA-2K 加採血瓶（SB-41：シスメックス株式会社）に血液を採取した。得られた血液について、次の表 3.-1)に記載した項目及び方法により検査した。なお、採血した全例について、May-Grünwald-Giemsa 染色法による血液塗抹標本を作製した。また、3.8%クエン酸ナトリウム溶液加試験管（血液 9 容に対し 1 容の割合）に採取した血液を遠心分離（3,000 rpm、1,600×g、10 分間）し、得られた血漿について表 3.-2)に記載の項目及び方法により検査した。交尾不成立雌動物についても採血し同様に検査したが、その成績は統計解析から除外した。

注：交配群雌の検査対象動物を以下に示した。

試験群	動物番号
対 照 群	1101、1104、1105、1107、1108
低用量群	2101、2102、2103、2107、2109
中用量群	3101、3103、3105、3107、3112
高用量群	4104、4105、4106、4109、4110

表 3.血液学検査の項目、測定法及び使用機器など

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

6.11.10 血液化学検査

血液学検査用試料と同時に採取した血液を凝固促進剤入り試験管（ベノジェクト II-オートセップ：テルモ株式会社）に採り、遠心分離（3,000 rpm、1,670×g、10 分間）し、得られた血清について表 4.-1)に記載の項目及び方法により検査した。また、ヘパリン加試験管（血液 1 mL 当たり約 20 単位のヘパリン）に採取した血液を遠心分離（3,000 rpm、1,600×g、10 分間）して得られた血漿について表 4.-2)に記載の項目及び方法により検査した。交尾不成立雌動物についても同様に検査したが、その成績は統計解析から除外した。血清の一部（交尾不成立雌動物を除く）は血中ホルモン測定に備え、約 0.5 mL×3 本をサンプルチューブに分注し、-80℃ の冷凍庫（許容範囲：-70℃ 以下）に保存した。

表 4.血液化学検査の項目、測定法及び使用機器など

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

6.11.11 血中ホルモン測定

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

6.11.12 病理学検査

1) 剖検及び器官重量測定

最終投与翌日及び回復期間終了日に全ての生存動物について、採血した動物は採血後に、その他の動物はイソフルラン麻酔下で、腹大動脈切断により放血致死させ、それぞれ体外表並びに頭部、胸部及び腹部の器官・組織の肉眼検査を行った。交尾不成立雌動物については、採血して放血致死させた後に剖検を行った。なお、母動物については剖検時に黄体数及び着床痕数を数えた。次いで、全例について、以下に示す器官の重量を測定した。それら器官重量（絶対重量）と剖検時の体重から体重 100 g 当たりの相対重量を算出した。なお、*印をつけた両側性の器官については左右別々に測定し、その合計値で評価した。また、交尾不成立雌動物についても同様に器官重量を測定したが、剖検日の体重も含め統計解析の対象から除外した。

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

2) 病理組織学検査

全ての個体について、以下に示す全検査対象器官/組織をリン酸緩衝 10%ホルマリン液で固定し、保存した。固定時に肺にはリン酸緩衝 10%ホルマリン液を注入した。ただし、眼球、視神経はリン酸緩衝液で調製した 3%グルタルアルデヒド・2.5%ホルマリン液で固定後、精巣及び精巣上体はブアン液で固定した後、リン酸緩衝 10%ホルマリン液に置換し保存した。次いで、投与終了時及び回復終了時の計画剖検時に採血を実施した各群雌雄各 5 匹（動物番号が若い順、ただし、交配群雌は分娩順の 5 匹）、並びに交尾不成立雌雄動物についてパラフィン包埋した後、切片とし（下線を施した器官・組織は固定・保存のみとした）、ヘマトキシリン・エオジン（H・E）染色標本作製した。鏡検は、まず投与終了時剖検群における対照群及び高用量群の採血を行った動物、並びに交尾不成立雌雄動物の全検査対象器官/組織について行った。両側性の器官については両側を摘出し、坐骨神経、眼球、副腎、顎下腺、腎臓、乳腺（鼠径部）、大腿骨（骨髓を含む）及び大腿部骨格筋は片側、甲状腺、上皮小体（ただし、一部の動物については片側で評価した）、精巣、卵巢、精巣上体及び精囊（凝固腺含む）は両側並びに子宮は両角部を鏡検した。なお、舌下腺、視神経及び皮膚（鼠径部）については、試験計画書に従い H・E 染色標本作製までとし、病理組織学検査は実施しなかった。その結果、高用量群の胃（雌雄）に被験物質投与による変化が疑われたことから、胃については投与終了時剖検群の低及び中用量群、並びに回復終了時剖検群についても検査を実施した。

大脳、小脳（橋を含む）、坐骨神経、脊髄（胸部）、眼球、視神経、ハーダー腺、下垂体、甲状腺、上皮小体、副腎、胸腺、脾臓、顎下リンパ節、腸間膜リンパ節、心臓、胸大動脈、気管、肺（気管支を含む）、舌、喉頭、食道、胃、十二指腸、

空腸、回腸（パイエル板を含む）、盲腸、結腸、直腸、顎下腺、舌下腺、肝臓、
 脾臓、腎臓、膀胱、精巣、卵巣、精巣上体、子宮、膣、前立腺、精囊（凝固腺を
 含む）、皮膚（鼠径部）、乳腺（鼠径部）、胸骨（骨髄を含む）、大腿骨（骨髄
 を含む）、大腿部骨格筋、個体識別部（耳標を装着した耳介）

6.12 統計解析

6.12.1 パラメータの算出

以下の式により性周期異常率、交尾率、授精率、受胎率及び出産率、生後 0 及び 4 日の性比を群ごとに、妊娠期間、着床前死亡率、着床率、分娩率、外表異常率、出生率、生後 4 日生存率を母動物（腹）ごとに算出した。なお、出生児の体重については母動物ごと雌雄別に平均値を求めた。

性周期異常率(%) = (性周期異常を示した個体数/観察雌個体数) × 100

交尾率(%) = (交尾動物数/同居動物数) × 100

授精率(%) = (雌を妊娠させた雄の数/交尾した雄の数) × 100

受胎率(%) = (妊娠した雌の数/交尾した雌の数) × 100

出産率(%) = (出生児出産雌数/妊娠雌数) × 100

妊娠期間(日) = 妊娠 0 日から分娩した日までの日数

着床前死亡率(%) = [(黄体数-着床痕数)/黄体数] × 100

着床率(%) = (着床痕数/黄体数) × 100

分娩率(%) = (出産児数/着床痕数) × 100

外表異常率(%) = (外表異常児数/出産児数) × 100

出生率(%) = (出生児数/出産児数) × 100

生後 4 日生存率(%) = (生後 4 日の生存児数/出生児数) × 100

生後 0 日（死産児含む）の性比(%) = (雄出産児数/出産児数) × 100

生後 0 日（出生児）の性比(%) = (雄出生児数/出生児数) × 100

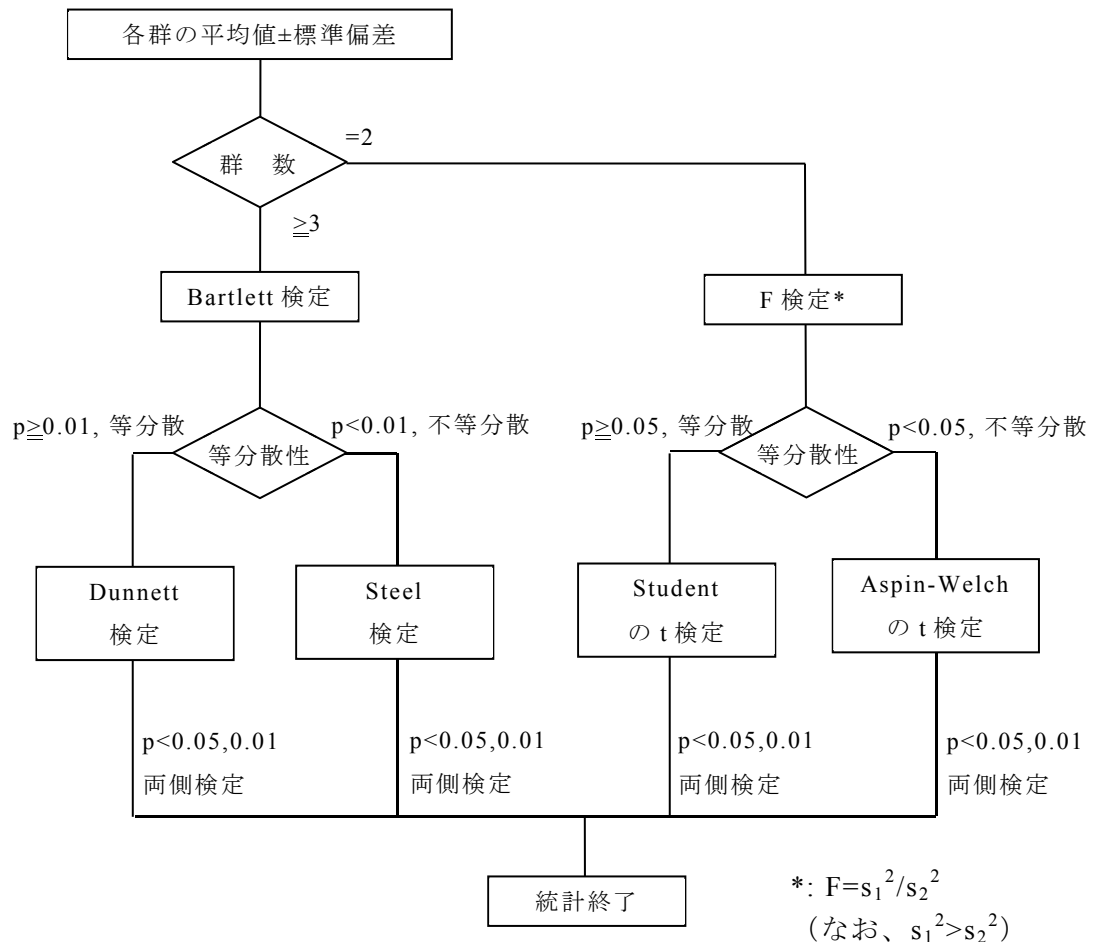
生後 4 日の性比(%) = (生後 4 日の雄生存児数/生後 4 日の生存児数) × 100

6.12.2 検定

対照群と各用量群との差について以下の手法により統計学的有意性の検定を行った。なお、交尾不成立雌は交尾率にのみ含め、交配開始後のデータは統計解析より除外した。解析には SAS Release 9.1.3 (SAS Institute Inc.) を使用した。

体重、体重増加量（雄及び非交配群雌：投与 1~42 日及び回復 1~14 日、交配群雌：投与 1~15 日、妊娠 0~20 日及び授乳 0~4 日、出生児：生後 0~4 日）、摂餌量（総摂餌量含む）、摂水量、発情期像発現回数、性周期（発情周期）、交尾までに要した日数、妊娠期間、黄体数、着床痕数、生存児数、オープンフィールド内観察（排糞数、立ち上がり回数）、機能検査（着地開脚幅）、握力及び自発運動量、尿検査の定量的項目、血液学検査、血液化学検査及び器官重量（含、剖検時体重）は、群ごとに平均値及び

標準偏差を求め、次に示す模式図の方法に従って検定した[3] [4] [5]。



着床前死亡率、着床率、分娩率、外表異常率、出生率及び生後4日生存率並びに空中正向反射スコアについては、母動物ごとに率を求めた後、群ごとに平均値及び標準偏差を求め、Wilcoxonの順位和検定（有意水準0.05及び0.01、両側）を行った[6]。

性周期異常率、交尾率、授精率、受胎率及び出産率、性比（生後0及び4日）並びに聴覚反応、接近反応、接触反応、痛覚反応及び瞳孔反射の各反応・反射スコアは、各群の性周期異常を示した個体数、交尾動物数、雌を妊娠させた雄動物数、妊娠雌動物数、出生児出産雌動物数、雌雄児数、正常反応・反射のみられた動物数より算出し、Fisherの直接確率計算法により検定（有意水準0.05及び0.01、両側）を行った[7]。

7. 試験結果

7.1 一般状態 (Table 1-1~1-11、Appendix 1-1~1-34)

いずれの投与群においても死亡動物はみられなかった。

1) 投与期間

雄及び非交配群雌では、いずれの動物にも異常はみられなかった。

交配群雌では、500 mg/kg 群の 1 例で投与 12~15 日に喘鳴がみられたが、1 例のみの一過性の変化であり、雄及び非交配群雌にはみられないことから、被験物質投与との関連はないと判断した。その他にはいずれの動物にも哺育状態を含め異常はみられなかった。

2) 回復期間

500 mg/kg 群の雄 1 例で回復 8~13 日に喘鳴がみられたが、1 例のみの一過性の変化であり、投与期間中の雄にはみられていないことから、被験物質投与との関連はないと判断した。その他にはいずれの動物にも異常はみられなかった。

7.2 詳細な一般状態の観察、機能検査、握力測定及び自発運動量の測定 (Fig. 1~5、Table 2-1~2-171、Appendix 2-1~2-344)

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

1) 投与期間

いずれの動物にも異常はみられなかった。

2) 回復期間

いずれの動物にも異常はみられなかった。

7.2.2 手に持った観察 (Table 2-24~2-82、Appendix 2-73~2-144)

1) 投与期間

いずれの動物にも妊娠中及び授乳中を含め、被験物質投与に関連すると考えられる異常はみられなかった。

2) 回復期間

500 mg/kg 群の雄 1 例で回復 2 週に異常呼吸（継続的な喘鳴）がみられたが、本例は一般状態で喘鳴がみられた個体であり、同様に被験物質投与との関連はないと判断した。その他、いずれの動物にも被験物質投与に関連すると考えられる異常はみられなかった。

7.2.3 オープンフィールド内観察 (Table 2-83~2-151、Appendix 2-145~2-288)

1) 投与期間

いずれの動物にも妊娠中及び授乳中を含め、被験物質投与に関連すると考えられる異常はみられなかった。雄及び交配群雌では、立ち上がり回数及び排糞の個数には対

照群と各被験物質投与群との間に有意差は認められなかった。なお、非交配群雌の 500 mg/kg 群で、投与 4 週の立ち上がり回数に対照群と比べ有意な低値が認められたが、1 時点のみの変化であり、対照群がわずかに増加したことによる相対的な低値と考えられ、偶発的な変化と判断した。

2) 回復期間

いずれの動物にも被験物質投与に関連すると考えられる異常はみられず、立ち上がり回数及び排糞の個数には 500 mg/kg 群の雌雄とも対照群との間に有意差は認められなかった。

7.2.4 機能検査 (Table 2-152~2-161、Appendix 2-289~2-316)

1) 投与期間終了週検査

いずれの動物にも聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射及び空中正向反射に異常はみられず、着地開脚幅には対照群と各被験物質投与群との間に有意差は認められなかった。

2) 回復期間終了週検査

いずれの動物にも聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射及び空中正向反射に異常はみられず、着地開脚幅には 500 mg/kg 群の雌雄とも対照群との間に有意差は認められなかった。

7.2.5 握力 (Table 2-162~2-166、Appendix 2-317~2-330)

1) 投与期間終了週測定

いずれの投与群にも被験物質投与に関連すると考えられる変化はみられなかった。なお、交配群雌の 50 mg/kg 群で対照群と比べ後肢の握力に有意な低値が認められたが、用量に関連しない変化であった。

2) 回復期間終了週測定

500 mg/kg 群の雌雄とも対照群との間に有意差は認められなかった。

7.2.6 自発運動量 (Fig. 1~5、Table 2-167~2-171、Appendix 2-331~2-344)

1) 投与期間終了週測定

いずれの投与群にも被験物質投与に関連すると考えられる変化はみられなかった。

なお、雄の 150 mg/kg 群で 30-40 分の間の運動量及び 0-60 分の間の総運動量に対照群と比べ有意な高値が認められたが、用量に関連しない変化であった。交配群雌の 500 mg/kg で 0-10 分の間の運動量に対照群と比べ有意な低値が認められたが、一過性の変動であり、0-60 分の間の総運動量には異常はみられず、雄及び非交配群雌に同様の変化はみられないことから、偶発的な変動と判断した。

2) 回復期間終了週測定

500 mg/kg 群の雄で 30-40 分の間の運動量に対照群と比べ有意な高値が認められた

が、一過性の変動であり、0-60 分の間の総運動量には異常はみられず、雌に同様の変化はみられないことから、偶発的な変動と判断した。

7.3 体重 (Fig. 6~12、Table 3-1~3-7、Appendix 3-1~3-22)

1) 投与期間

雄では、500 mg/kg 群で投与 42 日に対照群と比べ有意な低値が認められ、投与期間中の増加量も有意な低値を示した。

交配群雌では、500 mg/kg 群で妊娠 14 及び 20 日並びに授乳 0 及び 4 日に対照群と比べ有意な低値が認められた。

非交配群雌では、500 mg/kg 群と対照群との間に有意差は認められなかった。

2) 回復期間

500 mg/kg 群の雌雄とも対照群との間に有意差は認められなかった。

7.4 摂餌量 (Fig. 13~19、Table 4-1~4-7、Appendix 4-1~4-22)

1) 投与期間

雄では、各被験物質投与群ともに投与期間を通じて対照群と有意差は認められなかった。

交配群雌では、500 mg/kg 群で妊娠 7 日に対照群と比べ有意な低値が認められ、妊娠期間中の総摂餌量も有意な低値を示した。

非交配群雌では、500 mg/kg 群で投与 15 日に対照群と比べ有意な高値が認められたが、1 時点のみの変化であり、対照群値が低下したことによる相対的な高値と考えられ、偶発的な変化と判断した。

2) 回復期間

500 mg/kg 群の雌雄とも対照群との間に有意差は認められなかった。

7.5 尿検査 (摂水量測定を含む) (Table 5-1~5-24、Appendix 5-1~5-30)

1) 投与期間終了週検査

定性項目については、500 mg/kg 群の雄で尿 pH に低下傾向がみられた。なお、非交配群雌では異常はみられなかった。

定量項目については、いずれの検査項目においても被験物質投与群と対照群との間に有意差は認められなかった。

2) 回復期間終了週検査

定性項目については、いずれの動物にも異常はみられなかった。

定量項目については、いずれの検査項目においても 500 mg/kg 群の雌雄とも対照群との間に有意差は認められなかった。

7.6 血液学検査 (Table 6-1~6-7、Appendix 6-1~6-16)

1) 投与期間終了時検査

雄及び交配群雌では、いずれの検査項目においても各被験物質投与群と対照群との間に有意差は認められなかった。

非交配群雌では、500 mg/kg 群で対照群と比べ赤血球数に有意な高値、平均赤血球血色素量及び平均赤血球血色素濃度に有意な低値、血小板数に有意な高値が認められた。

2) 回復期間終了時検査

いずれの検査項目においても 500 mg/kg 群の雌雄とも対照群との間に有意差は認められなかった。

7.7 血液化学検査 (Table 7-1~7-7、Appendix 7-1~7-16)

1) 投与期間終了時検査

雄では、500 mg/kg 群で総タンパク質及びアルブミンに対照群と比べ有意な低値が認められた。なお、150 mg/kg 群で対照群と比べカリウムに有意な低値が認められたが、用量に関連しない変化であった。

交配群雌では、500 mg/kg 群でクレアチニンに対照群と比べ有意な低値が認められた。

非交配群雌では、500 mg/kg 群で総コレステロールに対照群と比べ有意な低値が認められた。

2) 回復期間終了時検査

いずれの検査項目においても 500 mg/kg 群の雌雄とも対照群との間に有意差は認められなかった。

7.8 器官重量 (Table 8-1~8-7、Appendix 8-1~8-32)

1) 投与期間終了時検査

雄では、500 mg/kg 群で対照群と比べ剖検時体重に有意な低値、脳の相対重量に有意な高値、心臓の絶対重量に有意な低値が認められ、交配群雌では、500 mg/kg 群で対照群と比べ剖検時体重に有意な低値、肝臓の絶対重量に有意な低値が認められたが、いずれも絶対あるいは相対重量のみの変化であり、剖検時体重の低値に伴う二次的な変化と考えられるため、毒性学的意義はないと判断した。

非交配群雌では、500 mg/kg 群で対照群と比べ脳及び卵巣の相対重量に有意な高値が認められたが、いずれも相対重量のみの変化であり、剖検時体重が対照群を下回ったことによる二次的な変化と考えられるため、毒性学的意義はないと判断した。

2) 回復期間終了時検査

500 mg/kg 群の雄では、対照群と比べ精巣上体の絶対及び相対重量に有意な低値、精囊の相対重量に有意な低値が認められた。

500 mg/kg 群の雌では、心臓の絶対及び相対重量に対照群と比べ有意な高値が認め

られたが、投与終了時検査には異常はみられず、いずれも試験施設の群平均値の背景データ（絶対重量：0.91±0.18、相対重量：0.32±0.04、Mean±2S.D.、38 試験、2010/04-2015/03）に収まる正常範囲内の変動であることから、毒性学的な意義は低いと考えられた。

7.9 剖検所見（Table 9-1~9-6、Appendix 9-1~9-116）

1) 投与期間終了時検査

交配群においては、被験物質投与によると考えられる変化として、前胃の壁肥厚が 500 mg/kg 群の雌雄に、前胃の隆起巣が 500 mg/kg 群の雌にみられた。その他の諸変化は発現状況から被験物質投与に関連しない変化と考えられた。また、交尾不成立であった 50 mg/kg 群の 2 例及び 150 mg/kg 群の 1 例では肉眼的異常はみられなかった。

非交配群においては、被験物質投与によると考えられる変化はみられなかった。

2) 回復期間終了時検査

投与終了時にみられた前胃における所見は 500 mg/kg 群のいずれの動物においてもみられなかった。なお、雄の 500 mg/kg 群で胸腺及び精囊の小型化が 1 例にみられた。他に被験物質投与に関連すると考えられる変化はみられなかった。

7.10 病理組織学検査（Table 10-1~10-14、Appendix 9-1~9-116）

1) 投与期間終了時検査

胃に被験物質投与によると考えられる変化がみられた。

交配群においては、前胃の扁平上皮細胞の過形成が 150 mg/kg 群の雄及び 500 mg/kg 群の雌雄にみられた。同変化は非交配群雌の 500 mg/kg 群にもみられた。

2) 交尾不成立動物

被験物質投与によると考えられる変化として、前胃の扁平上皮の過形成が 150 mg/kg 投与群の雌 1 例にみられた。なお、交尾不成立雌動物及び交配相手（雄）においては、交尾不成立の原因を示唆する組織学的変化はみられなかった。

3) 回復期間終了時検査

前胃の扁平上皮細胞の過形成が、500 mg/kg 群の雌雄で残存してみられた。

その他、諸臓器に組織学的変化がみられたが、その病理学的性状又は発現状況から被験物質投与に関連しない偶発的变化と考えられた。

7.11 性周期（Table 11、Appendix 10-1~10-8）

50、150 及び 500 mg/kg 群で各 2、2 及び 1 例に性周期異常がみられたが、性周期異常率、発情期像発現回数及び性周期（発情周期）には対照群と各被験物質投与群との間に有意差は認められなかった。

7.12 交配成績 (Table 12-1 及び 12-2、Appendix 11-1~11-8)

交尾不成立であった 50 及び 150 mg/kg の各 2 及び 1 例を除き、交配 7 日までに全例の交尾が成立し、交尾までに要した日数、交尾率及び受胎率には対照群と各被験物質投与群との間に有意差は認められなかった。

7.13 分娩成績 (Table 13、14-1、Appendix 12-1~12-4、13-1~13-4) 並びに分娩及び哺育状態 (Table 1-5 及び 1-6、Appendix 1-17~1-24)

妊娠期間、出産率、黄体数、着床痕数、着床前死亡率、着床率、分娩率、出生率、出産児数、出生児数、死産児数及び生後 0 日の性比 (出産児あるいは出生児) 並びに外表異常率には対照群と各被験物質投与群との間に有意差は認められなかった。

妊娠動物の分娩状態では妊娠 21 から 23 日に全例が分娩し、胎盤及び羊膜の処理は正常に行われた。哺育状態では、いずれの母動物にも児集め、営巣及び授乳行動に異常はみられなかった。

7.14 出生児の生存性及び性比 (Table 15、Appendix 14-1~14-4)

生後 4 日の生存率及び性比には対照群と各被験物質投与群との間に有意差は認められなかった。

7.15 出生児の体重 (Table 16-1 及び 16-2、Appendix 15-1~15-8)

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

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

いずれの死亡児にも肉眼的異常はみられなかった。

7.17 出生児の生後 4 日肉眼観察所見 (Table 14-2、Appendix 13-5~13-8)

いずれの出生児にも肉眼的異常はみられなかった。

8. 考察

クロトン酸の 0（対照群：コーン油）、50、150 及び 500 mg/kg を Sprague-Dawley 系 SPF ラットの雄には交配前 14 日間に加え交配期間を通して剖検前日まで（42 日間）、雌には交配前 14 日間に加え交配期間及び妊娠期間を通して授乳 4 日まで（41~48 日間）、非交配群雌には 42 日間強制経口投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0 及び 500 mg/kg 群の一部の動物については、雌雄ともに 42 日間投与した後 14 日間の回復期間を設け、毒性変化の可逆性を検討した。

8.1 反復投与毒性

いずれの投与群においても死亡動物はみられず、一般状態、詳細な一般状態、機能検査、握力、自発運動量には被験物質投与の影響は認められなかった。

体重及び摂餌量では、500 mg/kg 群の雄で投与期間中に体重増加抑制が認められ、被験物質投与による変化と考えられたが、摂餌量の変動を伴っていないことから、軽度な影響と考えられた。なお、回復期間中の体重及び摂餌量には対照群と明らかな差はみられず、可逆的な変化と考えられた。同用量の交配群雌で摂餌量の低下を伴った体重増加抑制が妊娠及び授乳期間中にみられた。非交配群雌では、体重及び摂餌量に被験物質投与の影響は認められなかった。

尿検査では、500 mg/kg 群の雄で尿 pH に低下傾向がみられたが、血液化学検査及び病理組織学検査に関連する変化はみられないことから、毒性学的意義はないと判断した。

血液学検査では、非交配群雌の 500 mg/kg 群で赤血球数の高値、平均赤血球血色素量及び平均赤血球血色素濃度の低値、血小板数の高値が認められ、被験物質投与による影響と考えられた。しかし、造血系の器官に病理組織学的な異常はみられないことから、その作用機序は明確にすることはできなかった。

血液化学検査では、500 mg/kg 群の雄で総タンパク質及びアルブミンに低値、交配群雌でクレアチニンに低値、非交配群雌で総コレステロールに低値が認められ、被験物質投与による影響と考えられた。しかし、肝臓あるいは腎臓に病理組織学的な異常はみられないことから、その作用機序は明確にすることはできなかった。

器官重量では、回復終了時に 500 mg/kg 群の雄で精巣上体と精囊の重量に低値が認められたが、投与終了時検査では精巣上体及び精囊の重量とそれらの病理組織に異常は認められず、また、同群の生殖機能に関するパラメータに被験物質投与の影響は認められないことから、重量低下の毒性学的な意義は低いと考えられた。

剖検及び病理組織学検査では、交配群で肉眼的に前胃の壁肥厚が 500 mg/kg 群の雌雄に、前胃の隆起巣が 500 mg/kg 群の雌にみられ、組織学的に前胃の扁平上皮細胞の過形成が交配群では 150 mg/kg 群の雄及び 500 mg/kg 群の雌雄でみられ、さらに非交配群雌の 500 mg/kg 群においてもみられた。クロトン酸は皮膚腐食性/刺激性を有し[8]、同様の変化は、刺激作用を有する化学物質が経口投与された場合、ラットの前胃にそ

の刺激に対する反応性変化としてみられることから[9]、本試験でみられた変化は経口投与による被験物質の直接的な刺激作用によって発生したものと考えられた。また、一部の動物で回復期間を設け、被験物質に起因した胃の変化の可逆性について検討した結果、回復群を設けた雄及び非交配群雌とも発現頻度及び程度の減弱がみられ、回復性が認められた。回復期間終了時に 500 mg/kg 群で雄 1 例に胸腺及び精嚢の小型化がみられたが、本例は喘鳴がみられ、著しい摂餌量の低下を伴った体重減少を示した個体であり、二次的な変化と推察され、被験物質投与との関連はないと判断した。

8.2 生殖発生毒性

500 mg/kg 群においても生殖機能に関するパラメータに被験物質投与の影響は認められないことから、雌雄動物の交尾能、授精能及び受胎能、母動物の妊娠維持、分娩及び哺育行動などへの影響はないと判断した。

500 mg/kg 群においても、出生児のいずれの検査項目にも被験物質投与による影響は認められないことから、児の子宮内発生、発育及び分化並びに生存性などへの影響はないと判断した。

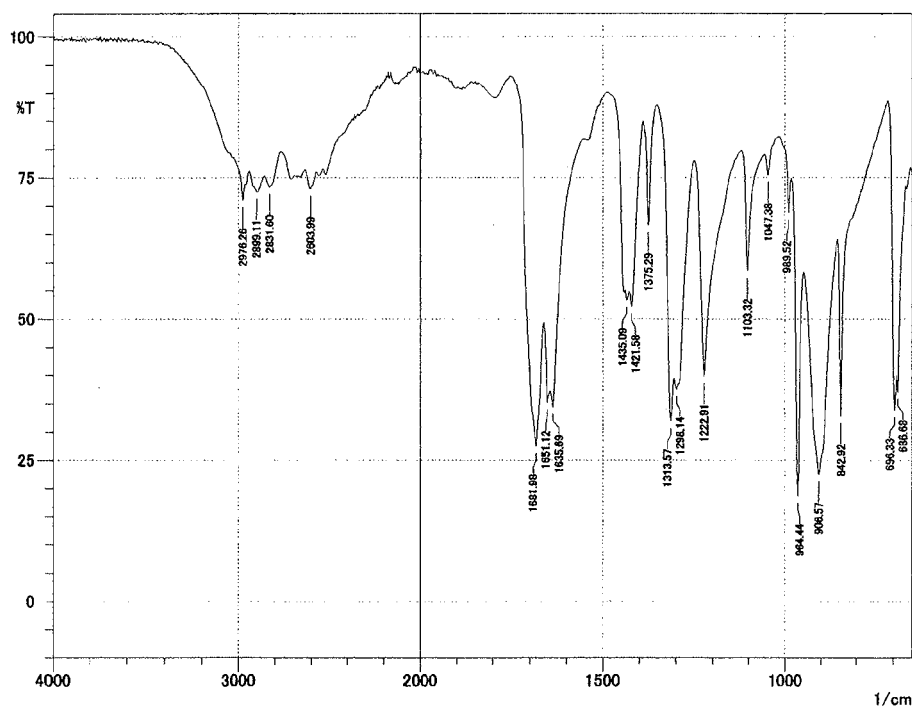
これらの結果から、本試験条件下でクロトン酸を反復経口投与することにより、被験物質に起因すると考えられる主な変化として雄の 500 mg/kg 群で体重増加抑制、総タンパク質及びアルブミンの低値、前胃の壁肥厚、150 mg/kg 以上の群で胃の扁平上皮細胞の過形成が、交配群雌の 500 mg/kg 群で摂餌量の低下を伴った体重増加抑制、クレアチニンの低値、前胃の壁肥厚及び隆起巣、胃の扁平上皮細胞の過形成が、非交配群雌の 500 mg/kg 群で赤血球数の高値、平均赤血球血色素量及び平均赤血球血色素濃度の低値、血小板数の高値、総コレステロールの低値、胃の扁平上皮細胞の過形成がみられた。したがって、本被験物質の反復投与毒性に対する雄での無影響量及び無毒性量は 50 mg/kg であり、雌ではいずれも 150 mg/kg と判断した。生殖発生毒性に対する無影響量及び無毒性量は雄親動物、母動物及び児動物でいずれも 500 mg/kg と判断した。

9. 文献

- [1] ■■■■■ : クロトン酸の IR を用いた特性試験及び安定性試験並びに GC を用いた被験液（媒体：コーン油）中濃度測定法バリデーション及び安定性・均一性試験（株式会社ボゾリサーチセンター 御殿場研究所、試験番号：A-2765、2015 年）
- [2] ■■■■■ : クロトン酸のラットを用いた 14 日間反復経口投与毒性試験（投与量設定試験）（株式会社ボゾリサーチセンター、試験番号：N-R051、2015 年）
- [3] Snedecor GW, Cochran WG. Statistical methods. 8th ed. Ames: Iowa State University Press; 1989.
- [4] Dunnett, CW. New tables for multiple comparisons with a control. Biometrics 20: 482-91. 1964.
- [5] Steel RGD. A multiple comparison rank sum test: Treatments versus control. Biometrics 15: 560-72. 1959.
- [6] Siegel S, Castellan NJ. Jr. Nonparametric statistics for the behavioral sciences. 2nd ed. New York: McGraw-Hill; 1988.
- [7] 佐久間昭（1981）：薬効評価－計画と分析－II, pp.23-27, 387-389, 東京大学出版会, 東京.
- [8] クロトン酸（CAS 番号 107-93-7）. 化学物質等安全データシート, 東京化成工業株式会社, 2013
- [9] 伊東信行発行、各論 4 章 消化管、毒性病理組織学、日本毒性病理学会編集、p 160、2000.

試験成績書
(クロトン酸の特性)

ステージ : 初期値
測定日 : 2015 年 9 月 3 日
被験物質 : クロトン酸
(ロット番号：MXJGG)
測定項目 : 赤外吸収スペクトル [全反射測定法 (ATR 法)]
結果 : 特性のスペクトルを以下に示す。



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

2015 年 9 月 10 日

試験責任者
株式会社ボゾリサーチセンター 御殿場研究所

試験成績書
(被験物質の安定性)

ステージ : 投与期間終了後

測定日 : 2015 年 12 月 16 日
2015 年 9 月 3 日 (特性のスペクトル)

被験物質 : クロトン酸
(ロット番号：MXJGG)

測定項目 : 赤外吸収スペクトル {全反射測定法 (ATR 法) }

判定基準 : 安定性のスペクトルを特性のスペクトル¹⁾と比較する
とき、同一波長のところに同様の強度の吸収を認める。

1) [REDACTED] クロトン酸の IR を用いた特性試験及び安定性試験並びに GC を用いた被験液 (媒体：コーン油) 中濃度測定法バリデーション及び安定性・均一性試験 (株式会社ボゾリサーチセンター 御殿場研究所、試験番号：A-2765)

結果 : 安定性のスペクトルを特性のスペクトルと比較したとき、同一波長のところに同様の強度の吸収を認めた。赤外吸収スペクトルは次のページに示す。

判定 : 適

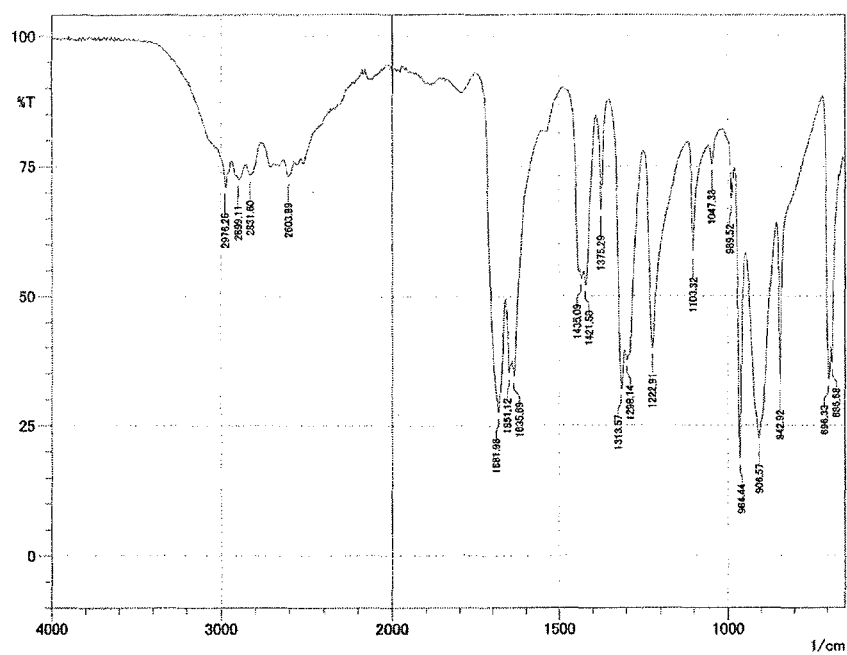
基準 : 「新規化学物質等に係る試験を実施する試験施設に関する基準」 (平成 23 年 3 月 31 日：薬食発 0331 第 8 号、平成 23・03・29 製局第 6 号、環企発第 110331010 号)

[REDACTED] 2016 年 1 月 4 日

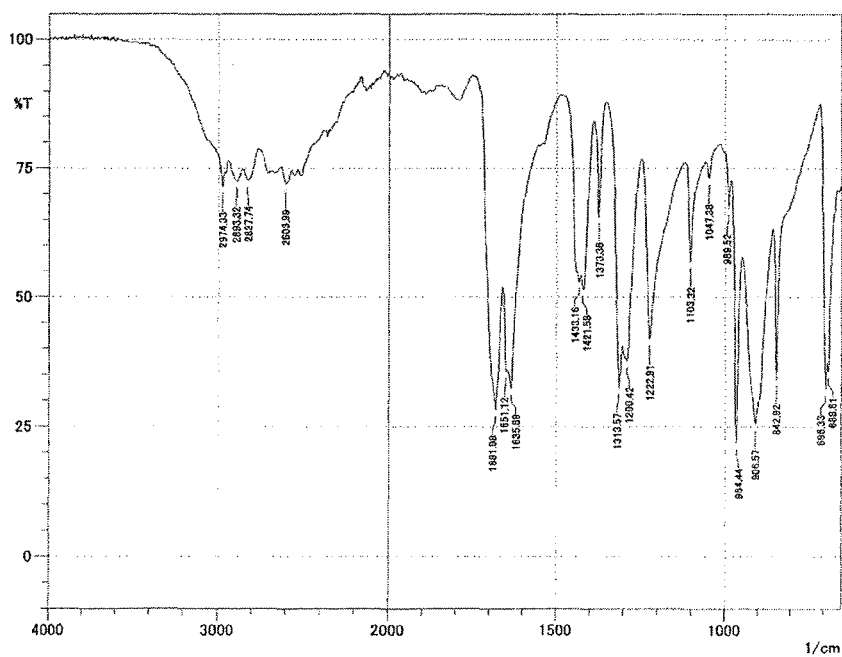
化学分析責任者
株式会社ボゾリサーチセンター 御殿場研究所

結果 : 赤外吸収スペクトル

(特性のスペクトル)



(安定性のスペクトル)



試験成績書
(被験液中クロトン酸の安定性・均一性)

被験物質 : クロトン酸
(ロット番号 : MXJGG)

媒体 : コーン油

形態 : 懸濁液

測定対象物質 : クロトン酸

保存条件 : 褐色ガラス瓶に入れ、冷所(冷蔵庫内、許容値:1~10℃)
及び室温にて保存

保存期間 : 冷所で8日間保存した後、室温で24時間保存

評価基準

安定性 : 残存率{調製日の測定濃度の平均値(100)に対する
保存後の測定濃度の平均値の割合}が100.0±10.0%以
内。

均一性 : 変動係数が10.0%以下。

結果 : 次ページに記載

判定 : 適

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

2015 年 10 月 6 日

試験責任者
株式会社ボゾリサーチセンター 御殿場研究所

試験成績書
(被験液中クロトン酸の安定性・均一性)

結果：

調製濃度 (mg/mL)	採取層	測定濃度 (mg/mL)	
		調製日	保存後
1.00	上層	1.02	1.01
	中層	1.01	1.01
	下層	0.997	0.980
	平均値	1.01	1.00
	標準偏差	0.01	0.02
	残存率 (%)	100	99.0
	変動係数 (%)	1.0	2.0
200	上層	203	198
	中層	197	197
	下層	200	192
	平均値	200	196
	標準偏差	3	3
	残存率 (%)	100	98.0
	変動係数 (%)	1.5	1.5

分析結果

試験番号 : R-1169
測定項目 : 濃度・均一性
ステージ : 初回投与
測定開始日 : 2015 年 10 月 8 日

測定試料

被験物質 : クロトン酸
(ロット番号 ; MXJGG)
形態 : 懸濁液
媒体 : コーン油
調製日 : 2015 年 10 月 8 日

測定対象物質 : クロトン酸

評価基準

濃度 : 表示値に対する割合 ; 100.0±10.0%
均一性 : 変動係数 (CV) ; 10.0%以下

結果 :

表示値 (mg/mL)	採取層	測定濃度 (mg/mL)	平均値±標準偏差	表示値に 対する割合 (%)	CV (%)
10	上層	9.45	9.59±0.13	95.9	1.4
	中層	9.71			
	下層	9.60			
30	上層	29.6	29.5±0.1	98.3	0.3
	中層	29.5			
	下層	29.5			
100	上層	100	101±1	101.0	1.0
	中層	102			
	下層	99.7			

判定 : 適

R-1169
Attached Data 5

分析結果

試験番号 : R-1169
測定項目 : 濃度・均一性
ステージ : 投与 6 週
測定開始日 : 2015 年 11 月 12 日

測定試料

被験物質 : クロトン酸
(ロット番号 ; MXJGG)
形態 : 懸濁液
媒体 : コーン油
調製日 : 2015 年 11 月 12 日

測定対象物質 : クロトン酸

評価基準

濃度 : 表示値に対する割合 ; $100.0 \pm 10.0\%$
均一性 : 変動係数 (CV) ; 10.0%以下

結果 :

表示値 (mg/mL)	採取層	測定濃度 (mg/mL)	平均値±標準偏差	表示値に 対する割合 (%)	CV (%)
10	上層	9.63	9.73±0.16	97.3	1.6
	中層	9.64			
	下層	9.92			
30	上層	29.5	29.6±0.3	98.7	1.0
	中層	30.0			
	下層	29.4			
100	上層	97.2	98.2±1.6	98.2	1.6
	中層	97.3			
	下層	100			

判定 : 適

クロトン酸のラットを用いた
14日間反復経口投与毒性試験（投与量設定試験）における所見

試験番号：N-R051

被験物質		媒体 ^{a)}	クロトン酸		
投与量(mg/kg)		0	250	500	1000
投与容量(mL/kg)		5	5	5	5
使用動物数 (♂/♀)		5/5	5/5	5/5	5/5
死亡動物数 (♂/♀)		0/0	0/0	0/0	0/1
死亡発現時期		—	—	—	投与 13 日 ^{b)}
一般 状態	生存	—	—	—	腹臥/横臥
	死亡				腹臥/横臥
体重	投与 7 日		—	↓(♂)	↓↓(♂), ↓(♀)
	投与 10 日		—	↓(♂)	↓↓(♂), ↓(♀)
	投与 14 日		—	↓(♂)	↓↓(♂), ↓(♀)
増加量	投与 1-14 日		—	↓(♂)	↓↓(♂), ↓(♀)
摂餌量	投与 4 日		—	—	↓↓(♂), ↓(♀)
	投与 7 日		—	—	↓↓(♂), ↓↓(♀)
	投与 10 日		—	—	↓↓(♂), ↓(♀)
	投与 14 日		—	—	↓↓(♂)
血液学 検査	赤血球数		—	—	↓(♂), ↓(♀)
	ヘモグロビン量		—	—	↓↓(♂), ↓(♀)
	ヘマトクリット値		—	—	↓↓(♂), ↓(♀)
	網赤血球数		—	—	↑(♂), ↑↑(♀)
	血小板数		—	↑↑(♂), ↑(♀)	↑↑(♂), ↑↑(♀)
	白血球数		—	↑(♀)	↑↑(♂), ↑(♀)
血液化学 検査	総タンパク質		—	↓↓(♂), ↓↓(♀)	↓↓(♂), ↓↓(♀)
	尿素窒素		—	—	↓↓(♀)
器官 重量	胸腺	絶対	—	—	↓↓(♂)
		相対	—	—	↓(♂)
	副腎	絶対	—	—	↑(♂)
		相対	—	—	↑↑(♂)
剖検	生存(♂)	—	前胃隆起巣, 腺胃赤色巣	前胃隆起巣, 腺胃赤色巣	食道壁肥厚, 前胃隆起巣, 腺胃赤色巣, 胸腺小型化
	生存(♀)	—		食道壁肥厚, 前胃隆起巣, 腺胃赤色巣, 肺暗赤色巣	食道壁肥厚, 前胃隆起巣, 胸腺小型化
	死亡				食道穿孔, 肺暗調化, 胸水貯留, 前胃隆起巣, 食道壁肥厚

a) : コーン油

b) : 投与過誤による死亡

— : 著変なし, / : データなし又は判別不明あるいは検定不能

↑又は↓; p<0.05, ↑↑又は↓↓; p<0.01, (対照群との間に有意差あり)

↑: 高値傾向, ↓: 低値傾向

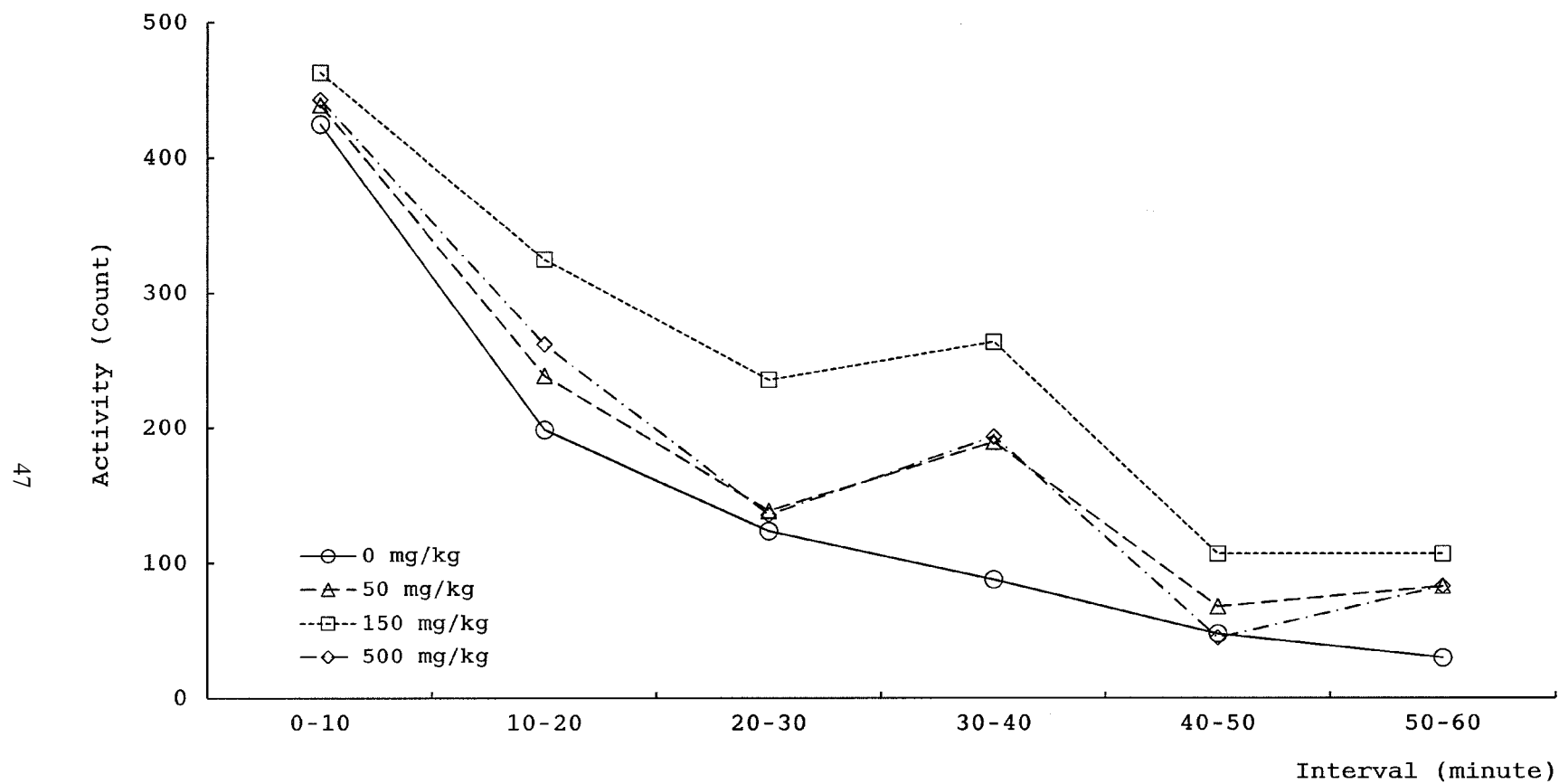


Fig.1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Motor activity of male rats (Week 6 of administration)

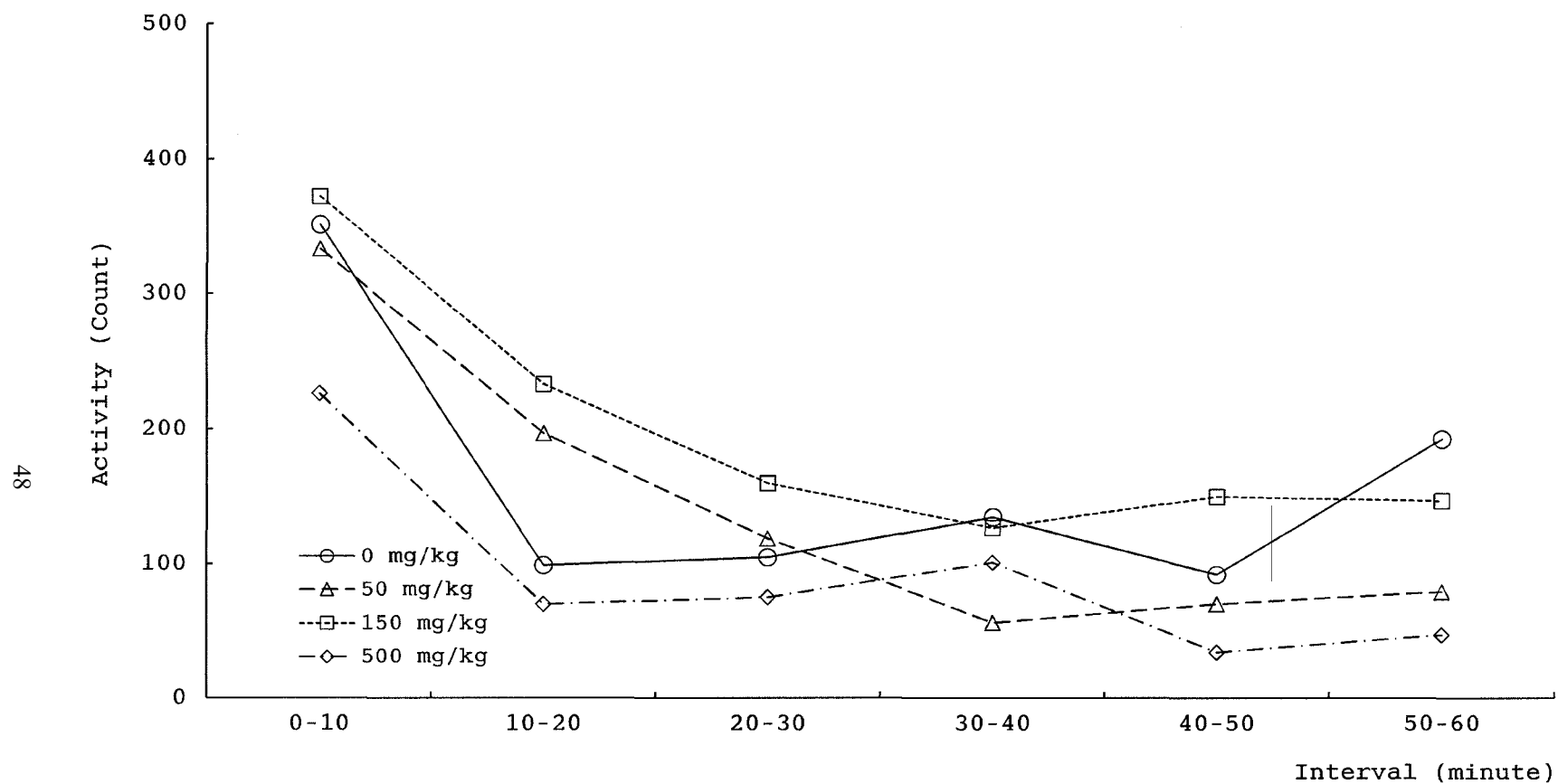


Fig.2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Motor activity of female rats (Lactation day 4)

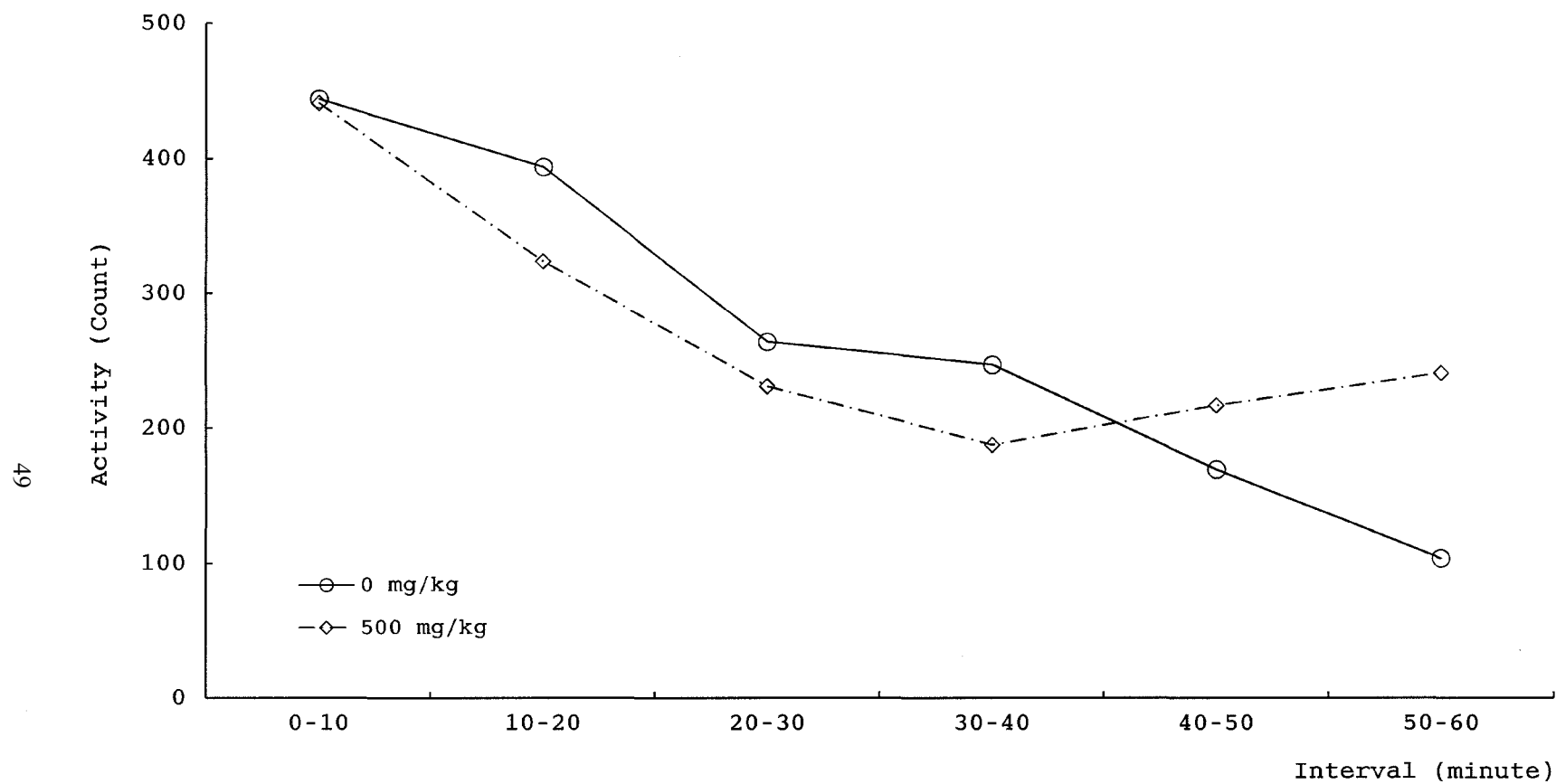


Fig.3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Motor activity of female rats (Week 6 of administration)

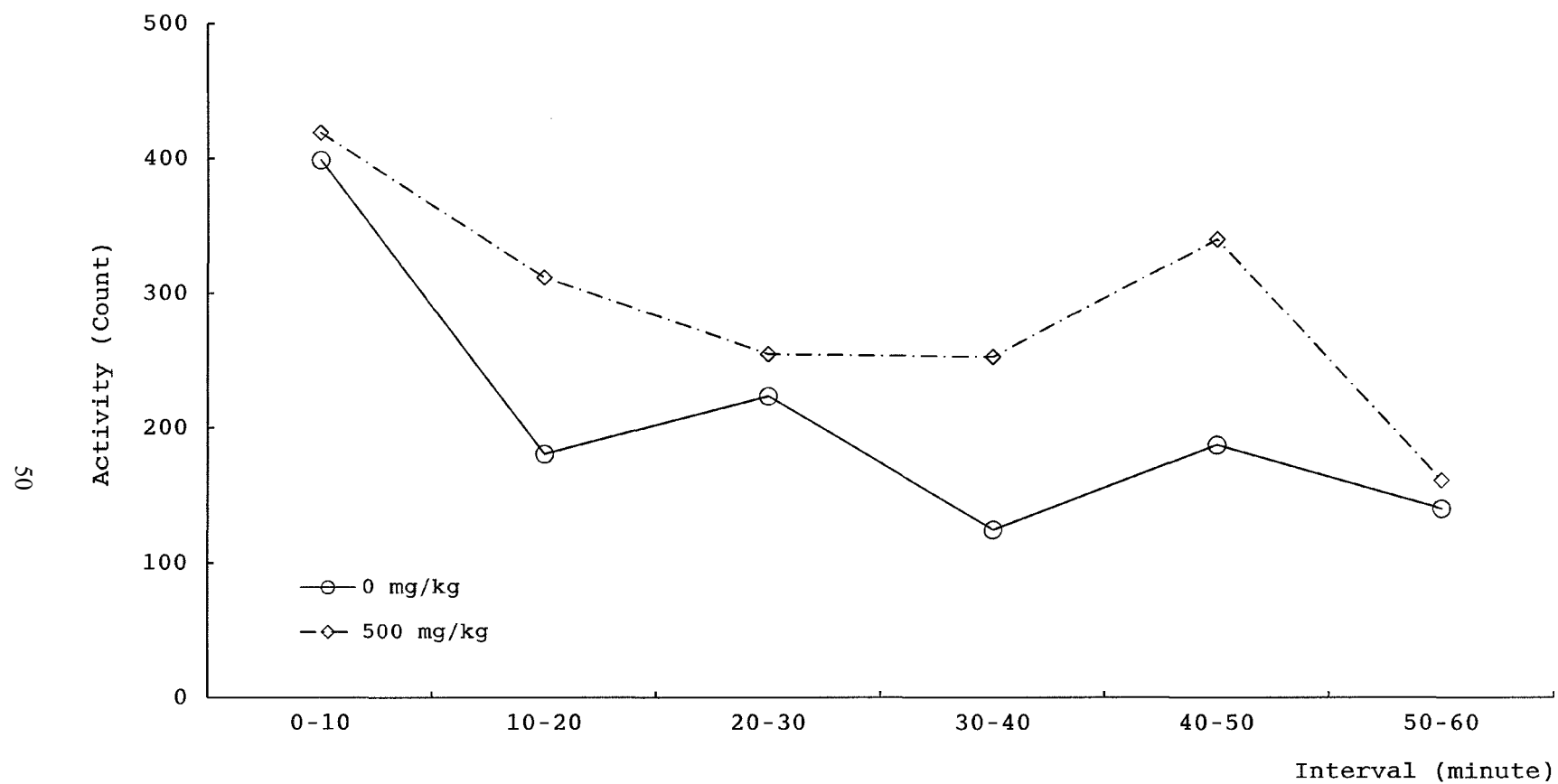


Fig.4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Motor activity of male rats (Week 2 of recovery)

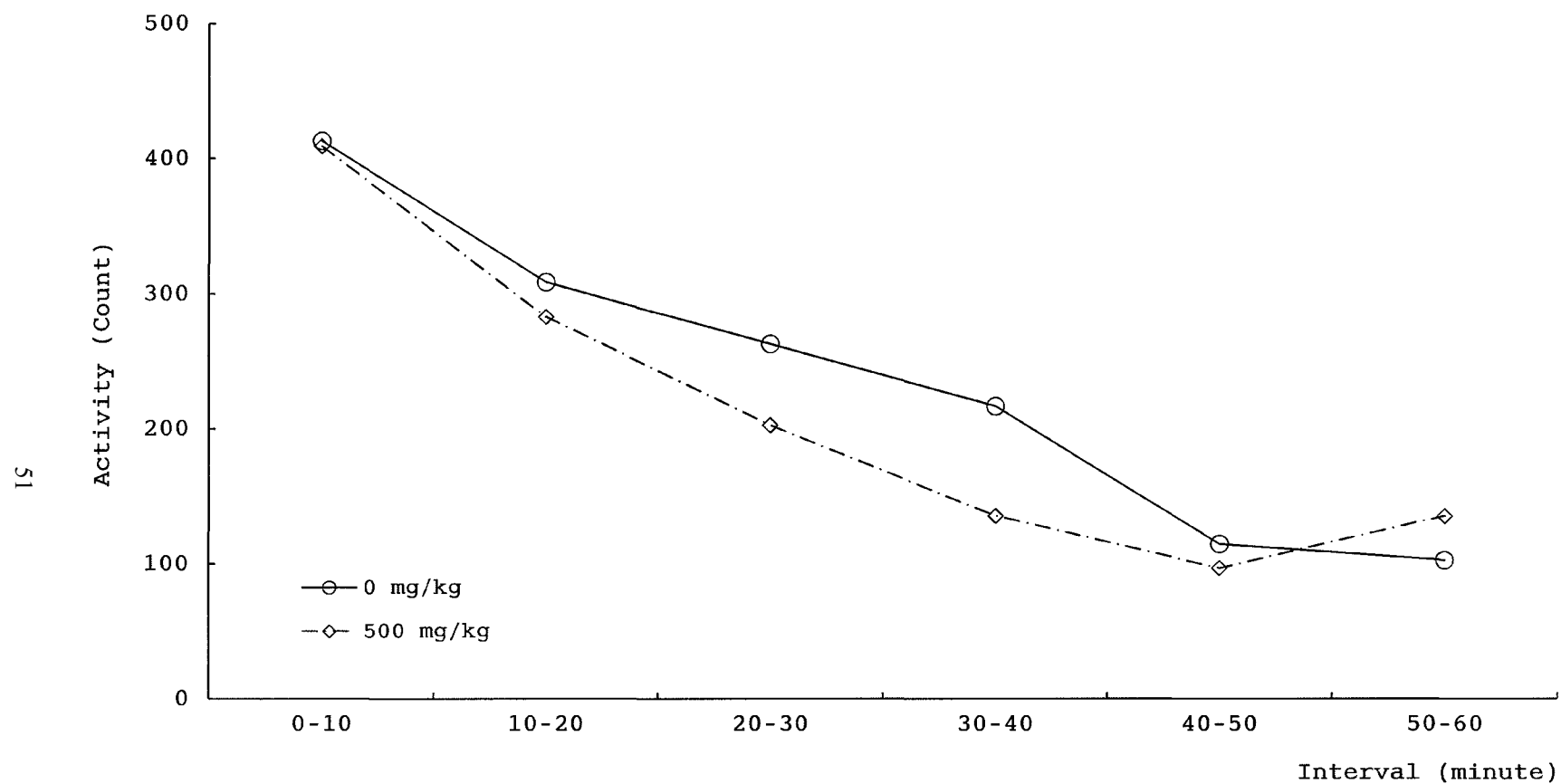


Fig.5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Motor activity of female rats (Week 2 of recovery)

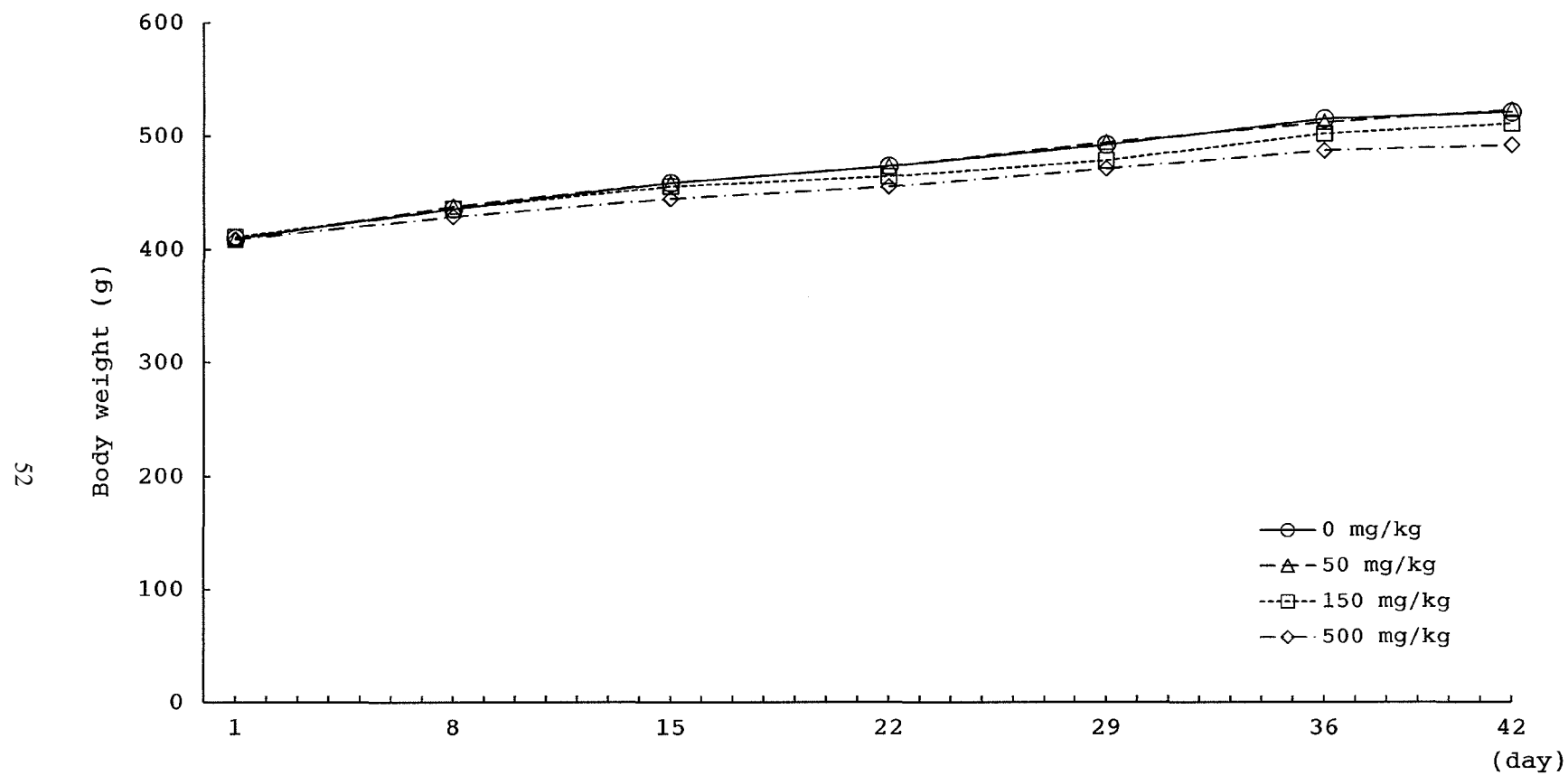


Fig.6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Body weight of male rats (F0 before mating Day 1-15, F0mating Day 15-43)

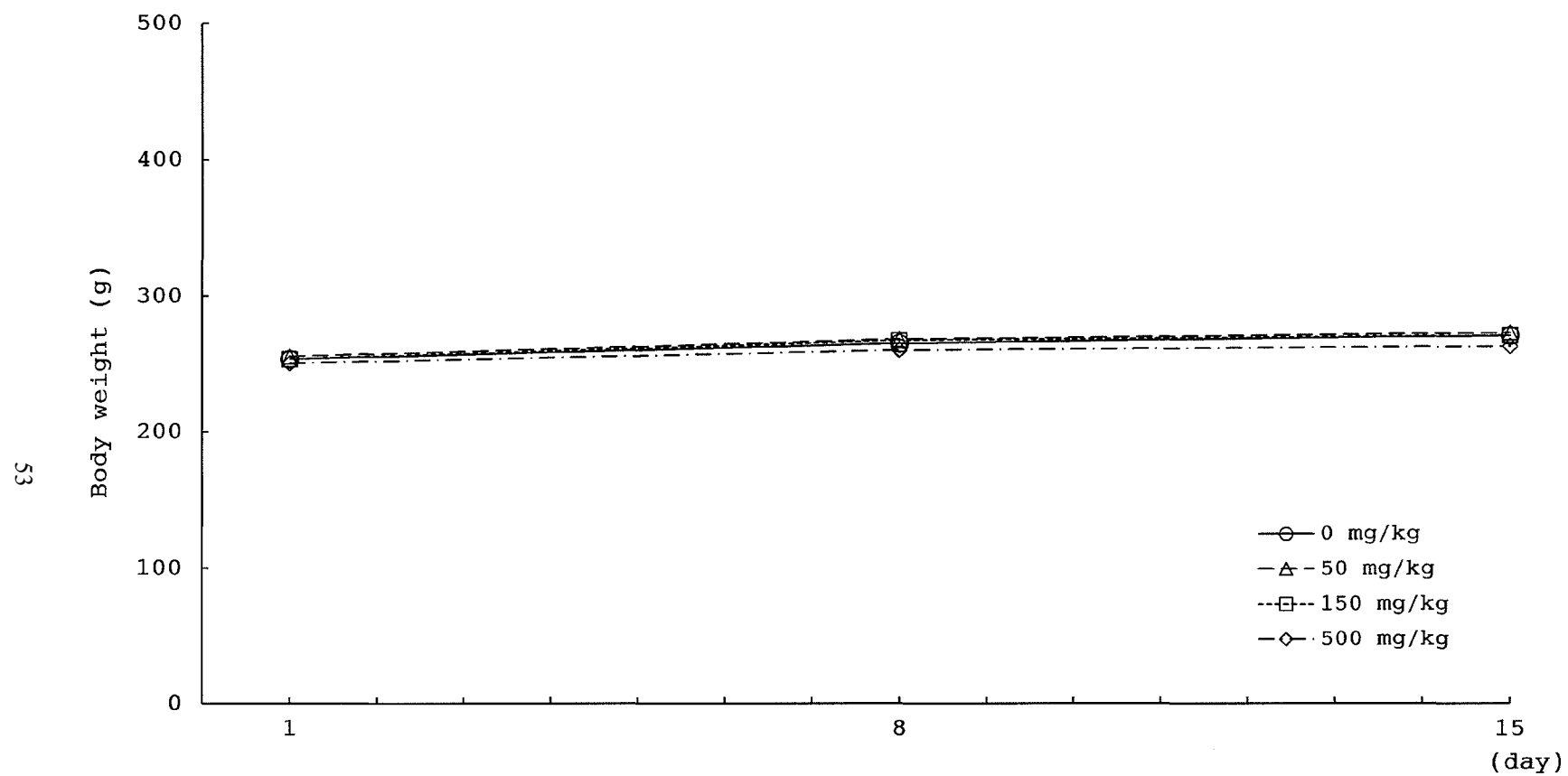


Fig.7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Body weight of female rats (F0 before mating Day 1-15)

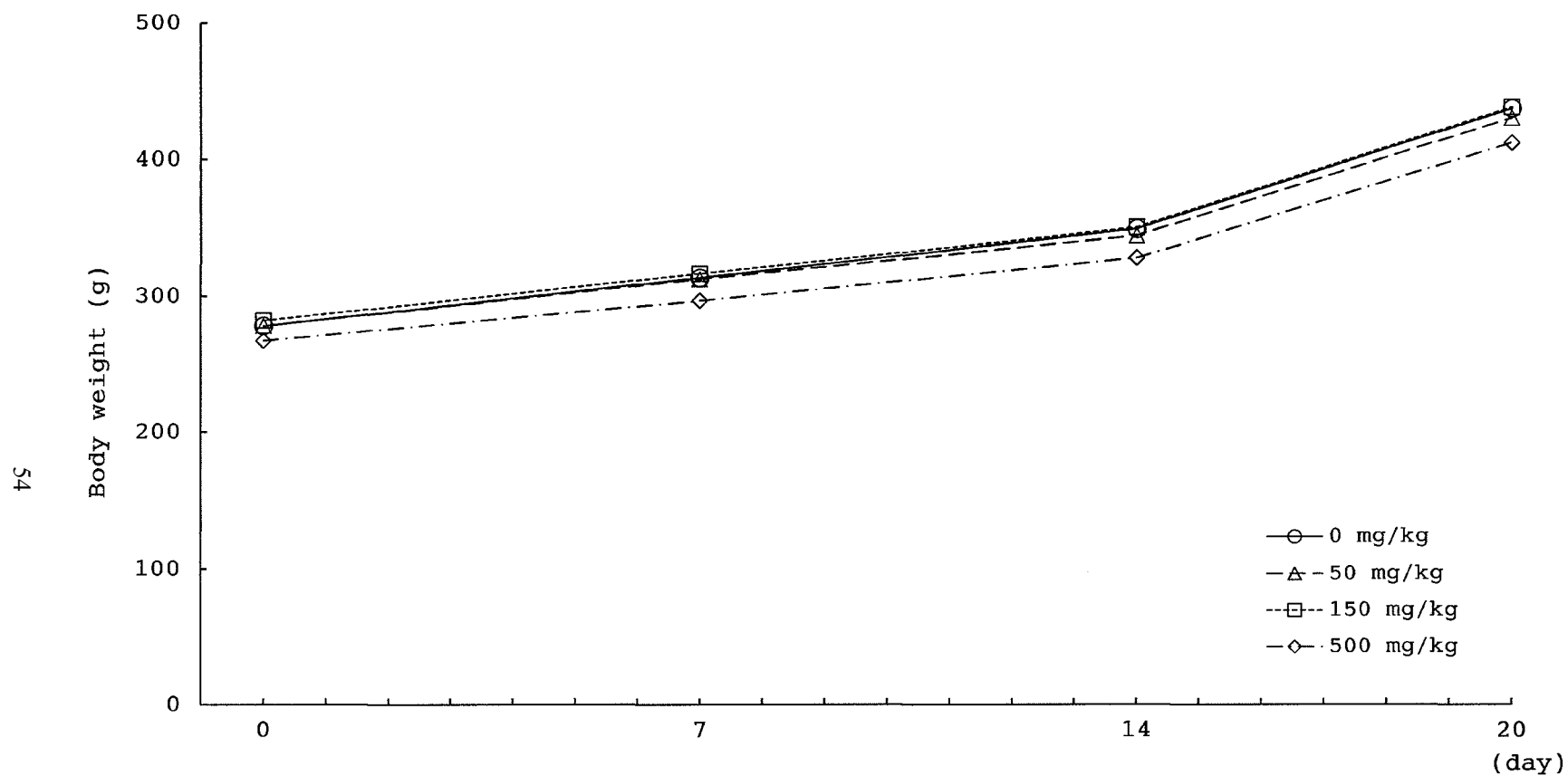


Fig.8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Body weight of dams (F0 gestation Day 0-25)

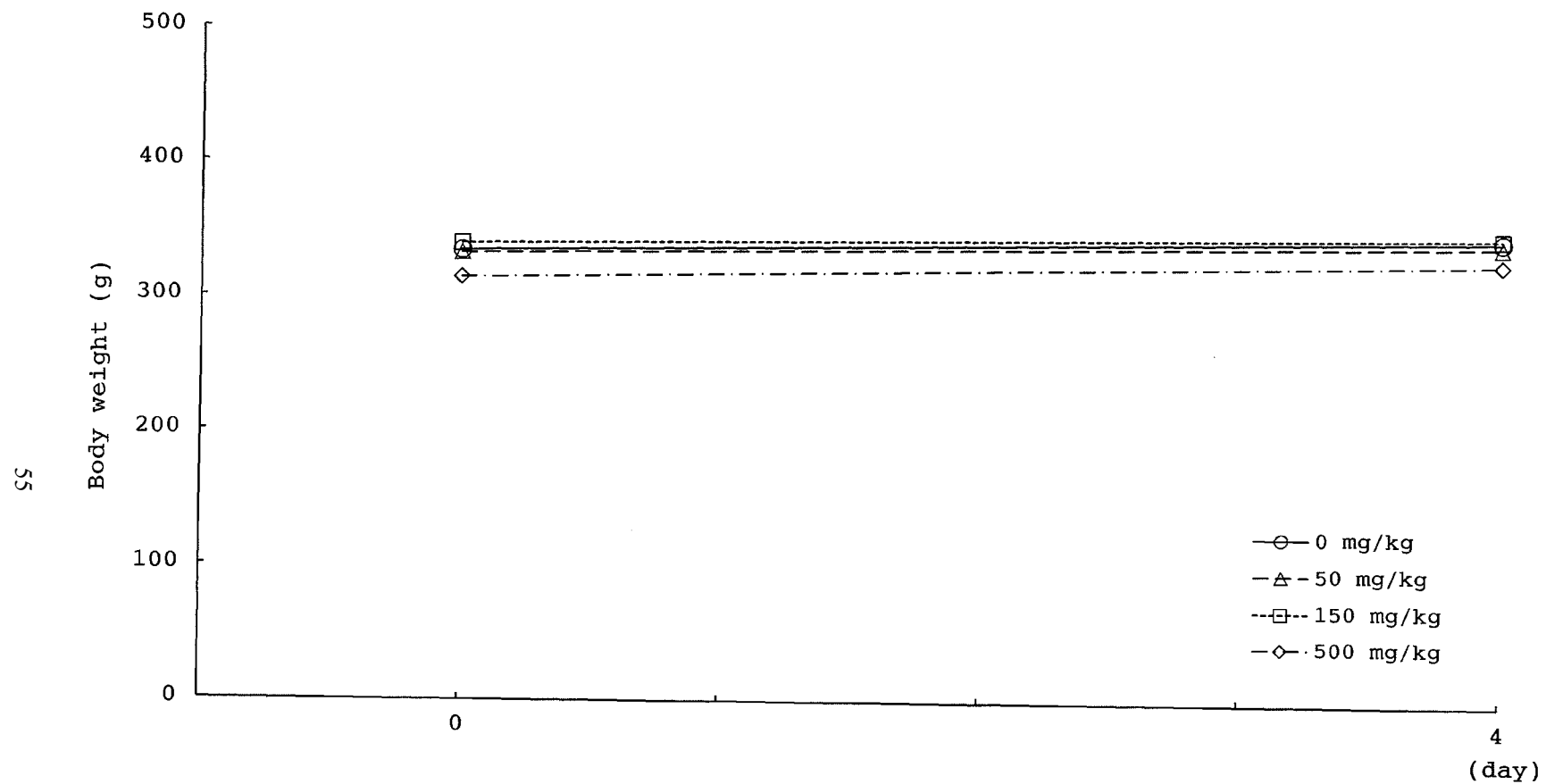


Fig.9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Body weight of dams (F0 lactation Day 0-5)

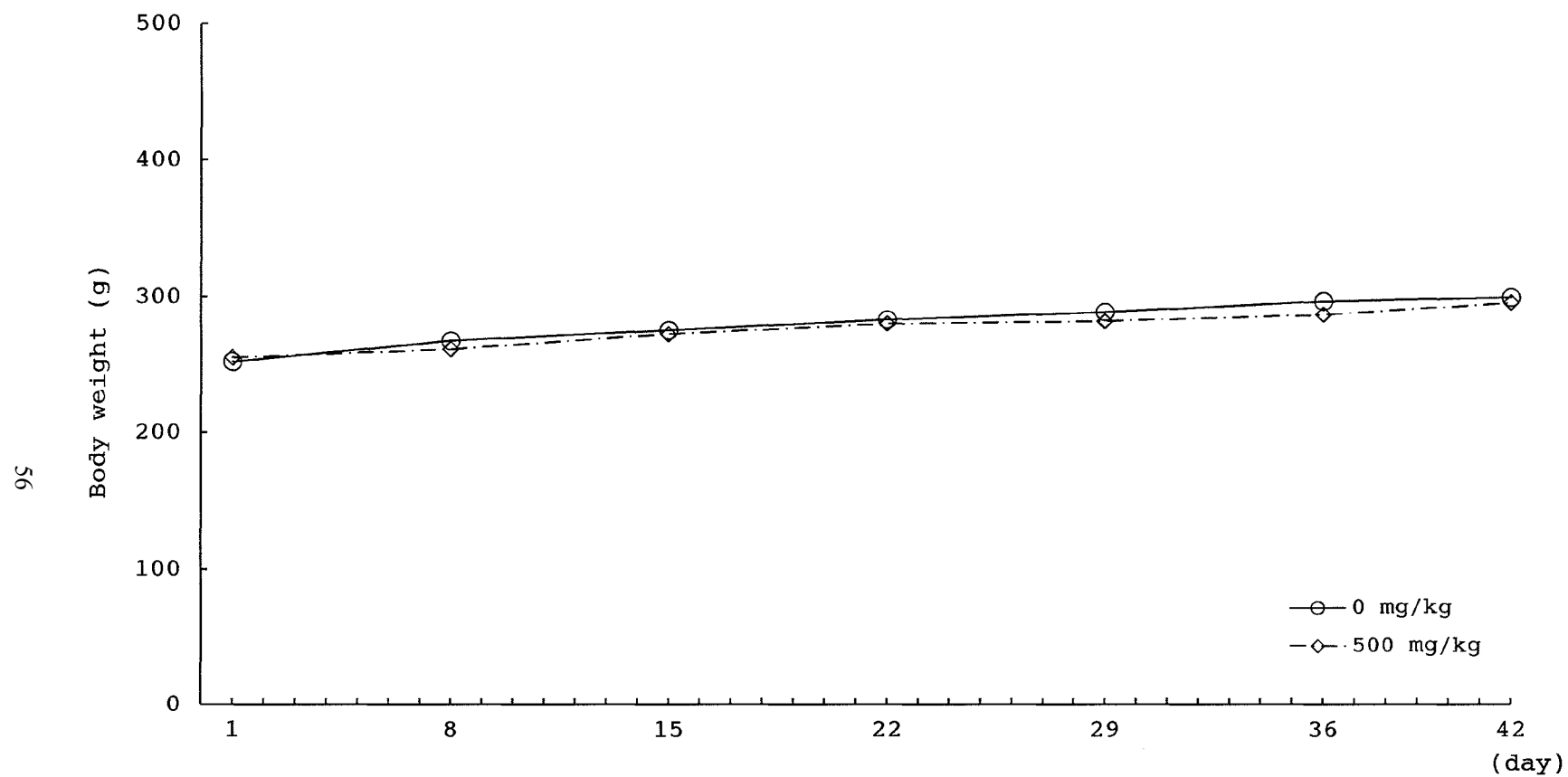


Fig.10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Body weight of female rats (Administration period)

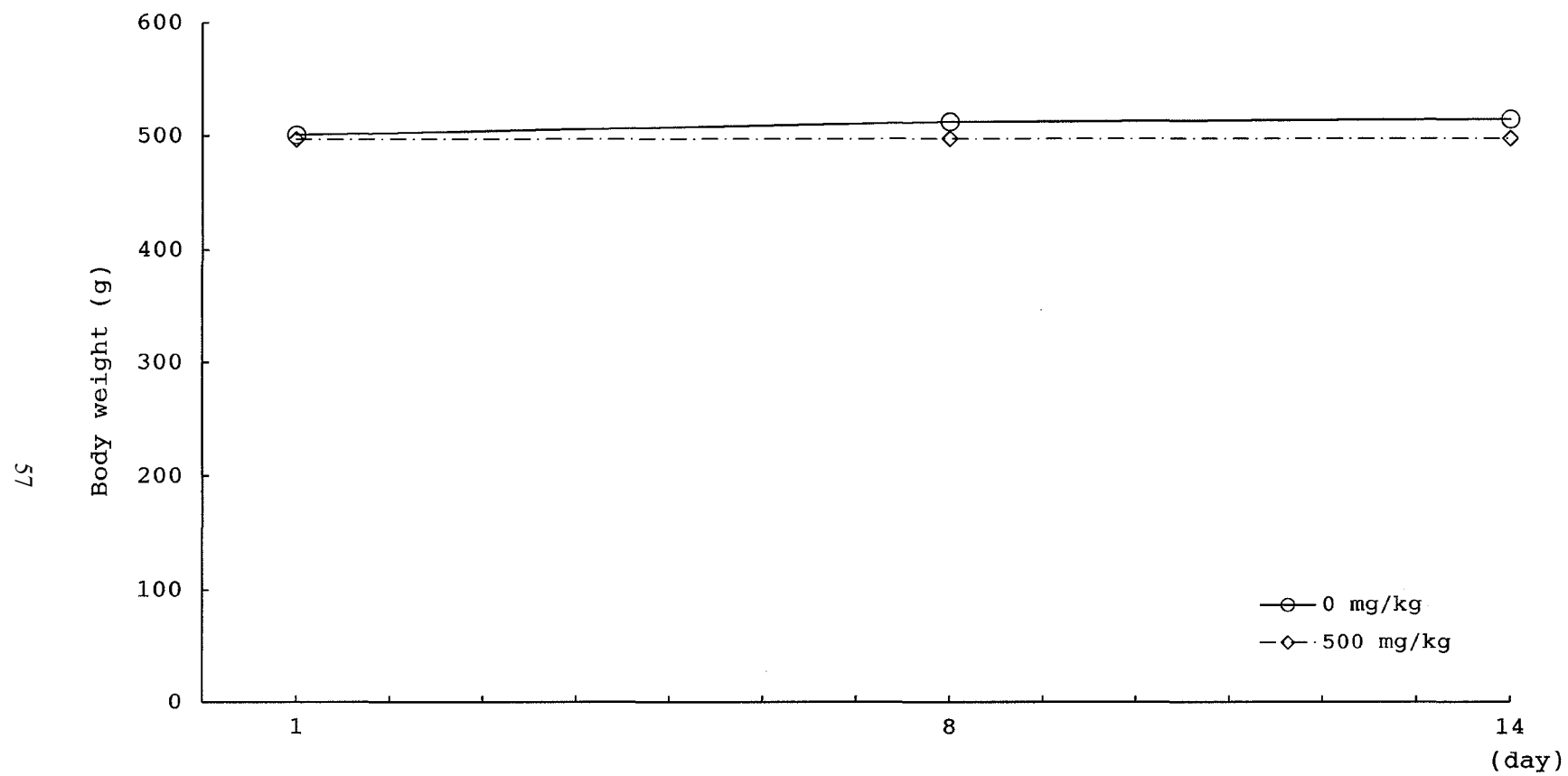


Fig.11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Body weight of male rats (Recovery period)

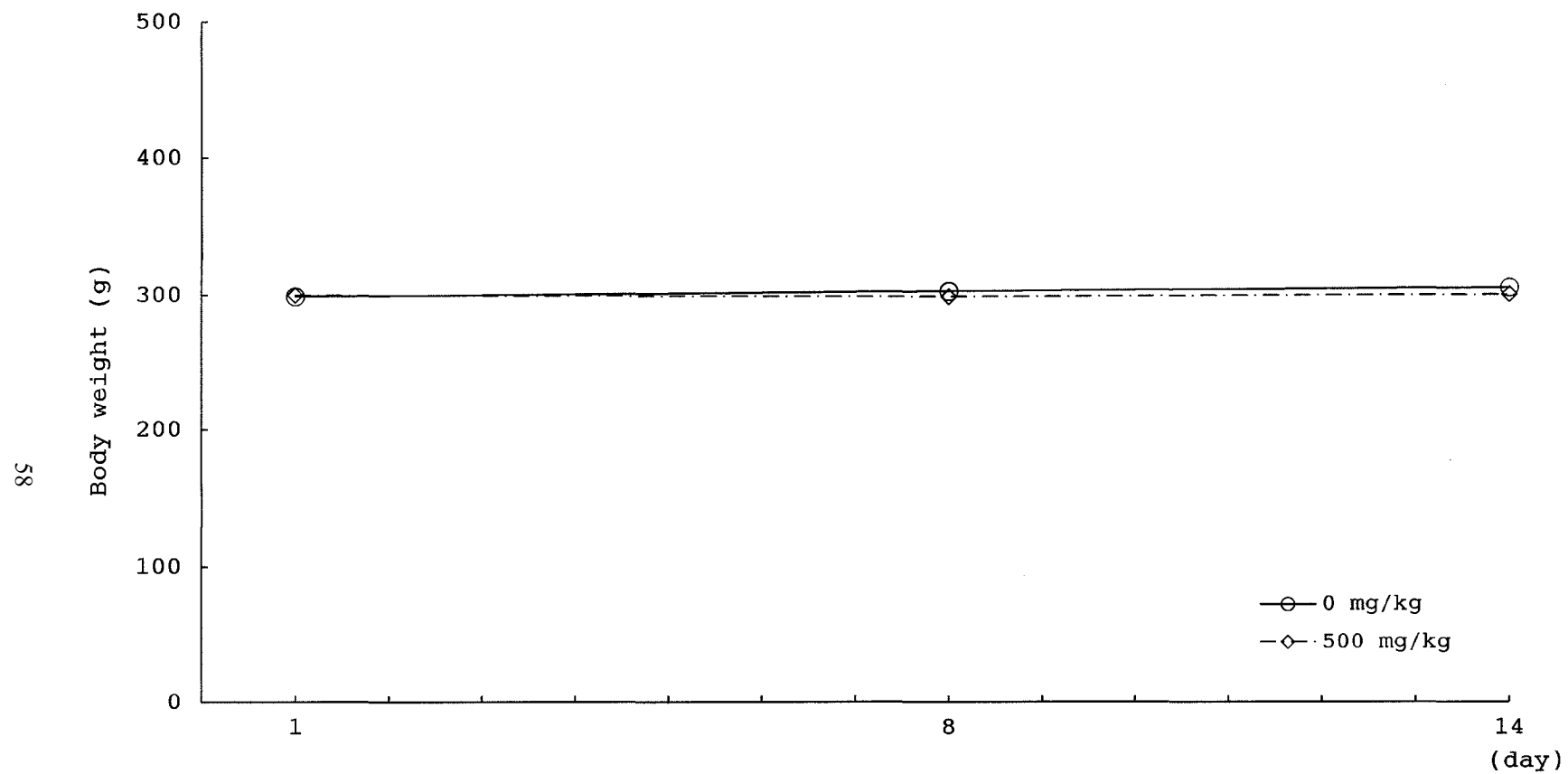


Fig.12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Body weight of female rats (Recovery period)

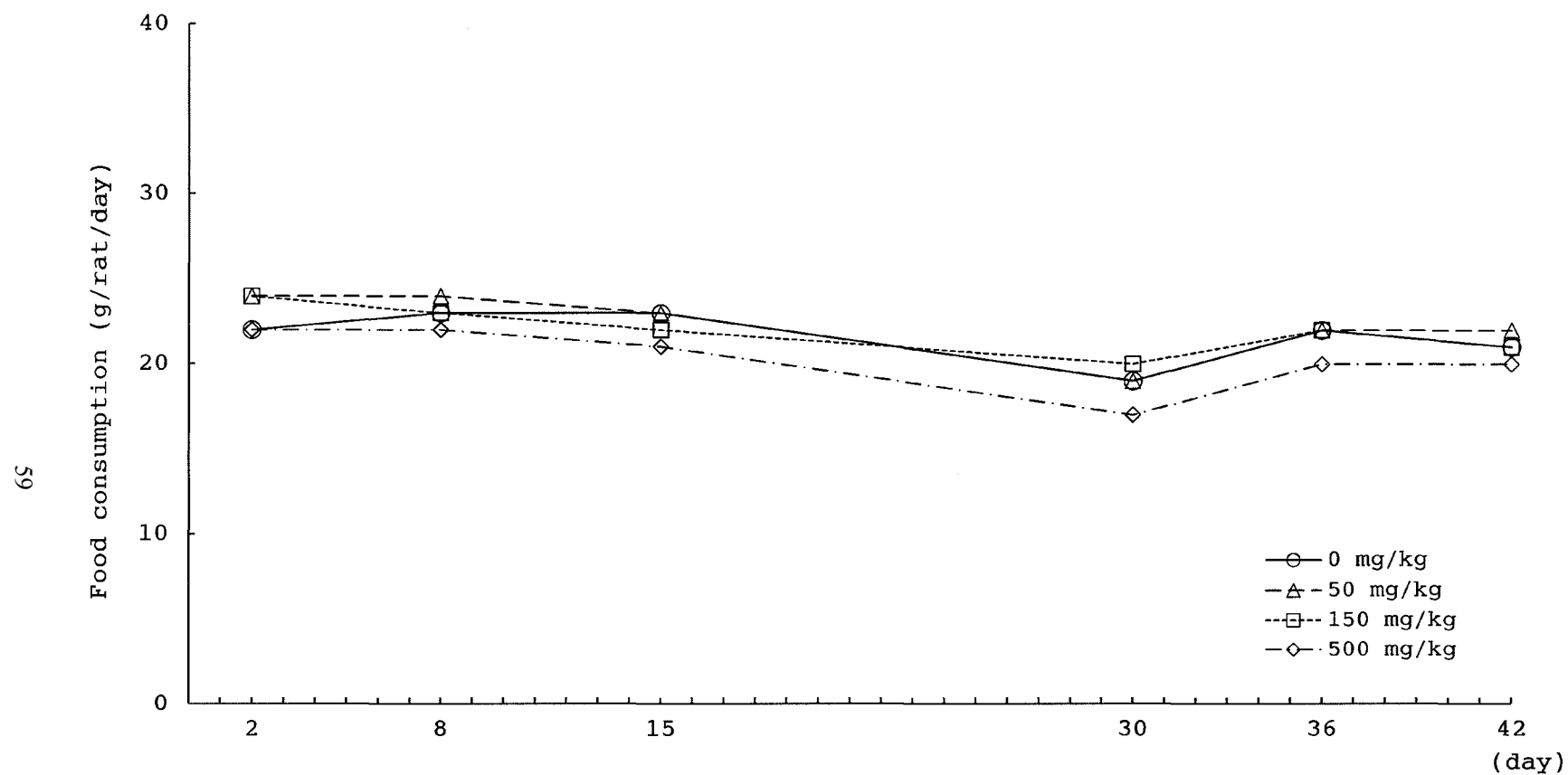


Fig.13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Food consumption of male rats (F0 before mating Day 1-15, F0mating Day 15-43)

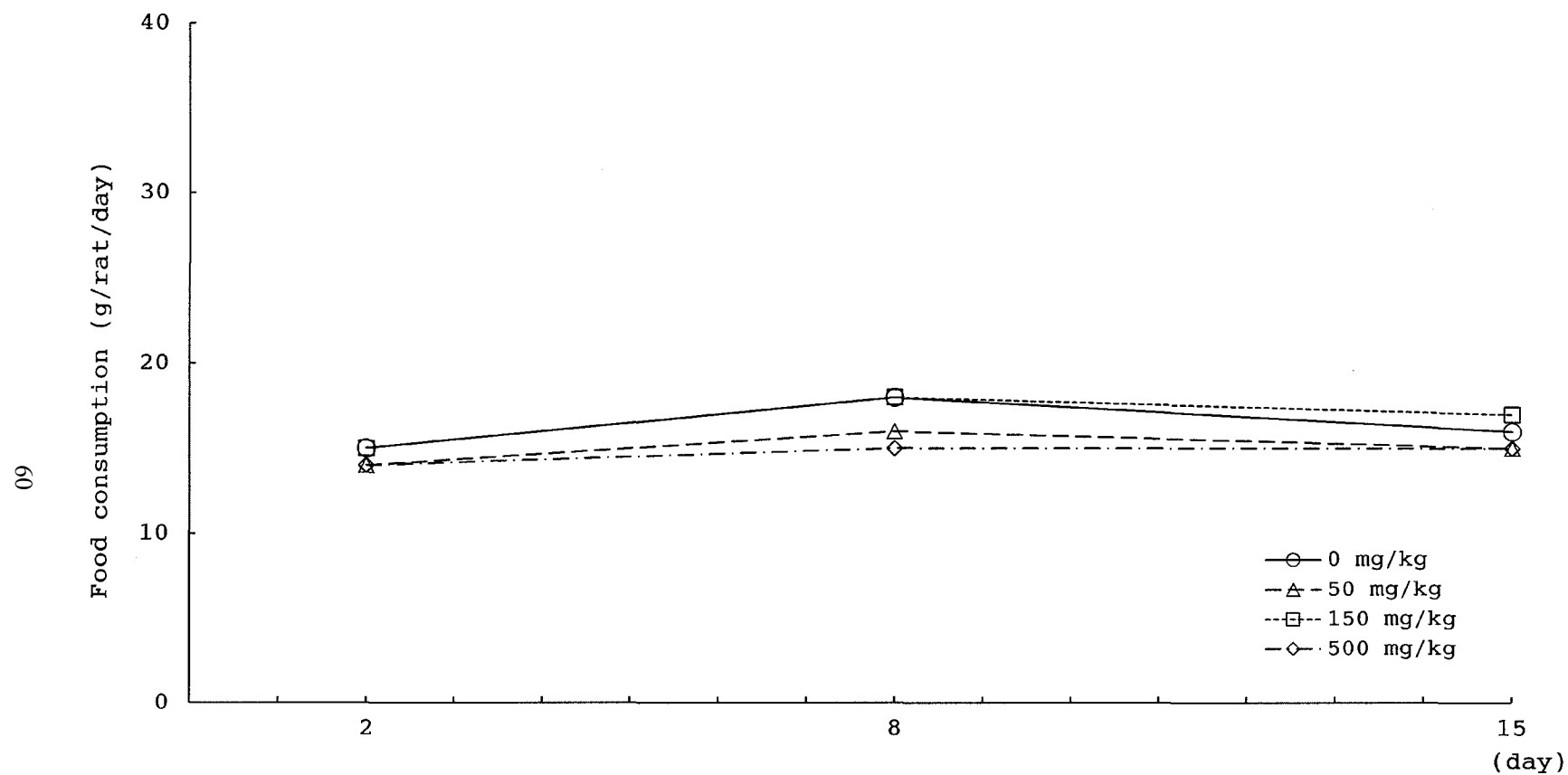


Fig.14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Food consumption of female rats (F0 before mating Day 1-15)

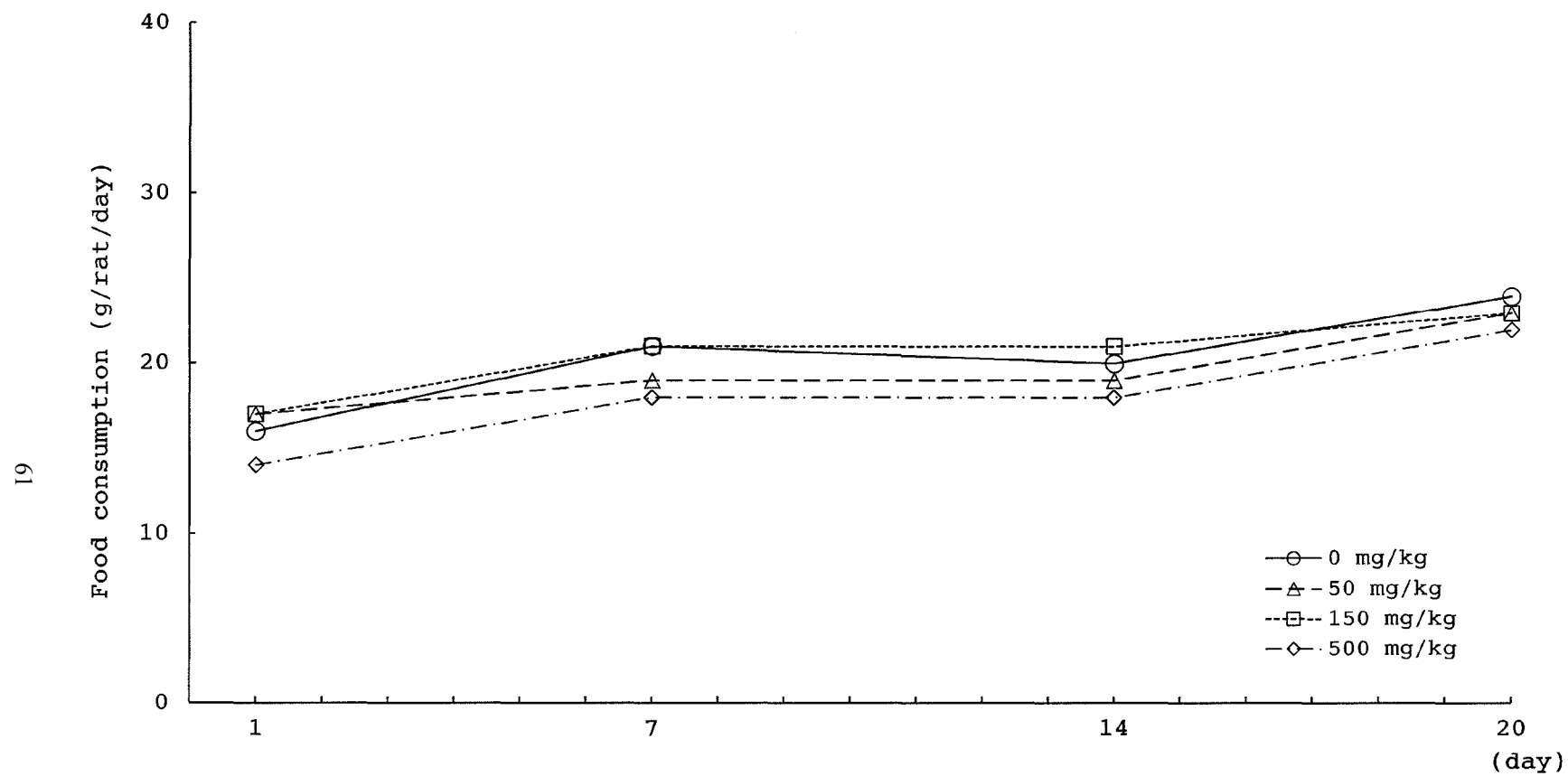


Fig.15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Food consumption of dams (F0 gestation Day 0-25)

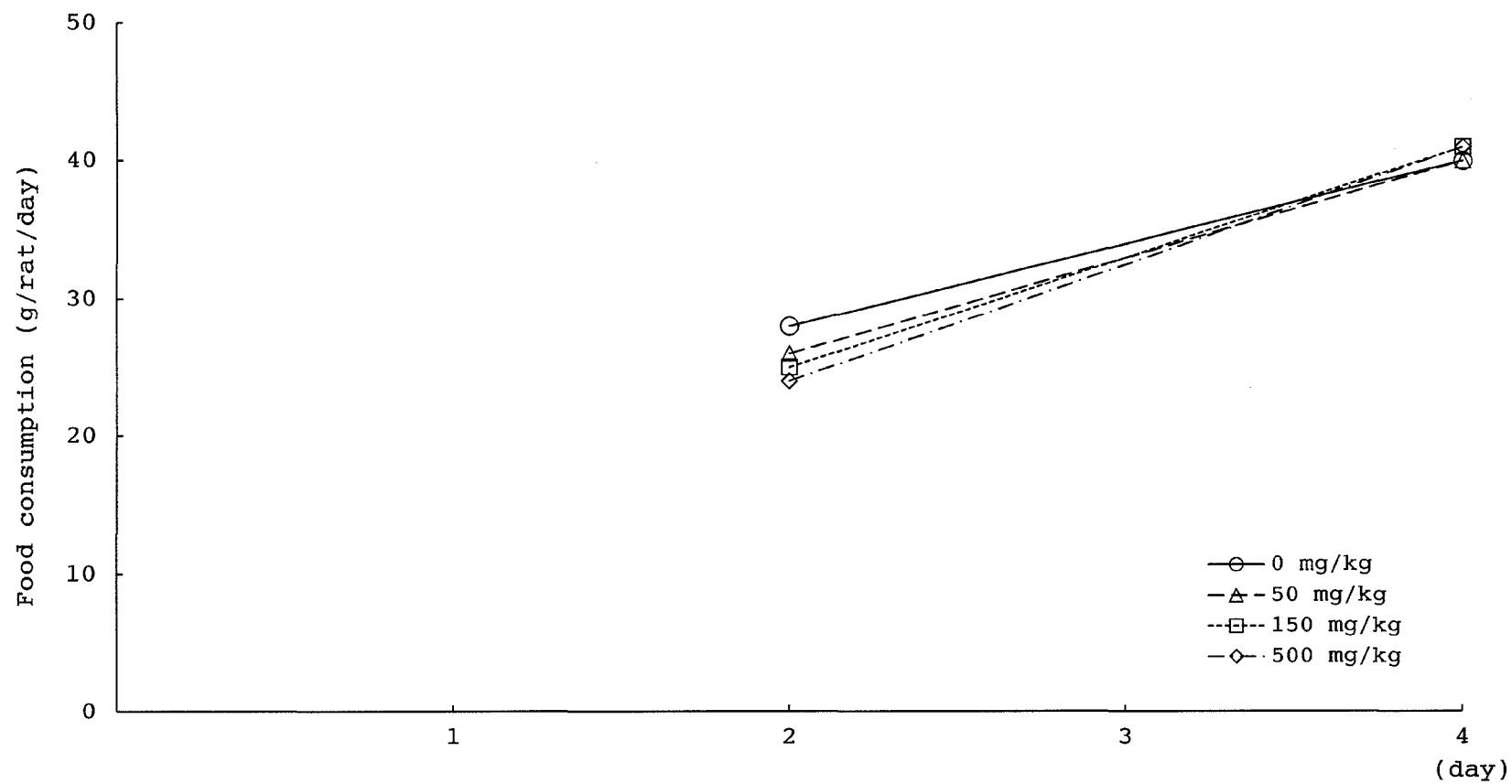


Fig.16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Food consumption of dams (F0 lactation Day 0-5)

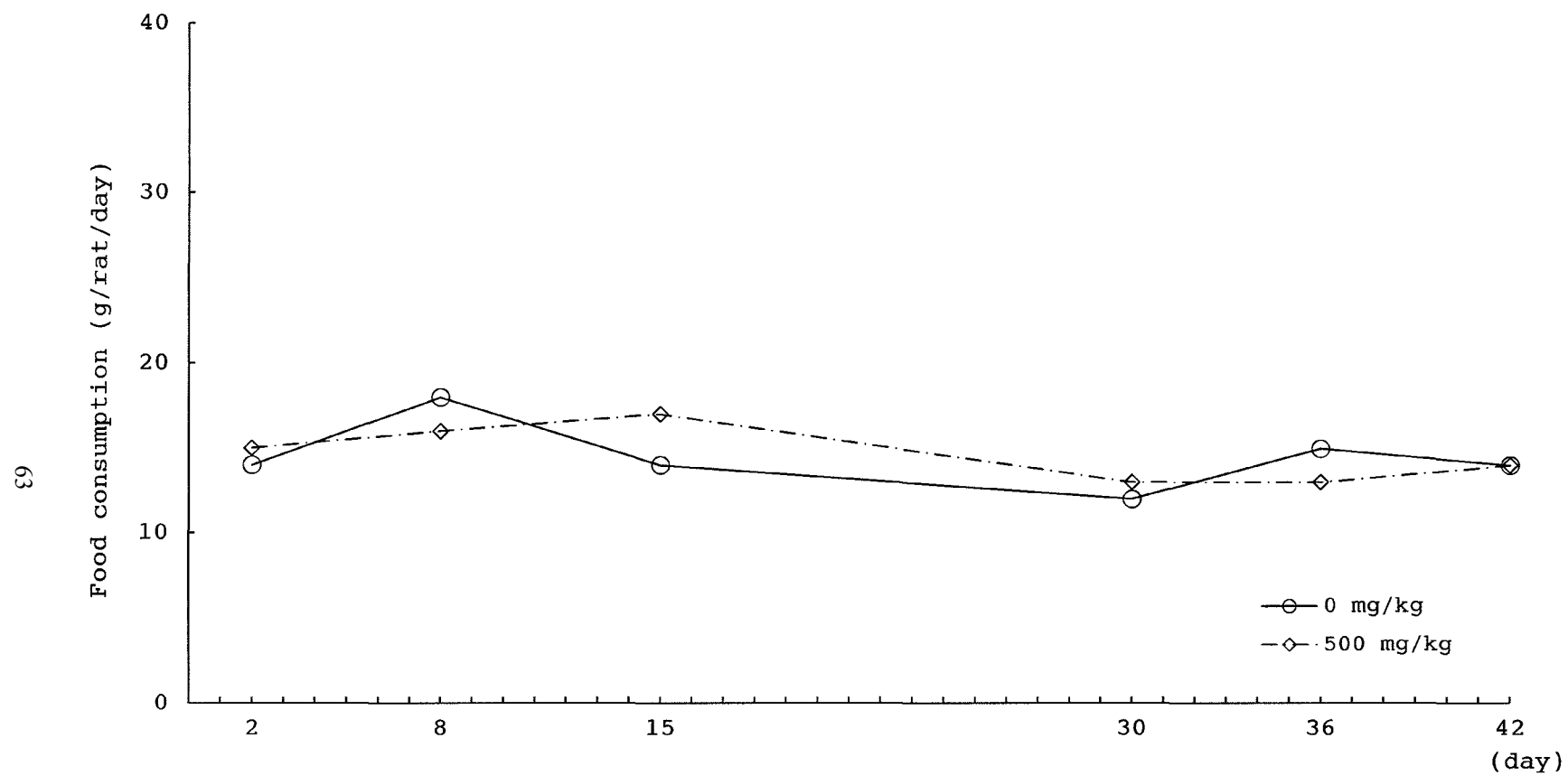


Fig.17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Food consumption of female rats (Administration period)

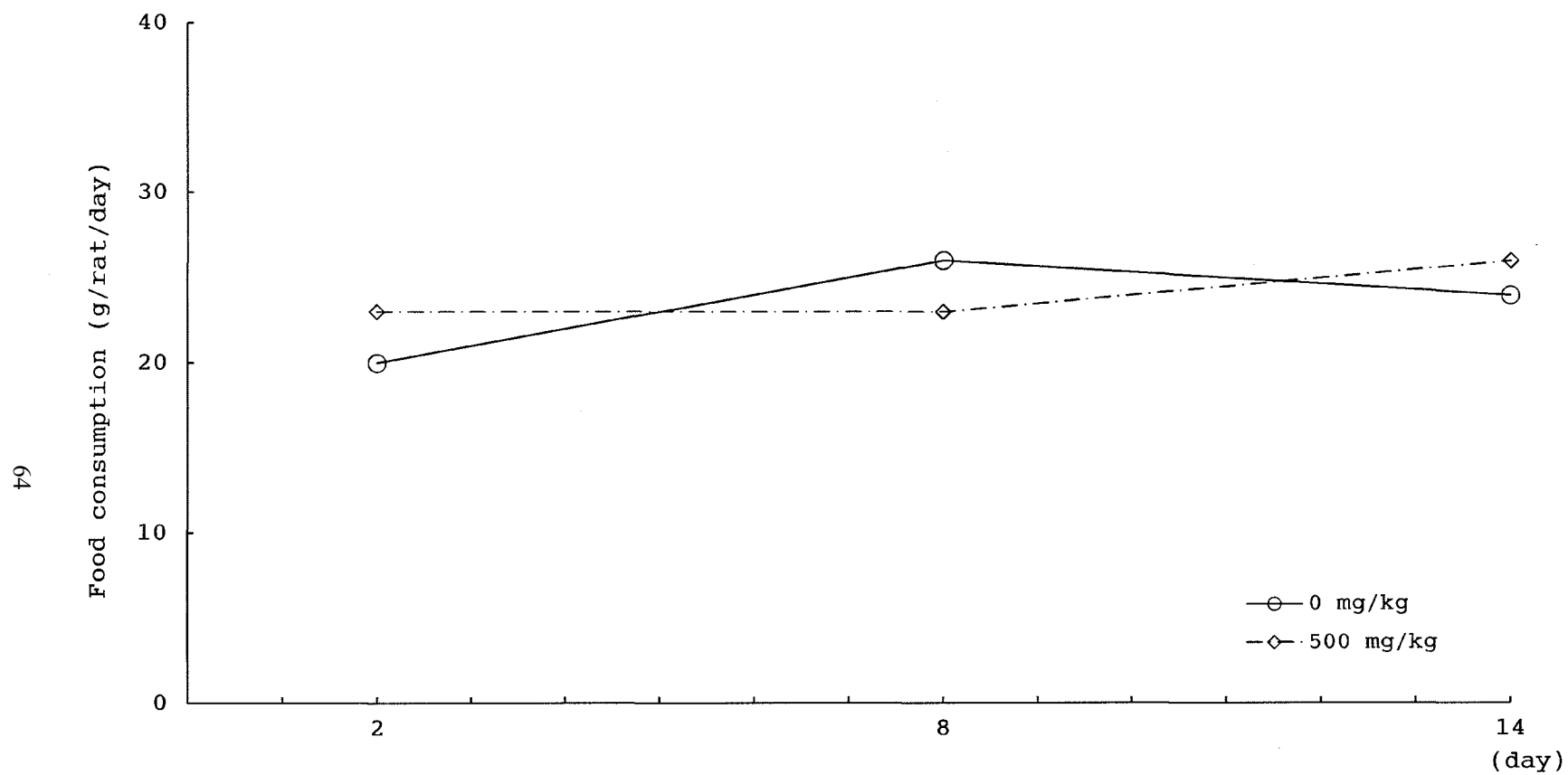


Fig.18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Food consumption of male rats (Recovery period)

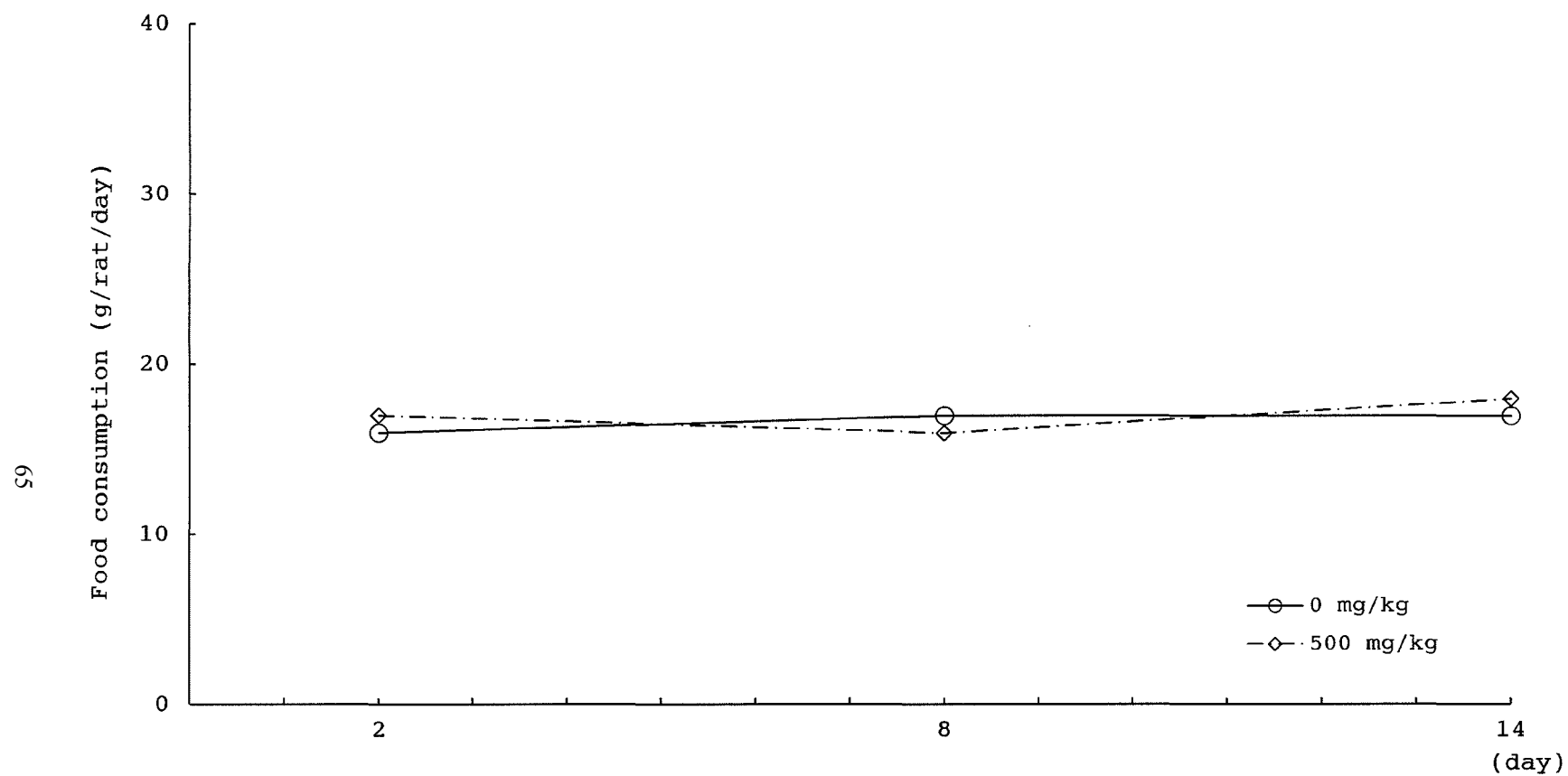


Fig.19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Food consumption of female rats (Recovery period)

Table 1-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs Period : F0 before mating Day 1-15, F0 mating Day 15-43
 Sex : Male

Species : Rat

Test article Dose	Signs	/Day													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
crotonic acid 0 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 50 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 150 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs Period : F0 before mating Day 1-15, F0 mating Day 15-43
 Sex : Male

Species : Rat

Test article Dose	Signs	/Day													
		15	16	17	18	19	20	21	22	23	24	25	26	27	28
crotonic acid 0 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 50 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 150 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs Period : F0 before mating Day 1-15, F0 mating Day 15-43
 Sex : Male

Species : Rat

Test article Dose	Signs	/Day														
		29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
crotonic acid 0 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 50 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 150 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a) : Day of necropsy

Table 1-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs Period : F0 before mating Day 1-15
 Sex : Female

Species : Rat

Test article Dose	Signs	/Day														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
crotonic acid 0 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 50 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 150 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
	Wheezing	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1

Table 1-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs Period : F0 gestation Day 0-25
 Sex : Female

Species : Rat

Test article Dose	Signs	/Day																							
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
crotonic acid 0 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	1	0
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 50 mg/kg	Number of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	3	0
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 150 mg/kg	Number of animals	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	1	0
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	2	0
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs Period : F0 lactation Day 0-5
 Sex : Female

Species : Rat

Test article Dose	Signs	/Day					
		0	1	2	3	4	5a)
crotonic acid 0 mg/kg	Number of animals	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0
crotonic acid 50 mg/kg	Number of animals	10	10	10	10	10	10
	Number of animals with abnormal findings	0	0	0	0	0	0
crotonic acid 150 mg/kg	Number of animals	11	11	11	11	11	11
	Number of animals with abnormal findings	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	12	12	12	12	12	12
	Number of animals with abnormal findings	0	0	0	0	0	0

a) : Day of necropsy

Table 1-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs Period : Administration Day 1-43
 Sex : Female

Species : Rat

Test article Dose	Signs	/Day													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
crotonic acid 0 mg/kg	Number of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female

Study No.: R-1169

Period : Administration Day 1-43

Species : Rat

Test article Dose	Signs	/Day													
		15	16	17	18	19	20	21	22	23	24	25	26	27	28
crotonic acid 0 mg/kg	Number of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs Period : Administration Day 1-43
 Sex : Female

Species : Rat

Test article Dose	Signs	/Day														
		29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
crotonic acid 0 mg/kg	Number of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a) : Day of necropsy

Table 1-10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Male

Study No.: R-1169

Species : Rat

Test article Dose	Signs	/Day														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
crotonic acid 0 mg/kg	Number of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Number of animals with abnormal findings	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0
	Wheezing	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0

a) : Day of necropsy

Table 1-11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female

Study No.: R-1169

Period : Recovery Day 1-15

Species : Rat

Test article Dose	Signs	/Day														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
crotonic acid 0 mg/kg	Number of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
crotonic acid 500 mg/kg	Number of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Number of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a) : Day of necropsy

Table 2 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid	n	12	0	0	12	0	0	0	0
0 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
50 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
150 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
500 mg/kg									
		Abnormal NC behavior							
Test article		0	1	2	3				
Dose									
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	12	0	0	0				
50 mg/kg									
crotonic acid	n	12	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid	n	12	0	0	12	0	0	0	0
0 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
50 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
150 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
500 mg/kg									
		Abnormal NC behavior							
Test article		0	1	2	3				
Dose									
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	12	0	0	0				
50 mg/kg									
crotonic acid	n	12	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 3

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid	n	12	0	0	0	12	0	0	0
0 mg/kg									
crotonic acid	n	12	0	0	0	12	0	0	0
50 mg/kg									
crotonic acid	n	12	0	0	0	12	0	0	0
150 mg/kg									
crotonic acid	n	12	0	0	0	12	0	0	0
500 mg/kg									
		Abnormal NC behavior							
Test article		0	1	2	3				
Dose									
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	12	0	0	0				
50 mg/kg									
crotonic acid	n	12	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 4

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid	n	12	0	0	12	0	0	0	0
0 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
50 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
150 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
500 mg/kg									
		Abnormal NC behavior							
Test article		0	1	2	3				
Dose									
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	12	0	0	0				
50 mg/kg									
crotonic acid	n	12	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid	n	12	0	0	12	0	0	0	0
0 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
50 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
150 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
500 mg/kg									
		Abnormal NC behavior							
Test article		0	1	2	3				
Dose									
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	12	0	0	0				
50 mg/kg									
crotonic acid	n	12	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid	n	12	0	0	12	0	0	0	0
0 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
50 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
150 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
500 mg/kg									
		Abnormal NC behavior							
Test article		0	1	2	3				
Dose									
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	12	0	0	0				
50 mg/kg									
crotonic acid	n	12	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched
 Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
 Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
 Not calculated : NC

Table 2 - 7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid	n	12	0	0	12	0	0	0	0
0 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
50 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
150 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
500 mg/kg									
		Abnormal NC behavior							
Test article		0	1	2	3				
Dose									
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	12	0	0	0				
50 mg/kg									
crotonic acid	n	12	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Species : Rat

		Posture NC			Convulsion NC				
Test article									
Dose		N	F	H	0	1	2	3	
crotonic acid	n	12	0	0	12	0	0	0	
0 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	
50 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	
150 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	
500 mg/kg									
		Abnormal NC behavior							
Test article									
Dose		0	1	2	3				
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	12	0	0	0				
50 mg/kg									
crotonic acid	n	12	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid	n	12	0	0		12	0	0	0
0 mg/kg									
crotonic acid	n	10	0	0		10	0	0	0
50 mg/kg									
crotonic acid	n	11	0	0		11	0	0	0
150 mg/kg									
crotonic acid	n	12	0	0		12	0	0	0
500 mg/kg									
		Abnormal NC behavior							
Test article		0	1	2	3				
Dose									
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	10	0	0	0				
50 mg/kg									
crotonic acid	n	11	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid 0 mg/kg	n	12	0	0		12	0	0	0
crotonic acid 50 mg/kg	n	10	0	0		10	0	0	0
crotonic acid 150 mg/kg	n	11	0	0		11	0	0	0
crotonic acid 500 mg/kg	n	12	0	0		12	0	0	0
		Abnormal NC behavior							
Test article		0	1	2		3			
Dose									
crotonic acid 0 mg/kg	n	12	0	0		0			
crotonic acid 50 mg/kg	n	10	0	0		0			
crotonic acid 150 mg/kg	n	11	0	0		0			
crotonic acid 500 mg/kg	n	12	0	0		0			

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Species : Rat

Test article Dose	n	Posture NC			Convulsion NC				
		N	F	H	0	1	2	3	
crotonic acid 0 mg/kg	n	12	0	0	12	0	0	0	
crotonic acid 50 mg/kg	n	10	0	0	10	0	0	0	
crotonic acid 150 mg/kg	n	11	0	0	11	0	0	0	
crotonic acid 500 mg/kg	n	12	0	0	12	0	0	0	
Abnormal NC behavior									
Test article Dose	n	0	1	2	3				
		0	1	2	3				
crotonic acid 0 mg/kg	n	12	0	0	0				
crotonic acid 50 mg/kg	n	10	0	0	0				
crotonic acid 150 mg/kg	n	11	0	0	0				
crotonic acid 500 mg/kg	n	12	0	0	0				

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid 0 mg/kg	n	12	0	0		12	0	0	0
crotonic acid 50 mg/kg	n	10	0	0		10	0	0	0
crotonic acid 150 mg/kg	n	11	0	0		11	0	0	0
crotonic acid 500 mg/kg	n	12	0	0		12	0	0	0
		Abnormal NC behavior							
Test article		0	1	2		3			
Dose									
crotonic acid 0 mg/kg	n	12	0	0		0			
crotonic acid 50 mg/kg	n	10	0	0		0			
crotonic acid 150 mg/kg	n	11	0	0		0			
crotonic acid 500 mg/kg	n	12	0	0		0			

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Species : Rat

		Posture NC				Convulsion NC			
Test article		N	F	H		0	1	2	3
Dose									
crotonic acid	n	12	0	0	12	0	0	0	0
0 mg/kg									
crotonic acid	n	10	0	0	10	0	0	0	0
50 mg/kg									
crotonic acid	n	11	0	0	11	0	0	0	0
150 mg/kg									
crotonic acid	n	12	0	0	12	0	0	0	0
500 mg/kg									
		Abnormal NC behavior							
Test article		0	1	2	3				
Dose									
crotonic acid	n	12	0	0	0				
0 mg/kg									
crotonic acid	n	10	0	0	0				
50 mg/kg									
crotonic acid	n	11	0	0	0				
150 mg/kg									
crotonic acid	n	12	0	0	0				
500 mg/kg									

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

		Abnormal NC behavior			
Test article		0	1	2	3
Dose					
crotonic acid	n	10	0	0	0
0 mg/kg					
crotonic acid	n	10	0	0	0
500 mg/kg					

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3:

Not calculated : NC

Not calculated . NC

Table 2 - 15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation		Sex : Female		Week : 2		Period : Administration		Species : Rat	
Generation : F0		Posture NC		Convulsion NC					
Test article		N		F		H			
Dose		0		1		2		3	
crotonic acid	n	10	0	0	0	10	0	0	0
0 mg/kg									
crotonic acid	n	10	0	0	0	10	0	0	0
500 mg/kg									
		Abnormal NC		behavior					
Test article		0		1		2		3	
Dose		0		1		2		3	
crotonic acid	n	10	0	0	0	0	0	0	0
0 mg/kg									
crotonic acid	n	10	0	0	0	0	0	0	0
500 mg/kg									
Posture) N: Normal, F: Flattened, H: Hunched									
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe									
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe									
Not calculated : NC									

Table 2 - 16

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation		Sex : Female		Week : 3		Period : Administration		Species : Rat	
Generation : F0		Posture NC		Convulsion NC					
Test article		N		F		H			
Dose		0		1		2		3	
crotonic acid	n	10	0	0	10	0	0	0	0
0 mg/kg									
crotonic acid	n	10	0	0	10	0	0	0	
500 mg/kg									
		Abnormal NC		behavior					
Test article		0		1		2		3	
Dose		0		1		2		3	
crotonic acid	n	10	0	0	0				
0 mg/kg									
crotonic acid	n	10	0	0	0				
500 mg/kg									
Posture) N: Normal, F: Flattened, H: Hunched									
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe									
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe									
Not calculated : NC									

Table 2 - 17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : Administration

Generation : F0

Sex : Female

Week : 4

Species : Rat

		Posture NC				Convulsion NC				
Test article										
Dose		N	F	H		0	1	2	3	
crotonic acid	n	10	0	0		10	0	0	0	
0 mg/kg										
crotonic acid	n	10	0	0		10	0	0	0	
500 mg/kg										
		Abnormal NC behavior								
Test article										
Dose		0	1	2	3					
crotonic acid	n	10	0	0	0					
0 mg/kg										
crotonic acid	n	10	0	0	0					
500 mg/kg										

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 18

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation		Sex : Female		Week : 5		Period : Administration					Species : Rat	
		Posture NC				Convulsion NC						
Test article												
Dose												
crotonic acid	n	N	F	H	0	1	2	3				
0 mg/kg		10	0	0	10	0	0	0				
crotonic acid	n	10	0	0	10	0	0	0				
500 mg/kg												
Abnormal NC behavior												
Test article												
Dose												
crotonic acid	n	0	1	2	3							
0 mg/kg		10	0	0	0							
crotonic acid	n	10	0	0	0							
500 mg/kg												
Posture) N: Normal, F: Flattened, H: Hunched												
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe												
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe												
Not calculated : NC												

Table 2 - 19

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : Administration

Generation : F0

Sex : Female

Week : 6

Species : Rat

		Posture NC				Convulsion NC				
Test article		N	F	H		0	1	2	3	
Dose										
crotonic acid	n	10	0	0		10	0	0	0	
0 mg/kg										
crotonic acid	n	10	0	0		10	0	0	0	
500 mg/kg										
		Abnormal NC behavior								
Test article		0	1	2	3					
Dose										
crotonic acid	n	10	0	0	0					
0 mg/kg										
crotonic acid	n	10	0	0	0					
500 mg/kg										

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 20

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : Recovery

Generation : F0

Sex : Male

Week : 1

Species : Rat

		Posture NC				Convulsion NC				
Test article										
Dose		N	F	H		0	1	2	3	
crotonic acid	n	5	0	0		5	0	0	0	
0 mg/kg										
crotonic acid	n	5	0	0		5	0	0	0	
500 mg/kg										
		Abnormal NC behavior								
Test article										
Dose		0	1	2	3					
crotonic acid	n	5	0	0	0					
0 mg/kg										
crotonic acid	n	5	0	0	0					
500 mg/kg										

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 21

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Species : Rat

		Posture NC				Convulsion NC				
Test article										
Dose		N	F	H		0	1	2	3	
crotonic acid	n	5	0	0		5	0	0	0	
0 mg/kg										
crotonic acid	n	5	0	0		5	0	0	0	
500 mg/kg										
		Abnormal NC behavior								
Test article										
Dose		0	1	2		3				
crotonic acid	n	5	0	0		0				
0 mg/kg										
crotonic acid	n	5	0	0		0				
500 mg/kg										

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Period : Recovery

Species : Rat

Convulsion NC

Abnormal NC behavior								
Test article Dose	n	N	F	H	0	1	2	3
crotonic acid 0 mg/kg	n	5	0	0	5	0	0	0
crotonic acid 500 mg/kg	n	5	0	0	5	0	0	0

Abnormal NC behavior					
Test article Dose	n	0	1	2	3
crotonic acid 0 mg/kg	n	5	0	0	0
crotonic acid 500 mg/kg	n	5	0	0	0

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 23

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Home cage observation

Period : Recovery

Generation : F0

Sex : Female

Week : 2

Species : Rat

		Posture NC				Convulsion NC				
Test article										
Dose		N	F	H		0	1	2	3	
crotonic acid	n	5	0	0		5	0	0	0	
0 mg/kg										
crotonic acid	n	5	0	0		5	0	0	0	
500 mg/kg										
		Abnormal NC behavior								
Test article										
Dose		0	1	2	3					
crotonic acid	n	5	0	0	0					
0 mg/kg										
crotonic acid	n	5	0	0	0					
500 mg/kg										

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 24

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Male		Week : 1		Period : F0 before mating		Species : Rat			
Generation : F0		Ease of removal from cage						Fur condition NC			
Test article	Dose	-1	0	1	2	3	0	1	2	3	
crotonic acid	0 mg/kg	n	0	12	0	0	0	12	0	0	
crotonic acid	50 mg/kg	n	0	12	0	0	0	12	0	0	
crotonic acid	150 mg/kg	n	0	12	0	0	0	12	0	0	
crotonic acid	500 mg/kg	n	0	12	0	0	0	12	0	0	
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC			
Test article	Dose	0	1	2	3	0	1	0	1		
crotonic acid	0 mg/kg	n	12	0	0	0	12	0	12	0	
crotonic acid	50 mg/kg	n	12	0	0	0	12	0	12	0	
crotonic acid	150 mg/kg	n	12	0	0	0	12	0	12	0	
crotonic acid	500 mg/kg	n	12	0	0	0	12	0	12	0	

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
 Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked
 Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe
 Secretions-Eye, Nose) 0: Absent, 1: Present
 Exophthalmos) 0: Absent, 1: Present
 Not calculated : NC

Table 2 - 25

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male		Week : 1		Period : F0 before mating		Species : Rat					
		Generation : F0				Palpebral NC closure				Mucosal NC membranes		Lacrimation NC			
Test article		0		1		2		3		0		1			
Dose		0		1		2		3		0		1			
crotonic acid 0 mg/kg	n	12	0	0	0	0	0	12	0	0	0	12	0		
crotonic acid 50 mg/kg	n	12	0	0	0	0	0	12	0	0	0	12	0		
crotonic acid 150 mg/kg	n	12	0	0	0	0	0	12	0	0	0	12	0		
crotonic acid 500 mg/kg	n	12	0	0	0	0	0	12	0	0	0	12	0		
Piloerection NC				Pupil size NC				Salivation NC							
Test article		0		1		-1		0		1		2		3	
Dose		0		1		-1		0		1		2		3	
crotonic acid 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	0
crotonic acid 50 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	0
crotonic acid 150 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	0
crotonic acid 500 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	0
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed															
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked															
Lacrimation) 0: Absent, 1: Present															
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Not calculated : NC															

Table 2 - 26

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Species : Rat

Test article Dose		Abnormal NC respiration					Vocalization NC				
		0	1	2	3		0	1	2	3	
crotonic acid 0 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 50 mg/kg	n	12	0	0	0		11	1	0	0	
crotonic acid 150 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 500 mg/kg	n	12	0	0	0		12	0	0	0	
Test article Dose		Reactivity to NC handling									
		-1	0	1	2	3					
crotonic acid 0 mg/kg	n	0	11	1	0	0					
crotonic acid 50 mg/kg	n	0	11	1	0	0					
crotonic acid 150 mg/kg	n	0	12	0	0	0					
crotonic acid 500 mg/kg	n	0	12	0	0	0					

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Not calculated : NC

Table 2 - 27

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		Period : F0 before mating										Species : Rat							
In-the-hand observation		Sex : Male		Week : 2		Ease of removal from cage						Fur condition NC							
Test article																			
Dose		-1		0		1		2		3		0		1		2		3	
crotonic acid 0 mg/kg	n		0		12		0		0		0		12		0		0		0
crotonic acid 50 mg/kg	n		0		12		0		0		0		12		0		0		0
crotonic acid 150 mg/kg	n		0		12		0		0		0		12		0		0		0
crotonic acid 500 mg/kg	n		0		12		0		0		0		12		0		0		0
		Skin NC						Secretions- NC Eye, Nose				Exophthalmos NC							
Test article		0		1		2		3		0		1		0		1			
crotonic acid 0 mg/kg	n		12		0		0		0		12		0		12		0		
crotonic acid 50 mg/kg	n		12		0		0		0		12		0		12		0		
crotonic acid 150 mg/kg	n		12		0		0		0		12		0		12		0		
crotonic acid 500 mg/kg	n		12		0		0		0		12		0		12		0		

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 28

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male		Week : 2		Period : F0 before mating		Species : Rat											
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC											
Test article		0		1		2		3		0		1		2		3					
Dose		0		1		2		3		0		1		2		3					
crotonic acid 0 mg/kg	n	12		0		0		0		12		0		0		0					
crotonic acid 50 mg/kg	n	12		0		0		0		12		0		0		0					
crotonic acid 150 mg/kg	n	12		0		0		0		12		0		0		0					
crotonic acid 500 mg/kg	n	12		0		0		0		12		0		0		0					
Piloerection NC						Pupil size NC						Salivation NC									
Test article		0		1		-1		0		1		2		0		1		2		3	
Dose		0		1		-1		0		1		2		0		1		2		3	
crotonic acid 0 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
crotonic acid 50 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
crotonic acid 150 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
crotonic acid 500 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed																					
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked																					
Lacrimation) 0: Absent, 1: Present																					
Piloerection) 0: Absent, 1: Present																					
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																					
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																					
Not calculated : NC																					

Table 2 - 29

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Species : Rat

		Abnormal NC respiration					Vocalization NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	12	0	0	0		11	1	0	0	
50 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											
		Reactivity to NC handling									
Test article		-1	0	1	2	3					
Dose											
crotonic acid	n	0	12	0	0	0					
0 mg/kg											
crotonic acid	n	0	12	0	0	0					
50 mg/kg											
crotonic acid	n	0	12	0	0	0					
150 mg/kg											
crotonic acid	n	0	12	0	0	0					
500 mg/kg											

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Not calculated : NC

Table 2 - 30

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

	In-the-hand observation	Sex : Male	Week : 3	Period : F0 mating				Species : Rat			
			Ease of remov- NC al from cage				Fur condition NC				
Test article											
Dose		-1	0	1	2	3	0	1	2	3	
crotonic acid 0 mg/kg	n	0	12	0	0	0	12	0	0	0	
crotonic acid 50 mg/kg	n	0	12	0	0	0	12	0	0	0	
crotonic acid 150 mg/kg	n	0	12	0	0	0	12	0	0	0	
crotonic acid 500 mg/kg	n	0	11	1	0	0	12	0	0	0	
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC			
Test article											
Dose		0	1	2	3	0	1	0	1		
crotonic acid 0 mg/kg	n	12	0	0	0	12	0	12	0		
crotonic acid 50 mg/kg	n	12	0	0	0	12	0	12	0		
crotonic acid 150 mg/kg	n	12	0	0	0	12	0	12	0		
crotonic acid 500 mg/kg	n	12	0	0	0	12	0	12	0		

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 31

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male		Week : 3		Period : F0 mating		Species : Rat			
		Palpebral NC closure						Mucosal NC membranes			Lacrimation NC		
Test article		0			1			2			3		
Dose		0			1			2			3		
crotonic acid	n	12	0	0	0	0	0	12	0	0	0	12	0
0 mg/kg													
crotonic acid	n	12	0	0	0	0	0	12	0	0	0	12	0
50 mg/kg													
crotonic acid	n	12	0	0	0	0	0	12	0	0	0	12	0
150 mg/kg													
crotonic acid	n	12	0	0	0	0	0	12	0	0	0	12	0
500 mg/kg													

Table 2 - 32

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male		Week : 3		Period : F0 mating		Species : Rat	
		Abnormal NC respiration				Vocalization NC					
Test article											
Dose		0	1	2	3	0	1	2	3		
crotonic acid 0 mg/kg	n	12	0	0	0	12	0	0	0		
crotonic acid 50 mg/kg	n	12	0	0	0	12	0	0	0		
crotonic acid 150 mg/kg	n	12	0	0	0	12	0	0	0		
crotonic acid 500 mg/kg	n	12	0	0	0	11	1	0	0		
Reactivity to NC handling											
Test article											
Dose		-1	0	1	2	3					
crotonic acid 0 mg/kg	n	0	12	0	0	0					
crotonic acid 50 mg/kg	n	0	12	0	0	0					
crotonic acid 150 mg/kg	n	0	12	0	0	0					
crotonic acid 500 mg/kg	n	0	12	0	0	0					
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe											
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive											
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward											
Not calculated : NC											

Table 2 - 33

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male	Week : 4		Period : F0 mating				Species : Rat								
						Ease of remov- NC al from cage				Fur condition NC									
Test article																			
Dose																			
crotonic acid 0 mg/kg	n	-1	0	0	12	1	0	2	0	3	0	0	12	1	0	2	0	3	0
crotonic acid 50 mg/kg	n		0		12		0		0		0		12		0		0		0
crotonic acid 150 mg/kg	n		0		12		0		0		0		12		0		0		0
crotonic acid 500 mg/kg	n		0		12		0		0		0		12		0		0		0
				Skin NC				Secretions- NC Eye, Nose				Exophthalmos NC							
Test article																			
Dose																			
crotonic acid 0 mg/kg	n	0	12	1	0	2	0	3	0	0	12	1	0	0	12	1	0		
crotonic acid 50 mg/kg	n		12		0		0		0		12		0		12		0		
crotonic acid 150 mg/kg	n		12		0		0		0		12		0		12		0		
crotonic acid 500 mg/kg	n		12		0		0		0		12		0		12		0		

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 34

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male		Week : 4		Period : F0 mating		Species : Rat																					
		Palpebral NC closure						Mucosal NC membranes			Lacrimation NC																				
Test article		0			1			2			3			0			1														
Dose		0			1			2			3			0			1														
crotonic acid	n	12			0			0			0			0			12			0											
0 mg/kg																															
crotonic acid	n	12			0			0			0			0			12			0											
50 mg/kg																															
crotonic acid	n	12			0			0			0			0			12			0											
150 mg/kg																															
crotonic acid	n	12			0			0			0			0			12			0											
500 mg/kg																															
		Piloerection NC						Pupil size NC						Salivation NC																	
Test article		0			1			-1			0			1			2			0			1			2			3		
Dose		0			1			-1			0			1			2			0			1			2			3		
crotonic acid	n	12			0			0			12			0			0			12			0			0			0		
0 mg/kg																															
crotonic acid	n	12			0			0			12			0			0			12			0			0			0		
50 mg/kg																															
crotonic acid	n	12			0			0			12			0			0			12			0			0			0		
150 mg/kg																															
crotonic acid	n	12			0			0			12			0			0			12			0			0			0		
500 mg/kg																															
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed																															
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked																															
Lacrimation) 0: Absent, 1: Present																															
Piloerection) 0: Absent, 1: Present																															
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																															
Not calculated : NC																															

Table 2 - 35

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male		Week : 4		Period : F0 mating		Species : Rat		
		Abnormal NC respiration				Vocalization NC						
Test article												
Dose		0	1	2	3	0	1	2	3			
crotonic acid 0 mg/kg	n	12	0	0	0	12	0	0	0			
crotonic acid 50 mg/kg	n	12	0	0	0	10	2	0	0			
crotonic acid 150 mg/kg	n	12	0	0	0	10	2	0	0			
crotonic acid 500 mg/kg	n	12	0	0	0	10	2	0	0			
		Reactivity to NC handling										
Test article												
Dose		-1	0	1	2	3						
crotonic acid 0 mg/kg	n	0	12	0	0	0						
crotonic acid 50 mg/kg	n	0	11	1	0	0						
crotonic acid 150 mg/kg	n	0	12	0	0	0						
crotonic acid 500 mg/kg	n	0	11	1	0	0						
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe												
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive												
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward												
Not calculated : NC												

Table 2 - 36

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Male		Week : 5		Period : F0 mating				Species : Rat	
Generation : F0				Ease of removal from cage				Fur condition NC			
Test article	Dose	-1	0	1	2	3	0	1	2	3	
crotonic acid	0 mg/kg	n	0	12	0	0	0	12	0	0	0
crotonic acid	50 mg/kg	n	0	12	0	0	0	12	0	0	0
crotonic acid	150 mg/kg	n	0	12	0	0	0	12	0	0	0
crotonic acid	500 mg/kg	n	0	12	0	0	0	12	0	0	0
		Skin NC		Secretions- NC Eye, Nose		Exophthalmos NC					
Test article	Dose	0	1	2	3	0	1	0	1		
crotonic acid	0 mg/kg	n	12	0	0	0	12	0	12	0	
crotonic acid	50 mg/kg	n	12	0	0	0	12	0	12	0	
crotonic acid	150 mg/kg	n	12	0	0	0	12	0	12	0	
crotonic acid	500 mg/kg	n	12	0	0	0	12	0	12	0	

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
 Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked
 Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe
 Secretions-Eye, Nose) 0: Absent, 1: Present
 Exophthalmos) 0: Absent, 1: Present
 Not calculated : NC

Table 2 - 37

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male		Week : 5		Period : F0 mating		Species : Rat					
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC					
Test article		0		1		2		3		0		1			
Dose		0		1		2		3		0		1			
crotonic acid 0 mg/kg	n	12		0		0		0		12		0			
crotonic acid 50 mg/kg	n	12		0		0		0		12		0			
crotonic acid 150 mg/kg	n	12		0		0		0		12		0			
crotonic acid 500 mg/kg	n	12		0		0		0		12		0			
Piloerection NC				Pupil size NC				Salivation NC							
Test article		0		1		-1		0		1		2		3	
Dose		0		1		-1		0		1		2		3	
crotonic acid 0 mg/kg	n	12		0		0		12		0		12		0	
crotonic acid 50 mg/kg	n	12		0		0		12		0		12		0	
crotonic acid 150 mg/kg	n	12		0		0		12		0		12		0	
crotonic acid 500 mg/kg	n	12		0		0		12		0		12		0	
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed															
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked															
Lacrimation) 0: Absent, 1: Present															
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Not calculated : NC															

Table 2 - 38

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Species : Rat

		Abnormal NC respiration					Vocalization NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
50 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											
		Reactivity to NC handling									
Test article		-1	0	1	2	3					
Dose											
crotonic acid	n	0	12	0	0	0					
0 mg/kg											
crotonic acid	n	0	12	0	0	0					
50 mg/kg											
crotonic acid	n	0	12	0	0	0					
150 mg/kg											
crotonic acid	n	0	12	0	0	0					
500 mg/kg											

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Not calculated : NC

Table 2 - 39

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Male		Week : 6		Period : F0 mating				Species : Rat	
Generation : F0				Ease of remov- NC				Fur condition NC			
				al from cage							
Test article	Dose	-1	0	1	2	3	0	1	2	3	
crotonic acid	0 mg/kg	n	0	12	0	0	0	12	0	0	0
crotonic acid	50 mg/kg	n	0	12	0	0	0	12	0	0	0
crotonic acid	150 mg/kg	n	0	11	1	0	0	12	0	0	0
crotonic acid	500 mg/kg	n	0	12	0	0	0	12	0	0	0
		Skin NC		Secretions- NC		Exophthalmos NC					
				Eye, Nose							
Test article	Dose	0	1	2	3	0	1	0	1		
crotonic acid	0 mg/kg	n	12	0	0	0	12	0	12	0	
crotonic acid	50 mg/kg	n	12	0	0	0	12	0	12	0	
crotonic acid	150 mg/kg	n	12	0	0	0	12	0	12	0	
crotonic acid	500 mg/kg	n	12	0	0	0	12	0	12	0	

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
 Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked
 Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe
 Secretions-Eye, Nose) 0: Absent, 1: Present
 Exophthalmos) 0: Absent, 1: Present
 Not calculated : NC

Table 2 - 40

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male		Week : 6		Period : F0 mating		Species : Rat							
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC							
Test article		0		1		2		3		0		1		2		3	
Dose		0		1		2		3		0		1		2		3	
crotonic acid	n	12		0		0		0		12		0		0		0	
0 mg/kg																	
crotonic acid	n	12		0		0		0		12		0		0		12	
50 mg/kg																	
crotonic acid	n	12		0		0		0		12		0		0		12	
150 mg/kg																	
crotonic acid	n	12		0		0		0		12		0		0		12	
500 mg/kg																	
		Piloerection NC				Pupil size NC				Salivation NC							
Test article		0		1		-1		0		1		2		0		1	
Dose		0		1		-1		0		1		2		0		1	
crotonic acid	n	12		0		0		12		0		0		12		0	
0 mg/kg																	
crotonic acid	n	12		0		0		12		0		0		12		0	
50 mg/kg																	
crotonic acid	n	12		0		0		12		0		0		12		0	
150 mg/kg																	
crotonic acid	n	12		0		0		12		0		0		12		0	
500 mg/kg																	
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed																	
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked																	
Lacrimation) 0: Absent, 1: Present																	
Piloerection) 0: Absent, 1: Present																	
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																	
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																	
Not calculated : NC																	

Table 2 - 41

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Species : Rat

Test article Dose		Abnormal NC respiration					Vocalization NC				
		0	1	2	3		0	1	2	3	
crotonic acid 0 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 50 mg/kg	n	12	0	0	0		11	1	0	0	
crotonic acid 150 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 500 mg/kg	n	12	0	0	0		12	0	0	0	
Test article Dose		Reactivity to NC handling									
		-1	0	1	2	3					
crotonic acid 0 mg/kg	n	0	12	0	0	0					
crotonic acid 50 mg/kg	n	0	12	0	0	0					
crotonic acid 150 mg/kg	n	0	11	1	0	0					
crotonic acid 500 mg/kg	n	0	12	0	0	0					

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Not calculated : NC

Table 2 - 42

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		Period : F0 before mating										Species : Rat				
In-the-hand observation		Sex : Female		Week : 1		Ease of removal from cage					Fur condition NC					
Test article	Dose	-1			0			1			2			3		
crotonic acid	0 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0	0		
crotonic acid	50 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0	0		
crotonic acid	150 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0	0		
crotonic acid	500 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0	0		
		Skin NC					Secretions- NC Eye, Nose			Exophthalmos NC						
Test article	Dose	0		1		2		3		0		1				
crotonic acid	0 mg/kg	n	12	0	0	0	0	12	0	0	12	0	0			
crotonic acid	50 mg/kg	n	12	0	0	0	0	12	0	0	12	0	0			
crotonic acid	150 mg/kg	n	12	0	0	0	0	12	0	0	12	0	0			
crotonic acid	500 mg/kg	n	12	0	0	0	0	12	0	0	12	0	0			

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 43

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Crotonic acid by oral administration in rats		In-the-hand observation		Sex : Female		Week : 1		Period : F0 before mating		Species : Rat							
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC							
Test article		0		1		2		3		0		1		2		3	
Dose		0		1		2		3		0		1		2		3	
crotonic acid 0 mg/kg	n	12		0		0		0		12		0		0		0	
crotonic acid 50 mg/kg	n	12		0		0		0		12		0		0		0	
crotonic acid 150 mg/kg	n	12		0		0		0		12		0		0		0	
crotonic acid 500 mg/kg	n	12		0		0		0		12		0		0		0	
		Piloerection NC				Pupil size NC				Salivation NC							
Test article		0		1		-1		0		1		2		0		1	
Dose		0		1		-1		0		1		2		0		1	
crotonic acid 0 mg/kg	n	12		0		0		12		0		0		12		0	
crotonic acid 50 mg/kg	n	12		0		0		12		0		0		12		0	
crotonic acid 150 mg/kg	n	12		0		0		12		0		0		12		0	
crotonic acid 500 mg/kg	n	12		0		0		12		0		0		12		0	
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed																	
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked																	
Lacrimation) 0: Absent, 1: Present																	
Piloerection) 0: Absent, 1: Present																	
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																	
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																	
Not calculated : NC																	

Table 2 - 44

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Week : 1		Period : F0 before mating				Species : Rat		
Generation : F0		Abnormal NC respiration		Vocalization NC								
Test article	Dose	0	1	2	3	0	1	2	3			
crotonic acid	0 mg/kg	n	12	0	0	0	12	0	0	0		
crotonic acid	50 mg/kg	n	12	0	0	0	12	0	0	0		
crotonic acid	150 mg/kg	n	12	0	0	0	12	0	0	0		
crotonic acid	500 mg/kg	n	12	0	0	0	12	0	0	0		
		Reactivity to NC handling										
Test article	Dose	-1	0	1	2	3						
crotonic acid	0 mg/kg	n	0	12	0	0	0					
crotonic acid	50 mg/kg	n	0	12	0	0	0					
crotonic acid	150 mg/kg	n	0	12	0	0	0					
crotonic acid	500 mg/kg	n	0	12	0	0	0					
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe												
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive												
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward												
Not calculated : NC												

Table 2 - 45

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Female		Week : 2		Period : F0 before mating		Species : Rat	
		Ease of remov- NC al from cage						Fur condition NC			
Test article											
Dose		-1	0	1	2	3	0	1	2	3	
crotonic acid 0 mg/kg	n	0	12	0	0	0	12	0	0	0	
crotonic acid 50 mg/kg	n	0	12	0	0	0	12	0	0	0	
crotonic acid 150 mg/kg	n	0	12	0	0	0	12	0	0	0	
crotonic acid 500 mg/kg	n	0	12	0	0	0	12	0	0	0	
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC			
Test article											
Dose		0	1	2	3	0	1	0	1		
crotonic acid 0 mg/kg	n	12	0	0	0	12	0	12	0		
crotonic acid 50 mg/kg	n	12	0	0	0	12	0	12	0		
crotonic acid 150 mg/kg	n	12	0	0	0	12	0	12	0		
crotonic acid 500 mg/kg	n	12	0	0	0	12	0	12	0		

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 46

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Crotonic acid by oral administration in rats		In-the-hand observation		Sex : Female		Week : 2		Period : F0 before mating		Species : Rat											
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC											
Test article		0		1		2		3		0		1		2		3					
Dose		0		1		2		3		0		1		2		3					
crotonic acid 0 mg/kg	n	12		0		0		0		12		0		0		0					
crotonic acid 50 mg/kg	n	12		0		0		0		12		0		0		0					
crotonic acid 150 mg/kg	n	12		0		0		0		12		0		0		0					
crotonic acid 500 mg/kg	n	12		0		0		0		12		0		0		0					
		Piloerection NC				Pupil size NC				Salivation NC											
Test article		0		1		-1		0		1		2		0		1		2		3	
Dose		0		1		-1		0		1		2		0		1		2		3	
crotonic acid 0 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
crotonic acid 50 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
crotonic acid 150 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
crotonic acid 500 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed																					
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked																					
Lacrimation) 0: Absent, 1: Present																					
Piloerection) 0: Absent, 1: Present																					
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																					
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																					
Not calculated : NC																					

Table 2 - 47

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Week : 2		Period : F0 before mating		Species : Rat	
Generation : F0		Abnormal NC respiration				Vocalization NC			
Test article	Dose	0	1	2	3	0	1	2	3
crotonic acid	0 mg/kg	n	12	0	0	0	12	0	0
crotonic acid	50 mg/kg	n	12	0	0	0	12	0	0
crotonic acid	150 mg/kg	n	12	0	0	0	12	0	0
crotonic acid	500 mg/kg	n	12	0	0	0	12	0	0
		Reactivity to NC handling							
Test article	Dose	-1	0	1	2	3			
crotonic acid	0 mg/kg	n	0	12	0	0	0		
crotonic acid	50 mg/kg	n	0	12	0	0	0		
crotonic acid	150 mg/kg	n	0	12	0	0	0		
crotonic acid	500 mg/kg	n	0	12	0	0	0		
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe									
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive									
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward									
Not calculated : NC									

Table 2 - 48

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Day : 1		Period : F0 gestation				Species : Rat			
Generation : F0						Ease of removal from cage				Fur condition NC			
Test article	Dose	-1	0	1	2	3	0	1	2	3			
crotonic acid	0 mg/kg	n	0	12	0	0	0	12	0	0	0		
crotonic acid	50 mg/kg	n	0	10	0	0	0	10	0	0	0		
crotonic acid	150 mg/kg	n	0	11	0	0	0	11	0	0	0		
crotonic acid	500 mg/kg	n	0	12	0	0	0	12	0	0	0		
		Skin NC		Secretions- NC Eye, Nose		Exophthalmos NC							
Test article	Dose	0	1	2	3	0	1	0	1				
crotonic acid	0 mg/kg	n	12	0	0	0	12	0	12	0			
crotonic acid	50 mg/kg	n	10	0	0	0	10	0	10	0			
crotonic acid	150 mg/kg	n	11	0	0	0	11	0	11	0			
crotonic acid	500 mg/kg	n	12	0	0	0	12	0	12	0			
Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult													
Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked													
Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe													
Secretions-Eye, Nose) 0: Absent, 1: Present													
Exophthalmos) 0: Absent, 1: Present													
Not calculated : NC													

Table 2 - 49

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Female		Day : 1		Period : F0 gestation		Species : Rat					
				Palpebral NC closure				Mucosal NC membranes		Lacrimation NC					
Test article		0		1		2		3		0		1			
Dose															
crotonic acid 0 mg/kg	n	12	0	0	0	0	0	12	0	0	0	12	0		
crotonic acid 50 mg/kg	n	10	0	0	0	0	0	10	0	0	0	10	0		
crotonic acid 150 mg/kg	n	11	0	0	0	0	0	11	0	0	0	11	0		
crotonic acid 500 mg/kg	n	12	0	0	0	0	0	12	0	0	0	12	0		
		Piloerection NC				Pupil size NC				Salivation NC					
Test article		0		1		-1		0		1		2		3	
Dose															
crotonic acid 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	0
crotonic acid 50 mg/kg	n	10	0	0	0	10	0	0	0	10	0	0	0	0	0
crotonic acid 150 mg/kg	n	11	0	0	0	11	0	0	0	11	0	0	0	0	0
crotonic acid 500 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	0
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed															
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked															
Lacrimation) 0: Absent, 1: Present															
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Not calculated : NC															

Table 2 - 50

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Species : Rat

Test article Dose		Abnormal NC respiration					Vocalization NC				
		0	1	2	3		0	1	2	3	
crotonic acid 0 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 50 mg/kg	n	10	0	0	0		10	0	0	0	
crotonic acid 150 mg/kg	n	11	0	0	0		11	0	0	0	
crotonic acid 500 mg/kg	n	12	0	0	0		12	0	0	0	
Test article Dose		Reactivity to NC handling									
		-1	0	1	2	3					
crotonic acid 0 mg/kg	n	0	12	0	0	0					
crotonic acid 50 mg/kg	n	0	10	0	0	0					
crotonic acid 150 mg/kg	n	0	11	0	0	0					
crotonic acid 500 mg/kg	n	0	12	0	0	0					

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Not calculated : NC

Table 2 - 51

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Day : 7		Period : F0 gestation				Species : Rat			
Generation : F0						Ease of removal from cage				Fur condition NC			
Test article	Dose	-1	0	1	2	3	0	1	2	3			
crotonic acid	0 mg/kg	n	0	12	0	0	0	12	0	0	0	0	0
crotonic acid	50 mg/kg	n	0	10	0	0	0	10	0	0	0	0	0
crotonic acid	150 mg/kg	n	0	11	0	0	0	11	0	0	0	0	0
crotonic acid	500 mg/kg	n	0	12	0	0	0	12	0	0	0	0	0
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC					
Test article	Dose	0	1	2	3	0	1	0	1				
crotonic acid	0 mg/kg	n	12	0	0	0	12	0	12	0	0	0	0
crotonic acid	50 mg/kg	n	10	0	0	0	10	0	10	0	0	0	0
crotonic acid	150 mg/kg	n	11	0	0	0	11	0	11	0	0	0	0
crotonic acid	500 mg/kg	n	12	0	0	0	12	0	12	0	0	0	0
Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult													
Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked													
Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe													
Secretions-Eye, Nose) 0: Absent, 1: Present													
Exophthalmos) 0: Absent, 1: Present													
Not calculated : NC													

Table 2 - 52

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Crotonic acid by oral administration in rats		In-the-hand observation		Sex : Female		Day : 7		Period : F0 gestation		Species : Rat							
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC							
Test article		0		1		2		3		0		1		2		3	
Dose		0		1		2		3		0		1		2		3	
crotonic acid 0 mg/kg	n	12		0		0		0		12		0		0		0	
crotonic acid 50 mg/kg	n	10		0		0		0		10		0		0		0	
crotonic acid 150 mg/kg	n	11		0		0		0		11		0		0		0	
crotonic acid 500 mg/kg	n	12		0		0		0		12		0		0		0	
		Piloerection NC				Pupil size NC				Salivation NC							
Test article		0		1		-1		0		1		2		0		1	
Dose		0		1		-1		0		1		2		0		1	
crotonic acid 0 mg/kg	n	12		0		0		12		0		0		12		0	
crotonic acid 50 mg/kg	n	10		0		0		10		0		0		10		0	
crotonic acid 150 mg/kg	n	11		0		0		11		0		0		11		0	
crotonic acid 500 mg/kg	n	12		0		0		12		0		0		12		0	
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed																	
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked																	
Lacrimation) 0: Absent, 1: Present																	
Piloerection) 0: Absent, 1: Present																	
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																	
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																	
Not calculated : NC																	

Table 2 - 53

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Species : Rat

Test article Dose		Abnormal NC respiration					Vocalization NC				
		0	1	2	3		0	1	2	3	
crotonic acid 0 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 50 mg/kg	n	10	0	0	0		10	0	0	0	
crotonic acid 150 mg/kg	n	11	0	0	0		11	0	0	0	
crotonic acid 500 mg/kg	n	12	0	0	0		12	0	0	0	
Test article Dose		Reactivity to NC handling									
		-1	0	1	2	3					
crotonic acid 0 mg/kg	n	0	12	0	0	0					
crotonic acid 50 mg/kg	n	0	10	0	0	0					
crotonic acid 150 mg/kg	n	0	11	0	0	0					
crotonic acid 500 mg/kg	n	0	12	0	0	0					

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Not calculated : NC

Table 2 - 54

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Species : Rat

		Ease of removal from cage					Fur condition NC				
Test article		-1	0	1	2	3	0	1	2	3	
Dose											
crotonic acid	n	0	12	0	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	10	0	0	0	10	0	0	0	
50 mg/kg											
crotonic acid	n	0	11	0	0	0	11	0	0	0	
150 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0	0	
500 mg/kg											
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC			
Test article		0	1	2	3	0	1	0	1		
Dose											
crotonic acid	n	12	0	0	0	12	0	12	0		
0 mg/kg											
crotonic acid	n	10	0	0	0	10	0	10	0		
50 mg/kg											
crotonic acid	n	11	0	0	0	11	0	11	0		
150 mg/kg											
crotonic acid	n	12	0	0	0	12	0	12	0		
500 mg/kg											

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 55

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Female		Day : 14		Period : F0 gestation		Species : Rat							
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC							
Test article		0		1		2		3		0		1		2		3	
Dose		0		1		2		3		0		1		2		3	
crotonic acid 0 mg/kg	n	12		0		0		0		12		0		0		0	
crotonic acid 50 mg/kg	n	10		0		0		0		10		0		0		0	
crotonic acid 150 mg/kg	n	11		0		0		0		11		0		0		0	
crotonic acid 500 mg/kg	n	12		0		0		0		12		0		0		0	
		Piloerection NC				Pupil size NC				Salivation NC							
Test article		0		1		-1		0		1		2		0		1	
Dose		0		1		-1		0		1		2		0		1	
crotonic acid 0 mg/kg	n	12		0		0		12		0		0		12		0	
crotonic acid 50 mg/kg	n	10		0		0		10		0		0		10		0	
crotonic acid 150 mg/kg	n	11		0		0		11		0		0		11		0	
crotonic acid 500 mg/kg	n	12		0		0		12		0		0		12		0	
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed																	
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked																	
Lacrimation) 0: Absent, 1: Present																	
Piloerection) 0: Absent, 1: Present																	
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																	
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																	
Not calculated : NC																	

Table 2 - 56

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Species : Rat

		Abnormal NC respiration					Vocalization NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	10	0	0	0		10	0	0	0	
50 mg/kg											
crotonic acid	n	11	0	0	0		11	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											
		Reactivity to NC handling									
Test article		-1	0	1	2	3					
Dose											
crotonic acid	n	0	12	0	0	0					
0 mg/kg											
crotonic acid	n	0	10	0	0	0					
50 mg/kg											
crotonic acid	n	0	11	0	0	0					
150 mg/kg											
crotonic acid	n	0	12	0	0	0					
500 mg/kg											

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Not calculated : NC

Table 2 - 57

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Day : 20		Period : F0 gestation				Species : Rat			
Generation : F0						Ease of removal from cage				Fur condition NC			
Test article	Dose	-1	0	1	2	3	0	1	2	3			
crotonic acid	0 mg/kg	n	0	12	0	0	0	12	0	0	0		
crotonic acid	50 mg/kg	n	0	10	0	0	0	10	0	0	0		
crotonic acid	150 mg/kg	n	0	11	0	0	0	11	0	0	0		
crotonic acid	500 mg/kg	n	0	12	0	0	0	12	0	0	0		
		Skin NC		Secretions- NC Eye, Nose		Exophthalmos NC							
Test article	Dose	0	1	2	3	0	1	0	1				
crotonic acid	0 mg/kg	n	12	0	0	0	12	0	12	0			
crotonic acid	50 mg/kg	n	10	0	0	0	10	0	10	0			
crotonic acid	150 mg/kg	n	11	0	0	0	11	0	11	0			
crotonic acid	500 mg/kg	n	12	0	0	0	12	0	12	0			

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 58

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Female		Day : 20		Period : F0 gestation		Species : Rat											
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC											
Test article		0		1		2		3		0		1		2		3					
Dose		0		1		2		3		0		1		2		3					
crotonic acid 0 mg/kg	n	12		0		0		0		12		0		0		0					
crotonic acid 50 mg/kg	n	10		0		0		0		10		0		0		0					
crotonic acid 150 mg/kg	n	11		0		0		0		11		0		0		0					
crotonic acid 500 mg/kg	n	12		0		0		0		12		0		0		0					
		Piloerection NC				Pupil size NC				Salivation NC											
Test article		0		1		-1		0		1		2		0		1		2		3	
Dose		0		1		-1		0		1		2		0		1		2		3	
crotonic acid 0 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
crotonic acid 50 mg/kg	n	10		0		0		10		0		0		10		0		0		0	
crotonic acid 150 mg/kg	n	11		0		0		11		0		0		11		0		0		0	
crotonic acid 500 mg/kg	n	12		0		0		12		0		0		12		0		0		0	
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed																					
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked																					
Lacrimation) 0: Absent, 1: Present																					
Piloerection) 0: Absent, 1: Present																					
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																					
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																					
Not calculated : NC																					

Table 2 - 59

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Species : Rat

		Abnormal NC respiration					Vocalization NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	10	0	0	0		10	0	0	0	
50 mg/kg											
crotonic acid	n	11	0	0	0		11	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											
		Reactivity to NC handling									
Test article		-1	0	1	2	3					
Dose											
crotonic acid	n	0	12	0	0	0					
0 mg/kg											
crotonic acid	n	0	10	0	0	0					
50 mg/kg											
crotonic acid	n	0	11	0	0	0					
150 mg/kg											
crotonic acid	n	0	12	0	0	0					
500 mg/kg											

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Not calculated : NC

Table 2 - 60

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
In-the-hand observation
Generation : F0 Sex : Female Day : 4 Period : F0 lactation

Study No. : R-1169

		Ease of removal- NC al from cage						Fur condition NC					
Test article													
Dose		-1	0	1	2	3		0	1	2	3		
crotonic acid	n	0	12	0	0	0		12	0	0	0		
0 mg/kg													
crotonic acid	n	0	10	0	0	0		10	0	0	0		
50 mg/kg													
crotonic acid	n	0	11	0	0	0		11	0	0	0		
150 mg/kg													
crotonic acid	n	0	12	0	0	0		12	0	0	0		
500 mg/kg													
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC					
Test article													
Dose		0	1	2	3	0	1	0	1				
crotonic acid	n	12	0	0	0	12	0	12	0				
0 mg/kg													
crotonic acid	n	10	0	0	0	10	0	10	0				
50 mg/kg													
crotonic acid	n	11	0	0	0	11	0	11	0				
150 mg/kg													
crotonic acid	n	12	0	0	0	12	0	12	0				
500 mg/kg													

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked
Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe
Secretions-Eye, Nose) 0: Absent, 1: Present
Exophthalmos) 0: Absent, 1: Present
Not calculated : NC

Table 2 - 61

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Female		Day : 4		Period : F0 lactation				Species : Rat										
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC												
Test article		0			1			2			3			0			1					
Dose		0			1			2			3			0			1					
crotonic acid	n	12			0			0			0			12			0					
0 mg/kg																						
crotonic acid	n	10			0			0			0			10			0					
50 mg/kg																						
crotonic acid	n	11			0			0			0			11			0					
150 mg/kg																						
crotonic acid	n	12			0			0			0			12			0					
500 mg/kg																						
Piloerection NC						Pupil size NC						Salivation NC										
Test article		0			1			-1			0			1			2			3		
Dose		0			1			-1			0			1			2			3		
crotonic acid	n	12			0			0			12			0			12			0		
0 mg/kg																						
crotonic acid	n	10			0			0			10			0			10			0		
50 mg/kg																						
crotonic acid	n	11			0			0			11			0			11			0		
150 mg/kg																						
crotonic acid	n	12			0			0			12			0			12			0		
500 mg/kg																						
Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed																						
Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked																						
Lacrimation) 0: Absent, 1: Present																						
Piloerection) 0: Absent, 1: Present																						
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																						
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																						
Not calculated : NC																						

Table 2 - 62

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
In-the-hand observation
Generation : F0 Sex : Female Day : 4 Period : F0 lactation

Study No. : R-1169

		Abnormal NC respiration					Vocalization NC					Species : Rat	
Test article	Dose	0	1	2	3		0	1	2	3			
crotonic acid	0 mg/kg	n	12	0	0	0	11	1	0	0			
crotonic acid	50 mg/kg	n	10	0	0	0	10	0	0	0			
crotonic acid	150 mg/kg	n	11	0	0	0	11	0	0	0			
crotonic acid	500 mg/kg	n	12	0	0	0	12	0	0	0			

		Reactivity to NC handling						
Test article	Dose	-1	0	1	2	3		
crotonic acid	0 mg/kg	n	0	12	0	0	0	
crotonic acid	50 mg/kg	n	0	10	0	0	0	
crotonic acid	150 mg/kg	n	0	11	0	0	0	
crotonic acid	500 mg/kg	n	0	12	0	0	0	

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward
Not calculated : NC

Table 2 - 63

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Week : 1		Period : Administration		Species : Rat					
Generation : F0													
		Ease of removal- NC					Fur condition NC						
		al from cage											
Test article													
Dose		-1	0	1	2	3	0	1	2	3			
crotonic acid	n	0	10	0	0	0	10	0	0	0			
0 mg/kg													
crotonic acid	n	0	10	0	0	0	10	0	0	0			
500 mg/kg													
		Skin NC					Secretions- NC		Exophthalmos NC				
							Eye, Nose						
Test article		0	1	2	3	0	1	0	1				
Dose													
crotonic acid	n	10	0	0	0	10	0	10	0				
0 mg/kg													
crotonic acid	n	10	0	0	0	10	0	10	0				
500 mg/kg													
		Palpebral NC					Mucosal NC					Lacrimation NC	
		closure					membranes						
Test article		0	1	2	3	0	1	2	3	0	1		
Dose													
crotonic acid	n	10	0	0	0	10	0	0	0	10	0		
0 mg/kg													
crotonic acid	n	10	0	0	0	10	0	0	0	10	0		
500 mg/kg													

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Normal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 64

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : Administration

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Piloerection NC			Pupil size NC					Salivation NC					
Test article	Dose	0		1	-1		0	1	2	0		1	2	3	
crotonic acid	0 mg/kg	n	10	0	0		10	0	0	10		0	0	0	
crotonic acid	500 mg/kg	n	10	0	0		10	0	0	10		0	0	0	
		Abnormal NC respiration					Vocalization NC								
Test article	Dose	0		1	2	3	0		1	2	3				
crotonic acid	0 mg/kg	n	10	0	0	0	10		0	0	0				
crotonic acid	500 mg/kg	n	10	0	0	0	9		1	0	0				
		Reactivity to NC handling													
Test article	Dose	-1		0	1	2	3								
crotonic acid	0 mg/kg	n	0	10	0	0	0								
crotonic acid	500 mg/kg	n	0	10	0	0	0								
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe															
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive															
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward															
Not calculated : NC															

Table 2 - 65

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Week : 2		Period : Administration		Species : Rat			
Generation : F0				Ease of removal- NC				Fur condition NC			
				al from cage							
Test article											
Dose		-1	0	1	2	3	0	1	2	3	
crotonic acid	n	0	10	0	0	0	10	0	0	0	
0 mg/kg											
crotonic acid	n	0	10	0	0	0	10	0	0	0	
500 mg/kg											
		Skin NC		Secretions- NC		Exophthalmos NC					
				Eye, Nose							
Test article		0	1	2	3	0	1	0	1		
Dose											
crotonic acid	n	10	0	0	0	10	0	10	0		
0 mg/kg											
crotonic acid	n	10	0	0	0	10	0	10	0		
500 mg/kg											
		Palpebral NC		Mucosal NC		Lacrimation NC					
		closure		membranes							
Test article		0	1	2	3	0	1	2	3	0	1
Dose											
crotonic acid	n	10	0	0	0	10	0	0	0	10	0
0 mg/kg											
crotonic acid	n	10	0	0	0	10	0	0	0	10	0
500 mg/kg											

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Normal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 66

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
In-the-hand observation
Generation : F0 Sex : Female Week : 2 Period : Administration

Study No. : R-1169

		Piloerection NC			Pupil size NC				Salivation NC						
Test article	Dose	0		1	-1		0	1	2	0		1	2	3	
crotonic acid	0 mg/kg	n	10	0	0		10	0	0	10		0	0	0	
crotonic acid	500 mg/kg	n	10	0	0		10	0	0	10		0	0	0	
		Abnormal NC respiration					Vocalization NC								
Test article	Dose	0		1	2	3	0		1	2	3				
crotonic acid	0 mg/kg	n	10	0	0	0	10		0	0	0				
crotonic acid	500 mg/kg	n	10	0	0	0	10		0	0	0				
		Reactivity to NC handling													
Test article	Dose	-1		0	1	2	3								
crotonic acid	0 mg/kg	n	0	10	0	0	0								
crotonic acid	500 mg/kg	n	0	10	0	0	0								
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe															
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive															
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward															
Not calculated : NC															

Table 2 - 67

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Week : 3		Period : Administration		Species : Rat			
Generation : F0				Ease of removal- NC al from cage				Fur condition NC			
Test article											
Dose		-1	0	1	2	3	0	1	2	3	
crotonic acid 0 mg/kg	n	0	10	0	0	0	10	0	0	0	
crotonic acid 500 mg/kg	n	0	10	0	0	0	10	0	0	0	
		Skin NC		Secretions- NC Eye, Nose		Exophthalmos NC					
Test article											
Dose		0	1	2	3	0	1	0	1		
crotonic acid 0 mg/kg	n	10	0	0	0	10	0	10	0		
crotonic acid 500 mg/kg	n	10	0	0	0	10	0	10	0		
		Palpebral NC closure		Mucosal NC membranes		Lacrimation NC					
Test article											
Dose		0	1	2	3	0	1	2	3	0	1
crotonic acid 0 mg/kg	n	10	0	0	0	10	0	0	0	10	0
crotonic acid 500 mg/kg	n	10	0	0	0	10	0	0	0	10	0

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Normal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 68

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : Administration

Generation : F0

Sex : Female

Week : 3

Species : Rat

		Piloerection NC			Pupil size NC					Salivation NC					
Test article	Dose	0		1	-1		0	1	2	0		1	2	3	
crotonic acid	0 mg/kg	n	10	0	0		10	0	0	10		0	0	0	
crotonic acid	500 mg/kg	n	10	0	0		10	0	0	10		0	0	0	
		Abnormal NC respiration					Vocalization NC								
Test article	Dose	0		1	2	3	0		1	2	3				
crotonic acid	0 mg/kg	n	10	0	0	0	10		0	0	0				
crotonic acid	500 mg/kg	n	10	0	0	0	10		0	0	0				
		Reactivity to NC handling													
Test article	Dose	-1		0	1	2	3								
crotonic acid	0 mg/kg	n	0	10	0	0	0								
crotonic acid	500 mg/kg	n	0	10	0	0	0								
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe															
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive															
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward															
Not calculated : NC															

Table 2 - 69

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

		In-the-hand observation		Sex : Female		Week : 4		Period : Administration				Species : Rat	
						Ease of remov- NC				Fur condition NC			
						al from cage							
Test article													
Dose		-1	0	0	1	2	3	0	1	2	3		
crotonic acid	n	0	10	0	0	0	0	10	0	0	0		
0 mg/kg													
crotonic acid	n	0	10	0	0	0	0	10	0	0	0		
500 mg/kg													
				Skin NC				Secretions- NC		Exophthalmos NC			
						Eye, Nose							
Test article		0	1	2	3	0	1	0	1	0 <td colspan="2"></td>			
Dose													
crotonic acid	n	10	0	0	0	10	0	10	0	0			
0 mg/kg													
crotonic acid	n	10	0	0	0	10	0	10	0	0			
500 mg/kg													
				Palpebral NC				Mucosal NC		Lacrimation NC			
				closure				membranes					
Test article		0	1	2	3	0	1	2	3	0			
Dose													
crotonic acid	n	10	0	0	0	10	0	0	0	10			
0 mg/kg													
crotonic acid	n	10	0	0	0	10	0	0	0	10			
500 mg/kg													

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Normal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 70

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
In-the-hand observation
Generation : F0 Sex : Female Week : 4 Period : Administration

Study No. : R-1169

		Generation : F0			Sex : Female		Week : 4		Species : Rat						
		Piloerection NC			Pupil size NC					Salivation NC					
Test article															
Dose		0	1		-1	0	0	1	2	0	0	1	2	3	0
crotonic acid	n	10	0		0		10	0	0		10	0	0		0
0 mg/kg															
crotonic acid	n	10	0		0		10	0	0		10	0	0		0
500 mg/kg															
		Abnormal NC respiration					Vocalization NC								
Test article															
Dose		0	1	2	3		0	1	2	3					
crotonic acid	n	10	0	0	0		10	0	0	0					
0 mg/kg															
crotonic acid	n	10	0	0	0		10	0	0	0					
500 mg/kg															
		Reactivity to NC handling													
Test article															
Dose		-1	0	1	2	3									
crotonic acid	n	0	10	0	0	0									
0 mg/kg															
crotonic acid	n	0	10	0	0	0									
500 mg/kg															
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe															
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive															
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward															
Not calculated : NC															

Table 2 - 71

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Week : 5		Period : Administration		Species : Rat										
Generation : F0																		
		Ease of removal- NC al from cage					Fur condition NC											
Test article	Dose																	
crotonic acid	0 mg/kg	n	-1	0	10	0	2	0	3	0	0	10	1	0	2	0	3	0
crotonic acid	500 mg/kg	n		0	10	0	0	0	0	10	0	0	0	0				0

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Normal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 72

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
In-the-hand observation
Generation : F0 Sex : Female Week : 5 Period : Administration

Study No. : R-1169

		Generation : F0			Sex : Female		Week : 5					Species : Rat		
		Piloerection NC						Pupil size NC			Salivation NC			
Test article														
Dose		0	1		-1	0	0	1	2	0	0	1	2	3
crotonic acid	n	10	0	0	0	10	0	0	0	10	0	0	0	0
0 mg/kg														
crotonic acid	n	10	0	0	0	10	0	0	0	10	0	0	0	0
500 mg/kg														
Abnormal NC respiration														
Vocalization NC														
Test article														
Dose		0	1	2	3	0	1	2	3	0				
crotonic acid	n	10	0	0	0	0	10	0	0	0				
0 mg/kg														
crotonic acid	n	10	0	0	0	0	10	0	0	0				
500 mg/kg														
Reactivity to NC handling														
Test article														
Dose		-1	0	1	2	3	0							
crotonic acid	n	0	10	0	0	0	0							
0 mg/kg														
crotonic acid	n	0	10	0	0	0	0							
500 mg/kg														
Piloerection) 0: Absent, 1: Present														
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis														
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked														
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe														
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive														
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward														
Not calculated : NC														

Table 2 - 73

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Week : 6		Period : Administration		Species : Rat				
Generation : F0												
		Ease of removal- NC al from cage					Fur condition NC					
Test article	Dose											
crotonic acid	0 mg/kg	n	-1	0	0	10	1	0	2	0	3	0
crotonic acid	500 mg/kg	n		0	10	0	0	0	10	0	0	0
Skin NC												
Secretions- NC Eye, Nose												
Exophthalmos NC												
Test article	Dose											
crotonic acid	0 mg/kg	n	0	1	2	3	0	1	0	1	0	
crotonic acid	500 mg/kg	n	10	0	0	0	10	0	10	0		
Palpebral NC closure												
Mucosal NC membranes												
Lacrimation NC												
Test article	Dose											
crotonic acid	0 mg/kg	n	0	1	2	3	0	1	2	3	0	1
crotonic acid	500 mg/kg	n	10	0	0	0	10	0	0	0	10	0

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Normal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 74

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
In-the-hand observation
Generation : F0 Sex : Female Week : 6 Period : Administration

Study No. : R-1169

		Generation : F0			Sex : Female		Week : 6		Species : Rat					
		Piloerection NC			Pupil size NC				Salivation NC					
Test article														
Dose		0	1		-1	0	1	2	0	0	1	2	3	
crotonic acid	n	10	0	0	0	10	0	0	10	0	0	0	0	
0 mg/kg														
crotonic acid	n	10	0	0	10	0	0	10	0	0	0	0	0	
500 mg/kg														
		Abnormal NC respiration				Vocalization NC								
Test article														
Dose		0	1	2	3	0	1	2	3					
crotonic acid	n	10	0	0	0	10	0	0	0					
0 mg/kg														
crotonic acid	n	10	0	0	0	10	0	0	0					
500 mg/kg														
		Reactivity to NC handling												
Test article														
Dose		-1	0	1	2	3								
crotonic acid	n	0	10	0	0	0								
0 mg/kg														
crotonic acid	n	0	10	0	0	0								
500 mg/kg														
Piloerection) 0: Absent, 1: Present														
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis														
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked														
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe														
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive														
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward														
Not calculated : NC														

Table 2 - 75

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Male		Week : 1		Period : Recovery		Species : Rat			
Generation : F0				Ease of removal- NC al from cage				Fur condition NC			
Test article											
Dose		-1	0	1	2	3	0	1	2	3	
crotonic acid 0 mg/kg	n	0	5	0	0	0	5	0	0	0	0
crotonic acid 500 mg/kg	n	0	5	0	0	0	5	0	0	0	
		Skin NC		Secretions- NC Eye, Nose		Exophthalmos NC					
Test article											
Dose		0	1	2	3	0	1	0	1		
crotonic acid 0 mg/kg	n	5	0	0	0	5	0	5	0		
crotonic acid 500 mg/kg	n	5	0	0	0	5	0	5	0		
		Palpebral NC closure		Mucosal NC membranes		Lacrimation NC					
Test article											
Dose		0	1	2	3	0	1	2	3	0	1
crotonic acid 0 mg/kg	n	5	0	0	0	5	0	0	0	5	0
crotonic acid 500 mg/kg	n	5	0	0	0	5	0	0	0	5	0

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Normal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 76

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
In-the-hand observation
Generation : F0 Sex : Male Week : 1 Period : Recovery

Study No. : R-1169

		Piloerection NC			Pupil size NC					Salivation NC							
Test article																	
Dose																	
crotonic acid	n	0	1	0	-1	0	0	1	2	0	0	1	0	2	0	3	0
0 mg/kg		5			0			5	0		5		0		0		0
crotonic acid	n	5	0	0	5	0	0	5	0	0	5	0	0	0	0		0
500 mg/kg																	
		Abnormal NC respiration					Vocalization NC										
Test article																	
Dose																	
crotonic acid	n	0	1	2	3	0	0	1	2	3	0						
0 mg/kg		5	0	0		0	5	0	0		0						
crotonic acid	n	5	0	0	0	5	0	0	0	0							
500 mg/kg																	
		Reactivity to NC handling															
Test article																	
Dose																	
crotonic acid	n	-1	0	1	2	3	0										
0 mg/kg		0	5	0	0		0										
crotonic acid	n	0	5	0	0	0											
500 mg/kg																	
Piloerection) 0: Absent, 1: Present																	
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis																	
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																	
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe																	
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive																	
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward																	
Not calculated : NC																	

Table 2 - 77

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		In-the-hand observation		Sex : Male		Week : 2		Period : Recovery				Species : Rat	
						Ease of remov- NC				Fur condition NC			
						al from cage							
Test article													
Dose		-1	0	0	1	2	3	0	1	2	3		
crotonic acid	n	0	5	0	0	0	0	5	0	0	0		
0 mg/kg													
crotonic acid	n	0	5	0	0	0	0	5	0	0	0		
500 mg/kg													
						Skin NC		Secretions- NC		Exophthalmos NC			
						Eye, Nose							
Test article													
Dose		0	1	2	3	0	1	0	1	0	1		
crotonic acid	n	5	0	0	0	5	0	5	0	5	0		
0 mg/kg													
crotonic acid	n	5	0	0	0	5	0	5	0				
500 mg/kg													
						Palpebral NC		Mucosal NC		Lacrimation NC			
						closure		membranes					
Test article													
Dose		0	1	2	3	0	1	2	3	0	1		
crotonic acid	n	5	0	0	0	5	0	0	0	5	0		
0 mg/kg													
crotonic acid	n	5	0	0	0	5	0	0	0	5	0		
500 mg/kg													

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Normal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 78

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Species : Rat

		Piloerection NC			Pupil size NC				Salivation NC					
Test article														
Dose		0	1		-1	0	1	2	0	1	2	3		
crotonic acid 0 mg/kg	n	5	0		0	5	0	0	5	0	0	0		
crotonic acid 500 mg/kg	n	5	0		0	5	0	0	5	0	0	0		
		Abnormal NC respiration				Vocalization NC								
Test article		0	1	2	3	0	1	2	3					
Dose														
crotonic acid 0 mg/kg	n	5	0	0	0	5	0	0	0					
crotonic acid 500 mg/kg	n	4	1	0	0	5	0	0	0					
		Reactivity to NC handling												
Test article		-1	0	1	2	3								
Dose														
crotonic acid 0 mg/kg	n	0	5	0	0	0								
crotonic acid 500 mg/kg	n	0	5	0	0	0								
Piloerection) 0: Absent, 1: Present														
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis														
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked														
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe														
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive														
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward														
Not calculated : NC														

Table 2 - 79

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation

Period : Recovery

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Ease of removal from cage					Fur condition NC				
Test article		-1	0	1	2	3	0	1	2	3	
Dose											
crotonic acid	n	0	5	0	0	0	5	0	0	0	
0 mg/kg											
crotonic acid	n	0	5	0	0	0	5	0	0	0	
500 mg/kg											
		Skin NC				Secretions- NC Eye, Nose			Exophthalmos NC		
Test article		0	1	2	3	0	1		0	1	
Dose											
crotonic acid	n	5	0	0	0	5	0		5	0	
0 mg/kg											
crotonic acid	n	5	0	0	0	5	0		5	0	
500 mg/kg											
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC	
Test article		0	1	2	3	0	1	2	3	0	1
Dose											
crotonic acid	n	5	0	0	0	5	0	0	0	5	0
0 mg/kg											
crotonic acid	n	5	0	0	0	5	0	0	0	5	0
500 mg/kg											

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Normal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Normal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 80

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Week : 1		Period : Recovery		Species : Rat	
Generation : F0		Piloerection NC		Pupil size NC		Salivation NC			
Test article		0		1		-1		0	
Dose		0		1		2		0	
crotonic acid	n	5	0	0	5	0	0	5	0
0 mg/kg									
crotonic acid	n	5	0	0	5	0	0	5	0
500 mg/kg									
		Abnormal NC		Vocalization NC					
		respiration							
Test article		0		1		2		3	
Dose		0		1		2		3	
crotonic acid	n	5	0	0	0	5	0	0	0
0 mg/kg									
crotonic acid	n	5	0	0	0	5	0	0	0
500 mg/kg									
		Reactivity to NC							
		handling							
Test article		-1		0		1		2	
Dose		-1		0		1		2	
crotonic acid	n	0	5	0	0	0	0	0	0
0 mg/kg									
crotonic acid	n	0	5	0	0	0	0	0	0
500 mg/kg									

Piloerection) 0: Absent, 1: Present
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward
Not calculated : NC

Table 2 - 81

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

In-the-hand observation		Sex : Female		Week : 2		Period : Recovery		Species : Rat			
Generation : F0				Ease of remov- NC al from cage				Fur condition NC			
Test article											
Dose		-1	0	1	2	3	0	1	2	3	
crotonic acid 0 mg/kg	n	0	5	0	0	0	5	0	0	0	
crotonic acid 500 mg/kg	n	0	5	0	0	0	5	0	0	0	
		Skin NC		Secretions- NC Eye, Nose		Exophthalmos NC					
Test article											
Dose		0	1	2	3	0	1	0	1		
crotonic acid 0 mg/kg	n	5	0	0	0	5	0	5	0		
crotonic acid 500 mg/kg	n	5	0	0	0	5	0	5	0		
		Palpebral NC closure		Mucosal NC membranes		Lacrimation NC					
Test article											
Dose		0	1	2	3	0	1	2	3	0	1
crotonic acid 0 mg/kg	n	5	0	0	0	5	0	0	0	5	0
crotonic acid 500 mg/kg	n	5	0	0	0	5	0	0	0	5	0

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Not calculated : NC

Table 2 - 82

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
In-the-hand observation
Generation : F0 Sex : Female Week : 2 Period : Recovery

Study No. : R-1169

		Piloerection NC			Pupil size NC				Salivation NC				
Test article													
Dose		0	1		-1	0	1	2	0	1	2	3	
crotonic acid	n	5	0		0	5	0	0	5	0	0	0	
0 mg/kg													
crotonic acid	n	5	0		0	5	0	0	5	0	0	0	
500 mg/kg													
		Abnormal NC respiration				Vocalization NC							
Test article													
Dose		0	1	2	3	0	1	2	3				
crotonic acid	n	5	0	0	0	5	0	0	0				
0 mg/kg													
crotonic acid	n	5	0	0	0	5	0	0	0				
500 mg/kg													
		Reactivity to NC handling											
Test article													
Dose		-1	0	1	2	3							
crotonic acid	n	0	5	0	0	0							
0 mg/kg													
crotonic acid	n	0	5	0	0	0							
500 mg/kg													
Piloerection) 0: Absent, 1: Present													
Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis													
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked													
Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe													
Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive													
Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward													
Not calculated : NC													

Table 2 - 83

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
50 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 84

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Male		Week : 1		Period : F0 before mating				Species : Rat			
		Gait NC				Posture NC							
Test article													
Dose		U	0	1	2	3	N	F	H				
crotonic acid 0 mg/kg	n	0	12	0	0	0	12	0	0				
crotonic acid 50 mg/kg	n	0	12	0	0	0	12	0	0				
crotonic acid 150 mg/kg	n	0	12	0	0	0	12	0	0				
crotonic acid 500 mg/kg	n	0	12	0	0	0	12	0	0				
		Grooming NC				Urination NC							
Test article													
Dose		0	1	2	0	1	2	3					
crotonic acid 0 mg/kg	n	12	0	0	12	0	0	0					
crotonic acid 50 mg/kg	n	12	0	0	9	3	0	0					
crotonic acid 150 mg/kg	n	12	0	0	12	0	0	0					
crotonic acid 500 mg/kg	n	12	0	0	12	0	0	0					
Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly													
Posture) N: Normal, F: Flattened, H: Hunched													
Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)													
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount													
Not calculated : NC													

Table 2 - 85

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats				Period : F0 before mating	
Open field observation		Sex : Male	Week : 1		Species : Rat
	Rearing	Defecation count			
Test article					
Dose					
crotonic acid 0 mg/kg	n	12	12		
	Mean	4	1		
	S.D.	2	1		
crotonic acid 50 mg/kg	n	12	12		
	Mean	4	0		
	S.D.	1	0		
crotonic acid 150 mg/kg	n	12	12		
	Mean	5	0		
	S.D.	2	0		
crotonic acid 500 mg/kg	n	12	12		
	Mean	5	0		
	S.D.	2	0		
Not significantly different from crotonic acid 0 mg/kg					

Table 2 - 86

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
50 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 87

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Male		Week : 2		Period : F0 before mating				Species : Rat			
Generation : F0				Gait NC				Posture NC					
Test article													
Dose		U	0	1	2	3	N	F	H				
crotonic acid 0 mg/kg	n	0	12	0	0	0	12	0	0				
crotonic acid 50 mg/kg	n	0	12	0	0	0	12	0	0				
crotonic acid 150 mg/kg	n	0	12	0	0	0	12	0	0				
crotonic acid 500 mg/kg	n	0	12	0	0	0	12	0	0				
		Grooming NC				Urination NC							
Test article													
Dose		0	1	2	0	1	2	3					
crotonic acid 0 mg/kg	n	12	0	0	10	2	0	0					
crotonic acid 50 mg/kg	n	12	0	0	10	1	1	0					
crotonic acid 150 mg/kg	n	12	0	0	11	1	0	0					
crotonic acid 500 mg/kg	n	12	0	0	12	0	0	0					
Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly													
Posture) N: Normal, F: Flattened, H: Hunched													
Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)													
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount													
Not calculated : NC													

Table 2 - 88

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Male Week : 2 Period : F0 before mating

Study No. : R-1169

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid 0 mg/kg	n	12	12
	Mean	4	0
	S.D.	2	1
crotonic acid 50 mg/kg	n	12	12
	Mean	5	0
	S.D.	3	0
crotonic acid 150 mg/kg	n	12	12
	Mean	5	0
	S.D.	3	0
crotonic acid 500 mg/kg	n	12	12
	Mean	4	0
	S.D.	2	0

Not significantly different from crotonic acid 0 mg/kg

Table 2 - 89

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 3

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
50 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe
Not calculated : NC

Table 2 - 90

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 3

Species : Rat

		Gait NC					Posture NC				
Test article		U	0	1	2	3	N	F	H		
Dose											
crotonic acid 0 mg/kg	n	0	12	0	0	0	12	0	0		
crotonic acid 50 mg/kg	n	0	12	0	0	0	12	0	0		
crotonic acid 150 mg/kg	n	0	12	0	0	0	12	0	0		
crotonic acid 500 mg/kg	n	0	12	0	0	0	12	0	0		
		Grooming NC				Urination NC					
Test article		0	1	2		0	1	2	3		
Dose											
crotonic acid 0 mg/kg	n	12	0	0		10	2	0	0		
crotonic acid 50 mg/kg	n	12	0	0		12	0	0	0		
crotonic acid 150 mg/kg	n	12	0	0		11	1	0	0		
crotonic acid 500 mg/kg	n	12	0	0		11	1	0	0		

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Not calculated : NC

Table 2 - 91

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats				Period : F0 mating
Open field observation		Sex : Male	Week : 3	Species : Rat
	Rearing	Defecation count		
Test article				
Dose				
crotonic acid 0 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
crotonic acid 50 mg/kg	n	12	12	
	Mean	5	0	
	S.D.	2	1	
crotonic acid 150 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	1	
crotonic acid 500 mg/kg	n	12	12	
	Mean	5	0	
	S.D.	2	0	
Not significantly different from crotonic acid 0 mg/kg				

Table 2 - 92

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 4

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
50 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 93

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Male		Week : 4		Period : F0 mating		Species : Rat			
		Gait NC					Posture NC				
Test article											
Dose		U	0	1	2	3	N	F	H		
crotonic acid 0 mg/kg	n	0	12	0	0	0	12	0	0		
crotonic acid 50 mg/kg	n	0	12	0	0	0	12	0	0		
crotonic acid 150 mg/kg	n	0	12	0	0	0	12	0	0		
crotonic acid 500 mg/kg	n	0	12	0	0	0	12	0	0		
Grooming NC					Urination NC						
Test article											
Dose		0	1	2	0	1	2	3			
crotonic acid 0 mg/kg	n	12	0	0	11	1	0	0			
crotonic acid 50 mg/kg	n	12	0	0	12	0	0	0			
crotonic acid 150 mg/kg	n	12	0	0	12	0	0	0			
crotonic acid 500 mg/kg	n	12	0	0	12	0	0	0			
Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly											
Posture) N: Normal, F: Flattened, H: Hunched											
Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)											
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount											
Not calculated : NC											

Table 2 - 94

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Male Week : 4 Period : F0 mating

Study No. : R-1169

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid 0 mg/kg	n	12	12
	Mean	5	0
	S.D.	2	0
crotonic acid 50 mg/kg	n	12	12
	Mean	4	0
	S.D.	2	0
crotonic acid 150 mg/kg	n	12	12
	Mean	4	0
	S.D.	2	0
crotonic acid 500 mg/kg	n	12	12
	Mean	4	0
	S.D.	1	0
			EF

Not significantly different from crotonic acid 0 mg/kg
EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 95

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Species : Rat

		Arousal NC					Convulsion NC				
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
crotonic acid 0 mg/kg	n	0	0	12	0	0	12	0	0	0	
crotonic acid 50 mg/kg	n	0	0	12	0	0	12	0	0	0	
crotonic acid 150 mg/kg	n	0	0	12	0	0	12	0	0	0	
crotonic acid 500 mg/kg	n	0	0	12	0	0	12	0	0	0	
		Abnormal NC behavior					Stereotypy NC				
Test article											
Dose		0	1	2	3		0	1	2	3	
crotonic acid 0 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 50 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 150 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 500 mg/kg	n	12	0	0	0		12	0	0	0	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 96

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Species : Rat

		Gait NC					Posture NC				
Test article		U	0	1	2	3	N	F	H		
Dose											
crotonic acid	n	0	12	0	0	0	12	0	0		
0 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
50 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
150 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
500 mg/kg											
		Grooming NC				Urination NC					
Test article		0	1	2		0	1	2	3		
Dose											
crotonic acid	n	12	0	0		10	2	0	0		
0 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
50 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
150 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
500 mg/kg											

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Not calculated : NC

Table 2 - 97

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Male Week : 5 Period : F0 mating

Study No. : R-1169

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid 0 mg/kg	n	12	12
	Mean	5	0
	S.D.	1	0
crotonic acid 50 mg/kg	n	12	12
	Mean	4	0
	S.D.	1	1
crotonic acid 150 mg/kg	n	12	12
	Mean	4	0
	S.D.	1	0
crotonic acid 500 mg/kg	n	12	12
	Mean	5	0
	S.D.	1	0

Not significantly different from crotonic acid 0 mg/kg

Table 2 - 98

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
50 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 99

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Species : Rat

		Gait NC					Posture NC				
Test article		U	0	1	2	3	N	F	H		
Dose											
crotonic acid	n	0	12	0	0	0	12	0	0		
0 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
50 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
150 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
500 mg/kg											
		Grooming NC				Urination NC					
Test article		0	1	2		0	1	2	3		
Dose											
crotonic acid	n	12	0	0		11	1	0	0		
0 mg/kg											
crotonic acid	n	12	0	0		9	3	0	0		
50 mg/kg											
crotonic acid	n	12	0	0		11	1	0	0		
150 mg/kg											
crotonic acid	n	12	0	0		10	2	0	0		
500 mg/kg											

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Not calculated : NC

Table 2 - 100

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Male Week : 6 Period : F0 mating

Study No. : R-1169

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid 0 mg/kg	n	12	12
	Mean	5	0
	S.D.	2	0
crotonic acid 50 mg/kg	n	12	12
	Mean	4	0
	S.D.	2	0
			EF
crotonic acid 150 mg/kg	n	12	12
	Mean	4	0
	S.D.	2	0
			EF
crotonic acid 500 mg/kg	n	12	12
	Mean	4	0
	S.D.	1	0
			EF

Not significantly different from crotonic acid 0 mg/kg
EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 101

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
50 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 102

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Gait NC					Posture NC				
Test article		U	0	1	2	3	N	F	H		
Dose											
crotonic acid	n	0	12	0	0	0	12	0	0		
0 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
50 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
150 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
500 mg/kg											
		Grooming NC				Urination NC					
Test article		0	1	2		0	1	2	3		
Dose											
crotonic acid	n	12	0	0		12	0	0	0		
0 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
50 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
150 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
500 mg/kg											

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly
Posture) N: Normal, F: Flattened, H: Hunched
Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 103

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid	n	12	12
0 mg/kg	Mean	6	0
	S.D.	1	0
crotonic acid	n	12	12
50 mg/kg	Mean	7	0
	S.D.	2	0
			EF
crotonic acid	n	12	12
150 mg/kg	Mean	6	0
	S.D.	2	0
			EF
crotonic acid	n	12	12
500 mg/kg	Mean	6	0
	S.D.	2	0
			EF

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 104

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Species : Rat

		Arousal NC					Convulsion NC				
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
crotonic acid 0 mg/kg	n	0	0	12	0	0	12	0	0	0	
crotonic acid 50 mg/kg	n	0	0	12	0	0	12	0	0	0	
crotonic acid 150 mg/kg	n	0	0	12	0	0	12	0	0	0	
crotonic acid 500 mg/kg	n	0	0	12	0	0	12	0	0	0	
		Abnormal NC behavior					Stereotypy NC				
Test article											
Dose		0	1	2	3		0	1	2	3	
crotonic acid 0 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 50 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 150 mg/kg	n	12	0	0	0		12	0	0	0	
crotonic acid 500 mg/kg	n	12	0	0	0		12	0	0	0	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 105

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Species : Rat

		Gait NC					Posture NC				
Test article		U	0	1	2	3	N	F	H		
Dose											
crotonic acid	n	0	12	0	0	0	12	0	0		
0 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
50 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
150 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
500 mg/kg											
		Grooming NC				Urination NC					
Test article		0	1	2		0	1	2	3		
Dose											
crotonic acid	n	12	0	0		11	1	0	0		
0 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
50 mg/kg											
crotonic acid	n	12	0	0		11	1	0	0		
150 mg/kg											
crotonic acid	n	12	0	0		11	1	0	0		
500 mg/kg											

Gait) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Not calculated : NC

Table 2 - 106

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Female Week : 2 Period : F0 before mating

Study No. : R-1169

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid 0 mg/kg	n	12	12
	Mean	6	0
	S.D.	2	0
crotonic acid 50 mg/kg	n	12	12
	Mean	7	0
	S.D.	2	0
			EF
crotonic acid 150 mg/kg	n	12	12
	Mean	7	0
	S.D.	3	0
			EF
crotonic acid 500 mg/kg	n	12	12
	Mean	6	0
	S.D.	2	0
			EF

Not significantly different from crotonic acid 0 mg/kg
EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 107

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	10	0	0	10	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	11	0	0	11	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	10	0	0	0		10	0	0	0	
50 mg/kg											
crotonic acid	n	11	0	0	0		11	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 108

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Female Day : 1 Period : F0 gestation

Study No. : R-1169

		Gait NC					Posture NC					Species : Rat	
Test article	Dose	U	0	1	2	3	N	F	H				
crotonic acid	0 mg/kg	n	0	12	0	0	0	12	0	0			
crotonic acid	50 mg/kg	n	0	10	0	0	0	10	0	0			
crotonic acid	150 mg/kg	n	0	11	0	0	0	11	0	0			
crotonic acid	500 mg/kg	n	0	12	0	0	0	12	0	0			

		Grooming NC			Urination NC				
Test article	Dose	0	1	2	0	1	2	3	
crotonic acid	0 mg/kg	n	12	0	0	11	1	0	0
crotonic acid	50 mg/kg	n	10	0	0	10	0	0	0
crotonic acid	150 mg/kg	n	11	0	0	10	1	0	0
crotonic acid	500 mg/kg	n	12	0	0	12	0	0	0

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly
Posture) N: Normal, F: Flattened, H: Hunched
Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 109

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Female Day : 1 Period : F0 gestation

Study No. : R-1169

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid	n	12	12
0 mg/kg	Mean	7	0
	S.D.	2	0
crotonic acid	n	10	10
50 mg/kg	Mean	8	0
	S.D.	2	0
			EF
crotonic acid	n	11	11
150 mg/kg	Mean	6	0
	S.D.	1	0
			EF
crotonic acid	n	12	12
500 mg/kg	Mean	6	0
	S.D.	2	0
			EF

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 110

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	10	0	0	10	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	11	0	0	11	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	10	0	0	0		10	0	0	0	
50 mg/kg											
crotonic acid	n	11	0	0	0		11	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 111

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Species : Rat

		Gait NC					Posture NC				
Test article		U	0	1	2	3	N	F	H		
Dose											
crotonic acid	n	0	12	0	0	0	12	0	0		
0 mg/kg											
crotonic acid	n	0	10	0	0	0	10	0	0		
50 mg/kg											
crotonic acid	n	0	11	0	0	0	11	0	0		
150 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
500 mg/kg											
		Grooming NC				Urination NC					
Test article		0	1	2		0	1	2	3		
Dose											
crotonic acid	n	12	0	0		12	0	0	0		
0 mg/kg											
crotonic acid	n	10	0	0		10	0	0	0		
50 mg/kg											
crotonic acid	n	11	0	0		11	0	0	0		
150 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
500 mg/kg											

Gait) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Not calculated : NC

Table 2 - 112

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Female Day : 7 Period : F0 gestation

Study No. : R-1169

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid 0 mg/kg	n	12	12
	Mean	7	0
	S.D.	2	0
crotonic acid 50 mg/kg	n	10	10
	Mean	8	0
	S.D.	1	0
			EF
crotonic acid 150 mg/kg	n	11	11
	Mean	7	0
	S.D.	2	0
			EF
crotonic acid 500 mg/kg	n	12	12
	Mean	7	0
	S.D.	2	0
			EF

Not significantly different from crotonic acid 0 mg/kg
EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 113

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	10	0	0	10	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	11	0	0	11	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	10	0	0	0		10	0	0	0	
50 mg/kg											
crotonic acid	n	11	0	0	0		11	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 114

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Female Day : 14 Period : F0 gestation

Study No. : R-1169

		Gait NC					Posture NC					Species : Rat	
Test article													
Dose		U	0	1	2	3	N	F	H				
crotonic acid 0 mg/kg	n	0	12	0	0	0	12	0	0				
crotonic acid 50 mg/kg	n	0	10	0	0	0	10	0	0				
crotonic acid 150 mg/kg	n	0	11	0	0	0	11	0	0				
crotonic acid 500 mg/kg	n	0	12	0	0	0	12	0	0				

		Grooming NC			Urination NC				
Test article									
Dose		0	1	2	0	1	2	3	
crotonic acid 0 mg/kg	n	12	0	0	12	0	0	0	
crotonic acid 50 mg/kg	n	10	0	0	10	0	0	0	
crotonic acid 150 mg/kg	n	11	0	0	11	0	0	0	
crotonic acid 500 mg/kg	n	12	0	0	12	0	0	0	

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly
Posture) N: Normal, F: Flattened, H: Hunched
Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 115

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Female Day : 14 Period : F0 gestation

Study No. : R-1169

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid	n	12	12
0 mg/kg	Mean	6	0
	S.D.	1	0
crotonic acid	n	10	10
50 mg/kg	Mean	7	0
	S.D.	2	0
			EF
crotonic acid	n	11	11
150 mg/kg	Mean	6	0
	S.D.	1	0
			EF
crotonic acid	n	12	12
500 mg/kg	Mean	6	0
	S.D.	1	0
			EF

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 116

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	10	0	0	10	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	11	0	0	11	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	10	0	0	0		10	0	0	0	
50 mg/kg											
crotonic acid	n	11	0	0	0		11	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 117

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Species : Rat

		Gait NC					Posture NC				
Test article		U	0	1	2	3	N	F	H		
Dose											
crotonic acid	n	0	12	0	0	0	12	0	0		
0 mg/kg											
crotonic acid	n	0	10	0	0	0	10	0	0		
50 mg/kg											
crotonic acid	n	0	11	0	0	0	11	0	0		
150 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
500 mg/kg											
		Grooming NC				Urination NC					
Test article		0	1	2		0	1	2	3		
Dose											
crotonic acid	n	12	0	0		12	0	0	0		
0 mg/kg											
crotonic acid	n	10	0	0		10	0	0	0		
50 mg/kg											
crotonic acid	n	11	0	0		11	0	0	0		
150 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
500 mg/kg											

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Not calculated : NC

Table 2 - 118

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid	n	12	12
0 mg/kg	Mean	4	0
	S.D.	1	0
crotonic acid	n	10	10
50 mg/kg	Mean	5	0
	S.D.	2	0
			EF
crotonic acid	n	11	11
150 mg/kg	Mean	3	0
	S.D.	1	0
			EF
crotonic acid	n	12	12
500 mg/kg	Mean	5	0
	S.D.	1	0
			EF

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 119

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Species : Rat

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	10	0	0	10	0	0	0	
50 mg/kg											
crotonic acid	n	0	0	11	0	0	11	0	0	0	
150 mg/kg											
crotonic acid	n	0	0	12	0	0	12	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	12	0	0	0		12	0	0	0	
0 mg/kg											
crotonic acid	n	10	0	0	0		10	0	0	0	
50 mg/kg											
crotonic acid	n	11	0	0	0		11	0	0	0	
150 mg/kg											
crotonic acid	n	12	0	0	0		12	0	0	0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Not calculated : NC

Table 2 - 120

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Species : Rat

		Gait NC					Posture NC				
Test article		U	0	1	2	3	N	F	H		
Dose											
crotonic acid	n	0	12	0	0	0	12	0	0		
0 mg/kg											
crotonic acid	n	0	10	0	0	0	10	0	0		
50 mg/kg											
crotonic acid	n	0	11	0	0	0	11	0	0		
150 mg/kg											
crotonic acid	n	0	12	0	0	0	12	0	0		
500 mg/kg											
		Grooming NC				Urination NC					
Test article		0	1	2		0	1	2	3		
Dose											
crotonic acid	n	12	0	0		12	0	0	0		
0 mg/kg											
crotonic acid	n	10	0	0		10	0	0	0		
50 mg/kg											
crotonic acid	n	11	0	0		11	0	0	0		
150 mg/kg											
crotonic acid	n	12	0	0		12	0	0	0		
500 mg/kg											

Gait) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Not calculated : NC

Table 2 - 121

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
crotonic acid	n	12	12
0 mg/kg	Mean	5	0
	S.D.	2	0
crotonic acid	n	10	10
50 mg/kg	Mean	6	0
	S.D.	2	0
			EF
crotonic acid	n	11	11
150 mg/kg	Mean	5	0
	S.D.	1	0
			EF
crotonic acid	n	12	12
500 mg/kg	Mean	6	0
	S.D.	2	0
			EF

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 122

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : Administration

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Arousal NC					Convulsion NC				
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
crotonic acid	n	0	0	10	0	0	10	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	10	0	0	10	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article											
Dose		0	1	2	3		0	1	2	3	
crotonic acid	n	10	0	0	0		10	0	0	0	
0 mg/kg											
crotonic acid	n	10	0	0	0		10	0	0	0	
500 mg/kg											
		Gait NC					Posture NC				
Test article											
Dose		U	0	1	2	3	N	F	H		
crotonic acid	n	0	10	0	0	0	10	0		0	
0 mg/kg											
crotonic acid	n	0	10	0	0	0	10	0		0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Not calculated : NC

Table 2 - 123

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 1		Period : Administration		Species : Rat	
Generation : F0		Grooming NC		Urination NC					
Test article	Dose	0	1	2	0	1	2	3	
crotonic acid	n	10	0	0	10	0	0	0	
0 mg/kg									
crotonic acid	n	10	0	0	10	0	0	0	
500 mg/kg									

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 124

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		Period : Administration		Species : Rat
Open field observation		Sex : Female	Week : 1	
Generation : F0				
Rearing				
Test article				
Dose				
crotonic acid 0 mg/kg	n	10	10	
	Mean	6	0	
	S.D.	1	0	
crotonic acid 500 mg/kg	n	10	10	
	Mean	5	0	
	S.D.	2	0	
			EF	

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 125

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 2		Period : Administration		Species : Rat			
Generation : F0		Arousal NC						Convulsion NC			
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
crotonic acid 0 mg/kg	n	0	0	10	0	0	10	0	0	0	
crotonic acid 500 mg/kg	n	0	0	10	0	0	10	0	0	0	
		Abnormal NC behavior						Stereotypy NC			
Test article											
Dose		0	1	2	3	0	1	2	3		
crotonic acid 0 mg/kg	n	10	0	0	0	10	0	0	0		
crotonic acid 500 mg/kg	n	10	0	0	0	10	0	0	0		
		Gait NC						Posture NC			
Test article											
Dose		U	0	1	2	3	N	F	H		
crotonic acid 0 mg/kg	n	0	10	0	0	0	10	0	0		
crotonic acid 500 mg/kg	n	0	10	0	0	0	10	0	0		

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Not calculated : NC

Table 2 - 126

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Period : Administration				Species : Rat			
Generation : F0		Sex : Female		Week : 2					
		Grooming NC		Urination NC					
Test article									
Dose		0	1	2		0	1	2	3
crotonic acid	n	10	0	0		10	0	0	0
0 mg/kg									
crotonic acid	n	10	0	0		10	0	0	0
500 mg/kg									

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 127

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		Period : Administration		Species : Rat
Open field observation		Sex : Female	Week : 2	
Generation : F0				
	Rearing	Defecation count		
Test article				
Dose				
crotonic acid	n	10	10	
0 mg/kg	Mean	7	0	
	S.D.	2	0	
crotonic acid	n	10	10	
500 mg/kg	Mean	5	0	
	S.D.	2	0	
			EF	

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 128

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 3		Period : Administration		Species : Rat			
Generation : F0		Arousal NC					Convulsion NC				
Test article											
Dose											
crotonic acid	n	-2	-1	0	1	2	0	1	2	3	
0 mg/kg		0	0	10	0	0	10	0	0	0	
crotonic acid	n	0	0	10	0	0	10	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article											
Dose											
crotonic acid	n	0	1	2	3	0	1	2	3		
0 mg/kg		10	0	0	0	10	0	0	0		
crotonic acid	n	10	0	0	0	10	0	0	0		
500 mg/kg											
		Gait NC					Posture NC				
Test article											
Dose											
crotonic acid	n	U	0	1	2	3	N	F	H		
0 mg/kg		0	10	0	0	0	10	0	0		
crotonic acid	n	0	10	0	0	0	10	0	0		
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Not calculated : NC

Table 2 - 129

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 3		Period : Administration		Species : Rat	
Generation : F0		Grooming NC		Urination NC					
Test article	Dose	0	1	2	0	1	2	3	
crotonic acid	n	10	0	0	9	1	0	0	
0 mg/kg									
crotonic acid	n	10	0	0	10	0	0	0	
500 mg/kg									

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 130

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		Period : Administration		Species : Rat
Open field observation		Sex : Female	Week : 3	
Generation : F0				
	Rearing	Defecation count		
Test article				
Dose				
crotonic acid 0 mg/kg	n	10	10	
	Mean	7	0	
	S.D.	3	0	
crotonic acid 500 mg/kg	n	10	10	
	Mean	6	0	
	S.D.	1	0	
			EF	

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 131

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Female Week : 4 Period : Administration

Study No. : R-1169

		Generation : F0		Sex : Female		Week : 4														Species : Rat	
		Arousal NC								Convulsion NC											
Test article																					
Dose		-2	-1	0	1	2	0	1	2	3											
crotonic acid 0 mg/kg	n	0	0	10	0	0	10	0	0	0											
crotonic acid 500 mg/kg	n	0	0	10	0	0	10	0	0	0											
		Abnormal NC behavior								Stereotypy NC											
Test article																					
Dose		0	1	2	3	0	1	2	3												
crotonic acid 0 mg/kg	n	10	0	0	0	10	0	0	0												
crotonic acid 500 mg/kg	n	10	0	0	0	10	0	0	0												
		Gait NC								Posture NC											
Test article																					
Dose		U	0	1	2	3	N	F	H												
crotonic acid 0 mg/kg	n	0	10	0	0	0	10	0	0												
crotonic acid 500 mg/kg	n	0	10	0	0	0	10	0	0												
Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert																					
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe																					
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe																					
Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe																					
Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly																					
Posture) N: Normal, F: Flattened, H: Hunched																					
Not calculated : NC																					

Table 2 - 132

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Period : Administration				Species : Rat			
Generation : F0		Sex : Female		Week : 4					
		Grooming NC		Urination NC					
Test article									
Dose		0	1	2		0	1	2	3
crotonic acid	n	10	0	0		10	0	0	0
0 mg/kg									
crotonic acid	n	10	0	0		8	2	0	0
500 mg/kg									

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 133

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 4		
	Rearing	Defecation count		
Test article				
Dose				
crotonic acid	n	10	10	
0 mg/kg	Mean	7	0	
	S.D.	2	0	
crotonic acid	n	10	10	
500 mg/kg	Mean	5	0	
	S.D.	2	0	
		T2 *	EF	

Significantly different from crotonic acid 0 mg/kg : * P<0.05

T2 : Student t-test (two-side)

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 134

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 5		Period : Administration		Species : Rat			
Generation : F0		Arousal NC					Convulsion NC				
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
crotonic acid 0 mg/kg	n	0	0	10	0	0	10	0	0	0	
crotonic acid 500 mg/kg	n	0	0	10	0	0	10	0	0	0	
		Abnormal NC behavior					Stereotypy NC				
Test article											
Dose		0	1	2	3	0	1	2	3		
crotonic acid 0 mg/kg	n	10	0	0	0	10	0	0	0		
crotonic acid 500 mg/kg	n	10	0	0	0	10	0	0	0		
		Gait NC					Posture NC				
Test article											
Dose		U	0	1	2	3	N	F	H		
crotonic acid 0 mg/kg	n	0	10	0	0	0	10	0	0		
crotonic acid 500 mg/kg	n	0	10	0	0	0	10	0	0		
Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert											
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe											
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe											
Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe											
Gait) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly											
Posture) N: Normal, F: Flattened, H: Hunched											
Not calculated : NC											

Table 2 - 135

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 5		Period : Administration		Species : Rat	
Generation : F0		Grooming NC		Urination NC					
Test article	Dose	0	1	2	0	1	2	3	
crotonic acid	n	10	0	0	9	1	0	0	
0 mg/kg									
crotonic acid	n	10	0	0	9	1	0	0	
500 mg/kg									

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 136

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		Period : Administration		Species : Rat
Open field observation		Sex : Female	Week : 5	
Generation : F0				
	Rearing	Defecation count		
Test article				
Dose				
crotonic acid	n	10	10	
0 mg/kg	Mean	6	0	
	S.D.	2	0	
crotonic acid	n	10	10	
500 mg/kg	Mean	5	0	
	S.D.	1	0	
			EF	

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 137

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : Administration

Generation : F0

Sex : Female

Week : 6

Species : Rat

		Arousal NC					Convulsion NC				
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
crotonic acid	n	0	0	10	0	0	10	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	10	0	0	10	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article											
Dose		0	1	2	3		0	1	2	3	
crotonic acid	n	10	0	0	0		10	0	0	0	
0 mg/kg											
crotonic acid	n	10	0	0	0		10	0	0	0	
500 mg/kg											
		Gait NC					Posture NC				
Test article											
Dose		U	0	1	2	3	N	F	H		
crotonic acid	n	0	10	0	0	0	10	0		0	
0 mg/kg											
crotonic acid	n	0	10	0	0	0	10	0		0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert
 Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
 Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
 Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe
 Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly
 Posture) N: Normal, F: Flattened, H: Hunched
 Not calculated : NC

Table 2 - 138

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 6		Period : Administration		Species : Rat	
Generation : F0		Grooming NC		Urination NC					
Test article	Dose	0	1	2	0	1	2	3	
crotonic acid	n	10	0	0	9	1	0	0	
0 mg/kg									
crotonic acid	n	10	0	0	10	0	0	0	
500 mg/kg									

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 139

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		Period : Administration		Species : Rat
Open field observation		Sex : Female	Week : 6	
Generation : F0				
	Rearing	Defecation count		
Test article				
Dose				
crotonic acid 0 mg/kg	n	10	10	
	Mean	6	0	
	S.D.	1	0	
crotonic acid 500 mg/kg	n	10	10	
	Mean	5	0	
	S.D.	1	0	
			EF	

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 140

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Male Week : 1 Period : Recovery

Study No. : R-1169

		Arousal NC					Convulsion NC					Species : Rat	
Test article													
Dose		-2	-1	0	1	2	0	1	2	3			
crotonic acid	n	0	0	5	0	0	5	0	0	0			
0 mg/kg													
crotonic acid	n	0	0	5	0	0	5	0	0	0			
500 mg/kg													
		Abnormal NC behavior					Stereotypy NC						
Test article													
Dose		0	1	2	3		0	1	2	3			
crotonic acid	n	5	0	0	0		5	0	0	0			
0 mg/kg													
crotonic acid	n	5	0	0	0		5	0	0	0			
500 mg/kg													
		Gait NC					Posture NC						
Test article													
Dose		U	0	1	2	3	N	F	H				
crotonic acid	n	0	5	0	0	0	5	0	0				
0 mg/kg													
crotonic acid	n	0	5	0	0	0	5	0	0				
500 mg/kg													
Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert													
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe													
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe													
Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe													
Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly													
Posture) N: Normal, F: Flattened, H: Hunched													
Not calculated : NC													

Table 2 - 141

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Male		Week : 1		Period : Recovery				Species : Rat	
Generation : F0		Grooming NC				Urination NC					
Test article	Dose	0	1	2	0	1	2	3			
crotonic acid	0 mg/kg	n	5	0	0	4	1	0	0		
crotonic acid	500 mg/kg	n	5	0	0	4	1	0	0		

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 142

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

	Open field observation		Period : Recovery	
	Generation : F0	Sex : Male	Week : 1	Species : Rat
	Rearing	Defecation count		
Test article				
Dose				
crotonic acid	n	5	5	
0 mg/kg	Mean	4	0	
	S.D.	1	0	
crotonic acid	n	5	5	
500 mg/kg	Mean	3	0	
	S.D.	1	0	
			EF	

Not significantly different from crotonic acid 0 mg/kg
EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 143

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Open field observation
Generation : F0 Sex : Male Week : 2 Period : Recovery

Study No. : R-1169

		Arousal NC					Convulsion NC				
Test article		-2	-1	0	1	2	0	1	2	3	
Dose											
crotonic acid	n	0	0	5	0	0	5	0	0	0	0
0 mg/kg											
crotonic acid	n	0	0	5	0	0	5	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
crotonic acid	n	5	0	0	0	5	0	0	0	0	
0 mg/kg											
crotonic acid	n	5	0	0	0	5	0	0	0		
500 mg/kg											
		Gait NC					Posture NC				
Test article		U	0	1	2	3	N	F	H		
Dose											
crotonic acid	n	0	5	0	0	0	5	0	0		
0 mg/kg											
crotonic acid	n	0	5	0	0	0	5	0	0		
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe
Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly
Posture) N: Normal, F: Flattened, H: Hunched
Not calculated : NC

Table 2 - 144

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Male		Week : 2		Period : Recovery				Species : Rat	
Generation : F0		Grooming NC				Urination NC					
Test article	Dose	0	1	2	0	1	2	3			
crotonic acid	0 mg/kg	n	5	0	0	4	1	0	0		
crotonic acid	500 mg/kg	n	5	0	0	4	1	0	0		

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 145

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats		Period : Recovery		Species : Rat
Open field observation		Sex : Male	Week : 2	
Generation : F0				
Rearing				
		Defecation count		
Test article				
Dose				
crotonic acid 0 mg/kg	n	5	5	
	Mean	6	0	
	S.D.	1	0	
crotonic acid 500 mg/kg	n	5	5	
	Mean	5	0	
	S.D.	2	0	
		EF		

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 146

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation

Period : Recovery

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Arousal NC					Convulsion NC				
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
crotonic acid	n	0	0	5	0	0	5	0	0	0	
0 mg/kg											
crotonic acid	n	0	0	5	0	0	5	0	0	0	
500 mg/kg											
		Abnormal NC behavior					Stereotypy NC				
Test article											
Dose		0	1	2	3		0	1	2	3	
crotonic acid	n	5	0	0	0		5	0	0	0	
0 mg/kg											
crotonic acid	n	5	0	0	0		5	0	0	0	
500 mg/kg											
		Gait NC					Posture NC				
Test article											
Dose		U	0	1	2	3	N	F	H		
crotonic acid	n	0	5	0	0	0	5	0		0	
0 mg/kg											
crotonic acid	n	0	5	0	0	0	5	0		0	
500 mg/kg											

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Not calculated : NC

Table 2 - 147

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 1		Period : Recovery				Species : Rat	
Generation : F0		Grooming NC				Urination NC					
Test article	Dose	0	1	2	0	1	2	3			
crotonic acid	0 mg/kg	n	5	0	0	5	0	0	0		
crotonic acid	500 mg/kg	n	5	0	0	5	0	0	0		

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 148

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

	Open field observation	Period : Recovery		
	Generation : F0	Sex : Female	Week : 1	Species : Rat
	Rearing	Defecation count		
Test article				
Dose				
crotonic acid	n	5	5	
0 mg/kg	Mean	6	0	
	S.D.	1	0	
crotonic acid	n	5	5	
500 mg/kg	Mean	4	0	
	S.D.	2	0	
			EF	

Not significantly different from crotonic acid 0 mg/kg
EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 149

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 2		Period : Recovery		Species : Rat			
Generation : F0		Arousal NC				Convulsion NC					
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
crotonic acid 0 mg/kg	n	0	0	5	0	0	5	0	0	0	
crotonic acid 500 mg/kg	n	0	0	5	0	0	5	0	0	0	
		Abnormal NC behavior				Stereotypy NC					
Test article											
Dose		0	1	2	3	0	1	2	3		
crotonic acid 0 mg/kg	n	5	0	0	0	5	0	0	0		
crotonic acid 500 mg/kg	n	5	0	0	0	5	0	0	0		
		Gait NC				Posture NC					
Test article											
Dose		U	0	1	2	3	N	F	H		
crotonic acid 0 mg/kg	n	0	5	0	0	0	5	0	0		
crotonic acid 500 mg/kg	n	0	5	0	0	0	5	0	0		
Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert											
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe											
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe											
Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe											
Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly											
Posture) N: Normal, F: Flattened, H: Hunched											
Not calculated : NC											

Table 2 - 150

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Sex : Female		Week : 2		Period : Recovery				Species : Rat	
Generation : F0		Grooming NC				Urination NC					
Test article	Dose	0	1	2	0	1	2	3			
crotonic acid	0 mg/kg	n	5	0	0	5	0	0	0		
crotonic acid	500 mg/kg	n	5	0	0	4	1	0	0		

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)
Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
Not calculated : NC

Table 2 - 151

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Open field observation		Period : Recovery		Species : Rat
Generation : F0		Sex : Female	Week : 2	
	Rearing	Defecation count		
Test article				
Dose				
crotonic acid	n	5	5	
0 mg/kg	Mean	6	0	
	S.D.	2	0	
crotonic acid	n	5	5	
500 mg/kg	Mean	5	0	
	S.D.	2	0	
			EF	

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 152

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Manipulative test		Sex : Male		Week : 6		Period : F0 mating				Species : Rat			
Generation : F0		Auditory response				Approach response				Touch response			
Test article													
Dose		-2	-1	0	1	-1	0	1	0	-1	0	1	0
crotonic acid	n	0	0	5	0	0	5	0	0	0	5	0	0
0 mg/kg													
crotonic acid	n	0	0	5	0	0	5	0	0	0	5	0	0
50 mg/kg													
crotonic acid	n	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF
150 mg/kg		0	0	5	0	0	5	0	0	0	5	0	0
crotonic acid	n	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF
500 mg/kg		0	0	5	0	0	5	0	0	0	5	0	0
		EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF
		Tail pinch response				Pupillary reflex							
Test article		-2	-1	0	1	P	F	L	R				
Dose													
crotonic acid	n	0	0	5	0	5	0	0	0				
0 mg/kg													
crotonic acid	n	0	0	5	0	5	0	0	0				
50 mg/kg													
crotonic acid	n	EF	EF	EF	EF	EF	EF	EF	EF				
150 mg/kg		0	0	5	0	5	0	0	0				
crotonic acid	n	EF	EF	EF	EF	EF	EF	EF	EF				
500 mg/kg		0	0	5	0	5	0	0	0				
		EF	EF	EF	EF	EF	EF	EF	EF				

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 153

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Manipulative test		Period : F0 mating		Species : Rat
Generation : F0		Sex : Male	Week : 6	
Test article		Aerial right- ing reflex	Landing foot splay mm	
Dose				
crotonic acid 0 mg/kg	n	5	5	
	Mean	0	87	
	S.D.	0	26	
crotonic acid 50 mg/kg	n	5	5	
	Mean	0	85	
	S.D.	0	11	
crotonic acid 150 mg/kg	n	5	5	
	Mean	0	72	
	S.D.	0	7	
crotonic acid 500 mg/kg	n	5	5	
	Mean	0	81	
	S.D.	0	36	
		EF		

Aerial righting reflex) Total score

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 154

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Manipulative test		Period : F0 lactation				Species : Rat			
Generation : F0		Sex : Female		Day : 4		Touch response			
		Auditory response				Approach response			
Test article									
Dose		-2	-1	0	1	-1	0	1	
crotonic acid 0 mg/kg	n	0	0	5	0	0	5	0	0
crotonic acid 50 mg/kg	n	0	0	5	0	0	5	0	0
crotonic acid 150 mg/kg	n	EF 0	EF 0	EF 5	EF 0	EF 0	EF 5	EF 0	EF 0
crotonic acid 500 mg/kg	n	EF 0	EF 0	EF 5	EF 0	EF 0	EF 5	EF 0	EF 0
		EF	EF	EF	EF	EF	EF	EF	EF
		Tail pinch response				Pupillary reflex			
Test article		-2	-1	0	1	P	F	L	R
crotonic acid 0 mg/kg	n	0	0	5	0	5	0	0	0
crotonic acid 50 mg/kg	n	0	0	5	0	5	0	0	0
crotonic acid 150 mg/kg	n	EF 0	EF 0	EF 5	EF 0	EF 5	EF 0	EF 0	EF 0
crotonic acid 500 mg/kg	n	EF 0	EF 0	EF 5	EF 0	EF 5	EF 0	EF 0	EF 0
		EF	EF	EF	EF	EF	EF	EF	EF

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 155

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Manipulative test

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Species : Rat

		Aerial right- ing reflex	Landing foot splay mm
Test article			
Dose			
crotonic acid	n	5	5
0 mg/kg	Mean	0	61
	S.D.	0	9
crotonic acid	n	5	5
50 mg/kg	Mean	0	52
	S.D.	0	18
		EF	
crotonic acid	n	5	5
150 mg/kg	Mean	0	72
	S.D.	0	12
		EF	
crotonic acid	n	5	5
500 mg/kg	Mean	0	52
	S.D.	0	4
		EF	

Aerial righting reflex) Total score

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 156

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Manipulative test		Period : Administration				Species : Rat			
Generation : F0		Sex : Female Week : 6				Touch response			
		Auditory response				Approach response			
Test article	Dose	-2	-1	0	1	-1	0	1	
crotonic acid	0 mg/kg	n	0	0	5	0	0	5	0
crotonic acid	500 mg/kg	n	0	0	5	0	0	5	0
		EF	EF	EF	EF	EF	EF	EF	EF
		Tail pinch response				Pupillary reflex			
Test article	Dose	-2	-1	0	1	P	F	L	R
crotonic acid	0 mg/kg	n	0	0	5	0	5	0	0
crotonic acid	500 mg/kg	n	0	0	5	0	5	0	0
		EF	EF	EF	EF	EF	EF	EF	EF

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 157

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Manipulative test		Period : Administration		Species : Rat
Generation : F0		Sex : Female	Week : 6	
Test article		Aerial right- ing reflex	Landing foot splay mm	
Dose				
crotonic acid 0 mg/kg	n	5	5	
	Mean	0	72	
	S.D.	0	27	
crotonic acid 500 mg/kg	n	5	5	
	Mean	0	71	
	S.D.	0	29	
		EF		

Aerial righting reflex) Total score

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 158

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Manipulative test
Generation : F0 Sex : Male Week : 2 Period : Recovery

Study No. : R-1169

		Auditory response				Approach response				Touch response			
Test article	Dose	-2	-1	0	1	-1	0	1		-1	0	1	
crotonic acid	0 mg/kg	n	0	0	5	0	0	5	0	0	0	5	0
crotonic acid	500 mg/kg	n	0	0	5	0	0	5	0	0	5	0	
		EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	
		Tail pinch response				Pupillary reflex							
Test article	Dose	-2	-1	0	1	P	F	L	R				
crotonic acid	0 mg/kg	n	0	0	5	0	5	0	0	0			
crotonic acid	500 mg/kg	n	0	0	5	0	5	0	0	0			
		EF	EF	EF	EF	EF	EF	EF	EF	EF			

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds
EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 159

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Manipulative test		Period : Recovery		Species : Rat
Generation : F0		Sex : Male	Week : 2	
Test article		Aerial right- ing reflex	Landing foot splay mm	
Dose				
crotonic acid 0 mg/kg	n	5	5	
	Mean	0	79	
	S.D.	0	14	
crotonic acid 500 mg/kg	n	5	5	
	Mean	0	75	
	S.D.	0	22	
		EF		

Aerial righting reflex) Total score

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 160

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats																	
Manipulative test		Sex : Female		Week : 2		Period : Recovery						Species : Rat					
		Auditory response						Approach response				Touch response					
Test article																	
Dose		-2		-1		0		1		-1		0		1		0	
crotonic acid 0 mg/kg		n	0	0	0	5	0	0	0	5	0	0	0	5	0	0	0
crotonic acid 500 mg/kg		n	0	0	5	0	0	5	0	0	5	0	0	5	0		
			EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF		
		Tail pinch response						Pupillary reflex									
Test article																	
Dose		-2		-1		0		1		P		F		L		R	
crotonic acid 0 mg/kg		n	0	0	5	0	0	5	0	0	0	0	0	0	0		
crotonic acid 500 mg/kg		n	0	0	5	0	5	0	0	0	0	0	0				
			EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF	EF			

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 161

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Manipulative test		Period : Recovery		Species : Rat
Generation : F0		Sex : Female	Week : 2	
Test article		Aerial right- ing reflex	Landing foot splay mm	
Dose				
crotonic acid 0 mg/kg	n	5	5	
	Mean	0	71	
	S.D.	0	20	
crotonic acid 500 mg/kg	n	5	5	
	Mean	0	55	
	S.D.	0	7	
		EF		

Aerial righting reflex) Total score

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 2 - 162

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Crotonic acid by oral administration in rats		Period : F0 mating		Species : Rat
Grip strength	Sex : Male	Week : 6		
Generation : F0	Grip strength of fore limb g	Grip strength of hind limb g		
Test article				
Dose				
crotonic acid 0 mg/kg	n	5	5	
	Mean	1845	1185	
	S.D.	224	117	
crotonic acid 50 mg/kg	n	5	5	
	Mean	1794	1157	
	S.D.	176	183	
crotonic acid 150 mg/kg	n	5	5	
	Mean	1823	1016	
	S.D.	134	120	
crotonic acid 500 mg/kg	n	5	5	
	Mean	1864	1003	
	S.D.	239	221	
Not significantly different from crotonic acid 0 mg/kg				

Table 2 - 163

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Grip strength
Generation : F0 Sex : Female Day : 4 Period : F0 lactation

Species : Rat

Test article Dose		Grip strength of fore limb g	Grip strength of hind limb g
crotonic acid 0 mg/kg	n Mean S.D.	5 1399 252	5 943 125
crotonic acid 50 mg/kg	n Mean S.D.	5 1224 204	5 690 72 DT **
crotonic acid 150 mg/kg	n Mean S.D.	5 1277 88	5 895 81
crotonic acid 500 mg/kg	n Mean S.D.	5 1324 77	5 837 110

Significantly different from crotonic acid 0 mg/kg : ** P<0.01

DT : Dunnett test (two-side)

Table 2 - 164

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Grip strength		Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 6		
	Grip strength of fore limb g	Grip strength of hind limb g		
Test article				
Dose				
crotonic acid	n	5	5	
0 mg/kg	Mean	1596	887	
	S.D.	153	205	
crotonic acid	n	5	5	
500 mg/kg	Mean	1471	869	
	S.D.	92	92	
Not significantly different from crotonic acid 0 mg/kg				

Table 2 - 165

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Grip strength		Sex : Male		Period : Recovery	Species : Rat
Generation : F0		Week : 2			
		Grip strength of fore limb g	Grip strength of hind limb g		
Test article	Dose				
crotonic acid 0 mg/kg	n	5	5		
	Mean	1853	1098		
	S.D.	156	237		
crotonic acid 500 mg/kg	n	5	5		
	Mean	1795	841		
	S.D.	143	239		
Not significantly different from crotonic acid 0 mg/kg					

Table 2 - 166

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Grip strength		Period : Recovery		Species : Rat
Generation : F0	Sex : Female	Week : 2		
Test article	Grip strength of fore limb g	Grip strength of hind limb g		
Dose				
crotonic acid	n	5	5	
0 mg/kg	Mean	1485	758	
	S.D.	151	153	
crotonic acid	n	5	5	
500 mg/kg	Mean	1342	791	
	S.D.	55	59	
Not significantly different from crotonic acid 0 mg/kg				

Table 2 - 167

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Motor activity		Period : F0 mating							Species : Rat
Generation : F0		Sex : Male	Week : 6						
		0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')	
Test article		Count	Count	Count	Count	Count	Count	Count	
Dose									
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	
	Mean	425	199	124	88	48	30	914	
	S.D.	30	82	51	80	42	32	96	
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5	
	Mean	439	239	139	190	68	83	1157	
	S.D.	58	82	105	80	74	48	343	
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5	
	Mean	463	325	236	264	107	107	1503	
	S.D.	48	103	123	63	119	88	458	
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	
	Mean	443	262	136	194	45	83	1163	
	S.D.	56	130	125	104	38	78	287	
		DT *							

Significantly different from crotonic acid 0 mg/kg : * P<0.05

DT : Dunnett test (two-side)

Table 2 - 168

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Motor activity		Period : F0 lactation						Species : Rat
Generation : F0		Sex : Female	Day : 4					
		0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Test article		Count	Count	Count	Count	Count	Count	Count
Dose								
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5
	Mean	351	99	105	135	92	193	975
	S.D.	74	67	101	93	125	174	457
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5
	Mean	333	197	119	56	70	79	856
	S.D.	110	165	73	88	88	94	395
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5
	Mean	372	233	160	127	150	147	1189
	S.D.	51	112	107	62	127	110	518
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5
	Mean	226	70	75	101	34	47	554
	S.D.	25	53	73	127	45	89	177
		DT *						

Significantly different from crotonic acid 0 mg/kg : * P<0.05

DT : Dunnett test (two-side)

Table 2 - 169

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Motor activity		Period : Administration						Species : Rat
Generation : F0	Sex : Female	Week : 6						
		0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Test article	Count	Count	Count	Count	Count	Count	Count	Count
Dose								
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5
	Mean	444	394	264	247	170	104	1622
	S.D.	59	58	100	105	141	118	414
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5
	Mean	441	324	231	188	217	241	1641
	S.D.	41	85	152	168	100	80	513

Not significantly different from crotonic acid 0 mg/kg

Table 2 - 170

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Motor activity		Period : Recovery						Species : Rat
Generation : F0	Sex : Male	Week : 2						
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')	
Test article	Count	Count	Count	Count	Count	Count	Count	
Dose								
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	
	Mean	399	181	224	125	188	1259	
	S.D.	61	125	118	96	78	510	
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	
	Mean	419	312	255	253	341	1743	
	S.D.	70	103	54	71	153	393	
T2 *								

Significantly different from crotonic acid 0 mg/kg : * P<0.05

T2 : Student t-test (two-side)

T2 *

Table 2 - 171

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Motor activity		Period : Recovery						Species : Rat
Generation : F0	Sex : Female	Week : 2						
		0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Test article		Count	Count	Count	Count	Count	Count	Count
Dose								
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5
	Mean	413	309	263	217	115	103	1419
	S.D.	47	139	93	90	133	127	541
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5
	Mean	409	283	203	136	97	136	1264
	S.D.	69	100	155	123	127	118	536

Not significantly different from crotonic acid 0 mg/kg

Table 3 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Body weight

Period : F0 before mating Day 1-15, F0 mating Day 15-42

Sex : Male

Unit : g

Species : Rat

Test article		/Day							Body weight
Dose		1	8	15	22	29	36	42	gain
crotonic acid 0 mg/kg	n	12	12	12	12	12	12	12	12
	Mean	410	436	459	474	493	516	522	112
	S.D.	16	19	25	30	36	35	37	29
crotonic acid 50 mg/kg	n	12	12	12	12	12	12	12	12
	Mean	409	438	459	474	495	513	524	115
	S.D.	11	12	16	15	21	21	21	16
crotonic acid 150 mg/kg	n	12	12	12	12	12	12	12	12
	Mean	411	436	456	465	479	503	512	102
	S.D.	13	13	13	20	21	24	25	19
crotonic acid 500 mg/kg	n	12	12	12	12	12	12	12	12
	Mean	409	429	445	456	472	488	493	84
	S.D.	14	21	25	26	27	29	29	20
								DT *	DT **

Significantly different from crotonic acid 0 mg/kg : * P<0.05, ** P<0.01

DT : Dunnett test (two-side)

Table 3 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Body weight

Period : F0 before mating Day 1-15

Sex : Female

Unit : g

Species : Rat

Test article Dose		/Day			Body weight gain
		1	8	15	
crotonic acid 0 mg/kg	n	12	12	12	12
	Mean	253	265	271	18
	S.D.	8	9	10	7
crotonic acid 50 mg/kg	n	12	12	12	12
	Mean	255	268	273	17
	S.D.	9	16	14	9
crotonic acid 150 mg/kg	n	12	12	12	12
	Mean	253	267	271	18
	S.D.	10	13	12	12
crotonic acid 500 mg/kg	n	12	12	12	12
	Mean	250	260	263	13
	S.D.	10	9	25	23

Not significantly different from crotonic acid 0 mg/kg

Table 3 - 3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Body weight
Sex : Female

Period : F0 gestation Day 0-25

Study No. : R-1169

Unit : g

Species : Rat

Test article Dose		/Day				Body weight gain
		0	7	14	20	
crotonic acid 0 mg/kg	n	12	12	12	12	12
	Mean	278	314	350	438	160
	S.D.	9	7	11	14	12
crotonic acid 50 mg/kg	n	10	10	10	10	10
	Mean	278	313	345	431	152
	S.D.	12	14	18	26	17
crotonic acid 150 mg/kg	n	11	11	11	11	11
	Mean	282	317	351	439	157
	S.D.	12	15	17	23	19
crotonic acid 500 mg/kg	n	12	12	12	12	12
	Mean	267	297	329	413	147
	S.D.	17	22	22	19	11
				DT *	DT *	

Significantly different from crotonic acid 0 mg/kg : * P<0.05

DT : Dunnett test (two-side)

Table 3 - 4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Body weight

Period : F0 lactation Day 0-5

Sex : Female

Unit : g

Species : Rat

Test article Dose		/Day		Body weight gain
		0	4	
crotonic acid 0 mg/kg	n	12	12	12
	Mean	335	347	12
	S.D.	15	6	13
crotonic acid 50 mg/kg	n	10	10	10
	Mean	333	343	10
	S.D.	18	16	18
crotonic acid 150 mg/kg	n	11	11	11
	Mean	340	349	9
	S.D.	19	17	21
crotonic acid 500 mg/kg	n	12	12	12
	Mean	315	330	16
	S.D.	21	17	10
		DT *	ST *	

Significantly different from crotonic acid 0 mg/kg : * P<0.05

DT : Dunnett test (two-side), ST : Steel test (two-side)

Table 3 - 5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Body weight
Sex : Female

Study No. : R-1169

		Period : Administration							Unit : g	Species : Rat
Test article	/Day	1	8	15	22	29	36	42	Body weight gain	
Dose										
crotonic acid	n	10	10	10	10	10	10	10	10	
0 mg/kg	Mean	252	267	275	283	289	297	300	48	
	S.D.	10	8	11	10	14	14	14	7	
crotonic acid	n	10	10	10	10	10	10	10	10	
500 mg/kg	Mean	255	261	272	280	282	287	296	41	
	S.D.	9	9	9	11	11	17	18	17	

Not significantly different from crotonic acid 0 mg/kg

Table 3 - 6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Body weight
Sex : Male

Period : Recovery Day 1-15

Study No. : R-1169

Unit : g

Species : Rat

Test article Dose		/Day			Body weight gain
		1	8	14	
crotonic acid 0 mg/kg	n	5	5	5	5
	Mean	501	513	516	15
	S.D.	23	27	25	8
crotonic acid 500 mg/kg	n	5	5	5	5
	Mean	497	498	499	2
	S.D.	24	63	78	68

Not significantly different from crotonic acid 0 mg/kg

Table 3 - 7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Body weight
Sex : Female

Period : Recovery Day 1-15

Study No. : R-1169

Unit : g

Species : Rat

Test article Dose		/Day			Body weight gain
		1	8	14	
crotonic acid 0 mg/kg	n	5	5	5	5
	Mean	299	303	306	7
	S.D.	15	17	22	9
crotonic acid 500 mg/kg	n	5	5	5	5
	Mean	300	299	301	1
	S.D.	25	18	14	11

Not significantly different from crotonic acid 0 mg/kg

Table 4 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Unit : g

Species : Rat

Test article		/Day						Total food
Dose		2	8	15	30	36	42	consumption
crotonic acid 0 mg/kg	n	12	12	12	12	12	12	12
	Mean	22	23	23	19	22	21	130
	S.D.	1	3	3	2	2	3	11
crotonic acid 50 mg/kg	n	12	12	12	12	12	12	12
	Mean	24	24	23	19	22	22	133
	S.D.	2	2	2	2	3	2	7
crotonic acid 150 mg/kg	n	12	12	12	12	12	12	12
	Mean	24	23	22	20	22	21	131
	S.D.	3	2	3	3	3	2	11
crotonic acid 500 mg/kg	n	12	12	12	12	12	12	12
	Mean	22	22	21	17	20	20	122
	S.D.	3	2	2	1	2	1	9

Not significantly different from crotonic acid 0 mg/kg

Table 4 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Food consumption

Period : F0 before mating Day 1-15

Sex : Female

Unit : g

Species : Rat

Test article Dose		/Day			Total food consumption
		2	8	15	
crotonic acid 0 mg/kg	n	12	12	12	12
	Mean	15	18	16	49
	S.D.	3	3	2	5
crotonic acid 50 mg/kg	n	12	12	12	12
	Mean	14	16	15	46
	S.D.	2	3	3	5
crotonic acid 150 mg/kg	n	12	12	12	12
	Mean	15	18	17	50
	S.D.	3	3	2	6
crotonic acid 500 mg/kg	n	12	12	12	12
	Mean	14	15	15	45
	S.D.	3	2	5	7

Not significantly different from crotonic acid 0 mg/kg

Table 4 - 3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Food consumption

Period : F0 gestation Day 0-25

Sex : Female

Unit : g

Species : Rat

Test article		/Day				Total food
Dose		1	7	14	20	consumption
crotonic acid 0 mg/kg	n	12	12	12	12	12
	Mean	16	21	20	24	81
	S.D.	2	3	2	2	5
crotonic acid 50 mg/kg	n	10	10	10	10	10
	Mean	17	19	19	23	78
	S.D.	2	5	3	2	8
crotonic acid 150 mg/kg	n	11	11	11	11	11
	Mean	17	21	21	23	82
	S.D.	3	2	2	2	6
crotonic acid 500 mg/kg	n	12	12	12	12	12
	Mean	14	18	18	22	72
	S.D.	3	3	3	3	7
			DT *			DT **

Significantly different from crotonic acid 0 mg/kg : * P<0.05, ** P<0.01

DT : Dunnett test (two-side)

Table 4 - 4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Food consumption

Period : F0 lactation Day 0-5

Sex : Female

Unit : g

Species : Rat

Test article Dose		/Day		Total food consumption
		2	4	
crotonic acid 0 mg/kg	n	12	12	12
	Mean	28	40	68
	S.D.	7	5	9
crotonic acid 50 mg/kg	n	10	10	10
	Mean	26	40	65
	S.D.	6	7	10
crotonic acid 150 mg/kg	n	11	11	11
	Mean	25	41	67
	S.D.	6	6	11
crotonic acid 500 mg/kg	n	12	12	12
	Mean	24	41	65
	S.D.	5	5	8

Not significantly different from crotonic acid 0 mg/kg

Table 4 - 5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Food consumption
Sex : Female

Study No. : R-1169

		Period : Administration						Unit : g	Species : Rat
Test article	/Day							Total food consumption	
Dose		2	8	15	30	36	42		
crotonic acid 0 mg/kg	n	10	10	10	10	10	10	10	
	Mean	14	18	14	12	15	14	86	
	S.D.	3	2	4	3	3	2	12	
crotonic acid 500 mg/kg	n	10	10	10	10	10	10	10	
	Mean	15	16	17	13	13	14	88	
	S.D.	2	3	2	3	5	2	13	

Significantly different from crotonic acid 0 mg/kg : * P<0.05
A2 : Welch test (two-side)

Table 4 - 6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Food consumption
Sex : Male

Study No. : R-1169

Period : Recovery Day 1-15

Unit : g

Species : Rat

Test article Dose		/Day			Total food consumption
		2	8	14	
crotonic acid 0 mg/kg	n	5	5	5	5
	Mean	20	26	24	70
	S.D.	3	3	1	6
crotonic acid 500 mg/kg	n	5	5	5	5
	Mean	23	23	26	73
	S.D.	3	13	3	18

Not significantly different from crotonic acid 0 mg/kg

Table 4 - 7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Food consumption
Sex : Female

Period : Recovery Day 1-15

Study No. : R-1169

Unit : g

Species : Rat

Test article Dose		/Day			Total food consumption
		2	8	14	
crotonic acid 0 mg/kg	n	5	5	5	5
	Mean	16	17	17	50
	S.D.	3	2	3	8
crotonic acid 500 mg/kg	n	5	5	5	5
	Mean	17	16	18	52
	S.D.	1	3	2	5

Not significantly different from crotonic acid 0 mg/kg

Table 5 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Urinalysis

Stage : Week 6 of administration

Sex : Male

Species : Rat

Sex : Male		pH										Species : Rat	
Test article													
Dose		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0			
crotonic acid 0 mg/kg	n	0	0	0	0	1	0	1	0	3			
crotonic acid 50 mg/kg	n	0	0	0	0	2	1	0	0	2			
crotonic acid 150 mg/kg	n	0	0	0	2	0	0	1	0	2			
crotonic acid 500 mg/kg	n	0	0	1	3	1	0	0	0	0			

Table 5 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Urinalysis

Stage : Week 6 of administration

Sex : Male

Species : Rat

		Glucose					Occult Blood				
Test article		-	1+	2+	3+	4+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid 0 mg/kg	n	5	0	0	0	0	3	2	0	0	0
crotonic acid 50 mg/kg	n	4	1	0	0	0	4	1	0	0	0
crotonic acid 150 mg/kg	n	4	1	0	0	0	4	1	0	0	0
crotonic acid 500 mg/kg	n	5	0	0	0	0	3	2	0	0	0

		Bilirubin				Urobilinogen			
Test article		-	1+	2+	3+	+/-	1+	2+	3+
Dose	n								
crotonic acid 0 mg/kg	n	4	1	0	0	5	0	0	0
crotonic acid 50 mg/kg	n	4	1	0	0	5	0	0	0
crotonic acid 150 mg/kg	n	4	1	0	0	5	0	0	0
crotonic acid 500 mg/kg	n	2	3	0	0	5	0	0	0

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Table 5 - 3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Male

Study No. : R-1169

Stage : Week 6 of administration

Species : Rat

		Color											
Test article													
Dose		LY	Y	DY	BR	RE	RB	WH	BL	CL	OT		
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0	0
0 mg/kg													
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0	0
50 mg/kg													
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0	0
150 mg/kg													
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0	0
500 mg/kg													
Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other													

Table 5 - 4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Male

Study No. : R-1169

Stage : Week 6 of administration

Species : Rat

		RBC					WBC				
Test article		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid 0 mg/kg	n	5	0	0	0	0	5	0	0	0	0
crotonic acid 50 mg/kg	n	5	0	0	0	0	5	0	0	0	0
crotonic acid 150 mg/kg	n	5	0	0	0	0	5	0	0	0	0
crotonic acid 500 mg/kg	n	5	0	0	0	0	5	0	0	0	0
		Squamous epithelial cells					Small round epithelial cells				
Test article		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid 0 mg/kg	n	0	5	0	0	0	5	0	0	0	0
crotonic acid 50 mg/kg	n	0	5	0	0	0	5	0	0	0	0
crotonic acid 150 mg/kg	n	0	5	0	0	0	5	0	0	0	0
crotonic acid 500 mg/kg	n	0	5	0	0	0	5	0	0	0	0

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Table 5 - 5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Male

Study No. : R-1169

Stage : Week 6 of administration

Species : Rat

		Cast					Crystal phosphate salts				
Test article		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid	n	5	0	0	0	0	0	5	0	0	0
0 mg/kg											
crotonic acid	n	5	0	0	0	0	1	4	0	0	0
50 mg/kg											
crotonic acid	n	5	0	0	0	0	1	4	0	0	0
150 mg/kg											
crotonic acid	n	5	0	0	0	0	1	4	0	0	0
500 mg/kg											
Crystal calcium oxalate											
Test article		-	+/-	1+	2+	3+					
Dose	n										
crotonic acid	n	5	0	0	0	0					
0 mg/kg											
crotonic acid	n	5	0	0	0	0					
50 mg/kg											
crotonic acid	n	5	0	0	0	0					
150 mg/kg											
crotonic acid	n	5	0	0	0	0					
500 mg/kg											

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Table 5 - 6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Urinalysis

Stage : Week 6 of administration

Sex : Male

Species : Rat

Test article		Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
Dose							
crotonic acid	n	5	5	5	5	5	5
0 mg/kg	Mean	40	13.0	1724	1.3	3.3	1.8
	S.D.	9	4.3	522	0.3	0.6	0.4
crotonic acid	n	5	5	5	5	5	5
50 mg/kg	Mean	43	13.8	1864	1.2	4.0	1.9
	S.D.	7	5.7	392	0.4	0.9	0.6
crotonic acid	n	5	5	5	5	5	5
150 mg/kg	Mean	40	10.8	2230	1.3	4.0	2.0
	S.D.	5	2.5	235	0.3	0.8	0.5
crotonic acid	n	5	5	5	5	5	5
500 mg/kg	Mean	49	15.2	1406	1.0	2.9	1.6
	S.D.	10	5.7	392	0.0	0.6	0.2

Not significantly different from crotonic acid 0 mg/kg

Table 5 - 7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Stage : Week 6 of administration

Study No. : R-1169

Species : Rat

		pH									
Test article											
Dose		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	
crotonic acid	n	0	0	1	1	0	1	0	0	2	
0 mg/kg											
crotonic acid	n	0	0	1	1	0	1	0	0	2	
500 mg/kg											
		Protein					Ketones				
Test article											
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
crotonic acid	n	1	2	2	0	0	3	2	0	0	0
0 mg/kg											
crotonic acid	n	3	1	1	0	0	3	2	0	0	0
500 mg/kg											

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL
Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Table 5 - 8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Study No. : R-1169

Stage : Week 6 of administration

Species : Rat

		Glucose					Occult Blood				
Test article											
Dose		-	1+	2+	3+	4+	-	+/-	1+	2+	3+
crotonic acid	n	5	0	0	0	0	5	0	0	0	0
0 mg/kg											
crotonic acid	n	5	0	0	0	0	5	0	0	0	0
500 mg/kg											
		Bilirubin				Urobilinogen					
Test article											
Dose		-	1+	2+	3+	+/-	1+	2+	3+		
crotonic acid	n	5	0	0	0	5	0	0	0		
0 mg/kg											
crotonic acid	n	5	0	0	0	5	0	0	0		
500 mg/kg											
Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL											
Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL											
Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL											
Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL											

Table 5 - 9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Study No. : R-1169

Stage : Week 6 of administration

Species : Rat

		Color											
Test article		LY	Y	DY	BR	RE	RB	WH	BL	CL	OT		
Dose													
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0	0
0 mg/kg													
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0	0
500 mg/kg													

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Table 5 - 10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Stage : Week 6 of administration

Study No. : R-1169

Species : Rat

		RBC					WBC				
Test article		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid	n	5	0	0	0	0	5	0	0	0	0
0 mg/kg											
crotonic acid	n	5	0	0	0	0	5	0	0	0	0
500 mg/kg											

		Squamous epithelial cells					Small round epithelial cells				
Test article		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid	n	0	5	0	0	0	5	0	0	0	0
0 mg/kg											
crotonic acid	n	0	5	0	0	0	5	0	0	0	0
500 mg/kg											

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Table 5 - 11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Study No. : R-1169

Stage : Week 6 of administration

Species : Rat

		Cast					Crystal phosphate salts				
Test article											
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
crotonic acid	n	5	0	0	0	0	1	4	0	0	0
0 mg/kg											
crotonic acid	n	5	0	0	0	0	2	3	0	0	0
500 mg/kg											
Crystal calcium oxalate											
Test article											
Dose		-	+/-	1+	2+	3+					
crotonic acid	n	5	0	0	0	0					
0 mg/kg											
crotonic acid	n	5	0	0	0	0					
500 mg/kg											

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Table 5 - 12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Study No. : R-1169

Stage : Week 6 of administration

Species : Rat

Test article		Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
Dose							
crotonic acid 0 mg/kg	n	5	5	5	5	5	5
	Mean	30	8.0	2093	0.9	2.3	1.2
	S.D.	8	3.6	703	0.3	0.6	0.4
crotonic acid 500 mg/kg	n	5	5	5	5	5	5
	Mean	31	10.3	1833	1.1	2.5	1.4
	S.D.	10	6.1	594	0.5	0.9	0.7

Not significantly different from crotonic acid 0 mg/kg

Table 5 - 13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Male

Study No. : R-1169

Stage : Week 2 of recovery

Species : Rat

		pH									
Test article											
Dose		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	
crotonic acid	n	0	0	0	0	0	0	0	2	3	
0 mg/kg											
crotonic acid	n	0	0	1	0	0	1	0	1	2	
500 mg/kg											
		Protein					Ketones				
Test article											
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
crotonic acid	n	1	2	2	0	0	4	1	0	0	0
0 mg/kg											
crotonic acid	n	1	1	2	1	0	2	2	1	0	0
500 mg/kg											
Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL											
Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL											

Table 5 - 14

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Male

Study No. : R-1169

Stage : Week 2 of recovery

Species : Rat

		Glucose					Occult Blood				
Test article		-	1+	2+	3+	4+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid 0 mg/kg	n	5	0	0	0	0	0	5	0	0	0
crotonic acid 500 mg/kg	n	5	0	0	0	0	2	3	0	0	0

		Bilirubin				Urobilinogen			
Test article		-	1+	2+	3+	+/-	1+	2+	3+
Dose	n								
crotonic acid 0 mg/kg	n	5	0	0	0	5	0	0	0
crotonic acid 500 mg/kg	n	4	1	0	0	5	0	0	0

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL
Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL
Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL
Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Table 5 - 15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Male

Study No. : R-1169

Stage : Week 2 of recovery

Species : Rat

		Color											
Test article		LY	Y	DY	BR	RE	RB	WH	BL	CL	OT		
Dose													
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0	0
0 mg/kg													
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0	0
500 mg/kg													

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Table 5 - 16

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Male

Study No. : R-1169

Stage : Week 2 of recovery

Species : Rat

		RBC					WBC				
Test article		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid	n	5	0	0	0	0	5	0	0	0	0
0 mg/kg											
crotonic acid	n	5	0	0	0	0	5	0	0	0	0
500 mg/kg											

		Squamous epithelial cells					Small round epithelial cells				
Test article		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid	n	0	5	0	0	0	5	0	0	0	0
0 mg/kg											
crotonic acid	n	0	5	0	0	0	5	0	0	0	0
500 mg/kg											

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Table 5 - 17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Male

Study No. : R-1169

Stage : Week 2 of recovery

Species : Rat

		Cast					Crystal phosphate salts				
Test article											
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
crotonic acid 0 mg/kg	n	5	0	0	0	0	0	5	0	0	0
crotonic acid 500 mg/kg	n	5	0	0	0	0	1	4	0	0	0
Crystal calcium oxalate											
Test article											
Dose		-	+/-	1+	2+	3+					
crotonic acid 0 mg/kg	n	5	0	0	0	0					
crotonic acid 500 mg/kg	n	5	0	0	0	0					
Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe											

Table 5 - 18

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Male

Study No. : R-1169

		Stage : Week 2 of recovery						Species : Rat
		Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h	
Test article	Dose							
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	
	Mean	49	18.3	1903	1.8	5.1	2.6	
	S.D.	6	7.5	434	0.4	0.3	0.5	
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	
	Mean	42	14.3	1853	1.3	3.9	2.0	
	S.D.	19	7.1	289	0.8	2.2	1.1	
Not significantly different from crotonic acid 0 mg/kg								

Table 5 - 19

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Study No. : R-1169

Stage : Week 2 of recovery

Species : Rat

		pH									
Test article											
Dose		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	
crotonic acid	n	0	0	0	2	0	0	2	0	1	
0 mg/kg											
crotonic acid	n	0	0	0	0	1	2	0	1	1	
500 mg/kg											
		Protein					Ketones				
Test article											
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
crotonic acid	n	3	1	1	0	0	4	1	0	0	0
0 mg/kg											
crotonic acid	n	3	2	0	0	0	2	3	0	0	0
500 mg/kg											

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL
Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Table 5 - 20

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Urinalysis

Stage : Week 2 of recovery

Sex : Female

Species : Rat

		Glucose					Occult Blood				
Test article		-	1+	2+	3+	4+	-	+/-	1+	2+	3+
Dose											
crotonic acid	n	4	1	0	0	0	5	0	0	0	0
0 mg/kg											
crotonic acid	n	4	1	0	0	0	5	0	0	0	0
500 mg/kg											
		Bilirubin					Urobilinogen				
Test article		-	1+	2+	3+		+/-	1+	2+	3+	
Dose											
crotonic acid	n	5	0	0	0	5	0	0	0	0	
0 mg/kg											
crotonic acid	n	5	0	0	0	5	0	0	0		
500 mg/kg											

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL
 Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL
 Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL
 Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Table 5 - 21

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Study No. : R-1169

Stage : Week 2 of recovery

Species : Rat

		Color										
Test article		LY	Y	DY	BR	RE	RB	WH	BL	CL	OT	
Dose												
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0
0 mg/kg												
crotonic acid	n	0	5	0	0	0	0	0	0	0	0	0
500 mg/kg												

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Table 5 - 22

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Study No. : R-1169

Stage : Week 2 of recovery

Species : Rat

		RBC					WBC				
Test article		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid	n	5	0	0	0	0	5	0	0	0	0
0 mg/kg											
crotonic acid	n	5	0	0	0	0	5	0	0	0	0
500 mg/kg											

		Squamous epithelial cells					Small round epithelial cells				
Test article		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Dose	n										
crotonic acid	n	0	5	0	0	0	5	0	0	0	0
0 mg/kg											
crotonic acid	n	0	5	0	0	0	5	0	0	0	0
500 mg/kg											

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Table 5 - 23

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Urinalysis
Sex : Female

Study No. : R-1169

Stage : Week 2 of recovery

Species : Rat

		Cast					Crystal phosphate salts				
Test article											
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
crotonic acid	n	5	0	0	0	0	1	4	0	0	0
0 mg/kg											
crotonic acid	n	5	0	0	0	0	0	5	0	0	0
500 mg/kg											
Crystal calcium oxalate											
Test article											
Dose		-	+/-	1+	2+	3+					
crotonic acid	n	5	0	0	0	0					
0 mg/kg											
crotonic acid	n	5	0	0	0	0					
500 mg/kg											

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe
Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Table 5 - 24

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Urinalysis

Stage : Week 2 of recovery

Sex : Female

Species : Rat

Test article		Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
Dose							
crotonic acid 0 mg/kg	n	5	5	5	5	5	5
	Mean	33	9.8	2192	1.1	2.9	1.5
	S.D.	6	5.2	587	0.2	0.4	0.3
crotonic acid 500 mg/kg	n	5	5	5	5	5	5
	Mean	32	8.3	2200	0.9	2.7	1.4
	S.D.	7	2.8	559	0.2	0.5	0.3

Not significantly different from crotonic acid 0 mg/kg

Table 6 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Hematology
Sex : Male

Stage : End of administration

Species : Rat

		RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP
		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%
Test article	Dose										
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	848	14.9	45.0	53.0	17.6	33.2	2.0	91.8	74.8	79.7
	S.D.	18	0.1	1.0	1.3	0.3	0.6	0.6	6.4	19.3	4.8
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	844	15.0	45.3	53.7	17.8	33.1	2.0	93.0	85.2	79.5
	S.D.	27	0.5	1.9	2.1	0.6	0.4	0.2	1.9	11.7	3.8
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	867	15.1	45.1	52.1	17.4	33.4	1.8	95.3	84.7	79.0
	S.D.	28	0.5	1.3	0.4	0.0	0.2	0.3	6.4	14.6	3.4
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	863	15.0	45.3	52.5	17.4	33.1	2.3	101.9	78.6	80.0
	S.D.	24	0.4	1.5	1.2	0.3	0.4	0.3	10.1	14.7	4.2
		NEUT	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO
		%	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
Test article	Dose										
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	16.1	1.6	0.3	1.7	0.5	59.2	12.4	1.2	0.3	1.3
	S.D.	4.9	0.3	0.1	0.3	0.1	13.6	6.1	0.2	0.1	0.5
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	17.4	1.0	0.4	1.4	0.4	67.6	14.9	0.8	0.3	1.2
	S.D.	3.9	0.1	0.1	0.2	0.2	9.2	4.3	0.2	0.1	0.4
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	17.4	1.2	0.3	1.5	0.7	66.9	14.6	1.0	0.3	1.3
	S.D.	4.1	0.5	0.1	0.4	0.4	12.0	3.2	0.5	0.1	0.6
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	15.9	1.5	0.4	1.4	0.8	62.5	12.9	1.1	0.3	1.1
	S.D.	4.4	0.6	0.1	0.4	0.3	10.3	5.4	0.3	0.1	0.4

Not significantly different from crotonic acid 0 mg/kg

Table 6 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Hematology

Stage : End of administration

Sex : Male

Species : Rat

		#LUC	PT	APTT	FIB
		10 ² /μL	s	s	mg/dL
Test article					
Dose					
crotonic acid	n	5	5	5	5
0 mg/kg	Mean	0.4	12.2	16.9	252
	S.D.	0.1	0.6	0.9	11
crotonic acid	n	5	5	5	5
50 mg/kg	Mean	0.3	12.4	16.5	254
	S.D.	0.1	0.5	1.1	21
crotonic acid	n	5	5	5	5
150 mg/kg	Mean	0.6	13.1	17.0	256
	S.D.	0.4	2.1	2.6	27
crotonic acid	n	5	5	5	5
500 mg/kg	Mean	0.6	13.0	17.7	243
	S.D.	0.3	1.9	1.7	34

Not significantly different from crotonic acid 0 mg/kg

Table 6 - 3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Hematology
Sex : Female

Stage : Lactation day 5

Species : Rat

		RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP
		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%
Test article Dose	n	5	5	5	5	5	5	5	5	5	5
	Mean	708	13.0	39.1	55.2	18.3	33.1	5.7	127.7	97.4	65.5
	S.D.	45	0.6	1.8	1.5	0.7	0.5	1.2	13.1	20.4	6.2
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	703	13.3	40.4	57.6	18.9	32.9	6.3	142.6	96.8	65.5
	S.D.	60	0.8	2.5	1.8	0.6	0.1	2.3	18.8	32.6	10.7
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	718	13.3	40.0	55.7	18.6	33.4	5.3	131.1	105.6	70.4
	S.D.	28	0.5	1.8	2.1	0.6	0.3	1.1	16.3	39.6	8.4
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	731	13.5	40.8	55.9	18.4	33.0	5.7	137.4	105.2	70.1
	S.D.	21	0.4	1.4	1.3	0.5	0.3	1.1	12.0	6.3	6.7
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	731	13.5	40.8	55.9	18.4	33.0	5.7	137.4	105.2	70.1
	S.D.	21	0.4	1.4	1.3	0.5	0.3	1.1	12.0	6.3	6.7

		NEUT	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO
		%	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
Test article Dose	n	5	5	5	5	5	5	5	5	5	5
	Mean	30.9	0.8	0.4	2.0	0.6	63.8	30.2	0.7	0.4	1.8
	S.D.	6.7	0.4	0.1	0.9	0.1	14.6	8.7	0.3	0.1	0.7
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	30.6	0.7	0.3	2.1	0.6	62.1	31.0	0.7	0.4	2.0
	S.D.	10.5	0.3	0.1	0.5	0.3	17.0	17.1	0.3	0.2	0.7
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	25.4	0.7	0.3	2.5	0.7	73.4	27.7	0.7	0.3	2.5
	S.D.	8.0	0.2	0.1	0.8	0.3	26.0	14.2	0.3	0.2	0.9
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	25.4	0.8	0.3	2.5	0.9	73.9	26.5	0.8	0.3	2.7
	S.D.	6.8	0.4	0.1	0.8	0.2	10.1	6.1	0.3	0.1	0.7
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	25.4	0.8	0.3	2.5	0.9	73.9	26.5	0.8	0.3	2.7
	S.D.	6.8	0.4	0.1	0.8	0.2	10.1	6.1	0.3	0.1	0.7

Not significantly different from crotonic acid 0 mg/kg

Table 6 - 4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Hematology

Stage : Lactation day 5

Sex : Female

Species : Rat

		#LUC	PT	APTT	FIB
		10 ² /μL	s	s	mg/dL
Test article					
Dose					
crotonic acid	n	5	5	5	5
0 mg/kg	Mean	0.6	12.8	16.7	314
	S.D.	0.2	0.8	0.7	65
crotonic acid	n	5	5	5	5
50 mg/kg	Mean	0.6	12.6	17.5	307
	S.D.	0.3	0.4	2.4	91
crotonic acid	n	5	5	5	5
150 mg/kg	Mean	0.8	12.8	14.2	304
	S.D.	0.5	1.0	2.5	66
crotonic acid	n	5	5	5	5
500 mg/kg	Mean	0.9	13.0	16.8	297
	S.D.	0.3	0.5	1.1	55

Not significantly different from crotonic acid 0 mg/kg

Table 6 - 5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

		Stage : End of administration							Species : Rat		
Hematology		RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP
Sex : Female											
Test article		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%
Dose											
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	783	14.9	42.6	54.5	19.0	34.9	2.0	96.7	57.2	75.5
	S.D.	30	0.2	1.1	1.1	0.6	0.6	0.6	7.1	12.6	9.1
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	840	15.1	44.7	53.2	18.0	33.8	2.1	127.0	66.6	84.2
	S.D.	44	0.7	2.4	0.3	0.2	0.4	0.3	7.7	13.8	2.2
		T2 *				A2 *	T2 **		T2 **		
		NEUT	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO
Test article		%	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
Dose											
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	20.3	1.7	0.3	1.6	0.5	43.2	11.5	1.0	0.2	0.9
	S.D.	9.8	0.5	0.1	0.6	0.3	11.0	5.3	0.5	0.1	0.3
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	12.2	1.2	0.3	1.5	0.6	56.0	8.2	0.8	0.2	1.0
	S.D.	1.6	0.4	0.1	0.4	0.1	11.2	2.3	0.4	0.1	0.3
		#LUC	PT	APTT	FIB						
Test article		10 ² /μL	s	s	mg/dL						
Dose											
crotonic acid 0 mg/kg	n	5	5	5	5						
	Mean	0.3	12.1	14.8	210						
	S.D.	0.2	0.7	1.5	27						
crotonic acid 500 mg/kg	n	5	5	5	5						
	Mean	0.4	12.1	14.8	200						
	S.D.	0.2	0.9	2.1	14						

Significantly different from crotonic acid 0 mg/kg : * P<0.05, ** P<0.01

A2 : Welch test (two-side), T2 : Student t-test (two-side)

Table 6 - 6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Hematology

Stage : End of recovery

Species : Rat

Sex : Male

		RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP
		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%
Test article Dose	n	5	5	5	5	5	5	5	5	5	5
	Mean	889	15.3	46.2	51.9	17.3	33.2	1.6	89.8	79.9	82.3
	S.D.	43	0.6	2.2	1.5	0.5	0.5	0.3	5.8	11.1	4.9
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	888	15.8	47.2	53.2	17.9	33.6	1.4	83.1	78.4	73.1
	S.D.	56	1.1	2.6	0.9	0.4	0.5	0.4	28.0	17.8	21.0
		NEUT	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO
		%	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
Test article Dose	n	5	5	5	5	5	5	5	5	5	5
	Mean	13.2	1.5	0.4	2.0	0.6	66.1	10.3	1.2	0.3	1.5
	S.D.	4.2	0.4	0.1	0.5	0.2	12.3	2.7	0.3	0.1	0.3
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	22.7	1.2	0.4	1.9	0.7	59.1	16.1	0.9	0.3	1.4
	S.D.	20.5	0.5	0.1	1.2	0.1	26.3	12.4	0.4	0.2	0.7
		#LUC	PT	APTT	FIB						
		10 ² /μL	s	s	mg/dL						
Test article Dose	n	5	5	5	5						
	Mean	0.5	12.6	17.3	235						
	S.D.	0.2	0.4	2.4	13						
crotonic acid 500 mg/kg	n	5	5	5	5						
	Mean	0.6	13.2	17.5	241						
	S.D.	0.2	0.4	2.3	20						

Not significantly different from crotonic acid 0 mg/kg

Table 6 - 7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Hematology
Sex : Female

Study No. : R-1169

		Stage : End of recovery								Species : Rat	
		RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP
Test article		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%
Dose											
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	796	14.6	41.9	52.7	18.4	34.9	2.0	103.7	59.7	79.5
	S.D.	55	0.7	2.4	1.2	0.6	0.6	0.4	9.2	29.2	6.3
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	814	14.9	43.7	53.8	18.3	34.1	1.9	99.6	59.9	81.8
	S.D.	33	0.5	1.5	2.1	0.6	0.6	0.5	6.1	10.1	4.3
		NEUT	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO
Test article		%	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
Dose											
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	16.1	2.0	0.4	1.6	0.5	46.8	10.1	1.2	0.3	1.0
	S.D.	5.9	0.4	0.2	0.4	0.2	20.5	8.3	0.8	0.2	0.7
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	13.6	1.8	0.4	1.6	0.7	49.0	8.3	1.1	0.3	1.0
	S.D.	4.6	0.9	0.2	0.5	0.3	8.4	3.4	0.4	0.1	0.3
		#LUC	PT	APTT	FIB						
Test article		10 ² /μL	s	s	mg/dL						
Dose											
crotonic acid 0 mg/kg	n	5	5	5	5						
	Mean	0.3	12.7	15.2	201						
	S.D.	0.2	0.4	0.9	18						
crotonic acid 500 mg/kg	n	5	5	5	5						
	Mean	0.4	12.8	15.2	196						
	S.D.	0.2	0.4	1.2	17						

Not significantly different from crotonic acid 0 mg/kg

Table 7 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

		Blood chemistry								
		Stage : End of administration								
		Species : Rat								
		Sex : Male								
		AST	ALT	LDH	γ-GTP	ALP	T-BA	T-CHO	TG	T-BIL
Test article		IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL
Dose										
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	66	47	50	1	389	13.4	59	24	90
	S.D.	6	10	9	0	79	3.8	10	7	10
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	60	48	46	1	506	13.9	57	28	90
	S.D.	6	5	15	0	147	5.7	9	14	13
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	60	39	44	1	508	14.3	52	20	84
	S.D.	7	6	6	0	100	6.0	8	10	11
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	59	40	44	1	418	12.9	60	34	94
	S.D.	6	7	7	0	81	6.3	7	5	10
		GLU	BUN	CRNN	Na	K	Cl	Ca	P	TP
		mg/dL	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	164	17	0.25	143	4.6	106	9.6	5.9	5.9
	S.D.	23	2	0.05	1	0.2	1	0.1	0.3	0.3
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	148	16	0.24	143	4.5	107	9.6	6.1	5.7
	S.D.	8	2	0.03	1	0.1	1	0.3	0.4	0.3
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	150	17	0.26	143	4.3	107	9.6	5.7	5.8
	S.D.	5	2	0.04	1	0.2	2	0.2	0.3	0.2
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	144	16	0.25	143	4.7	107	9.5	6.0	5.4
	S.D.	18	1	0.04	1	0.1	1	0.3	0.2	0.2
		DT **								
		DT *								

Significantly different from crotonic acid 0 mg/kg : * P<0.05, ** P<0.01

DT : Dunnett test (two-side)

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 7 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Blood chemistry
Sex : Male

Study No. : R-1169

Stage : End of administration

Species : Rat

A/G		
Test article		
Dose		
crotonic acid 0 mg/kg	n	5
	Mean	1.1
	S.D.	0.1
crotonic acid 50 mg/kg	n	5
	Mean	1.2
	S.D.	0.1
crotonic acid 150 mg/kg	n	5
	Mean	1.1
	S.D.	0.1
crotonic acid 500 mg/kg	n	5
	Mean	1.2
	S.D.	0.1

Not significantly different from crotonic acid 0 mg/kg

Table 7 - 3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Blood chemistry

Stage : Lactation day 5

Sex : Female

Species : Rat

		AST	ALT	LDH	γ-GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL
		IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL
Test article Dose	n	5	5	5	5	5	5	5	5	5	5
	Mean	76	65	39	1	309	21.8	48	68	105	0.1
	S.D.	14	3	9	0	121	6.2	8	28	10	0.0
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	72	57	41	1	246	40.5	58	75	119	0.1
	S.D.	11	13	6	0	44	50.5	6	37	15	0.0
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	88	69	43	1	325	19.7	57	94	122	0.1
	S.D.	27	17	18	0	154	8.6	8	34	17	0.0
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	71	61	37	1	190	17.7	53	113	120	0.1
	S.D.	11	9	14	0	9	4.3	3	26	7	0.0
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	133	24	0.27	141	4.4	106	10.5	6.9	6.1	3.4
	S.D.	26	2	0.02	0	0.2	2	0.3	1.1	0.2	0.1
		GLU	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB
		mg/dL	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
Test article Dose	n	5	5	5	5	5	5	5	5	5	5
	Mean	133	24	0.27	141	4.4	106	10.5	6.9	6.1	3.4
	S.D.	26	2	0.02	0	0.2	2	0.3	1.1	0.2	0.1
crotonic acid 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	131	20	0.23	141	4.5	106	10.5	7.1	6.2	3.4
	S.D.	14	4	0.03	1	0.1	1	0.6	0.4	0.4	0.2
crotonic acid 50 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	147	20	0.25	141	4.3	106	10.3	7.1	5.9	3.2
	S.D.	12	6	0.03	1	0.4	3	0.4	1.1	0.2	0.1
crotonic acid 150 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	118	20	0.22	140	4.4	105	10.5	6.7	6.1	3.4
	S.D.	5	4	0.01	2	0.4	1	0.2	0.3	0.1	0.1
crotonic acid 500 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	118	20	0.22	140	4.4	105	10.5	6.7	6.1	3.4
	S.D.	5	4	0.01	2	0.4	1	0.2	0.3	0.1	0.1

Significantly different from crotonic acid 0 mg/kg : * P<0.05

DT : Dunnett test (two-side)

DT *

Table 7 - 4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Blood chemistry

Stage : Lactation day 5

Sex : Female

Species : Rat

A/G		
Test article		
Dose		
crotonic acid	n	5
0 mg/kg	Mean	1.3
	S.D.	0.1
crotonic acid	n	5
50 mg/kg	Mean	1.2
	S.D.	0.1
crotonic acid	n	5
150 mg/kg	Mean	1.2
	S.D.	0.1
crotonic acid	n	5
500 mg/kg	Mean	1.2
	S.D.	0.0

Not significantly different from crotonic acid 0 mg/kg

Table 7 - 5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Blood chemistry

Stage : End of administration

Sex : Female

Species : Rat

		AST	ALT	LDH	γ-GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL
		IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL
Test article											
Dose											
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	59	40	30	1	249	40.2	66	17	129	0.1
	S.D.	7	13	2	0	75	40.5	7	3	17	0.0
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	58	41	35	1	263	22.5	56	23	119	0.1
	S.D.	8	18	7	0	137	12.5	6	6	9	0.0
T2 *											EF
		GLU	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB
		mg/dL	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
Test article											
Dose											
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	131	18	0.29	140	3.8	107	9.8	4.2	6.2	3.5
	S.D.	13	5	0.04	1	0.4	1	0.2	0.5	0.4	0.3
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	129	19	0.31	143	4.1	108	9.7	4.1	5.8	3.4
	S.D.	11	5	0.03	2	0.2	2	0.2	0.6	0.2	0.2
A/G											
Test article											
Dose											
crotonic acid	n	5									
0 mg/kg	Mean	1.3									
	S.D.	0.1									
crotonic acid	n	5									
500 mg/kg	Mean	1.4									
	S.D.	0.2									

Significantly different from crotonic acid 0 mg/kg : * P<0.05

T2 : Student t-test (two-side)

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 7 - 6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Blood chemistry

Stage : End of recovery

Sex : Male

Species : Rat

		AST	ALT	LDH	γ-GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL
		IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL
Test article											
Dose											
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	62	45	46	1	351	15.8	49	45	83	0.1
	S.D.	7	7	12	0	57	17.4	5	23	11	0.0
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	111	66	55	1	369	17.7	52	38	85	0.1
	S.D.	103	39	23	0	52	16.0	15	11	17	0.0
EF											
		GLU	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB
		mg/dL	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
Test article											
Dose											
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	162	18	0.22	142	4.7	106	9.3	5.2	5.7	3.0
	S.D.	28	2	0.01	1	0.3	2	0.2	0.2	0.3	0.2
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	155	20	0.24	143	4.5	105	9.5	5.2	5.7	2.9
	S.D.	20	3	0.02	1	0.5	2	0.2	0.4	0.5	0.2
A/G											
Test article											
Dose											
crotonic acid	n	5									
0 mg/kg	Mean	1.1									
	S.D.	0.1									
crotonic acid	n	5									
500 mg/kg	Mean	1.1									
	S.D.	0.1									

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 7 - 7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Blood chemistry
Sex : Female

Stage : End of recovery

Species : Rat

		AST	ALT	LDH	γ-GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL
		IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL
Test article											
Dose											
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	54	32	35	1	215	12.4	58	30	120	0.1
	S.D.	5	4	4	1	85	3.7	13	27	22	0.0
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	62	35	42	1	202	25.9	59	27	125	0.1
	S.D.	9	5	10	0	65	18.9	11	9	18	0.0
											EF
		GLU	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB
		mg/dL	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
Test article											
Dose											
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	153	19	0.27	141	4.3	107	9.8	4.8	6.2	3.5
	S.D.	27	1	0.03	2	0.2	1	0.1	0.4	0.1	0.1
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	158	19	0.30	141	4.4	108	9.8	5.0	6.3	3.5
	S.D.	20	3	0.05	1	0.4	0	0.4	1.0	0.4	0.3
A/G											
Test article											
Dose											
crotonic acid	n	5									
0 mg/kg	Mean	1.3									
	S.D.	0.1									
crotonic acid	n	5									
500 mg/kg	Mean	1.3									
	S.D.	0.1									

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 8 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Organ weight

Stage : End of administration

Species : Rat

Sex : Male

		Sex : Male	Body weight		Brain		Pituitary		Thyroid-RL		Thymus	
Test article												
Dose		g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
crotonic acid	n	7	7	7	7	7	7	7	7	7	7	7
0 mg/kg	Mean	525	2.13	0.41	13.5	2.6	20.7	4.0	271	52		
	S.D.	31	0.04	0.02	1.5	0.4	6.0	1.3	54	10		
crotonic acid	n	12	12	12	12	12	12	12	12	12	12	12
50 mg/kg	Mean	507	2.16	0.43	13.3	2.6	23.0	4.5	331	65		
	S.D.	20	0.10	0.03	2.0	0.3	3.1	0.6	60	12		
crotonic acid	n	12	12	12	12	12	12	12	12	12	12	12
150 mg/kg	Mean	497	2.13	0.43	13.0	2.6	22.9	4.6	281	56		
	S.D.	24	0.11	0.03	0.9	0.2	2.0	0.4	74	13		
crotonic acid	n	7	7	7	7	7	7	7	7	7	7	7
500 mg/kg	Mean	477	2.13	0.45	13.2	2.8	21.9	4.6	257	54		
	S.D.	32	0.10	0.03	1.8	0.3	3.6	0.9	55	13		
		DT **		DT *								
		Heart		Liver		Spleen		Kidney-RL		Adrenal-RL		
Test article												
Dose		AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	
crotonic acid	n	7	7	7	7	7	7	7	7	7	7	7
0 mg/kg	Mean	1.56	0.29	13.64	2.60	0.76	0.14	3.36	0.64	59	11	
	S.D.	0.14	0.02	1.25	0.15	0.13	0.02	0.21	0.05	10	2	
crotonic acid	n	12	12	12	12	12	12	12	12	12	12	12
50 mg/kg	Mean	1.49	0.29	13.07	2.57	0.75	0.15	3.30	0.65	62	12	
	S.D.	0.12	0.02	1.53	0.22	0.13	0.02	0.24	0.03	11	2	
crotonic acid	n	12	12	12	12	12	12	12	12	12	12	12
150 mg/kg	Mean	1.44	0.29	12.78	2.58	0.70	0.14	3.20	0.64	58	12	
	S.D.	0.08	0.02	1.05	0.19	0.12	0.03	0.26	0.05	8	2	
crotonic acid	n	7	7	7	7	7	7	7	7	7	7	7
500 mg/kg	Mean	1.33	0.28	12.62	2.65	0.72	0.15	3.22	0.68	58	12	
	S.D.	0.10	0.03	1.06	0.12	0.09	0.02	0.24	0.06	8	1	
		DT **										

AB : Absolute weight, RE : Relative weight by body weight

Significantly different from crotonic acid 0 mg/kg : * P<0.05, ** P<0.01

DT : Dunnett test (two-side)

Table 8 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Crotonic acid by oral administration in rats		Stage : End of administration								Species : Rat
Organ weight		Testis-RL		Epididymis-RL		Prostate		Seminalvesicle		
Sex : Male		AB	RE	AB	RE	AB	RE	AB	RE	
Test article		g	g/100g	mg	mg/100g	g	g/100g	g	g/100g	
Dose										
crotonic acid 0 mg/kg	n	7	7	7	7	7	7	7	7	
	Mean	3.34	0.64	1244	237	1.24	0.24	1.77	0.34	
	S.D.	0.21	0.06	75	15	0.19	0.04	0.23	0.03	
crotonic acid 50 mg/kg	n	12	12	12	12	12	12	12	12	
	Mean	3.36	0.66	1299	256	1.27	0.25	1.72	0.34	
	S.D.	0.18	0.03	84	16	0.15	0.03	0.27	0.05	
crotonic acid 150 mg/kg	n	12	12	12	12	12	12	12	12	
	Mean	3.25	0.66	1255	254	1.25	0.25	1.79	0.36	
	S.D.	0.25	0.07	98	29	0.26	0.06	0.30	0.07	
crotonic acid 500 mg/kg	n	7	7	7	7	7	7	7	7	
	Mean	3.22	0.68	1223	257	1.14	0.24	1.81	0.38	
	S.D.	0.24	0.07	82	15	0.15	0.02	0.31	0.07	

AB : Absolute weight, RE : Relative weight by body weight

Not significantly different from crotonic acid 0 mg/kg

Table 8 - 3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Organ weight

Stage : Lactation day 5

Sex : Female

Species : Rat

		Sex : Female	Body weight			Brain		Pituitary		Thyroid-RL		Thymus	
Test article Dose		g	AB	RE	AB	RE	AB	RE	AB	RE			
			g	g/100g	mg	mg/100g	mg	mg/100g	mg	mg/100g			
crotonic acid 0 mg/kg	n	12	12	12	12	12	12	12	12	12			
	Mean	327	1.97	0.60	18.4	5.7	16.3	5.0	210	64			
	S.D.	7	0.08	0.03	3.3	1.0	3.2	1.0	39	11			
crotonic acid 50 mg/kg	n	10	10	10	10	10	10	10	10	10			
	Mean	321	1.97	0.62	17.5	5.4	17.2	5.4	214	67			
	S.D.	16	0.12	0.06	2.7	0.7	3.0	1.0	54	18			
crotonic acid 150 mg/kg	n	11	11	11	11	11	11	11	11	11			
	Mean	329	1.96	0.60	17.9	5.5	14.9	4.5	219	67			
	S.D.	15	0.10	0.05	2.5	0.9	2.0	0.6	44	13			
crotonic acid 500 mg/kg	n	12	12	12	12	12	12	12	12	12			
	Mean	309	1.96	0.63	18.3	5.9	16.0	5.2	181	58			
	S.D.	14	0.03	0.03	3.7	1.3	2.7	0.9	44	13			
		DT **											

		Heart		Liver		Spleen		Kidney-RL		Adrenal-RL	
Test article Dose		AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
		g	g/100g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
crotonic acid 0 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	1.03	0.32	10.98	3.36	0.65	0.20	2.28	0.70	74	23
	S.D.	0.08	0.02	0.74	0.20	0.12	0.04	0.18	0.05	12	4
crotonic acid 50 mg/kg	n	10	10	10	10	10	10	10	10	10	10
	Mean	1.05	0.33	10.58	3.30	0.66	0.20	2.22	0.69	73	23
	S.D.	0.07	0.03	0.45	0.13	0.07	0.02	0.16	0.05	8	2
crotonic acid 150 mg/kg	n	11	11	11	11	11	11	11	11	11	11
	Mean	1.10	0.34	10.83	3.30	0.67	0.20	2.29	0.70	79	24
	S.D.	0.11	0.04	0.63	0.24	0.07	0.02	0.16	0.05	10	3
crotonic acid 500 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	1.02	0.33	10.11	3.27	0.62	0.20	2.16	0.70	78	25
	S.D.	0.09	0.02	0.62	0.18	0.08	0.02	0.12	0.04	10	3
		DT **									

AB : Absolute weight, RE : Relative weight by body weight

Significantly different from crotonic acid 0 mg/kg : ** P<0.01

DT : Dunnett test (two-side)

Table 8 - 4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Organ weight

Stage : Lactation day 5

Sex : Female

Species : Rat

		Ovary-RL		Uterus	
Test article		AB	RE	AB	RE
Dose		mg	mg/100g	mg	mg/100g
crotonic acid 0 mg/kg	n	12	12	12	12
	Mean	107.0	32.8	741	227
	S.D.	13.9	4.3	130	40
crotonic acid 50 mg/kg	n	10	10	10	10
	Mean	99.0	30.9	751	234
	S.D.	9.1	3.0	124	32
crotonic acid 150 mg/kg	n	11	11	11	11
	Mean	104.0	31.6	802	244
	S.D.	7.9	2.4	108	36
crotonic acid 500 mg/kg	n	12	12	12	12
	Mean	102.7	33.2	722	233
	S.D.	11.7	3.8	77	21

AB : Absolute weight, RE : Relative weight by body weight

Not significantly different from crotonic acid 0 mg/kg

Table 8 - 5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Organ weight

Stage : End of administration

Species : Rat

Sex : Female

Sex : Female		Species : Rat									
		Body weight	Brain		Pituitary		Thyroid-RL		Thymus		
Test article			AB	RE	AB	RE	AB	RE	AB	RE	
Dose		g	g	g/100g	mg	mg/100g	mg	mg/100g	mg	mg/100g	
crotonic acid	n	5	5	5	5	5	5	5	5	5	
0 mg/kg	Mean	296	1.94	0.65	16.9	5.7	17.3	5.8	263	89	
	S.D.	5	0.07	0.02	2.1	0.7	2.9	0.9	37	12	
crotonic acid	n	5	5	5	5	5	5	5	5	5	
500 mg/kg	Mean	279	1.96	0.70	16.8	6.0	16.6	6.0	289	104	
	S.D.	17	0.06	0.04	4.6	1.5	1.6	0.7	37	19	
T2 *											
		Heart		Liver		Spleen		Kidney-RL		Adrenal-RL	
Test article		AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
Dose		g	g/100g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	0.92	0.31	7.56	2.55	0.54	0.18	1.84	0.62	69	23
	S.D.	0.06	0.02	0.80	0.24	0.11	0.04	0.09	0.03	8	3
crotonic acid	n	5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	0.88	0.31	6.96	2.49	0.48	0.17	1.84	0.66	70	25
	S.D.	0.08	0.02	0.61	0.10	0.07	0.03	0.18	0.05	5	1
		Ovary-RL		Uterus							
Test article		AB	RE	AB	RE						
Dose		mg	mg/100g	mg	mg/100g						
crotonic acid	n	5	5	5	5						
0 mg/kg	Mean	77.3	26.1	483	163						
	S.D.	8.7	2.8	86	27						
crotonic acid	n	5	5	5	5						
500 mg/kg	Mean	86.7	31.1	639	227						
	S.D.	7.7	2.6	228	74						
T2 *											

AB : Absolute weight, RE : Relative weight by body weight

Significantly different from crotonic acid 0 mg/kg : * P<0.05

T2 : Student t-test (two-side)

Table 8 - 6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

		Organ weight		Stage : End of recovery								Species : Rat	
		Sex : Male		Body weight		Brain		Pituitary		Thyroid-RL		Thymus	
Test article				AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
Dose		g		g	g/100g	mg	mg/100g	mg	mg/100g	mg	mg/100g	mg	mg/100g
crotonic acid	n	5		5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	498		2.16	0.43	14.0	2.8	22.9	4.6	240	49		
	S.D.	23		0.12	0.02	3.9	0.7	5.4	1.0	70	16		
crotonic acid	n	5		5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	480		2.13	0.46	13.0	2.7	22.9	4.8	203	41		
	S.D.	77		0.05	0.09	1.7	0.2	3.9	0.9	111	20		
		Heart		Liver		Spleen		Kidney-RL		Adrenal-RL			
Test article		AB	RE	AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
Dose		g	g/100g	g	g/100g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
crotonic acid	n	5		5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	1.46		0.29	12.15	2.44	0.72	0.14	3.43	0.69	53	11	
	S.D.	0.16		0.02	1.38	0.20	0.05	0.01	0.65	0.10	3	1	
crotonic acid	n	5		5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	1.46		0.31	11.39	2.38	0.61	0.12	3.21	0.67	61	13	
	S.D.	0.09		0.04	1.86	0.14	0.19	0.03	0.50	0.05	15	6	
		Testis-RL		Epididymis-RL		Prostate		Seminalvesicle					
Test article		AB	RE	AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
Dose		g	g/100g	mg	mg/100g	g	g/100g	g	g/100g	g	g/100g	g	g/100g
crotonic acid	n	5		5	5	5	5	5	5	5	5	5	5
0 mg/kg	Mean	3.42		0.69	1481	298	1.31	0.27	1.96	0.39			
	S.D.	0.16		0.06	97	29	0.15	0.03	0.18	0.03			
crotonic acid	n	5		5	5	5	5	5	5	5	5	5	5
500 mg/kg	Mean	3.26		0.69	1219	253	1.21	0.25	1.32	0.26			
	S.D.	0.28		0.09	230	15	0.40	0.05	0.56	0.09			
					T2 *	T2 *				T2 *			

AB : Absolute weight, RE : Relative weight by body weight

Significantly different from crotonic acid 0 mg/kg : * P<0.05

T2 : Student t-test (two-side)

Table 8 - 7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

crotonic acid by oral administration in rats				Stage : End of recovery								Species : Rat	
Organ weight		Sex : Female		Body weight		Brain		Pituitary		Thyroid-RL		Thymus	
Test article	Dose	n	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g		
crotonic acid 0 mg/kg		n	5	5	5	5	5	5	5	5	5		
	Mean		293	1.96	0.67	16.0	5.5	16.6	5.7	236	81		
	S.D.		21	0.07	0.06	3.7	1.5	2.8	1.0	64	22		
crotonic acid 500 mg/kg		n	5	5	5	5	5	5	5	5	5		
	Mean		289	1.99	0.69	16.6	5.8	17.6	6.1	271	94		
	S.D.		17	0.06	0.05	1.5	0.6	4.3	1.6	53	19		
		Heart		Liver		Spleen		Kidney-RL		Adrenal-RL			
Test article	Dose	n	g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g		
crotonic acid 0 mg/kg		n	5	5	5	5	5	5	5	5	5		
	Mean		0.90	0.31	7.07	2.41	0.52	0.18	1.95	0.66	66		
	S.D.		0.04	0.02	0.56	0.07	0.03	0.01	0.24	0.06	8		
crotonic acid 500 mg/kg		n	5	5	5	5	5	5	5	5	5		
	Mean		1.00	0.35	7.17	2.48	0.54	0.19	1.92	0.66	69		
	S.D.		0.06	0.01	0.53	0.14	0.08	0.02	0.06	0.02	13		
			T2 *	T2 **									
		Ovary-RL		Uterus									
Test article	Dose	n	mg	AB mg	RE mg/100g	AB mg	RE mg/100g						
crotonic acid 0 mg/kg		n	5	5	5	5	5						
	Mean		87.1	29.6	766	263							
	S.D.		23.3	6.5	140	56							
crotonic acid 500 mg/kg		n	5	5	5	5							
	Mean		92.0	31.8	654	227							
	S.D.		20.5	7.0	192	69							

AB : Absolute weight, RE : Relative weight by body weight

Significantly different from crotonic acid 0 mg/kg : * P<0.05, ** P<0.01

T2 : Student t-test (two-side)

Table 9-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Gross pathological findings (End of administration period (D42))

		Species : Rat			
Organs	Sex:	M	M	M	M
	Dose (mg/kg) :	0	50	150	500
Findings	Number:	7	12	12	7
Kidney					
Focus, white		0	0	0	1
Dilatation, pelvic		0	0	1	0
Seminal vesicle (coagulating gland)					
Small		0	0	1	0
Stomach					
Thickening, wall, forestomach		0	0	0	2
Focus, dark red, glandular stomach		0	3	1	0

M : Male

Study No. : R-1169

Table 9-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Gross pathological findings (End of administration period (D42))

Species : Rat

Organs	Sex:	F	F
	Dose (mg/kg) :	0	500
Findings	Number:	5	5
Stomach			
Focus, dark red, glandular stomach		1	0

F : Female

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

		Species : Rat			
Organs	Sex:	F	F	F	F
	Dose (mg/kg) :	0	50	150	500
Findings	Number:	12	10	11	12
Stomach					
Focus, raised, forestomach		0	0	0	3
Thickening, wall, forestomach		0	0	0	1
Focus, dark red, glandular stomach		3	0	0	0

F : Female

Study No. : R-1169

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

Species : Rat

Organs	Sex:	M	M
	Dose (mg/kg) :	0	500
Findings	Number:	5	5
Seminal vesicle(coagulating gland)			
Small		0	1
Thymus			
Small		0	1

M : Male

Table 9-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Gross pathological findings (End of recovery period)

Species : Rat

Organs	Sex:	F	F
	Dose (mg/kg) :	0	500
Findings	Number:	5	5
Stomach			
Focus, dark red, glandular stomach		1	0

F : Female

Table 9-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Gross pathological findings (Undelivered)

Species : Rat

Organs	Sex:	F	F
	Dose (mg/kg) :	50	150
Findings	Number:	2	1
All tissues			
Not remarkable		2	1

F : Female

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

Species : Rat

Organs	Sex:	M	M	M	M
	Dose (mg/kg) :	0	50	150	500
Findings	Number:	7	12	12	7
Adrenal					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Bone+Bone marrow, femoral					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Cerebellum (pons)					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Cerebrum					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Epididymis					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Eye					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Heart					
Number examined		5	2	1	5
Not remarkable		4	2	1	3
Cell infiltration		1	0	0	2
minimal		1	0	0	2
Intestine, duodenum					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Intestine, jejunum					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Intestine, ileum (Peyer's patch)					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Intestine, cecum					
Number examined		5	2	1	5
Not remarkable		4	2	0	5
Cell infiltration, mucosal		1	0	1	0
minimal		1	0	1	0
Intestine, colon					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Intestine, rectum					
Number examined		5	2	1	5
Not remarkable		5	2	1	5

M : Male

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

Species : Rat

Organs	Sex:	M	M	M	M
	Dose (mg/kg) :	0	50	150	500
Findings	Number:	7	12	12	7
Kidney					
Number examined		5	2	1	5
Not remarkable		3	1	1	3
Basophilia,tubular		1	1	0	0
minimal		1	1	0	0
Urinary cast,hyaline		1	0	0	2
minimal		1	0	0	2
Liver					
Number examined		5	2	1	5
Not remarkable		4	2	0	5
Microgranuloma		1	0	1	0
minimal		1	0	1	0
Lung(bronchus)					
Number examined		5	2	1	5
Not remarkable		4	2	1	5
Aggregation,alveolar macrophage		1	0	0	0
minimal		1	0	0	0
Lymph node,mesenteric					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Lymph node,submandibular					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Mammary gland,inguinal					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Pancreas					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Parathyroid					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Pituitary					
Number examined		5	2	1	5
Not remarkable		4	2	1	5
Cyst,pars distalis		1	0	0	0
minimal		1	0	0	0
Prostate					
Number examined		5	2	1	5
Not remarkable		3	1	0	4
Cell infiltration,interstitial		2	1	1	1
minimal		1	1	1	0
mild		1	0	0	1
Salivary gland,submandibular					
Number examined		5	2	1	5
Not remarkable		5	2	1	5

M : Male

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

Species : Rat

Organs	Sex:	M	M	M	M
	Dose (mg/kg) :	0	50	150	500
Findings	Number:	7	12	12	7
Sciatic nerve					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Seminal vesicle(coagulating gland)					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Skeletal muscle,femoral					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Spinal cord,thoracic					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Spleen					
Number examined		5	2	1	5
Not remarkable		5	2	1	4
Aggregation,macrophage		0	0	0	1
mild		0	0	0	1
Stomach					
Number examined		5	6	6	5
Not remarkable		5	5	2	0
Erosion/Ulcer,glandular stomach		0	1	0	1
minimal		0	1	0	1
Hyperplasia,squamous,forestomach		0	0	4	5
minimal		0	0	4	0
mild		0	0	0	2
moderate		0	0	0	3
Testis					
Number examined		5	2	1	5
Not remarkable		4	2	1	5
Atrophy,seminiferous tubular		1	0	0	0
minimal		1	0	0	0
Thymus					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Thyroid					
Number examined		5	2	1	5
Not remarkable		4	2	1	4
Cyst,ultimobranchial		1	0	0	1
minimal		1	0	0	1
Trachea					
Number examined		5	2	1	5
Not remarkable		5	2	1	5
Urinary bladder					
Number examined		5	2	1	5
Not remarkable		5	2	1	5

M : Male

Table 10-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Histopathological findings (End of administration period (D42))

		Species : Rat	
Organs	Sex:	F	F
	Dose (mg/kg) :	0	500
Findings	Number:	5	5
Adrenal			
Number examined		5	5
Not remarkable		5	5
Bone+Bone marrow, femoral			
Number examined		5	5
Not remarkable		5	5
Cerebellum (pons)			
Number examined		5	5
Not remarkable		5	5
Cerebrum			
Number examined		5	5
Not remarkable		5	5
Eye			
Number examined		5	5
Not remarkable		5	5
Heart			
Number examined		5	5
Not remarkable		5	5
Intestine, duodenum			
Number examined		5	5
Not remarkable		5	5
Intestine, jejunum			
Number examined		5	5
Not remarkable		5	5
Intestine, ileum (Peyer's patch)			
Number examined		5	5
Not remarkable		5	5
Intestine, cecum			
Number examined		5	5
Not remarkable		5	4
Cell infiltration, mucosal		0	1
minimal		0	1
Intestine, colon			
Number examined		5	5
Not remarkable		5	5
Intestine, rectum			
Number examined		5	5
Not remarkable		5	5
Kidney			
Number examined		5	5
Not remarkable		4	4
Basophilia, tubular		1	1
minimal		1	1

F : Female

Table 10-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Histopathological findings (End of administration period (D42))

		Species : Rat	
Organs	Sex:	F	F
	Dose (mg/kg) :	0	500
Findings	Number:	5	5
Liver			
Number examined		5	5
Not remarkable		4	3
Microgranuloma		1	2
minimal		1	2
Lung (bronchus)			
Number examined		5	5
Not remarkable		5	5
Lymph node, mesenteric			
Number examined		5	5
Not remarkable		5	5
Lymph node, submandibular			
Number examined		5	5
Not remarkable		5	5
Mammary gland, inguinal			
Number examined		5	5
Not remarkable		5	5
Ovary			
Number examined		5	5
Not remarkable		5	5
Pancreas			
Number examined		5	5
Not remarkable		4	5
Atrophy, acinar, focal		1	0
minimal		1	0
Parathyroid			
Number examined		5	4
Not remarkable		5	4
No sample		0	1
Pituitary			
Number examined		5	5
Not remarkable		5	5
Salivary gland, submandibular			
Number examined		5	5
Not remarkable		5	5
Sciatic nerve			
Number examined		5	5
Not remarkable		5	5
Skeletal muscle, femoral			
Number examined		5	5
Not remarkable		4	5
Cell infiltration, focal		1	0
minimal		1	0

F : Female

Table 10-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Histopathological findings (End of administration period (D42))

		Species : Rat	
Organs	Sex:	F	F
	Dose (mg/kg) :	0	500
Findings	Number:	5	5
Spinal cord, thoracic			
Number examined		5	5
Not remarkable		5	5
Spleen			
Number examined		5	5
Not remarkable		5	5
Stomach			
Number examined		5	5
Not remarkable		4	0
Erosion/Ulcer, glandular stomach		1	0
minimal		1	0
Hyperplasia, squamous, forestomach		0	5
mild		0	2
moderate		0	3
Thymus			
Number examined		5	5
Not remarkable		5	5
Thyroid			
Number examined		5	5
Not remarkable		3	3
Cyst, ultimobranchial		2	2
minimal		2	2
Trachea			
Number examined		5	5
Not remarkable		5	5
Urinary bladder			
Number examined		5	5
Not remarkable		5	5
Uterus			
Number examined		5	5
Not remarkable		5	5
Vagina			
Number examined		5	5
Not remarkable		4	5
Mucification		1	0
mild		1	0

F : Female

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

Species : Rat

Organs	Sex:	F	F	F	F
	Dose (mg/kg) :	0	50	150	500
Findings	Number:	12	10	11	12
Adrenal					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Bone+Bone marrow, femoral					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Cerebellum (pons)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Cerebrum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Eye					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Heart					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine, duodenum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine, jejunum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine, ileum (Peyer's patch)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine, cecum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine, colon					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine, rectum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Kidney					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Liver					
Number examined		5	0	0	5
Not remarkable		4	0	0	3
Microgranuloma		1	0	0	2
minimal		1	0	0	2

F : Female

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

Species : Rat

Organs	Sex:	F	F	F	F
	Dose (mg/kg) :	0	50	150	500
Findings	Number:	12	10	11	12
Lung (bronchus)					
Number examined		5	0	0	5
Not remarkable		4	0	0	3
Aggregation, alveolar macrophage		1	0	0	2
minimal		1	0	0	2
Lymph node, mesenteric					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Lymph node, submandibular					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Mammary gland, inguinal					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Ovary					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pancreas					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Parathyroid					
Number examined		5	0	0	4
Not remarkable		5	0	0	4
No sample		0	0	0	1
Pituitary					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Salivary gland, submandibular					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Sciatic nerve					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Skeletal muscle, femoral					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spinal cord, thoracic					
Number examined		5	0	0	5
Not remarkable		5	0	0	5

F : Female

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

Species : Rat

Organs	Sex:	F	F	F	F
	Dose (mg/kg) :	0	50	150	500
Findings	Number:	12	10	11	12
Spleen					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Stomach					
Number examined		5	5	5	5
Not remarkable		4	5	5	0
Erosion/Ulcer, glandular stomach		1	0	0	1
minimal		0	0	0	1
mild		1	0	0	0
Hyperplasia, squamous, forestomach		0	0	0	5
minimal		0	0	0	1
mild		0	0	0	1
moderate		0	0	0	3
Thymus					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Thyroid					
Number examined		5	0	0	5
Not remarkable		3	0	0	2
Cyst, ultimobranchial		2	0	0	3
minimal		2	0	0	3
Trachea					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Urinary bladder					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Uterus					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Vagina					
Number examined		5	0	0	5
Not remarkable		5	0	0	5

F : Female

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

			Species : Rat
Organs	Sex:	M	M
	Dose (mg/kg) :	0	500
Findings	Number:	5	5
Stomach			
Number examined		5	5
Not remarkable		5	3
Hyperplasia, squamous, forestomach		0	2
mild		0	2

M : Male

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

			Species : Rat
Organs	Sex:	F	F
	Dose (mg/kg) :	0	500
Findings	Number:	5	5
Stomach			
Number examined		5	5
Not remarkable		4	2
Erosion/Ulcer, glandular stomach		1	0
mild		1	0
Hyperplasia, squamous, forestomach		0	3
mild		0	3

F : Female

Table 10-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Histopathological findings (Undelivered)

		Species : Rat	
Organs	Sex:	F	F
Findings	Dose (mg/kg) : Number:	50 2	150 1
Adrenal			
Number examined		2	1
Not remarkable		2	1
Bone+Bone marrow, femoral			
Number examined		2	1
Not remarkable		2	1
Cerebellum (pons)			
Number examined		2	1
Not remarkable		2	1
Cerebrum			
Number examined		2	1
Not remarkable		2	1
Eye			
Number examined		2	1
Not remarkable		2	1
Heart			
Number examined		2	1
Not remarkable		2	1
Intestine, duodenum			
Number examined		2	1
Not remarkable		2	1
Intestine, jejunum			
Number examined		2	1
Not remarkable		2	1
Intestine, ileum (Peyer's patch)			
Number examined		2	1
Not remarkable		2	1
Intestine, cecum			
Number examined		2	1
Not remarkable		2	1
Intestine, colon			
Number examined		2	1
Not remarkable		2	1
Intestine, rectum			
Number examined		2	1
Not remarkable		2	1
Kidney			
Number examined		2	1
Not remarkable		2	1
Liver			
Number examined		2	1
Not remarkable		2	1

F : Female

Table 10-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Histopathological findings (Undelivered)

		Species : Rat	
Organs	Sex:	F	F
Findings	Dose (mg/kg) : Number:	50 2	150 1
Lung (bronchus)			
Number examined		2	1
Not remarkable		2	1
Lymph node, mesenteric			
Number examined		2	1
Not remarkable		2	1
Lymph node, submandibular			
Number examined		2	1
Not remarkable		2	1
Mammary gland, inguinal			
Number examined		2	1
Not remarkable		2	1
Ovary			
Number examined		2	1
Not remarkable		2	1
Pancreas			
Number examined		2	1
Not remarkable		2	1
Parathyroid			
Number examined		2	1
Not remarkable		2	1
Pituitary			
Number examined		2	1
Not remarkable		2	1
Salivary gland, submandibular			
Number examined		2	1
Not remarkable		2	1
Sciatic nerve			
Number examined		2	1
Not remarkable		2	1
Skeletal muscle, femoral			
Number examined		2	1
Not remarkable		2	1
Spinal cord, thoracic			
Number examined		2	1
Not remarkable		2	1
Spleen			
Number examined		2	1
Not remarkable		2	1
Stomach			
Number examined		2	1
Not remarkable		2	0
Hyperplasia, squamous, forestomach		0	1
minimal		0	1

F : Female

Table 10-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
Histopathological findings (Undelivered)

		Species : Rat	
Organs	Sex:	F	F
	Dose (mg/kg) :	50	150
Findings	Number:	2	1
Thymus			
Number examined		2	1
Not remarkable		2	1
Thyroid			
Number examined		2	1
Not remarkable		2	1
Trachea			
Number examined		2	1
Not remarkable		2	1
Urinary bladder			
Number examined		2	1
Not remarkable		2	1
Uterus			
Number examined		2	1
Not remarkable		2	1
Vagina			
Number examined		2	1
Not remarkable		2	1

F : Female

Table 11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Estrus cycles

Generation : F0

Species : Rat

		Generation : F6			Species : Rat	
Test article Dose		/Before mating	Number of estrus	Number of animals with abnormal estrous cycle	Abnormal estrous cycle index	
		Mean estrous cycle (Days)				
crotonic acid 0 mg/kg	n	12	12	12	0.0	
	Mean	4.2	3.8	(0)		
	S.D.	0.3	0.5			
crotonic acid 50 mg/kg	n	11	12	12	16.7	
	Mean	4.2	3.3	(2)		
	S.D.	0.5	0.9			
crotonic acid 150 mg/kg	n	12	12	12	16.7	
	Mean	4.9	3.7	(2)		
	S.D.	2.6	0.7			
crotonic acid 500 mg/kg	n	12	12	12	8.3	
	Mean	4.1	3.4	(1)		
	S.D.	0.3	0.5			

() : Values in brackets represent number of animals with abnormal estrous cycle.

Abnormal estrous cycle index = (No. of animals with abnormal estrous cycle / No. of animals examined) × 100

Not significantly different from crotonic acid 0 mg/kg

Table 12 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Reproductive performance

Generation : F0 Sex : Male

Species : Rat

Test article Dose		Number of pairs	Elapsed day of conceiving	1st mating	
				Copulation index (%) a)	Fertility index (%) b)
crotonic acid 0 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.9	100.0	100.0
	S.D.		1.7		
crotonic acid 50 mg/kg	n	12	10	(10/12)	(10/10)
	Mean		2.3	83.3	100.0
	S.D.		1.3		
crotonic acid 150 mg/kg	n	12	11	(11/12)	(11/11)
	Mean		3.3	91.7	100.0
	S.D.		0.6		
crotonic acid 500 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		1.9	100.0	100.0
	S.D.		0.9		
EF					

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

a): (Number of copulated animals / Number of mated animals)×100

b): (Number of males which impregnated females / Number of copulated males)×100

Table 12 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

Reproductive performance

Generation : F0

Sex : Female

Species : Rat

Test article Dose		Number of pairs	Elapsed day of conceiving	1st mating	
				Copulation index (%) a)	Fertility index (%) b)
crotonic acid 0 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.9	100.0	100.0
	S.D.		1.7		
crotonic acid 50 mg/kg	n	12	10	(10/12)	(10/10)
	Mean		2.3	83.3	100.0
	S.D.		1.3		
crotonic acid 150 mg/kg	n	12	11	(11/12)	(11/11)
	Mean		3.3	91.7	100.0
	S.D.		0.6		
crotonic acid 500 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		1.9	100.0	100.0
	S.D.		0.9		
EF					

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

a): (Number of copulated animals / Number of mated animals)×100

b): (Number of pregnant females / Number of copulated females)×100

Table 13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Study No. : R-1169

Delivery data

Generation : F0

Species : Rat

Test article Dose		Gestation period (day)	Gestation index (%) a)	Number of corpora lutea	Number of implan- tation	Preimplan- tation loss (%) b)	Implantation index (%) c)	Delivery index (%) d)	Live birth index (%) e)	Number of offspring	Number of live newborns			Sex ratio (%)		Number of dead newborns
											M	F	Total	live- borns f)	delivered pups g)	
crotonic acid 0 mg/kg	n	12	12/12	12	12	12	12	12	12	12	12	12	12	94/183	94/183	12
	Mean	22.0	100.0	16.1	15.8	2.2	97.8	97.0	100.0	15.3	7.8	7.4	15.3	51.4	51.4	0.0
	S.D.	0.3		1.4	1.6	3.2	3.2	5.5	0.0	1.5	1.8	2.0	1.5			0.0
crotonic acid 50 mg/kg	n	10	10/10	10	10	10	10	10	10	10	10	10	10	71/139	72/141	10
	Mean	22.2	100.0	15.6	15.5	0.7	99.3	90.8	98.7	14.1	7.1	6.8	13.9	51.1	51.1	0.2
	S.D.	0.5		1.2	1.3	2.1	2.1	10.4	2.7	2.0	2.3	0.9	1.9			0.4
EF																
crotonic acid 150 mg/kg	n	11	11/11	11	11	11	11	11	11	11	11	11	11	87/168	87/168	11
	Mean	22.0	100.0	16.9	15.8	6.2	93.8	96.7	100.0	15.3	7.9	7.4	15.3	51.8	51.8	0.0
	S.D.	0.4		1.8	2.4	12.5	12.5	6.1	0.0	2.4	2.3	3.0	2.4			0.0
EF																
crotonic acid 500 mg/kg	n	12	12/12	12	12	12	12	12	12	12	12	12	12	79/170	79/173	12
	Mean	22.1	100.0	15.3	15.1	1.5	98.5	95.5	98.3	14.4	6.6	7.6	14.2	46.5	45.7	0.3
	S.D.	0.3		0.9	0.7	3.7	3.7	6.8	3.2	1.3	2.4	1.8	1.4			0.5
EF																

M : Male, F : Female

Not significantly different from crotonic acid 0 mg/kg

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

a): (Number of females which delivered liveborns / Number of pregnant females)×100

b): [(Number of corpora lutea - Number of implantation) / Number of corpora lutea]×100

c): (Number of implantation / Number of corpora lutea)×100

d): (Number of delivered pups / Number of implantation)×100

e): (Number of liveborns / Number of delivered pups)×100

f): (Number of liveborn males / Number of liveborns)×100

g): (Number of delivered males / Number of delivered pups)×100

Table 14 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
External examination of offspring
Generation : F0

Study No. : R-1169

Days after birth : 0
Species : Rat

Test article	crotonic acid	crotonic acid	crotonic acid	crotonic acid
Dose	0 mg/kg	50 mg/kg	150 mg/kg	500 mg/kg
Number of dams	12	10	11	12
Number of offspring	183	141	168	173
Number of offspring with any anomaly (incidence %a)	0(0.0)	0(0.0) EF	0(0.0) EF	0(0.0) EF

Not significantly different from crotonic acid 0 mg/kg

a) : (Number of offspring with any anomaly / Number of offspring) x 100

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

Table 14 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
External examination of offspring
Generation : F0

Study No. : R-1169

Days after birth : 4
Species : Rat

Test article	crotonic acid	crotonic acid	crotonic acid	crotonic acid
Dose	0 mg/kg	50 mg/kg	150 mg/kg	500 mg/kg
Number of dams	12	10	11	12
Number of offspring	182	139	165	168
Number of offspring with any anomaly	0	0	0	0

Table 15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Viability index and sex ratio of offspring on day 4 after birth
Generation : F0

Study No. : R-1169

Species : Rat

Test article Dose		Number of live offspring		Viability index (%)a)	Sex ratio (%)b)
		Day 0	Day 4		
crotonic acid 0 mg/kg	n	12	12	12	93/182
	Mean	15.3	15.2	99.5	51.1
	S.D.	1.5	1.5	1.8	
crotonic acid 50 mg/kg	n	10	10	10	71/139
	Mean	13.9	13.9	100.0	51.1
	S.D.	1.9	1.9	0.0	
crotonic acid 150 mg/kg	n	11	11	11	86/165
	Mean	15.3	15.0	98.5	52.1
	S.D.	2.4	2.1	3.6	
crotonic acid 500 mg/kg	n	12	12	12	78/168
	Mean	14.2	14.0	98.8	46.4
	S.D.	1.4	1.4	2.7	

a) : (Number of live offspring on day 4 after birth / Number of live newborns) × 100

b) : (Number of live males on day 4 after birth / Number of live offspring on day 4 after birth) × 100

Not significantly different from crotonic acid 0 mg/kg

Table 16 - 1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Body weight of offspring
Generation : F0

Study No. : R-1169

Generation : F0			Unit : g		Species : Rat	
Test article Dose			/Days after birth			
			0	4/Pre-culled		
crotonic acid 0 mg/kg	Male	n	12	12		
		Mean	6.5	10.1		
		S.D.	0.4	0.5		
	Female	n	12	12		
		Mean	6.1	9.5		
		S.D.	0.4	0.6		
crotonic acid 50 mg/kg	Male	n	10	10		
		Mean	6.9	10.8		
		S.D.	0.7	1.0		
	Female	n	10	10		
		Mean	6.6	10.3		
		S.D.	0.7	1.1		
crotonic acid 150 mg/kg	Male	n	11	11		
		Mean	6.5	10.2		
		S.D.	0.3	1.2		
	Female	n	11	11		
		Mean	6.2	9.9		
		S.D.	0.5	1.3		
crotonic acid 500 mg/kg	Male	n	12	12		
		Mean	6.7	10.5		
		S.D.	0.4	0.8		
	Female	n	12	12		
		Mean	6.3	9.9		
		S.D.	0.4	0.7		
Not significantly different from crotonic acid 0 mg/kg						

Table 16 - 2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Body weight gain of offspring
Generation : F0

Study No. : R-1169

Base : Day 4 after birth

Unit : g

Species : Rat

Test article Dose			/Days after birth /Before culling	
			0-4	
crotonic acid 0 mg/kg	Male	n	12	
		Mean	3.6	
		S.D.	0.6	
	Female	n	12	
		Mean	3.4	
		S.D.	0.6	
crotonic acid 50 mg/kg	Male	n	10	
		Mean	3.9	
		S.D.	0.6	
	Female	n	10	
		Mean	3.7	
		S.D.	0.7	
crotonic acid 150 mg/kg	Male	n	11	
		Mean	3.7	
		S.D.	1.0	
	Female	n	11	
		Mean	3.7	
		S.D.	1.0	
crotonic acid 500 mg/kg	Male	n	12	
		Mean	3.7	
		S.D.	0.5	
	Female	n	12	
		Mean	3.6	
		S.D.	0.4	

Not significantly different from crotonic acid 0 mg/kg

Table 17

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
External examination of dead offspring
Generation : F0

Study No. : R-1169

Test article					Species : Rat
Dose	crotonic acid 0 mg/kg	crotonic acid 50 mg/kg	crotonic acid 150 mg/kg	crotonic acid 500 mg/kg	
Number of dams	12	10	11	12	
Number of offspring	1	0	3	2	
Number of offspring with any anomaly	0	0	0	0	

Appendix 1-1

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-2

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-3

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy

- : No abnormal findings

Appendix 1-4

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 50 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-5

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Male
Period : F0 before mating Day 1-15, F0 mating Day 15-43
Dose : crotonic acid 50 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 50 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy

- : No abnormal findings

Appendix 1-7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 150 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 150 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
3001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-9

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 150 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
3001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy

- : No abnormal findings

Appendix 1-10

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 500 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-11

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 500 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
4001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-12

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Dose : crotonic acid 500 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
4001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy

- : No abnormal findings

Appendix 1-13

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Female

Period : F0 before mating Day 1-15

Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-14

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Female

Period : F0 before mating Day 1-15

Dose : crotonic acid 50 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-15

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Female

Period : F0 before mating Day 1-15

Dose : crotonic acid 150 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
3101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-16

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : F0 before mating Day 1-15
Dose : crotonic acid 500 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
4101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4108	-	-	-	-	-	-	-	-	-	-	-	A	A	A	A
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

A : Wheezing

Animal No.	/Day																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	

- : No abnormal findings

d : Delivery

/d : Found delivery after the observation of general conditions.

Animal No.	/Day																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	

- : No abnormal findings

d : Delivery

/d : Found delivery after the observation of general conditions.

Animal No. 2105 : Not copulated

Animal No. 2108 : Not copulated

Animal No.	/Day																								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
3101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
3102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d	
3107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
3108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		

- : No abnormal findings

d : Delivery

/d : Found delivery after the observation of general conditions.

Animal No. 3109 : Not copulated

Animal No.	/Day																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
4101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d
4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d
4105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d
4107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d

- : No abnormal findings

d : Delivery

/d : Found delivery after the observation of general conditions.

Appendix 1-21

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : F0 lactation Day 0-5
Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day					
	0	1	2	3	4	5a)
1101	-	-	-	-	-	-
1102	-	-	-	-	-	-
1103	-	-	-	-	-	-
1104	-	-	-	-	-	-
1105	-	-	-	-	-	-
1106	-	-	-	-	-	-
1107	-	-	-	-	-	-
1108	-	-	-	-	-	-
1109	-	-	-	-	-	-
1110	-	-	-	-	-	-
1111	-	-	-	-	-	-
1112	-	-	-	-	-	-

a) : Day of necropsy
- : No abnormal findings

Appendix 1-22

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs
 Sex : Female
 Period : F0 lactation Day 0-5
 Dose : crotonic acid 50 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day					
	0	1	2	3	4	5a)
2101	-	-	-	-	-	-
2102	-	-	-	-	-	-
2103	-	-	-	-	-	-
2104	-	-	-	-	-	-
2106	-	-	-	-	-	-
2107	-	-	-	-	-	-
2109	-	-	-	-	-	-
2110	-	-	-	-	-	-
2111	-	-	-	-	-	-
2112	-	-	-	-	-	-

a) : Day of necropsy
 - : No abnormal findings
 Animal No. 2105 : Not copulated
 Animal No. 2108 : Not copulated

Appendix 1-23

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Female

Period : F0 lactation Day 0-5

Dose : crotonic acid 150 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day					
	0	1	2	3	4	5a)
3101	-	-	-	-	-	-
3102	-	-	-	-	-	-
3103	-	-	-	-	-	-
3104	-	-	-	-	-	-
3105	-	-	-	-	-	-
3106	-	-	-	-	-	-
3107	-	-	-	-	-	-
3108	-	-	-	-	-	-
3110	-	-	-	-	-	-
3111	-	-	-	-	-	-
3112	-	-	-	-	-	-

a) : Day of necropsy

- : No abnormal findings

Animal No. 3109 : Not copulated

Appendix 1-24

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : F0 lactation Day 0-5
Dose : crotonic acid 500 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day					
	0	1	2	3	4	5a)
4101	-	-	-	-	-	-
4102	-	-	-	-	-	-
4103	-	-	-	-	-	-
4104	-	-	-	-	-	-
4105	-	-	-	-	-	-
4106	-	-	-	-	-	-
4107	-	-	-	-	-	-
4108	-	-	-	-	-	-
4109	-	-	-	-	-	-
4110	-	-	-	-	-	-
4111	-	-	-	-	-	-
4112	-	-	-	-	-	-

a) : Day of necropsy
- : No abnormal findings

Appendix 1-25

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Clinical signs

Sex : Female

Period : Administration Day 1-43

Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
5101	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5102	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5103	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5104	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5105	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5106	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5107	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5108	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5109	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5110	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-26

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : Administration Day 1-43
Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
5101	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5102	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5103	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5104	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5105	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5106	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5107	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5108	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5109	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5110	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-27

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : Administration Day 1-43
Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
5101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy
- : No abnormal findings

Appendix 1-28

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : Administration Day 1-43
Dose : crotonic acid 500 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
6101	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6102	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6103	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6104	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6105	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6106	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6107	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6108	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6109	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6110	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-29

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : Administration Day 1-43
Dose : crotonic acid 500 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
6101	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6102	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6103	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6104	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6105	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6106	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6107	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6108	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6109	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6110	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal findings

Appendix 1-30

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : Administration Day 1-43
Dose : crotonic acid 500 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
6101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy
- : No abnormal findings

Appendix 1-31

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats
 Clinical signs
 Sex : Male
 Period : Recovery Day 1-15
 Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy
 - : No abnormal findings

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
4008	-	-	-	-	-	-	-	A	A	A	A	A	A	-	-
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy

- : No abnormal findings

A : Wheezing

Appendix 1-33

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : Recovery Day 1-15
Dose : crotonic acid 0 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
5106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy
- : No abnormal findings

Appendix 1-34

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Clinical signs
Sex : Female
Period : Recovery Day 1-15
Dose : crotonic acid 500 mg/kg

Study No.: R-1169

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
6106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a) : Day of necropsy
- : No abnormal findings

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : crotonic acid 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
1001	N	0	0
1002	N	0	0
1003	N	0	0
1004	N	0	0
1005	N	0	0
1006	N	0	0
1007	N	0	0
1008	N	0	0
1009	N	0	0
1010	N	0	0
1011	N	0	0
1012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 before mating		Species : Rat
Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 50 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
2001	N	0	0	
2002	N	0	0	
2003	N	0	0	
2004	N	0	0	
2005	N	0	0	
2006	N	0	0	
2007	N	0	0	
2008	N	0	0	
2009	N	0	0	
2010	N	0	0	
2011	N	0	0	
2012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : crotonic acid 150 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
3001	N	0	0
3002	N	0	0
3003	N	0	0
3004	N	0	0
3005	N	0	0
3006	N	0	0
3007	N	0	0
3008	N	0	0
3009	N	0	0
3010	N	0	0
3011	N	0	0
3012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : crotonic acid 500 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
4001	N	0	0
4002	N	0	0
4003	N	0	0
4004	N	0	0
4005	N	0	0
4006	N	0	0
4007	N	0	0
4008	N	0	0
4009	N	0	0
4010	N	0	0
4011	N	0	0
4012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Generation : F0

Sex : Male

Week : 2

Period : F0 before mating

Dose : crotonic acid 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
1001	N	0	0
1002	N	0	0
1003	N	0	0
1004	N	0	0
1005	N	0	0
1006	N	0	0
1007	N	0	0
1008	N	0	0
1009	N	0	0
1010	N	0	0
1011	N	0	0
1012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 before mating		Species : Rat
Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 50 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
2001	N	0	0	
2002	N	0	0	
2003	N	0	0	
2004	N	0	0	
2005	N	0	0	
2006	N	0	0	
2007	N	0	0	
2008	N	0	0	
2009	N	0	0	
2010	N	0	0	
2011	N	0	0	
2012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : crotonic acid 150 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
3001	N	0	0
3002	N	0	0
3003	N	0	0
3004	N	0	0
3005	N	0	0
3006	N	0	0
3007	N	0	0
3008	N	0	0
3009	N	0	0
3010	N	0	0
3011	N	0	0
3012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : crotonic acid 500 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
4001	N	0	0
4002	N	0	0
4003	N	0	0
4004	N	0	0
4005	N	0	0
4006	N	0	0
4007	N	0	0
4008	N	0	0
4009	N	0	0
4010	N	0	0
4011	N	0	0
4012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : crotonic acid 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
1001	N	0	0
1002	N	0	0
1003	N	0	0
1004	N	0	0
1005	N	0	0
1006	N	0	0
1007	N	0	0
1008	N	0	0
1009	N	0	0
1010	N	0	0
1011	N	0	0
1012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Crotonic acid by oral administration in rats				Species : Rat
Home cage observation		Period : F0 mating		
Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 50 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
2001	N	0	0	
2002	N	0	0	
2003	N	0	0	
2004	N	0	0	
2005	N	0	0	
2006	N	0	0	
2007	N	0	0	
2008	N	0	0	
2009	N	0	0	
2010	N	0	0	
2011	N	0	0	
2012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 150 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
3001	N	0	0	
3002	N	0	0	
3003	N	0	0	
3004	N	0	0	
3005	N	0	0	
3006	N	0	0	
3007	N	0	0	
3008	N	0	0	
3009	N	0	0	
3010	N	0	0	
3011	N	0	0	
3012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 500 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
4001	N	0	0	
4002	N	0	0	
4003	N	0	0	
4004	N	0	0	
4005	N	0	0	
4006	N	0	0	
4007	N	0	0	
4008	N	0	0	
4009	N	0	0	
4010	N	0	0	
4011	N	0	0	
4012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 0 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
1001	N	0	0	
1002	N	0	0	
1003	N	0	0	
1004	N	0	0	
1005	N	0	0	
1006	N	0	0	
1007	N	0	0	
1008	N	0	0	
1009	N	0	0	
1010	N	0	0	
1011	N	0	0	
1012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 50 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
2001	N	0	0	
2002	N	0	0	
2003	N	0	0	
2004	N	0	0	
2005	N	0	0	
2006	N	0	0	
2007	N	0	0	
2008	N	0	0	
2009	N	0	0	
2010	N	0	0	
2011	N	0	0	
2012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 150 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
3001	N	0	0	
3002	N	0	0	
3003	N	0	0	
3004	N	0	0	
3005	N	0	0	
3006	N	0	0	
3007	N	0	0	
3008	N	0	0	
3009	N	0	0	
3010	N	0	0	
3011	N	0	0	
3012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 4

Dose : crotonic acid 500 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
4001	N	0	0
4002	N	0	0
4003	N	0	0
4004	N	0	0
4005	N	0	0
4006	N	0	0
4007	N	0	0
4008	N	0	0
4009	N	0	0
4010	N	0	0
4011	N	0	0
4012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 mating	Species : Rat
Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 0 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
1001	N	0	0	
1002	N	0	0	
1003	N	0	0	
1004	N	0	0	
1005	N	0	0	
1006	N	0	0	
1007	N	0	0	
1008	N	0	0	
1009	N	0	0	
1010	N	0	0	
1011	N	0	0	
1012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : crotonic acid 50 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
2001	N	0	0
2002	N	0	0
2003	N	0	0
2004	N	0	0
2005	N	0	0
2006	N	0	0
2007	N	0	0
2008	N	0	0
2009	N	0	0
2010	N	0	0
2011	N	0	0
2012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 150 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
3001	N	0	0	
3002	N	0	0	
3003	N	0	0	
3004	N	0	0	
3005	N	0	0	
3006	N	0	0	
3007	N	0	0	
3008	N	0	0	
3009	N	0	0	
3010	N	0	0	
3011	N	0	0	
3012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : crotonic acid 500 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
4001	N	0	0
4002	N	0	0
4003	N	0	0
4004	N	0	0
4005	N	0	0
4006	N	0	0
4007	N	0	0
4008	N	0	0
4009	N	0	0
4010	N	0	0
4011	N	0	0
4012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 0 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
1001	N	0	0	
1002	N	0	0	
1003	N	0	0	
1004	N	0	0	
1005	N	0	0	
1006	N	0	0	
1007	N	0	0	
1008	N	0	0	
1009	N	0	0	
1010	N	0	0	
1011	N	0	0	
1012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 50 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
2001	N	0	0	
2002	N	0	0	
2003	N	0	0	
2004	N	0	0	
2005	N	0	0	
2006	N	0	0	
2007	N	0	0	
2008	N	0	0	
2009	N	0	0	
2010	N	0	0	
2011	N	0	0	
2012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 150 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
3001	N	0	0	
3002	N	0	0	
3003	N	0	0	
3004	N	0	0	
3005	N	0	0	
3006	N	0	0	
3007	N	0	0	
3008	N	0	0	
3009	N	0	0	
3010	N	0	0	
3011	N	0	0	
3012	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : crotonic acid 500 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
4001	N	0	0
4002	N	0	0
4003	N	0	0
4004	N	0	0
4005	N	0	0
4006	N	0	0
4007	N	0	0
4008	N	0	0
4009	N	0	0
4010	N	0	0
4011	N	0	0
4012	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : crotonic acid 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
1101	N	0	0
1102	N	0	0
1103	N	0	0
1104	N	0	0
1105	N	0	0
1106	N	0	0
1107	N	0	0
1108	N	0	0
1109	N	0	0
1110	N	0	0
1111	N	0	0
1112	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : crotonic acid 50 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
2101	N	0	0
2102	N	0	0
2103	N	0	0
2104	N	0	0
2105	N	0	0
2106	N	0	0
2107	N	0	0
2108	N	0	0
2109	N	0	0
2110	N	0	0
2111	N	0	0
2112	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 before mating	Species : Rat
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 150 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
3101	N	0	0	
3102	N	0	0	
3103	N	0	0	
3104	N	0	0	
3105	N	0	0	
3106	N	0	0	
3107	N	0	0	
3108	N	0	0	
3109	N	0	0	
3110	N	0	0	
3111	N	0	0	
3112	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 before mating	Species : Rat
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
4101	N	0	0	
4102	N	0	0	
4103	N	0	0	
4104	N	0	0	
4105	N	0	0	
4106	N	0	0	
4107	N	0	0	
4108	N	0	0	
4109	N	0	0	
4110	N	0	0	
4111	N	0	0	
4112	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : crotonic acid 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
1101	N	0	0
1102	N	0	0
1103	N	0	0
1104	N	0	0
1105	N	0	0
1106	N	0	0
1107	N	0	0
1108	N	0	0
1109	N	0	0
1110	N	0	0
1111	N	0	0
1112	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : crotonic acid 50 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
2101	N	0	0
2102	N	0	0
2103	N	0	0
2104	N	0	0
2105	N	0	0
2106	N	0	0
2107	N	0	0
2108	N	0	0
2109	N	0	0
2110	N	0	0
2111	N	0	0
2112	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Generation : F0

Sex : Female

Week : 2

Period : F0 before mating

Dose : crotonic acid 150 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
3101	N	0	0
3102	N	0	0
3103	N	0	0
3104	N	0	0
3105	N	0	0
3106	N	0	0
3107	N	0	0
3108	N	0	0
3109	N	0	0
3110	N	0	0
3111	N	0	0
3112	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : crotonic acid 500 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
4101	N	0	0
4102	N	0	0
4103	N	0	0
4104	N	0	0
4105	N	0	0
4106	N	0	0
4107	N	0	0
4108	N	0	0
4109	N	0	0
4110	N	0	0
4111	N	0	0
4112	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 gestation	Species : Rat
Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 0 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
1101	N	0	0	
1102	N	0	0	
1103	N	0	0	
1104	N	0	0	
1105	N	0	0	
1106	N	0	0	
1107	N	0	0	
1108	N	0	0	
1109	N	0	0	
1110	N	0	0	
1111	N	0	0	
1112	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 gestation	Species : Rat
Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 50 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
2101	N	0	0	
2102	N	0	0	
2103	N	0	0	
2104	N	0	0	
2106	N	0	0	
2107	N	0	0	
2109	N	0	0	
2110	N	0	0	
2111	N	0	0	
2112	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Animal No.2105,2108: Not copulated

Home cage observation			Period : F0 gestation	Species : Rat
Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 150 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
3101	N	0	0	
3102	N	0	0	
3103	N	0	0	
3104	N	0	0	
3105	N	0	0	
3106	N	0	0	
3107	N	0	0	
3108	N	0	0	
3110	N	0	0	
3111	N	0	0	
3112	N	0	0	
n	11	11	11	

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Animal No.3109: Not copulated

Home cage observation			Period : F0 gestation		Species : Rat
Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 500 mg/kg		
Animal No.	Posture	Convulsion	Abnormal behavior		
4101	N	0	0		
4102	N	0	0		
4103	N	0	0		
4104	N	0	0		
4105	N	0	0		
4106	N	0	0		
4107	N	0	0		
4108	N	0	0		
4109	N	0	0		
4110	N	0	0		
4111	N	0	0		
4112	N	0	0		
n	12	12	12		

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : crotonic acid 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
1101	N	0	0
1102	N	0	0
1103	N	0	0
1104	N	0	0
1105	N	0	0
1106	N	0	0
1107	N	0	0
1108	N	0	0
1109	N	0	0
1110	N	0	0
1111	N	0	0
1112	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 gestation	Species : Rat
Generation : F0	Sex : Female	Day : 7	Dose : crotonic acid 50 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
2101	N	0	0	
2102	N	0	0	
2103	N	0	0	
2104	N	0	0	
2106	N	0	0	
2107	N	0	0	
2109	N	0	0	
2110	N	0	0	
2111	N	0	0	
2112	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Animal No.2105,2108: Not copulated

Home cage observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : crotonic acid 150 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
3101	N	0	0
3102	N	0	0
3103	N	0	0
3104	N	0	0
3105	N	0	0
3106	N	0	0
3107	N	0	0
3108	N	0	0
3110	N	0	0
3111	N	0	0
3112	N	0	0
n	11	11	11

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Animal No.3109: Not copulated

Home cage observation		Period : F0 gestation		Species : Rat
Generation : F0	Sex : Female	Day : 7	Dose : crotonic acid 500 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
4101	N	0	0	
4102	N	0	0	
4103	N	0	0	
4104	N	0	0	
4105	N	0	0	
4106	N	0	0	
4107	N	0	0	
4108	N	0	0	
4109	N	0	0	
4110	N	0	0	
4111	N	0	0	
4112	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 gestation	Species : Rat
Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 0 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
1101	N	0	0	
1102	N	0	0	
1103	N	0	0	
1104	N	0	0	
1105	N	0	0	
1106	N	0	0	
1107	N	0	0	
1108	N	0	0	
1109	N	0	0	
1110	N	0	0	
1111	N	0	0	
1112	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 gestation	Species : Rat
Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 50 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
2101	N	0	0	
2102	N	0	0	
2103	N	0	0	
2104	N	0	0	
2106	N	0	0	
2107	N	0	0	
2109	N	0	0	
2110	N	0	0	
2111	N	0	0	
2112	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Animal No.2105,2108: Not copulated

Home cage observation			Period : F0 gestation	Species : Rat
Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 150 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
3101	N	0	0	
3102	N	0	0	
3103	N	0	0	
3104	N	0	0	
3105	N	0	0	
3106	N	0	0	
3107	N	0	0	
3108	N	0	0	
3110	N	0	0	
3111	N	0	0	
3112	N	0	0	
n	11	11	11	

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Animal No.3109: Not copulated

Home cage observation		Period : F0 gestation		Species : Rat
Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 500 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
4101	N	0	0	
4102	N	0	0	
4103	N	0	0	
4104	N	0	0	
4105	N	0	0	
4106	N	0	0	
4107	N	0	0	
4108	N	0	0	
4109	N	0	0	
4110	N	0	0	
4111	N	0	0	
4112	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Dose : crotonic acid 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
1101	N	0	0
1102	N	0	0
1103	N	0	0
1104	N	0	0
1105	N	0	0
1106	N	0	0
1107	N	0	0
1108	N	0	0
1109	N	0	0
1110	N	0	0
1111	N	0	0
1112	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 gestation	Species : Rat
Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 50 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
2101	N	0	0	
2102	N	0	0	
2103	N	0	0	
2104	N	0	0	
2106	N	0	0	
2107	N	0	0	
2109	N	0	0	
2110	N	0	0	
2111	N	0	0	
2112	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Animal No.2105,2108: Not copulated

Home cage observation			Period : F0 gestation	Species : Rat
Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 150 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
3101	N	0	0	
3102	N	0	0	
3103	N	0	0	
3104	N	0	0	
3105	N	0	0	
3106	N	0	0	
3107	N	0	0	
3108	N	0	0	
3110	N	0	0	
3111	N	0	0	
3112	N	0	0	
n	11	11	11	

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe
Animal No.3109: Not copulated

Home cage observation		Period : F0 gestation		Species : Rat
Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 500 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
4101	N	0	0	
4102	N	0	0	
4103	N	0	0	
4104	N	0	0	
4105	N	0	0	
4106	N	0	0	
4107	N	0	0	
4108	N	0	0	
4109	N	0	0	
4110	N	0	0	
4111	N	0	0	
4112	N	0	0	
n	12	12	12	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Dose : crotonic acid 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
1101	N	0	0
1102	N	0	0
1103	N	0	0
1104	N	0	0
1105	N	0	0
1106	N	0	0
1107	N	0	0
1108	N	0	0
1109	N	0	0
1110	N	0	0
1111	N	0	0
1112	N	0	0
n	12	12	12

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : F0 lactation	Species : Rat
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 50 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
2101	N	0	0	
2102	N	0	0	
2103	N	0	0	
2104	N	0	0	
2106	N	0	0	
2107	N	0	0	
2109	N	0	0	
2110	N	0	0	
2111	N	0	0	
2112	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Animal No.2105,2108: Not copulated

Home cage observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Dose : crotonic acid 150 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
3101	N	0	0
3102	N	0	0
3103	N	0	0
3104	N	0	0
3105	N	0	0
3106	N	0	0
3107	N	0	0
3108	N	0	0
3110	N	0	0
3111	N	0	0
3112	N	0	0
n	11	11	11

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Animal No.3109: Not copulated

Crotonic acid by oral administration in rats				Period : F0 lactation	Species : Rat
Home cage observation				Dose : crotonic acid 500 mg/kg	
Generation : F0	Sex : Female	Day : 4			
	Posture	Convulsion	Abnormal behavior		
Animal No.					
4101	N	0	0		
4102	N	0	0		
4103	N	0	0		
4104	N	0	0		
4105	N	0	0		
4106	N	0	0		
4107	N	0	0		
4108	N	0	0		
4109	N	0	0		
4110	N	0	0		
4111	N	0	0		
4112	N	0	0		
n	12	12	12		

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Administration	Species : Rat
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 0 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
5101	N	0	0	
5102	N	0	0	
5103	N	0	0	
5104	N	0	0	
5105	N	0	0	
5106	N	0	0	
5107	N	0	0	
5108	N	0	0	
5109	N	0	0	
5110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Administration	Species : Rat
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
6101	N	0	0	
6102	N	0	0	
6103	N	0	0	
6104	N	0	0	
6105	N	0	0	
6106	N	0	0	
6107	N	0	0	
6108	N	0	0	
6109	N	0	0	
6110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Administration	Species : Rat
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
5101	N	0	0	
5102	N	0	0	
5103	N	0	0	
5104	N	0	0	
5105	N	0	0	
5106	N	0	0	
5107	N	0	0	
5108	N	0	0	
5109	N	0	0	
5110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Administration	Species : Rat
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
6101	N	0	0	
6102	N	0	0	
6103	N	0	0	
6104	N	0	0	
6105	N	0	0	
6106	N	0	0	
6107	N	0	0	
6108	N	0	0	
6109	N	0	0	
6110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Administration	Species : Rat
Generation : F0	Sex : Female	Week : 3	Dose : crotonic acid 0 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
5101	N	0	0	
5102	N	0	0	
5103	N	0	0	
5104	N	0	0	
5105	N	0	0	
5106	N	0	0	
5107	N	0	0	
5108	N	0	0	
5109	N	0	0	
5110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 3	Dose : crotonic acid 500 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
6101	N	0	0	
6102	N	0	0	
6103	N	0	0	
6104	N	0	0	
6105	N	0	0	
6106	N	0	0	
6107	N	0	0	
6108	N	0	0	
6109	N	0	0	
6110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Administration	Species : Rat
Generation : F0	Sex : Female	Week : 4	Dose : crotonic acid 0 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
5101	N	0	0	
5102	N	0	0	
5103	N	0	0	
5104	N	0	0	
5105	N	0	0	
5106	N	0	0	
5107	N	0	0	
5108	N	0	0	
5109	N	0	0	
5110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 4	Dose : crotonic acid 500 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
6101	N	0	0	
6102	N	0	0	
6103	N	0	0	
6104	N	0	0	
6105	N	0	0	
6106	N	0	0	
6107	N	0	0	
6108	N	0	0	
6109	N	0	0	
6110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 5	Dose : crotonic acid 0 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
5101	N	0	0	
5102	N	0	0	
5103	N	0	0	
5104	N	0	0	
5105	N	0	0	
5106	N	0	0	
5107	N	0	0	
5108	N	0	0	
5109	N	0	0	
5110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Administration	Species : Rat
Generation : F0	Sex : Female	Week : 5	Dose : crotonic acid 500 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
6101	N	0	0	
6102	N	0	0	
6103	N	0	0	
6104	N	0	0	
6105	N	0	0	
6106	N	0	0	
6107	N	0	0	
6108	N	0	0	
6109	N	0	0	
6110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Administration	Species : Rat
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 0 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
5101	N	0	0	
5102	N	0	0	
5103	N	0	0	
5104	N	0	0	
5105	N	0	0	
5106	N	0	0	
5107	N	0	0	
5108	N	0	0	
5109	N	0	0	
5110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Administration	Species : Rat
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 500 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
6101	N	0	0	
6102	N	0	0	
6103	N	0	0	
6104	N	0	0	
6105	N	0	0	
6106	N	0	0	
6107	N	0	0	
6108	N	0	0	
6109	N	0	0	
6110	N	0	0	
n	10	10	10	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : Recovery		Species : Rat
Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 0 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
1008	N	0	0	
1009	N	0	0	
1010	N	0	0	
1011	N	0	0	
1012	N	0	0	
n	5	5	5	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : Recovery		Species : Rat
Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 500 mg/kg	
	Posture	Convulsion	Abnormal behavior	
Animal No.				
4008	N	0	0	
4009	N	0	0	
4010	N	0	0	
4011	N	0	0	
4012	N	0	0	
n	5	5	5	

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : Recovery		Species : Rat
Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 0 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
1008	N	0	0	
1009	N	0	0	
1010	N	0	0	
1011	N	0	0	
1012	N	0	0	
n	5	5	5	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : Recovery		Species : Rat
Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 500 mg/kg	
Animal No.	Posture	Convulsion	Abnormal behavior	
4008	N	0	0	
4009	N	0	0	
4010	N	0	0	
4011	N	0	0	
4012	N	0	0	
n	5	5	5	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Recovery		Species : Rat
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 0 mg/kg		
Posture	Convulsion	Abnormal behavior			
Animal No.					
5106	N	0	0		
5107	N	0	0		
5108	N	0	0		
5109	N	0	0		
5110	N	0	0		
n	5	5	5		

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : Recovery		Species : Rat
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg	
	Posture	Convulsion	Abnormal behavior	
Animal No.				
6106	N	0	0	
6107	N	0	0	
6108	N	0	0	
6109	N	0	0	
6110	N	0	0	
n	5	5	5	

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation			Period : Recovery	Species : Rat
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg	
Posture	Convulsion	Abnormal behavior		
Animal No.				
5106	N	0	0	
5107	N	0	0	
5108	N	0	0	
5109	N	0	0	
5110	N	0	0	
n	5	5	5	

Posture) N: Normal, F: Flattened, H: Hunched

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Home cage observation		Period : Recovery		Species : Rat
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg	
	Posture	Convulsion	Abnormal behavior	
Animal No.				
6106	N	0	0	
6107	N	0	0	
6108	N	0	0	
6109	N	0	0	
6110	N	0	0	
n	5	5	5	

Posture) N: Normal, F: Flattened, H: Hunched
Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe
Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1001	0	0	0	0	0	0	0	0
1002	0	0	0	0	0	0	0	0
1003	0	0	0	0	0	0	0	0
1004	0	0	0	0	0	0	0	0
1005	0	0	0	0	0	0	0	0
1006	0	0	0	0	0	0	0	0
1007	0	0	0	0	0	0	0	0
1008	0	0	0	0	0	0	0	0
1009	0	0	0	0	0	0	0	0
1010	0	0	0	0	0	0	0	0
1011	0	0	0	0	0	0	0	0
1012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1001	0	0	0	0	0	0
1002	0	0	0	0	0	0
1003	0	0	0	0	0	0
1004	0	0	0	0	0	0
1005	0	0	0	0	0	0
1006	0	0	0	0	0	1
1007	0	0	0	0	0	0
1008	0	0	0	0	0	0
1009	0	0	0	0	0	0
1010	0	0	0	0	0	0
1011	0	0	0	0	0	0
1012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2001	0	0	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0
2004	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	0
2008	0	0	0	0	0	0	0	0
2009	0	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0	0
2011	0	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2001	0	0	0	0	0	0
2002	0	0	0	0	0	0
2003	0	0	0	0	0	0
2004	0	0	0	0	0	0
2005	0	0	0	0	0	0
2006	0	0	0	0	0	0
2007	0	0	0	0	0	0
2008	0	0	0	0	0	0
2009	0	0	0	0	0	0
2010	0	0	0	0	0	0
2011	0	0	0	0	1	1
2012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3001	0	0	0	0	0	0	0	0
3002	0	0	0	0	0	0	0	0
3003	0	0	0	0	0	0	0	0
3004	0	0	0	0	0	0	0	0
3005	0	0	0	0	0	0	0	0
3006	0	0	0	0	0	0	0	0
3007	0	0	0	0	0	0	0	0
3008	0	0	0	0	0	0	0	0
3009	0	0	0	0	0	0	0	0
3010	0	0	0	0	0	0	0	0
3011	0	0	0	0	0	0	0	0
3012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3001	0	0	0	0	0	0
3002	0	0	0	0	0	0
3003	0	0	0	0	0	0
3004	0	0	0	0	0	0
3005	0	0	0	0	0	0
3006	0	0	0	0	0	0
3007	0	0	0	0	0	0
3008	0	0	0	0	0	0
3009	0	0	0	0	0	0
3010	0	0	0	0	0	0
3011	0	0	0	0	0	0
3012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4001	0	0	0	0	0	0	0	0
4002	0	0	0	0	0	0	0	0
4003	0	0	0	0	0	0	0	0
4004	0	0	0	0	0	0	0	0
4005	0	0	0	0	0	0	0	0
4006	0	0	0	0	0	0	0	0
4007	0	0	0	0	0	0	0	0
4008	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4001	0	0	0	0	0	0
4002	0	0	0	0	0	0
4003	0	0	0	0	0	0
4004	0	0	0	0	0	0
4005	0	0	0	0	0	0
4006	0	0	0	0	0	0
4007	0	0	0	0	0	0
4008	0	0	0	0	0	0
4009	0	0	0	0	0	0
4010	0	0	0	0	0	0
4011	0	0	0	0	0	0
4012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1001	0	0	0	0	0	0	0	0
1002	0	0	0	0	0	0	0	0
1003	0	0	0	0	0	0	0	0
1004	0	0	0	0	0	0	0	0
1005	0	0	0	0	0	0	0	0
1006	0	0	0	0	0	0	0	0
1007	0	0	0	0	0	0	0	0
1008	0	0	0	0	0	0	0	0
1009	0	0	0	0	0	0	0	0
1010	0	0	0	0	0	0	0	0
1011	0	0	0	0	0	0	0	0
1012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1001	0	0	0	0	0	0
1002	0	0	0	0	0	0
1003	0	0	0	0	0	0
1004	0	0	0	0	0	0
1005	0	0	0	0	0	0
1006	0	0	0	0	0	0
1007	0	0	0	0	0	0
1008	0	0	0	0	0	0
1009	0	0	0	0	0	0
1010	0	0	0	0	0	0
1011	0	0	0	0	0	0
1012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2001	0	0	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0
2004	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	0
2008	0	0	0	0	0	0	0	0
2009	0	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0	0
2011	0	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2001	0	0	0	0	0	0
2002	0	0	0	0	0	0
2003	0	0	0	0	0	0
2004	0	0	0	0	0	0
2005	0	0	0	0	0	0
2006	0	0	0	0	0	0
2007	0	0	0	0	0	0
2008	0	0	0	0	0	0
2009	0	0	0	0	0	0
2010	0	0	0	0	0	0
2011	0	0	0	0	0	0
2012	0	0	0	0	1	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3001	0	0	0	0	0	0	0	0
3002	0	0	0	0	0	0	0	0
3003	0	0	0	0	0	0	0	0
3004	0	0	0	0	0	0	0	0
3005	0	0	0	0	0	0	0	0
3006	0	0	0	0	0	0	0	0
3007	0	0	0	0	0	0	0	0
3008	0	0	0	0	0	0	0	0
3009	0	0	0	0	0	0	0	0
3010	0	0	0	0	0	0	0	0
3011	0	0	0	0	0	0	0	0
3012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3001	0	0	0	0	0	0
3002	0	0	0	0	0	0
3003	0	0	0	0	0	0
3004	0	0	0	0	0	0
3005	0	0	0	0	0	0
3006	0	0	0	0	0	0
3007	0	0	0	0	0	0
3008	0	0	0	0	0	0
3009	0	0	0	0	0	0
3010	0	0	0	0	0	0
3011	0	0	0	0	0	0
3012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4001	0	0	0	0	0	0	0	0
4002	0	0	0	0	0	0	0	0
4003	0	0	0	0	0	0	0	0
4004	0	0	0	0	0	0	0	0
4005	0	0	0	0	0	0	0	0
4006	0	0	0	0	0	0	0	0
4007	0	0	0	0	0	0	0	0
4008	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4001	0	0	0	0	0	0
4002	0	0	0	0	0	0
4003	0	0	0	0	0	0
4004	0	0	0	0	0	0
4005	0	0	0	0	0	0
4006	0	0	0	0	0	0
4007	0	0	0	0	0	0
4008	0	0	0	0	0	0
4009	0	0	0	0	0	0
4010	0	0	0	0	0	0
4011	0	0	0	0	0	0
4012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat				
	Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 0 mg/kg					
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation	
1001	0	0	0	0	0	0	0	0	
1002	0	0	0	0	0	0	0	0	
1003	0	0	0	0	0	0	0	0	
1004	0	0	0	0	0	0	0	0	
1005	0	0	0	0	0	0	0	0	
1006	0	0	0	0	0	0	0	0	
1007	0	0	0	0	0	0	0	0	
1008	0	0	0	0	0	0	0	0	
1009	0	0	0	0	0	0	0	0	
1010	0	0	0	0	0	0	0	0	
1011	0	0	0	0	0	0	0	0	
1012	0	0	0	0	0	0	0	0	
n	12	12	12	12	12	12	12	12	

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1001	0	0	0	0	0	0
1002	0	0	0	0	0	0
1003	0	0	0	0	0	0
1004	0	0	0	0	0	0
1005	0	0	0	0	0	0
1006	0	0	0	0	0	0
1007	0	0	0	0	0	0
1008	0	0	0	0	0	0
1009	0	0	0	0	0	0
1010	0	0	0	0	0	0
1011	0	0	0	0	0	0
1012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2001	0	0	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0
2004	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	0
2008	0	0	0	0	0	0	0	0
2009	0	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0	0
2011	0	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2001	0	0	0	0	0	0
2002	0	0	0	0	0	0
2003	0	0	0	0	0	0
2004	0	0	0	0	0	0
2005	0	0	0	0	0	0
2006	0	0	0	0	0	0
2007	0	0	0	0	0	0
2008	0	0	0	0	0	0
2009	0	0	0	0	0	0
2010	0	0	0	0	0	0
2011	0	0	0	0	0	0
2012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3001	0	0	0	0	0	0	0	0
3002	0	0	0	0	0	0	0	0
3003	0	0	0	0	0	0	0	0
3004	0	0	0	0	0	0	0	0
3005	0	0	0	0	0	0	0	0
3006	0	0	0	0	0	0	0	0
3007	0	0	0	0	0	0	0	0
3008	0	0	0	0	0	0	0	0
3009	0	0	0	0	0	0	0	0
3010	0	0	0	0	0	0	0	0
3011	0	0	0	0	0	0	0	0
3012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3001	0	0	0	0	0	0
3002	0	0	0	0	0	0
3003	0	0	0	0	0	0
3004	0	0	0	0	0	0
3005	0	0	0	0	0	0
3006	0	0	0	0	0	0
3007	0	0	0	0	0	0
3008	0	0	0	0	0	0
3009	0	0	0	0	0	0
3010	0	0	0	0	0	0
3011	0	0	0	0	0	0
3012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4001	0	0	0	0	0	0	0	0
4002	0	0	0	0	0	0	0	0
4003	0	0	0	0	0	0	0	0
4004	0	0	0	0	0	0	0	0
4005	0	0	0	0	0	0	0	0
4006	1	0	0	0	0	0	0	0
4007	0	0	0	0	0	0	0	0
4008	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4001	0	0	0	0	0	0
4002	0	0	0	0	0	0
4003	0	0	0	0	0	0
4004	0	0	0	0	0	0
4005	0	0	0	0	0	0
4006	0	0	0	0	1	0
4007	0	0	0	0	0	0
4008	0	0	0	0	0	0
4009	0	0	0	0	0	0
4010	0	0	0	0	0	0
4011	0	0	0	0	0	0
4012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1001	0	0	0	0	0	0	0	0
1002	0	0	0	0	0	0	0	0
1003	0	0	0	0	0	0	0	0
1004	0	0	0	0	0	0	0	0
1005	0	0	0	0	0	0	0	0
1006	0	0	0	0	0	0	0	0
1007	0	0	0	0	0	0	0	0
1008	0	0	0	0	0	0	0	0
1009	0	0	0	0	0	0	0	0
1010	0	0	0	0	0	0	0	0
1011	0	0	0	0	0	0	0	0
1012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1001	0	0	0	0	0	0
1002	0	0	0	0	0	0
1003	0	0	0	0	0	0
1004	0	0	0	0	0	0
1005	0	0	0	0	0	0
1006	0	0	0	0	0	0
1007	0	0	0	0	0	0
1008	0	0	0	0	0	0
1009	0	0	0	0	0	0
1010	0	0	0	0	0	0
1011	0	0	0	0	0	0
1012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2001	0	0	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0
2004	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	0
2008	0	0	0	0	0	0	0	0
2009	0	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0	0
2011	0	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2001	0	0	0	0	0	0
2002	0	0	0	0	1	0
2003	0	0	0	0	0	0
2004	0	0	0	0	0	0
2005	0	0	0	0	0	0
2006	0	0	0	0	0	0
2007	0	0	0	0	0	0
2008	0	0	0	0	1	1
2009	0	0	0	0	0	0
2010	0	0	0	0	0	0
2011	0	0	0	0	0	0
2012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3001	0	0	0	0	0	0	0	0
3002	0	0	0	0	0	0	0	0
3003	0	0	0	0	0	0	0	0
3004	0	0	0	0	0	0	0	0
3005	0	0	0	0	0	0	0	0
3006	0	0	0	0	0	0	0	0
3007	0	0	0	0	0	0	0	0
3008	0	0	0	0	0	0	0	0
3009	0	0	0	0	0	0	0	0
3010	0	0	0	0	0	0	0	0
3011	0	0	0	0	0	0	0	0
3012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3001	0	0	0	0	0	0
3002	0	0	0	0	0	0
3003	0	0	0	0	0	0
3004	0	0	0	0	0	0
3005	0	0	0	0	0	0
3006	0	0	0	0	0	0
3007	0	0	0	0	1	0
3008	0	0	0	0	1	0
3009	0	0	0	0	0	0
3010	0	0	0	0	0	0
3011	0	0	0	0	0	0
3012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4001	0	0	0	0	0	0	0	0
4002	0	0	0	0	0	0	0	0
4003	0	0	0	0	0	0	0	0
4004	0	0	0	0	0	0	0	0
4005	0	0	0	0	0	0	0	0
4006	0	0	0	0	0	0	0	0
4007	0	0	0	0	0	0	0	0
4008	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4001	0	0	0	0	0	0
4002	0	0	0	0	0	0
4003	0	0	0	0	0	0
4004	0	0	0	0	0	0
4005	0	0	0	0	0	0
4006	0	0	0	0	1	0
4007	0	0	0	0	0	0
4008	0	0	0	0	0	0
4009	0	0	0	0	0	0
4010	0	0	0	0	0	0
4011	0	0	0	0	0	0
4012	0	0	0	0	1	1
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1001	0	0	0	0	0	0	0	0
1002	0	0	0	0	0	0	0	0
1003	0	0	0	0	0	0	0	0
1004	0	0	0	0	0	0	0	0
1005	0	0	0	0	0	0	0	0
1006	0	0	0	0	0	0	0	0
1007	0	0	0	0	0	0	0	0
1008	0	0	0	0	0	0	0	0
1009	0	0	0	0	0	0	0	0
1010	0	0	0	0	0	0	0	0
1011	0	0	0	0	0	0	0	0
1012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1001	0	0	0	0	0	0
1002	0	0	0	0	0	0
1003	0	0	0	0	0	0
1004	0	0	0	0	0	0
1005	0	0	0	0	0	0
1006	0	0	0	0	0	0
1007	0	0	0	0	0	0
1008	0	0	0	0	0	0
1009	0	0	0	0	0	0
1010	0	0	0	0	0	0
1011	0	0	0	0	0	0
1012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2001	0	0	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0
2004	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	0
2008	0	0	0	0	0	0	0	0
2009	0	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0	0
2011	0	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2001	0	0	0	0	0	0
2002	0	0	0	0	0	0
2003	0	0	0	0	0	0
2004	0	0	0	0	0	0
2005	0	0	0	0	0	0
2006	0	0	0	0	0	0
2007	0	0	0	0	0	0
2008	0	0	0	0	0	0
2009	0	0	0	0	0	0
2010	0	0	0	0	0	0
2011	0	0	0	0	0	0
2012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3001	0	0	0	0	0	0	0	0
3002	0	0	0	0	0	0	0	0
3003	0	0	0	0	0	0	0	0
3004	0	0	0	0	0	0	0	0
3005	0	0	0	0	0	0	0	0
3006	0	0	0	0	0	0	0	0
3007	0	0	0	0	0	0	0	0
3008	0	0	0	0	0	0	0	0
3009	0	0	0	0	0	0	0	0
3010	0	0	0	0	0	0	0	0
3011	0	0	0	0	0	0	0	0
3012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3001	0	0	0	0	0	0
3002	0	0	0	0	0	0
3003	0	0	0	0	0	0
3004	0	0	0	0	0	0
3005	0	0	0	0	0	0
3006	0	0	0	0	0	0
3007	0	0	0	0	0	0
3008	0	0	0	0	0	0
3009	0	0	0	0	0	0
3010	0	0	0	0	0	0
3011	0	0	0	0	0	0
3012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4001	0	0	0	0	0	0	0	0
4002	0	0	0	0	0	0	0	0
4003	0	0	0	0	0	0	0	0
4004	0	0	0	0	0	0	0	0
4005	0	0	0	0	0	0	0	0
4006	0	0	0	0	0	0	0	0
4007	0	0	0	0	0	0	0	0
4008	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4001	0	0	0	0	0	0
4002	0	0	0	0	0	0
4003	0	0	0	0	0	0
4004	0	0	0	0	0	0
4005	0	0	0	0	0	0
4006	0	0	0	0	0	0
4007	0	0	0	0	0	0
4008	0	0	0	0	0	0
4009	0	0	0	0	0	0
4010	0	0	0	0	0	0
4011	0	0	0	0	0	0
4012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1001	0	0	0	0	0	0	0	0
1002	0	0	0	0	0	0	0	0
1003	0	0	0	0	0	0	0	0
1004	0	0	0	0	0	0	0	0
1005	0	0	0	0	0	0	0	0
1006	0	0	0	0	0	0	0	0
1007	0	0	0	0	0	0	0	0
1008	0	0	0	0	0	0	0	0
1009	0	0	0	0	0	0	0	0
1010	0	0	0	0	0	0	0	0
1011	0	0	0	0	0	0	0	0
1012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1001	0	0	0	0	0	0
1002	0	0	0	0	0	0
1003	0	0	0	0	0	0
1004	0	0	0	0	0	0
1005	0	0	0	0	0	0
1006	0	0	0	0	0	0
1007	0	0	0	0	0	0
1008	0	0	0	0	0	0
1009	0	0	0	0	0	0
1010	0	0	0	0	0	0
1011	0	0	0	0	0	0
1012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2001	0	0	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0
2004	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	0
2008	0	0	0	0	0	0	0	0
2009	0	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0	0
2011	0	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2001	0	0	0	0	0	0
2002	0	0	0	0	0	0
2003	0	0	0	0	0	0
2004	0	0	0	0	0	0
2005	0	0	0	0	0	0
2006	0	0	0	0	0	0
2007	0	0	0	0	0	0
2008	0	0	0	0	0	0
2009	0	0	0	0	0	0
2010	0	0	0	0	0	0
2011	0	0	0	0	0	0
2012	0	0	0	0	1	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3001	0	0	0	0	0	0	0	0
3002	0	0	0	0	0	0	0	0
3003	0	0	0	0	0	0	0	0
3004	0	0	0	0	0	0	0	0
3005	0	0	0	0	0	0	0	0
3006	0	0	0	0	0	0	0	0
3007	0	0	0	0	0	0	0	0
3008	0	0	0	0	0	0	0	0
3009	1	0	0	0	0	0	0	0
3010	0	0	0	0	0	0	0	0
3011	0	0	0	0	0	0	0	0
3012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3001	0	0	0	0	0	0
3002	0	0	0	0	0	0
3003	0	0	0	0	0	0
3004	0	0	0	0	0	0
3005	0	0	0	0	0	0
3006	0	0	0	0	0	0
3007	0	0	0	0	0	0
3008	0	0	0	0	0	0
3009	0	0	0	0	0	1
3010	0	0	0	0	0	0
3011	0	0	0	0	0	0
3012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 mating		Species : Rat			
	Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4001	0	0	0	0	0	0	0	0
4002	0	0	0	0	0	0	0	0
4003	0	0	0	0	0	0	0	0
4004	0	0	0	0	0	0	0	0
4005	0	0	0	0	0	0	0	0
4006	0	0	0	0	0	0	0	0
4007	0	0	0	0	0	0	0	0
4008	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4001	0	0	0	0	0	0
4002	0	0	0	0	0	0
4003	0	0	0	0	0	0
4004	0	0	0	0	0	0
4005	0	0	0	0	0	0
4006	0	0	0	0	0	0
4007	0	0	0	0	0	0
4008	0	0	0	0	0	0
4009	0	0	0	0	0	0
4010	0	0	0	0	0	0
4011	0	0	0	0	0	0
4012	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1101	0	0	0	0	0	0	0	0
1102	0	0	0	0	0	0	0	0
1103	0	0	0	0	0	0	0	0
1104	0	0	0	0	0	0	0	0
1105	0	0	0	0	0	0	0	0
1106	0	0	0	0	0	0	0	0
1107	0	0	0	0	0	0	0	0
1108	0	0	0	0	0	0	0	0
1109	0	0	0	0	0	0	0	0
1110	0	0	0	0	0	0	0	0
1111	0	0	0	0	0	0	0	0
1112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1101	0	0	0	0	0	0
1102	0	0	0	0	0	0
1103	0	0	0	0	0	0
1104	0	0	0	0	0	0
1105	0	0	0	0	0	0
1106	0	0	0	0	0	0
1107	0	0	0	0	0	0
1108	0	0	0	0	0	0
1109	0	0	0	0	0	0
1110	0	0	0	0	0	0
1111	0	0	0	0	0	0
1112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2101	0	0	0	0	0	0	0	0
2102	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0
2104	0	0	0	0	0	0	0	0
2105	0	0	0	0	0	0	0	0
2106	0	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0	0
2108	0	0	0	0	0	0	0	0
2109	0	0	0	0	0	0	0	0
2110	0	0	0	0	0	0	0	0
2111	0	0	0	0	0	0	0	0
2112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2101	0	0	0	0	0	0
2102	0	0	0	0	0	0
2103	0	0	0	0	0	0
2104	0	0	0	0	0	0
2105	0	0	0	0	0	0
2106	0	0	0	0	0	0
2107	0	0	0	0	0	0
2108	0	0	0	0	0	0
2109	0	0	0	0	0	0
2110	0	0	0	0	0	0
2111	0	0	0	0	0	0
2112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3101	0	0	0	0	0	0	0	0
3102	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0
3109	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3101	0	0	0	0	0	0
3102	0	0	0	0	0	0
3103	0	0	0	0	0	0
3104	0	0	0	0	0	0
3105	0	0	0	0	0	0
3106	0	0	0	0	0	0
3107	0	0	0	0	0	0
3108	0	0	0	0	0	0
3109	0	0	0	0	0	0
3110	0	0	0	0	0	0
3111	0	0	0	0	0	0
3112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4101	0	0	0	0	0	0	0	0
4102	0	0	0	0	0	0	0	0
4103	0	0	0	0	0	0	0	0
4104	0	0	0	0	0	0	0	0
4105	0	0	0	0	0	0	0	0
4106	0	0	0	0	0	0	0	0
4107	0	0	0	0	0	0	0	0
4108	0	0	0	0	0	0	0	0
4109	0	0	0	0	0	0	0	0
4110	0	0	0	0	0	0	0	0
4111	0	0	0	0	0	0	0	0
4112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4101	0	0	0	0	0	0
4102	0	0	0	0	0	0
4103	0	0	0	0	0	0
4104	0	0	0	0	0	0
4105	0	0	0	0	0	0
4106	0	0	0	0	0	0
4107	0	0	0	0	0	0
4108	0	0	0	0	0	0
4109	0	0	0	0	0	0
4110	0	0	0	0	0	0
4111	0	0	0	0	0	0
4112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1101	0	0	0	0	0	0	0	0
1102	0	0	0	0	0	0	0	0
1103	0	0	0	0	0	0	0	0
1104	0	0	0	0	0	0	0	0
1105	0	0	0	0	0	0	0	0
1106	0	0	0	0	0	0	0	0
1107	0	0	0	0	0	0	0	0
1108	0	0	0	0	0	0	0	0
1109	0	0	0	0	0	0	0	0
1110	0	0	0	0	0	0	0	0
1111	0	0	0	0	0	0	0	0
1112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1101	0	0	0	0	0	0
1102	0	0	0	0	0	0
1103	0	0	0	0	0	0
1104	0	0	0	0	0	0
1105	0	0	0	0	0	0
1106	0	0	0	0	0	0
1107	0	0	0	0	0	0
1108	0	0	0	0	0	0
1109	0	0	0	0	0	0
1110	0	0	0	0	0	0
1111	0	0	0	0	0	0
1112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2101	0	0	0	0	0	0	0	0
2102	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0
2104	0	0	0	0	0	0	0	0
2105	0	0	0	0	0	0	0	0
2106	0	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0	0
2108	0	0	0	0	0	0	0	0
2109	0	0	0	0	0	0	0	0
2110	0	0	0	0	0	0	0	0
2111	0	0	0	0	0	0	0	0
2112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2101	0	0	0	0	0	0
2102	0	0	0	0	0	0
2103	0	0	0	0	0	0
2104	0	0	0	0	0	0
2105	0	0	0	0	0	0
2106	0	0	0	0	0	0
2107	0	0	0	0	0	0
2108	0	0	0	0	0	0
2109	0	0	0	0	0	0
2110	0	0	0	0	0	0
2111	0	0	0	0	0	0
2112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3101	0	0	0	0	0	0	0	0
3102	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0
3109	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3101	0	0	0	0	0	0
3102	0	0	0	0	0	0
3103	0	0	0	0	0	0
3104	0	0	0	0	0	0
3105	0	0	0	0	0	0
3106	0	0	0	0	0	0
3107	0	0	0	0	0	0
3108	0	0	0	0	0	0
3109	0	0	0	0	0	0
3110	0	0	0	0	0	0
3111	0	0	0	0	0	0
3112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4101	0	0	0	0	0	0	0	0
4102	0	0	0	0	0	0	0	0
4103	0	0	0	0	0	0	0	0
4104	0	0	0	0	0	0	0	0
4105	0	0	0	0	0	0	0	0
4106	0	0	0	0	0	0	0	0
4107	0	0	0	0	0	0	0	0
4108	0	0	0	0	0	0	0	0
4109	0	0	0	0	0	0	0	0
4110	0	0	0	0	0	0	0	0
4111	0	0	0	0	0	0	0	0
4112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4101	0	0	0	0	0	0
4102	0	0	0	0	0	0
4103	0	0	0	0	0	0
4104	0	0	0	0	0	0
4105	0	0	0	0	0	0
4106	0	0	0	0	0	0
4107	0	0	0	0	0	0
4108	0	0	0	0	0	0
4109	0	0	0	0	0	0
4110	0	0	0	0	0	0
4111	0	0	0	0	0	0
4112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1101	0	0	0	0	0	0	0	0
1102	0	0	0	0	0	0	0	0
1103	0	0	0	0	0	0	0	0
1104	0	0	0	0	0	0	0	0
1105	0	0	0	0	0	0	0	0
1106	0	0	0	0	0	0	0	0
1107	0	0	0	0	0	0	0	0
1108	0	0	0	0	0	0	0	0
1109	0	0	0	0	0	0	0	0
1110	0	0	0	0	0	0	0	0
1111	0	0	0	0	0	0	0	0
1112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1101	0	0	0	0	0	0
1102	0	0	0	0	0	0
1103	0	0	0	0	0	0
1104	0	0	0	0	0	0
1105	0	0	0	0	0	0
1106	0	0	0	0	0	0
1107	0	0	0	0	0	0
1108	0	0	0	0	0	0
1109	0	0	0	0	0	0
1110	0	0	0	0	0	0
1111	0	0	0	0	0	0
1112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation			Period : F0 gestation			Species : Rat		
Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 50 mg/kg					
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation	
Animal No.								
2101	0	0	0	0	0	0	0	
2102	0	0	0	0	0	0	0	
2103	0	0	0	0	0	0	0	
2104	0	0	0	0	0	0	0	
2106	0	0	0	0	0	0	0	
2107	0	0	0	0	0	0	0	
2109	0	0	0	0	0	0	0	
2110	0	0	0	0	0	0	0	
2111	0	0	0	0	0	0	0	
2112	0	0	0	0	0	0	0	
n	10	10	10	10	10	10	10	

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
Animal No.					
2101	0	0	0	0	0
2102	0	0	0	0	0
2103	0	0	0	0	0
2104	0	0	0	0	0
2106	0	0	0	0	0
2107	0	0	0	0	0
2109	0	0	0	0	0
2110	0	0	0	0	0
2111	0	0	0	0	0
2112	0	0	0	0	0
n	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.2105,2108: Not copulated

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3101	0	0	0	0	0	0	0	0
3102	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0
n	11	11	11	11	11	11	11	11

Animal No.	Piloerection		Pupil size		Salivation		Abnormal respiration		Vocalization		Reactivity to handling	
3101	0	0	0	0	0	0	0	0	0	0	0	0
3102	0	0	0	0	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0	0	0	0	0
n	11	11	11	11	11	11	11	11	11	11	11	11

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.3109: Not copulated

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4101	0	0	0	0	0	0	0	0
4102	0	0	0	0	0	0	0	0
4103	0	0	0	0	0	0	0	0
4104	0	0	0	0	0	0	0	0
4105	0	0	0	0	0	0	0	0
4106	0	0	0	0	0	0	0	0
4107	0	0	0	0	0	0	0	0
4108	0	0	0	0	0	0	0	0
4109	0	0	0	0	0	0	0	0
4110	0	0	0	0	0	0	0	0
4111	0	0	0	0	0	0	0	0
4112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4101	0	0	0	0	0	0
4102	0	0	0	0	0	0
4103	0	0	0	0	0	0
4104	0	0	0	0	0	0
4105	0	0	0	0	0	0
4106	0	0	0	0	0	0
4107	0	0	0	0	0	0
4108	0	0	0	0	0	0
4109	0	0	0	0	0	0
4110	0	0	0	0	0	0
4111	0	0	0	0	0	0
4112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 7	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1101	0	0	0	0	0	0	0	0
1102	0	0	0	0	0	0	0	0
1103	0	0	0	0	0	0	0	0
1104	0	0	0	0	0	0	0	0
1105	0	0	0	0	0	0	0	0
1106	0	0	0	0	0	0	0	0
1107	0	0	0	0	0	0	0	0
1108	0	0	0	0	0	0	0	0
1109	0	0	0	0	0	0	0	0
1110	0	0	0	0	0	0	0	0
1111	0	0	0	0	0	0	0	0
1112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1101	0	0	0	0	0	0
1102	0	0	0	0	0	0
1103	0	0	0	0	0	0
1104	0	0	0	0	0	0
1105	0	0	0	0	0	0
1106	0	0	0	0	0	0
1107	0	0	0	0	0	0
1108	0	0	0	0	0	0
1109	0	0	0	0	0	0
1110	0	0	0	0	0	0
1111	0	0	0	0	0	0
1112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 7	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2101	0	0	0	0	0	0	0	0
2102	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0
2104	0	0	0	0	0	0	0	0
2106	0	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0	0
2109	0	0	0	0	0	0	0	0
2110	0	0	0	0	0	0	0	0
2111	0	0	0	0	0	0	0	0
2112	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2101	0	0	0	0	0	0
2102	0	0	0	0	0	0
2103	0	0	0	0	0	0
2104	0	0	0	0	0	0
2106	0	0	0	0	0	0
2107	0	0	0	0	0	0
2109	0	0	0	0	0	0
2110	0	0	0	0	0	0
2111	0	0	0	0	0	0
2112	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.2105,2108: Not copulated

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 7	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3101	0	0	0	0	0	0	0	0
3102	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0
n	11	11	11	11	11	11	11	11

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3101	0	0	0	0	0	0
3102	0	0	0	0	0	0
3103	0	0	0	0	0	0
3104	0	0	0	0	0	0
3105	0	0	0	0	0	0
3106	0	0	0	0	0	0
3107	0	0	0	0	0	0
3108	0	0	0	0	0	0
3110	0	0	0	0	0	0
3111	0	0	0	0	0	0
3112	0	0	0	0	0	0
n	11	11	11	11	11	11

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.3109: Not copulated

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 7	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4101	0	0	0	0	0	0	0	0
4102	0	0	0	0	0	0	0	0
4103	0	0	0	0	0	0	0	0
4104	0	0	0	0	0	0	0	0
4105	0	0	0	0	0	0	0	0
4106	0	0	0	0	0	0	0	0
4107	0	0	0	0	0	0	0	0
4108	0	0	0	0	0	0	0	0
4109	0	0	0	0	0	0	0	0
4110	0	0	0	0	0	0	0	0
4111	0	0	0	0	0	0	0	0
4112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4101	0	0	0	0	0	0
4102	0	0	0	0	0	0
4103	0	0	0	0	0	0
4104	0	0	0	0	0	0
4105	0	0	0	0	0	0
4106	0	0	0	0	0	0
4107	0	0	0	0	0	0
4108	0	0	0	0	0	0
4109	0	0	0	0	0	0
4110	0	0	0	0	0	0
4111	0	0	0	0	0	0
4112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat				
	Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 0 mg/kg					
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation	
1101	0	0	0	0	0	0	0	0	
1102	0	0	0	0	0	0	0	0	
1103	0	0	0	0	0	0	0	0	
1104	0	0	0	0	0	0	0	0	
1105	0	0	0	0	0	0	0	0	
1106	0	0	0	0	0	0	0	0	
1107	0	0	0	0	0	0	0	0	
1108	0	0	0	0	0	0	0	0	
1109	0	0	0	0	0	0	0	0	
1110	0	0	0	0	0	0	0	0	
1111	0	0	0	0	0	0	0	0	
1112	0	0	0	0	0	0	0	0	
n	12	12	12	12	12	12	12	12	

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1101	0	0	0	0	0	0
1102	0	0	0	0	0	0
1103	0	0	0	0	0	0
1104	0	0	0	0	0	0
1105	0	0	0	0	0	0
1106	0	0	0	0	0	0
1107	0	0	0	0	0	0
1108	0	0	0	0	0	0
1109	0	0	0	0	0	0
1110	0	0	0	0	0	0
1111	0	0	0	0	0	0
1112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 50 mg/kg					
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation	
Animal No.								
2101	0	0	0	0	0	0	0	0
2102	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0
2104	0	0	0	0	0	0	0	0
2106	0	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0	0
2109	0	0	0	0	0	0	0	0
2110	0	0	0	0	0	0	0	0
2111	0	0	0	0	0	0	0	0
2112	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling	
Animal No.						
2101	0	0	0	0	0	
2102	0	0	0	0	0	
2103	0	0	0	0	0	
2104	0	0	0	0	0	
2106	0	0	0	0	0	
2107	0	0	0	0	0	
2109	0	0	0	0	0	
2110	0	0	0	0	0	
2111	0	0	0	0	0	
2112	0	0	0	0	0	
n	10	10	10	10	10	

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.2105,2108: Not copulated

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3101	0	0	0	0	0	0	0	0
3102	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0
n	11	11	11	11	11	11	11	11

Animal No.	Piloerection		Pupil size		Salivation		Abnormal respiration		Vocalization		Reactivity to handling	
3101	0	0	0	0	0	0	0	0	0	0	0	0
3102	0	0	0	0	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0	0	0	0	0
n	11	11	11	11	11	11	11	11	11	11	11	11

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.3109: Not copulated

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4101	0	0	0	0	0	0	0	0
4102	0	0	0	0	0	0	0	0
4103	0	0	0	0	0	0	0	0
4104	0	0	0	0	0	0	0	0
4105	0	0	0	0	0	0	0	0
4106	0	0	0	0	0	0	0	0
4107	0	0	0	0	0	0	0	0
4108	0	0	0	0	0	0	0	0
4109	0	0	0	0	0	0	0	0
4110	0	0	0	0	0	0	0	0
4111	0	0	0	0	0	0	0	0
4112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4101	0	0	0	0	0	0
4102	0	0	0	0	0	0
4103	0	0	0	0	0	0
4104	0	0	0	0	0	0
4105	0	0	0	0	0	0
4106	0	0	0	0	0	0
4107	0	0	0	0	0	0
4108	0	0	0	0	0	0
4109	0	0	0	0	0	0
4110	0	0	0	0	0	0
4111	0	0	0	0	0	0
4112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1101	0	0	0	0	0	0	0	0
1102	0	0	0	0	0	0	0	0
1103	0	0	0	0	0	0	0	0
1104	0	0	0	0	0	0	0	0
1105	0	0	0	0	0	0	0	0
1106	0	0	0	0	0	0	0	0
1107	0	0	0	0	0	0	0	0
1108	0	0	0	0	0	0	0	0
1109	0	0	0	0	0	0	0	0
1110	0	0	0	0	0	0	0	0
1111	0	0	0	0	0	0	0	0
1112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1101	0	0	0	0	0	0
1102	0	0	0	0	0	0
1103	0	0	0	0	0	0
1104	0	0	0	0	0	0
1105	0	0	0	0	0	0
1106	0	0	0	0	0	0
1107	0	0	0	0	0	0
1108	0	0	0	0	0	0
1109	0	0	0	0	0	0
1110	0	0	0	0	0	0
1111	0	0	0	0	0	0
1112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 50 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
2101	0	0	0	0	0	0	0	0
2102	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0
2104	0	0	0	0	0	0	0	0
2106	0	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0	0
2109	0	0	0	0	0	0	0	0
2110	0	0	0	0	0	0	0	0
2111	0	0	0	0	0	0	0	0
2112	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
2101	0	0	0	0	0	0
2102	0	0	0	0	0	0
2103	0	0	0	0	0	0
2104	0	0	0	0	0	0
2106	0	0	0	0	0	0
2107	0	0	0	0	0	0
2109	0	0	0	0	0	0
2110	0	0	0	0	0	0
2111	0	0	0	0	0	0
2112	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.2105,2108: Not copulated

crotonic acid by oral administration in rats			Period : F0 gestation			Species : Rat		
In-the-hand observation		Sex : Female	Day : 20	Dose : crotonic acid 150 mg/kg				
	Ease of remov- al from cage	Fur condition	Skin	Secretions- Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
Animal No.								
3101	0	0	0	0	0	0	0	0
3102	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0
n	11	11	11	11	11	11	11	11
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
Animal No.								
3101	0	0	0	0	0	0		
3102	0	0	0	0	0	0		
3103	0	0	0	0	0	0		
3104	0	0	0	0	0	0		
3105	0	0	0	0	0	0		
3106	0	0	0	0	0	0		
3107	0	0	0	0	0	0		
3108	0	0	0	0	0	0		
3110	0	0	0	0	0	0		
3111	0	0	0	0	0	0		
3112	0	0	0	0	0	0		
n	11	11	11	11	11	11		

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.3109: Not copulated

Animal No.	In-the-hand observation		Period : F0 gestation		Species : Rat			
	Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4101	0	0	0	0	0	0	0	0
4102	0	0	0	0	0	0	0	0
4103	0	0	0	0	0	0	0	0
4104	0	0	0	0	0	0	0	0
4105	0	0	0	0	0	0	0	0
4106	0	0	0	0	0	0	0	0
4107	0	0	0	0	0	0	0	0
4108	0	0	0	0	0	0	0	0
4109	0	0	0	0	0	0	0	0
4110	0	0	0	0	0	0	0	0
4111	0	0	0	0	0	0	0	0
4112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4101	0	0	0	0	0	0
4102	0	0	0	0	0	0
4103	0	0	0	0	0	0
4104	0	0	0	0	0	0
4105	0	0	0	0	0	0
4106	0	0	0	0	0	0
4107	0	0	0	0	0	0
4108	0	0	0	0	0	0
4109	0	0	0	0	0	0
4110	0	0	0	0	0	0
4111	0	0	0	0	0	0
4112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : F0 lactation		Species : Rat			
	Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1101	0	0	0	0	0	0	0	0
1102	0	0	0	0	0	0	0	0
1103	0	0	0	0	0	0	0	0
1104	0	0	0	0	0	0	0	0
1105	0	0	0	0	0	0	0	0
1106	0	0	0	0	0	0	0	0
1107	0	0	0	0	0	0	0	0
1108	0	0	0	0	0	0	0	0
1109	0	0	0	0	0	0	0	0
1110	0	0	0	0	0	0	0	0
1111	0	0	0	0	0	0	0	0
1112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1101	0	0	0	0	0	0
1102	0	0	0	0	0	0
1103	0	0	0	0	0	0
1104	0	0	0	0	0	0
1105	0	0	0	0	0	0
1106	0	0	0	0	0	0
1107	0	0	0	0	0	0
1108	0	0	0	0	1	0
1109	0	0	0	0	0	0
1110	0	0	0	0	0	0
1111	0	0	0	0	0	0
1112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation			Period : F0 lactation			Species : Rat		
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 50 mg/kg					
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation	
Animal No.								
2101	0	0	0	0	0	0	0	0
2102	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0
2104	0	0	0	0	0	0	0	0
2106	0	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0	0
2109	0	0	0	0	0	0	0	0
2110	0	0	0	0	0	0	0	0
2111	0	0	0	0	0	0	0	0
2112	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
Animal No.					
2101	0	0	0	0	0
2102	0	0	0	0	0
2103	0	0	0	0	0
2104	0	0	0	0	0
2106	0	0	0	0	0
2107	0	0	0	0	0
2109	0	0	0	0	0
2110	0	0	0	0	0
2111	0	0	0	0	0
2112	0	0	0	0	0
n	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.2105,2108: Not copulated

Animal No.	In-the-hand observation		Period : F0 lactation		Species : Rat			
	Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 150 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
3101	0	0	0	0	0	0	0	0
3102	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0
n	11	11	11	11	11	11	11	11

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
3101	0	0	0	0	0	0
3102	0	0	0	0	0	0
3103	0	0	0	0	0	0
3104	0	0	0	0	0	0
3105	0	0	0	0	0	0
3106	0	0	0	0	0	0
3107	0	0	0	0	0	0
3108	0	0	0	0	0	0
3110	0	0	0	0	0	0
3111	0	0	0	0	0	0
3112	0	0	0	0	0	0
n	11	11	11	11	11	11

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.3109: Not copulated

Animal No.	In-the-hand observation		Period : F0 lactation		Species : Rat			
	Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4101	0	0	0	0	0	0	0	0
4102	0	0	0	0	0	0	0	0
4103	0	0	0	0	0	0	0	0
4104	0	0	0	0	0	0	0	0
4105	0	0	0	0	0	0	0	0
4106	0	0	0	0	0	0	0	0
4107	0	0	0	0	0	0	0	0
4108	0	0	0	0	0	0	0	0
4109	0	0	0	0	0	0	0	0
4110	0	0	0	0	0	0	0	0
4111	0	0	0	0	0	0	0	0
4112	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12

Animal No.						
	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4101	0	0	0	0	0	0
4102	0	0	0	0	0	0
4103	0	0	0	0	0	0
4104	0	0	0	0	0	0
4105	0	0	0	0	0	0
4106	0	0	0	0	0	0
4107	0	0	0	0	0	0
4108	0	0	0	0	0	0
4109	0	0	0	0	0	0
4110	0	0	0	0	0	0
4111	0	0	0	0	0	0
4112	0	0	0	0	0	0
n	12	12	12	12	12	12

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
5101	0	0	0	0	0	0	0	0
5102	0	0	0	0	0	0	0	0
5103	0	0	0	0	0	0	0	0
5104	0	0	0	0	0	0	0	0
5105	0	0	0	0	0	0	0	0
5106	0	0	0	0	0	0	0	0
5107	0	0	0	0	0	0	0	0
5108	0	0	0	0	0	0	0	0
5109	0	0	0	0	0	0	0	0
5110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
5101	0	0	0	0	0	0
5102	0	0	0	0	0	0
5103	0	0	0	0	0	0
5104	0	0	0	0	0	0
5105	0	0	0	0	0	0
5106	0	0	0	0	0	0
5107	0	0	0	0	0	0
5108	0	0	0	0	0	0
5109	0	0	0	0	0	0
5110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
6101	0	0	0	0	0	0	0	0
6102	0	0	0	0	0	0	0	0
6103	0	0	0	0	0	0	0	0
6104	0	0	0	0	0	0	0	0
6105	0	0	0	0	0	0	0	0
6106	0	0	0	0	0	0	0	0
6107	0	0	0	0	0	0	0	0
6108	0	0	0	0	0	0	0	0
6109	0	0	0	0	0	0	0	0
6110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
6101	0	0	0	0	0	0
6102	0	0	0	0	0	0
6103	0	0	0	0	0	0
6104	0	0	0	0	0	0
6105	0	0	0	0	1	0
6106	0	0	0	0	0	0
6107	0	0	0	0	0	0
6108	0	0	0	0	0	0
6109	0	0	0	0	0	0
6110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
5101	0	0	0	0	0	0	0	0
5102	0	0	0	0	0	0	0	0
5103	0	0	0	0	0	0	0	0
5104	0	0	0	0	0	0	0	0
5105	0	0	0	0	0	0	0	0
5106	0	0	0	0	0	0	0	0
5107	0	0	0	0	0	0	0	0
5108	0	0	0	0	0	0	0	0
5109	0	0	0	0	0	0	0	0
5110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
5101	0	0	0	0	0	0
5102	0	0	0	0	0	0
5103	0	0	0	0	0	0
5104	0	0	0	0	0	0
5105	0	0	0	0	0	0
5106	0	0	0	0	0	0
5107	0	0	0	0	0	0
5108	0	0	0	0	0	0
5109	0	0	0	0	0	0
5110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
6101	0	0	0	0	0	0	0	0
6102	0	0	0	0	0	0	0	0
6103	0	0	0	0	0	0	0	0
6104	0	0	0	0	0	0	0	0
6105	0	0	0	0	0	0	0	0
6106	0	0	0	0	0	0	0	0
6107	0	0	0	0	0	0	0	0
6108	0	0	0	0	0	0	0	0
6109	0	0	0	0	0	0	0	0
6110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
6101	0	0	0	0	0	0
6102	0	0	0	0	0	0
6103	0	0	0	0	0	0
6104	0	0	0	0	0	0
6105	0	0	0	0	0	0
6106	0	0	0	0	0	0
6107	0	0	0	0	0	0
6108	0	0	0	0	0	0
6109	0	0	0	0	0	0
6110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 3	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
5101	0	0	0	0	0	0	0	0
5102	0	0	0	0	0	0	0	0
5103	0	0	0	0	0	0	0	0
5104	0	0	0	0	0	0	0	0
5105	0	0	0	0	0	0	0	0
5106	0	0	0	0	0	0	0	0
5107	0	0	0	0	0	0	0	0
5108	0	0	0	0	0	0	0	0
5109	0	0	0	0	0	0	0	0
5110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
5101	0	0	0	0	0	0
5102	0	0	0	0	0	0
5103	0	0	0	0	0	0
5104	0	0	0	0	0	0
5105	0	0	0	0	0	0
5106	0	0	0	0	0	0
5107	0	0	0	0	0	0
5108	0	0	0	0	0	0
5109	0	0	0	0	0	0
5110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 3	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
6101	0	0	0	0	0	0	0	0
6102	0	0	0	0	0	0	0	0
6103	0	0	0	0	0	0	0	0
6104	0	0	0	0	0	0	0	0
6105	0	0	0	0	0	0	0	0
6106	0	0	0	0	0	0	0	0
6107	0	0	0	0	0	0	0	0
6108	0	0	0	0	0	0	0	0
6109	0	0	0	0	0	0	0	0
6110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
6101	0	0	0	0	0	0
6102	0	0	0	0	0	0
6103	0	0	0	0	0	0
6104	0	0	0	0	0	0
6105	0	0	0	0	0	0
6106	0	0	0	0	0	0
6107	0	0	0	0	0	0
6108	0	0	0	0	0	0
6109	0	0	0	0	0	0
6110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 4	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
5101	0	0	0	0	0	0	0	0
5102	0	0	0	0	0	0	0	0
5103	0	0	0	0	0	0	0	0
5104	0	0	0	0	0	0	0	0
5105	0	0	0	0	0	0	0	0
5106	0	0	0	0	0	0	0	0
5107	0	0	0	0	0	0	0	0
5108	0	0	0	0	0	0	0	0
5109	0	0	0	0	0	0	0	0
5110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
5101	0	0	0	0	0	0
5102	0	0	0	0	0	0
5103	0	0	0	0	0	0
5104	0	0	0	0	0	0
5105	0	0	0	0	0	0
5106	0	0	0	0	0	0
5107	0	0	0	0	0	0
5108	0	0	0	0	0	0
5109	0	0	0	0	0	0
5110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 4	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
6101	0	0	0	0	0	0	0	0
6102	0	0	0	0	0	0	0	0
6103	0	0	0	0	0	0	0	0
6104	0	0	0	0	0	0	0	0
6105	0	0	0	0	0	0	0	0
6106	0	0	0	0	0	0	0	0
6107	0	0	0	0	0	0	0	0
6108	0	0	0	0	0	0	0	0
6109	0	0	0	0	0	0	0	0
6110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
6101	0	0	0	0	0	0
6102	0	0	0	0	0	0
6103	0	0	0	0	0	0
6104	0	0	0	0	0	0
6105	0	0	0	0	0	0
6106	0	0	0	0	0	0
6107	0	0	0	0	0	0
6108	0	0	0	0	0	0
6109	0	0	0	0	0	0
6110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 5	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
5101	0	0	0	0	0	0	0	0
5102	0	0	0	0	0	0	0	0
5103	0	0	0	0	0	0	0	0
5104	0	0	0	0	0	0	0	0
5105	0	0	0	0	0	0	0	0
5106	0	0	0	0	0	0	0	0
5107	0	0	0	0	0	0	0	0
5108	0	0	0	0	0	0	0	0
5109	0	0	0	0	0	0	0	0
5110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
5101	0	0	0	0	0	0
5102	0	0	0	0	0	0
5103	0	0	0	0	0	0
5104	0	0	0	0	0	0
5105	0	0	0	0	0	0
5106	0	0	0	0	0	0
5107	0	0	0	0	0	0
5108	0	0	0	0	0	0
5109	0	0	0	0	0	0
5110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 5	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
6101	0	0	0	0	0	0	0	0
6102	0	0	0	0	0	0	0	0
6103	0	0	0	0	0	0	0	0
6104	0	0	0	0	0	0	0	0
6105	0	0	0	0	0	0	0	0
6106	0	0	0	0	0	0	0	0
6107	0	0	0	0	0	0	0	0
6108	0	0	0	0	0	0	0	0
6109	0	0	0	0	0	0	0	0
6110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
6101	0	0	0	0	0	0
6102	0	0	0	0	0	0
6103	0	0	0	0	0	0
6104	0	0	0	0	0	0
6105	0	0	0	0	0	0
6106	0	0	0	0	0	0
6107	0	0	0	0	0	0
6108	0	0	0	0	0	0
6109	0	0	0	0	0	0
6110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 0 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
5101	0	0	0	0	0	0	0	0
5102	0	0	0	0	0	0	0	0
5103	0	0	0	0	0	0	0	0
5104	0	0	0	0	0	0	0	0
5105	0	0	0	0	0	0	0	0
5106	0	0	0	0	0	0	0	0
5107	0	0	0	0	0	0	0	0
5108	0	0	0	0	0	0	0	0
5109	0	0	0	0	0	0	0	0
5110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
5101	0	0	0	0	0	0
5102	0	0	0	0	0	0
5103	0	0	0	0	0	0
5104	0	0	0	0	0	0
5105	0	0	0	0	0	0
5106	0	0	0	0	0	0
5107	0	0	0	0	0	0
5108	0	0	0	0	0	0
5109	0	0	0	0	0	0
5110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Animal No.	In-the-hand observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 500 mg/kg				
	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
6101	0	0	0	0	0	0	0	0
6102	0	0	0	0	0	0	0	0
6103	0	0	0	0	0	0	0	0
6104	0	0	0	0	0	0	0	0
6105	0	0	0	0	0	0	0	0
6106	0	0	0	0	0	0	0	0
6107	0	0	0	0	0	0	0	0
6108	0	0	0	0	0	0	0	0
6109	0	0	0	0	0	0	0	0
6110	0	0	0	0	0	0	0	0
n	10	10	10	10	10	10	10	10

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
6101	0	0	0	0	0	0
6102	0	0	0	0	0	0
6103	0	0	0	0	0	0
6104	0	0	0	0	0	0
6105	0	0	0	0	0	0
6106	0	0	0	0	0	0
6107	0	0	0	0	0	0
6108	0	0	0	0	0	0
6109	0	0	0	0	0	0
6110	0	0	0	0	0	0
n	10	10	10	10	10	10

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation		Period : Recovery		Species : Rat				
Generation : F0		Sex : Male	Week : 1	Dose : crotonic acid 0 mg/kg				
Animal No.	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1008	0	0	0	0	0	0	0	0
1009	0	0	0	0	0	0	0	0
1010	0	0	0	0	0	0	0	0
1011	0	0	0	0	0	0	0	0
1012	0	0	0	0	0	0	0	0
n	5	5	5	5	5	5	5	5

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1008	0	0	0	0	0	0
1009	0	0	0	0	0	0
1010	0	0	0	0	0	0
1011	0	0	0	0	0	0
1012	0	0	0	0	0	0
n	5	5	5	5	5	5

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation		Period : Recovery		Species : Rat				
Generation : F0		Sex : Male	Week : 1	Dose : crotonic acid 500 mg/kg				
Animal No.	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4008	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0
n	5	5	5	5	5	5	5	5

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4008	0	0	0	0	0	0
4009	0	0	0	0	0	0
4010	0	0	0	0	0	0
4011	0	0	0	0	0	0
4012	0	0	0	0	0	0
n	5	5	5	5	5	5

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation		Period : Recovery		Species : Rat				
Generation : F0		Sex : Male	Week : 2	Dose : crotonic acid 0 mg/kg				
Animal No.	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
1008	0	0	0	0	0	0	0	0
1009	0	0	0	0	0	0	0	0
1010	0	0	0	0	0	0	0	0
1011	0	0	0	0	0	0	0	0
1012	0	0	0	0	0	0	0	0
n	5	5	5	5	5	5	5	5

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
1008	0	0	0	0	0	0
1009	0	0	0	0	0	0
1010	0	0	0	0	0	0
1011	0	0	0	0	0	0
1012	0	0	0	0	0	0
n	5	5	5	5	5	5

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation		Period : Recovery		Species : Rat				
Generation : F0		Sex : Male	Week : 2	Dose : crotonic acid 500 mg/kg				
Animal No.	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
4008	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0
n	5	5	5	5	5	5	5	5

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
4008	0	0	0	1 a)	0	0
4009	0	0	0	0	0	0
4010	0	0	0	0	0	0
4011	0	0	0	0	0	0
4012	0	0	0	0	0	0
n	5	5	5	5	5	5

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

a) Consecutive wheezing

In-the-hand observation		Period : Recovery		Species : Rat				
Generation : F0		Sex : Female	Week : 1	Dose : crotonic acid 0 mg/kg				
Animal No.	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
5106	0	0	0	0	0	0	0	0
5107	0	0	0	0	0	0	0	0
5108	0	0	0	0	0	0	0	0
5109	0	0	0	0	0	0	0	0
5110	0	0	0	0	0	0	0	0
n	5	5	5	5	5	5	5	5

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
5106	0	0	0	0	0	0
5107	0	0	0	0	0	0
5108	0	0	0	0	0	0
5109	0	0	0	0	0	0
5110	0	0	0	0	0	0
n	5	5	5	5	5	5

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation		Period : Recovery		Species : Rat				
Generation : F0		Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg				
Animal No.	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
6106	0	0	0	0	0	0	0	0
6107	0	0	0	0	0	0	0	0
6108	0	0	0	0	0	0	0	0
6109	0	0	0	0	0	0	0	0
6110	0	0	0	0	0	0	0	0
n	5	5	5	5	5	5	5	5

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
6106	0	0	0	0	0	0
6107	0	0	0	0	0	0
6108	0	0	0	0	0	0
6109	0	0	0	0	0	0
6110	0	0	0	0	0	0
n	5	5	5	5	5	5

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation		Period : Recovery		Species : Rat				
Generation : F0		Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg				
Animal No.	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
5106	0	0	0	0	0	0	0	0
5107	0	0	0	0	0	0	0	0
5108	0	0	0	0	0	0	0	0
5109	0	0	0	0	0	0	0	0
5110	0	0	0	0	0	0	0	0
n	5	5	5	5	5	5	5	5

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
5106	0	0	0	0	0	0
5107	0	0	0	0	0	0
5108	0	0	0	0	0	0
5109	0	0	0	0	0	0
5110	0	0	0	0	0	0
n	5	5	5	5	5	5

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

In-the-hand observation		Period : Recovery		Species : Rat				
Generation : F0		Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg				
Animal No.	Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation
6106	0	0	0	0	0	0	0	0
6107	0	0	0	0	0	0	0	0
6108	0	0	0	0	0	0	0	0
6109	0	0	0	0	0	0	0	0
6110	0	0	0	0	0	0	0	0
n	5	5	5	5	5	5	5	5

Animal No.	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
6106	0	0	0	0	0	0
6107	0	0	0	0	0	0
6108	0	0	0	0	0	0
6109	0	0	0	0	0	0
6110	0	0	0	0	0	0
n	5	5	5	5	5	5

Ease of removal from cage) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult

Fur condition) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Skin) 0: Nomal, 1: Slight, 2: Moderate, 3: Severe

Secretions-Eye, Nose) 0: Absent, 1: Present

Exophthalmos) 0: Absent, 1: Present

Palpebral closure) 0: Nomal, 1: Slightly closed, 2: Half closed, 3: Completely closed

Mucosal membranes) 0: Nomal, 1: Slight, 2: Moderate, 3: Marked

Lacrimation) 0: Absent, 1: Present

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Nomal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Abnormal respiration) 0: None, 1: Slight, 2: Moderate, 3: Severe

Vocalization) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive

Reactivity to handling) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Awkward, 3: Very Awkward

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1001	0	0	0	0	N	0	0	
1002	0	0	0	0	N	0	0	
1003	0	0	0	0	N	0	0	
1004	0	0	0	0	N	0	0	
1005	0	0	0	0	N	0	0	
1006	0	0	0	0	N	0	0	
1007	0	0	0	0	N	0	0	
1008	0	0	0	0	N	0	0	
1009	0	0	0	0	N	0	0	
1010	0	0	0	0	N	0	0	
1011	0	0	0	0	N	0	0	
1012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	5	0
1002	4	0
1003	5	0
1004	5	0
1005	2	0
1006	1	4
1007	5	0
1008	4	0
1009	5	2
1010	1	0
1011	5	0
1012	4	0
n	12	12
Mean	4	1
S.D.	2	1

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2001	0	0	0	0	N	0	0	
2002	0	0	0	0	N	0	0	
2003	0	0	0	0	N	0	1	
2004	0	0	0	0	N	0	0	
2005	0	0	0	0	N	0	0	
2006	0	0	0	0	N	0	0	
2007	0	0	0	0	N	0	0	
2008	0	0	0	0	N	0	1	
2009	0	0	0	0	N	0	0	
2010	0	0	0	0	N	0	0	
2011	0	0	0	0	N	0	1	
2012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	4	0
2002	3	0
2003	5	0
2004	4	0
2005	4	0
2006	7	0
2007	6	0
2008	4	1
2009	4	0
2010	2	0
2011	5	0
2012	4	0
n	12	12
Mean	4	0
S.D.	1	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3001	0	0	0	0	N	0	0	
3002	0	0	0	0	N	0	0	
3003	0	0	0	0	N	0	0	
3004	0	0	0	0	N	0	0	
3005	0	0	0	0	N	0	0	
3006	0	0	0	0	N	0	0	
3007	0	0	0	0	N	0	0	
3008	0	0	0	0	N	0	0	
3009	0	0	0	0	N	0	0	
3010	0	0	0	0	N	0	0	
3011	0	0	0	0	N	0	0	
3012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	5	0
3002	6	0
3003	4	0
3004	2	0
3005	8	0
3006	4	0
3007	2	0
3008	4	0
3009	5	0
3010	6	0
3011	6	0
3012	3	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4001	0	0	0	0	N	0	0	
4002	0	0	0	0	N	0	0	
4003	0	0	0	0	N	0	0	
4004	0	0	0	0	N	0	0	
4005	0	0	0	0	N	0	0	
4006	0	0	0	0	N	0	0	
4007	0	0	0	0	N	0	0	
4008	0	0	0	0	N	0	0	
4009	0	0	0	0	N	0	0	
4010	0	0	0	0	N	0	0	
4011	0	0	0	0	N	0	0	
4012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	6	0
4002	6	0
4003	2	0
4004	3	0
4005	5	0
4006	2	0
4007	5	0
4008	3	0
4009	6	0
4010	9	0
4011	4	0
4012	4	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1001	0	0	0	0	N	0	0	
1002	0	0	0	0	N	0	1	
1003	0	0	0	0	N	0	1	
1004	0	0	0	0	N	0	0	
1005	0	0	0	0	N	0	0	
1006	0	0	0	0	N	0	0	
1007	0	0	0	0	N	0	0	
1008	0	0	0	0	N	0	0	
1009	0	0	0	0	N	0	0	
1010	0	0	0	0	N	0	0	
1011	0	0	0	0	N	0	0	
1012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	5	0
1002	6	0
1003	7	0
1004	7	0
1005	3	0
1006	1	2
1007	5	0
1008	3	0
1009	6	0
1010	0	0
1011	6	0
1012	4	0
n	12	12
Mean	4	0
S.D.	2	1

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2001	0	0	0	0	N	0	0	
2002	0	0	0	0	N	0	0	
2003	0	0	0	0	N	0	0	
2004	0	0	0	0	N	0	0	
2005	0	0	0	0	N	0	0	
2006	0	0	0	0	N	0	1	
2007	0	0	0	0	N	0	0	
2008	0	0	0	0	N	0	2	
2009	0	0	0	0	N	0	0	
2010	0	0	0	0	N	0	0	
2011	0	0	0	0	N	0	0	
2012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	8	0
2002	1	0
2003	5	0
2004	4	0
2005	2	0
2006	5	0
2007	4	0
2008	7	0
2009	8	0
2010	4	0
2011	10	0
2012	4	0
n	12	12
Mean	5	0
S.D.	3	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3001	0	0	0	0	N	0	0	
3002	0	0	0	0	N	0	0	
3003	0	0	0	0	N	0	0	
3004	0	0	0	0	N	0	0	
3005	0	0	0	0	N	0	0	
3006	0	0	0	0	N	0	1	
3007	0	0	0	0	N	0	0	
3008	0	0	0	0	N	0	0	
3009	0	0	0	0	N	0	0	
3010	0	0	0	0	N	0	0	
3011	0	0	0	0	N	0	0	
3012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	7	0
3002	6	0
3003	4	0
3004	4	0
3005	3	0
3006	1	0
3007	3	0
3008	4	1
3009	12	0
3010	6	0
3011	3	0
3012	4	0
n	12	12
Mean	5	0
S.D.	3	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4001	0	0	0	0	N	0	0	
4002	0	0	0	0	N	0	0	
4003	0	0	0	0	N	0	0	
4004	0	0	0	0	N	0	0	
4005	0	0	0	0	N	0	0	
4006	0	0	0	0	N	0	0	
4007	0	0	0	0	N	0	0	
4008	0	0	0	0	N	0	0	
4009	0	0	0	0	N	0	0	
4010	0	0	0	0	N	0	0	
4011	0	0	0	0	N	0	0	
4012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	8	0
4002	6	0
4003	3	0
4004	2	0
4005	8	0
4006	5	0
4007	4	0
4008	2	0
4009	4	0
4010	3	0
4011	5	0
4012	3	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0		Sex : Male		Week : 3		Dose : crotonic acid 0 mg/kg		
Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
1001	0	0	0	0	0	N	0	0
1002	0	0	0	0	0	N	0	0
1003	0	0	0	0	0	N	0	1
1004	0	0	0	0	0	N	0	0
1005	0	0	0	0	0	N	0	0
1006	0	0	0	0	0	N	0	1
1007	0	0	0	0	0	N	0	0
1008	0	0	0	0	0	N	0	0
1009	0	0	0	0	0	N	0	0
1010	0	0	0	0	0	N	0	0
1011	0	0	0	0	0	N	0	0
1012	0	0	0	0	0	N	0	0
n	12	12	12	12	12	12	12	12

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	10	0
1002	4	0
1003	7	0
1004	1	0
1005	3	0
1006	4	1
1007	5	0
1008	4	0
1009	4	0
1010	4	0
1011	4	0
1012	1	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2001	0	0	0	0	N	0	0	
2002	0	0	0	0	N	0	0	
2003	0	0	0	0	N	0	0	
2004	0	0	0	0	N	0	0	
2005	0	0	0	0	N	0	0	
2006	0	0	0	0	N	0	0	
2007	0	0	0	0	N	0	0	
2008	0	0	0	0	N	0	0	
2009	0	0	0	0	N	0	0	
2010	0	0	0	0	N	0	0	
2011	0	0	0	0	N	0	0	
2012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	6	0
2002	1	0
2003	5	0
2004	4	0
2005	3	2
2006	9	0
2007	5	0
2008	3	3
2009	5	0
2010	7	0
2011	8	0
2012	5	0
n	12	12
Mean	5	0
S.D.	2	1

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3001	0	0	0	0	N	0	0	
3002	0	0	0	0	N	0	0	
3003	0	0	0	0	N	0	0	
3004	0	0	0	0	N	0	0	
3005	0	0	0	0	N	0	0	
3006	0	0	0	0	N	0	0	
3007	0	0	0	0	N	0	0	
3008	0	0	0	0	N	0	1	
3009	0	0	0	0	N	0	0	
3010	0	0	0	0	N	0	0	
3011	0	0	0	0	N	0	0	
3012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	5	0
3002	4	0
3003	7	0
3004	2	2
3005	5	1
3006	3	0
3007	7	1
3008	5	0
3009	3	0
3010	4	0
3011	1	0
3012	4	0
n	12	12
Mean	4	0
S.D.	2	1

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 3	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4001	0	0	0	0	N	0	0	
4002	0	0	0	0	N	0	0	
4003	0	0	0	0	N	0	0	
4004	0	0	0	0	N	0	0	
4005	0	0	0	0	N	0	0	
4006	0	0	0	0	N	0	0	
4007	0	0	0	0	N	0	0	
4008	0	0	0	0	N	0	0	
4009	0	0	0	0	N	0	0	
4010	0	0	0	0	N	0	0	
4011	0	0	0	0	N	0	1	
4012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	6	0
4002	3	0
4003	5	0
4004	4	0
4005	5	0
4006	3	0
4007	8	0
4008	5	0
4009	6	0
4010	6	0
4011	3	0
4012	3	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1001	0	0	0	0	N	0	1	
1002	0	0	0	0	N	0	0	
1003	0	0	0	0	N	0	0	
1004	0	0	0	0	N	0	0	
1005	0	0	0	0	N	0	0	
1006	0	0	0	0	N	0	0	
1007	0	0	0	0	N	0	0	
1008	0	0	0	0	N	0	0	
1009	0	0	0	0	N	0	0	
1010	0	0	0	0	N	0	0	
1011	0	0	0	0	N	0	0	
1012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 4

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	7	0
1002	4	0
1003	7	0
1004	4	0
1005	3	0
1006	3	0
1007	7	0
1008	4	0
1009	7	0
1010	4	0
1011	4	0
1012	2	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2001	0	0	0	0	N	0	0	
2002	0	0	0	0	N	0	0	
2003	0	0	0	0	N	0	0	
2004	0	0	0	0	N	0	0	
2005	0	0	0	0	N	0	0	
2006	0	0	0	0	N	0	0	
2007	0	0	0	0	N	0	0	
2008	0	0	0	0	N	0	0	
2009	0	0	0	0	N	0	0	
2010	0	0	0	0	N	0	0	
2011	0	0	0	0	N	0	0	
2012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 4

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	7	0
2002	0	0
2003	4	0
2004	3	0
2005	2	0
2006	6	0
2007	4	0
2008	1	0
2009	6	0
2010	5	0
2011	5	0
2012	0	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3001	0	0	0	0	N	0	0	
3002	0	0	0	0	N	0	0	
3003	0	0	0	0	N	0	0	
3004	0	0	0	0	N	0	0	
3005	0	0	0	0	N	0	0	
3006	0	0	0	0	N	0	0	
3007	0	0	0	0	N	0	0	
3008	0	0	0	0	N	0	0	
3009	0	0	0	0	N	0	0	
3010	0	0	0	0	N	0	0	
3011	0	0	0	0	N	0	0	
3012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 4

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	6	0
3002	5	0
3003	4	0
3004	2	0
3005	6	0
3006	3	0
3007	1	0
3008	3	0
3009	1	0
3010	4	0
3011	2	0
3012	6	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 4	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4001	0	0	0	0	N	0	0	
4002	0	0	0	0	N	0	0	
4003	0	0	0	0	N	0	0	
4004	0	0	0	0	N	0	0	
4005	0	0	0	0	N	0	0	
4006	0	0	0	0	N	0	0	
4007	0	0	0	0	N	0	0	
4008	0	0	0	0	N	0	0	
4009	0	0	0	0	N	0	0	
4010	0	0	0	0	N	0	0	
4011	0	0	0	0	N	0	0	
4012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 4

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	6	0
4002	4	0
4003	1	0
4004	3	0
4005	5	0
4006	5	0
4007	5	0
4008	2	0
4009	5	0
4010	4	0
4011	3	0
4012	4	0
n	12	12
Mean	4	0
S.D.	1	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1001	0	0	0	0	N	0	0	
1002	0	0	0	0	N	0	0	
1003	0	0	0	0	N	0	0	
1004	0	0	0	0	N	0	1	
1005	0	0	0	0	N	0	0	
1006	0	0	0	0	N	0	1	
1007	0	0	0	0	N	0	0	
1008	0	0	0	0	N	0	0	
1009	0	0	0	0	N	0	0	
1010	0	0	0	0	N	0	0	
1011	0	0	0	0	N	0	0	
1012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	7	0
1002	5	0
1003	5	0
1004	5	0
1005	3	0
1006	3	0
1007	5	0
1008	6	0
1009	6	0
1010	4	0
1011	7	0
1012	3	0
n	12	12
Mean	5	0
S.D.	1	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2001	0	0	0	0	N	0	0	
2002	0	0	0	0	N	0	0	
2003	0	0	0	0	N	0	0	
2004	0	0	0	0	N	0	0	
2005	0	0	0	0	N	0	0	
2006	0	0	0	0	N	0	0	
2007	0	0	0	0	N	0	0	
2008	0	0	0	0	N	0	0	
2009	0	0	0	0	N	0	0	
2010	0	0	0	0	N	0	0	
2011	0	0	0	0	N	0	0	
2012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	5	0
2002	3	0
2003	4	0
2004	4	0
2005	3	0
2006	6	0
2007	5	0
2008	2	2
2009	3	0
2010	5	0
2011	6	0
2012	5	0
n	12	12
Mean	4	0
S.D.	1	1

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3001	0	0	0	0	N	0	0	
3002	0	0	0	0	N	0	0	
3003	0	0	0	0	N	0	0	
3004	0	0	0	0	N	0	0	
3005	0	0	0	0	N	0	0	
3006	0	0	0	0	N	0	0	
3007	0	0	0	0	N	0	0	
3008	0	0	0	0	N	0	0	
3009	0	0	0	0	N	0	0	
3010	0	0	0	0	N	0	0	
3011	0	0	0	0	N	0	0	
3012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	3	0
3002	5	0
3003	5	0
3004	3	0
3005	4	0
3006	3	0
3007	4	0
3008	3	0
3009	3	0
3010	4	0
3011	3	0
3012	5	0
n	12	12
Mean	4	0
S.D.	1	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 5	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4001	0	0	0	0	N	0	0	
4002	0	0	0	0	N	0	0	
4003	0	0	0	0	N	0	0	
4004	0	0	0	0	N	0	0	
4005	0	0	0	0	N	0	0	
4006	0	0	0	0	N	0	0	
4007	0	0	0	0	N	0	0	
4008	0	0	0	0	N	0	0	
4009	0	0	0	0	N	0	0	
4010	0	0	0	0	N	0	0	
4011	0	0	0	0	N	0	0	
4012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	4	0
4002	4	0
4003	3	0
4004	3	0
4005	5	0
4006	5	0
4007	8	0
4008	4	0
4009	4	0
4010	7	0
4011	4	0
4012	5	0
n	12	12
Mean	5	0
S.D.	1	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1001	0	0	0	0	N	0	0	
1002	0	0	0	0	N	0	0	
1003	0	0	0	0	N	0	0	
1004	0	0	0	0	N	0	0	
1005	0	0	0	0	N	0	0	
1006	0	0	0	0	N	0	0	
1007	0	0	0	0	N	0	0	
1008	0	0	0	0	N	0	0	
1009	0	0	0	0	N	0	0	
1010	0	0	0	0	N	0	0	
1011	0	0	0	0	N	0	0	
1012	0	0	0	0	N	0	1	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	5	0
1002	2	0
1003	3	0
1004	6	0
1005	3	0
1006	3	0
1007	6	0
1008	5	0
1009	7	0
1010	5	0
1011	6	0
1012	5	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2001	0	0	0	0	N	0	0	
2002	0	0	0	0	N	0	1	
2003	0	0	0	0	N	0	0	
2004	0	0	0	0	N	0	0	
2005	0	0	0	0	N	0	0	
2006	0	0	0	0	N	0	0	
2007	0	0	0	0	N	0	0	
2008	0	0	0	0	N	0	1	
2009	0	0	0	0	N	0	0	
2010	0	0	0	0	N	0	1	
2011	0	0	0	0	N	0	0	
2012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	7	0
2002	2	0
2003	4	0
2004	3	0
2005	4	0
2006	3	0
2007	3	0
2008	2	0
2009	5	0
2010	2	0
2011	5	0
2012	2	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3001	0	0	0	0	N	0	0	
3002	0	0	0	0	N	0	0	
3003	0	0	0	0	N	0	0	
3004	0	0	0	0	N	0	0	
3005	0	0	0	0	N	0	0	
3006	0	0	0	0	N	0	0	
3007	0	0	0	0	N	0	0	
3008	0	0	0	0	N	0	1	
3009	0	0	0	0	N	0	0	
3010	0	0	0	0	N	0	0	
3011	0	0	0	0	N	0	0	
3012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	6	0
3002	3	0
3003	2	0
3004	2	0
3005	3	0
3006	1	0
3007	2	0
3008	5	0
3009	2	0
3010	4	0
3011	6	0
3012	6	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Species : Rat				
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4001	0	0	0	0	N	0	0	
4002	0	0	0	0	N	0	0	
4003	0	0	0	0	N	0	0	
4004	0	0	0	0	N	0	0	
4005	0	0	0	0	N	0	0	
4006	0	0	0	0	N	0	1	
4007	0	0	0	0	N	0	0	
4008	0	0	0	0	N	0	0	
4009	0	0	0	0	N	0	0	
4010	0	0	0	0	N	0	0	
4011	0	0	0	0	N	0	1	
4012	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	4	0
4002	3	0
4003	4	0
4004	3	0
4005	3	0
4006	2	0
4007	5	0
4008	3	0
4009	4	0
4010	5	0
4011	5	0
4012	7	0
n	12	12
Mean	4	0
S.D.	1	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1101	0	0	0	0	N	0	0	
1102	0	0	0	0	N	0	0	
1103	0	0	0	0	N	0	0	
1104	0	0	0	0	N	0	0	
1105	0	0	0	0	N	0	0	
1106	0	0	0	0	N	0	0	
1107	0	0	0	0	N	0	0	
1108	0	0	0	0	N	0	0	
1109	0	0	0	0	N	0	0	
1110	0	0	0	0	N	0	0	
1111	0	0	0	0	N	0	0	
1112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	5	0
1102	3	0
1103	4	0
1104	5	0
1105	5	0
1106	8	0
1107	7	0
1108	6	0
1109	6	0
1110	6	0
1111	5	0
1112	7	0
n	12	12
Mean	6	0
S.D.	1	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2101	0	0	0	0	N	0	0	
2102	0	0	0	0	N	0	0	
2103	0	0	0	0	N	0	0	
2104	0	0	0	0	N	0	0	
2105	0	0	0	0	N	0	0	
2106	0	0	0	0	N	0	0	
2107	0	0	0	0	N	0	0	
2108	0	0	0	0	N	0	0	
2109	0	0	0	0	N	0	0	
2110	0	0	0	0	N	0	0	
2111	0	0	0	0	N	0	0	
2112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	7	0
2102	7	0
2103	6	0
2104	6	0
2105	6	0
2106	8	0
2107	7	0
2108	5	0
2109	5	0
2110	12	0
2111	6	0
2112	7	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3101	0	0	0	0	N	0	0	
3102	0	0	0	0	N	0	0	
3103	0	0	0	0	N	0	0	
3104	0	0	0	0	N	0	0	
3105	0	0	0	0	N	0	0	
3106	0	0	0	0	N	0	0	
3107	0	0	0	0	N	0	0	
3108	0	0	0	0	N	0	0	
3109	0	0	0	0	N	0	0	
3110	0	0	0	0	N	0	0	
3111	0	0	0	0	N	0	0	
3112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	5	0
3102	8	0
3103	4	0
3104	8	0
3105	8	0
3106	5	0
3107	6	0
3108	6	0
3109	7	0
3110	2	0
3111	9	0
3112	6	0
n	12	12
Mean	6	0
S.D.	2	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0		Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg				
Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
4101	0	0	0	0	0	N	0	0
4102	0	0	0	0	0	N	0	0
4103	0	0	0	0	0	N	0	0
4104	0	0	0	0	0	N	0	0
4105	0	0	0	0	0	N	0	0
4106	0	0	0	0	0	N	0	0
4107	0	0	0	0	0	N	0	0
4108	0	0	0	0	0	N	0	0
4109	0	0	0	0	0	N	0	0
4110	0	0	0	0	0	N	0	0
4111	0	0	0	0	0	N	0	0
4112	0	0	0	0	0	N	0	0
n	12	12	12	12	12	12	12	12

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	7	0
4102	6	0
4103	6	0
4104	6	0
4105	4	0
4106	6	0
4107	6	0
4108	5	0
4109	6	0
4110	10	0
4111	4	0
4112	8	0
n	12	12
Mean	6	0
S.D.	2	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1101	0	0	0	0	N	0	0	
1102	0	0	0	0	N	0	0	
1103	0	0	0	0	N	0	0	
1104	0	0	0	0	N	0	0	
1105	0	0	0	0	N	0	0	
1106	0	0	0	0	N	0	1	
1107	0	0	0	0	N	0	0	
1108	0	0	0	0	N	0	0	
1109	0	0	0	0	N	0	0	
1110	0	0	0	0	N	0	0	
1111	0	0	0	0	N	0	0	
1112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	4	0
1102	4	0
1103	8	0
1104	6	0
1105	7	0
1106	8	0
1107	5	0
1108	5	0
1109	8	0
1110	6	0
1111	5	0
1112	10	0
n	12	12
Mean	6	0
S.D.	2	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2101	0	0	0	0	N	0	0	
2102	0	0	0	0	N	0	0	
2103	0	0	0	0	N	0	0	
2104	0	0	0	0	N	0	0	
2105	0	0	0	0	N	0	0	
2106	0	0	0	0	N	0	0	
2107	0	0	0	0	N	0	0	
2108	0	0	0	0	N	0	0	
2109	0	0	0	0	N	0	0	
2110	0	0	0	0	N	0	0	
2111	0	0	0	0	N	0	0	
2112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	9	0
2102	7	0
2103	7	0
2104	8	0
2105	3	0
2106	9	0
2107	8	0
2108	3	0
2109	7	0
2110	10	0
2111	4	0
2112	5	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3101	0	0	0	0	N	0	0	
3102	0	0	0	0	N	0	0	
3103	0	0	0	0	N	0	0	
3104	0	0	0	0	N	0	1	
3105	0	0	0	0	N	0	0	
3106	0	0	0	0	N	0	0	
3107	0	0	0	0	N	0	0	
3108	0	0	0	0	N	0	0	
3109	0	0	0	0	N	0	0	
3110	0	0	0	0	N	0	0	
3111	0	0	0	0	N	0	0	
3112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	5	0
3102	8	0
3103	4	0
3104	13	0
3105	11	0
3106	3	0
3107	7	0
3108	5	0
3109	7	0
3110	4	0
3111	4	0
3112	8	0
n	12	12
Mean	7	0
S.D.	3	0

Open field observation		Period : F0 before mating		Species : Rat				
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4101	0	0	0	0	N	0	0	
4102	0	0	0	0	N	0	0	
4103	0	0	0	0	N	0	0	
4104	0	0	0	0	N	0	0	
4105	0	0	0	0	N	0	0	
4106	0	0	0	0	N	0	0	
4107	0	0	0	0	N	0	0	
4108	0	0	0	0	N	0	1	
4109	0	0	0	0	N	0	0	
4110	0	0	0	0	N	0	0	
4111	0	0	0	0	N	0	0	
4112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	5	0
4102	5	0
4103	5	0
4104	7	0
4105	4	0
4106	7	0
4107	6	0
4108	2	0
4109	6	0
4110	11	0
4111	5	0
4112	9	0
n	12	12
Mean	6	0
S.D.	2	0

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0		Sex : Female	Day : 1	Dose : crotonic acid 0 mg/kg				
Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
1101	0	0	0	0	0	N	0	0
1102	0	0	0	0	0	N	0	1
1103	0	0	0	0	0	N	0	0
1104	0	0	0	0	0	N	0	0
1105	0	0	0	0	0	N	0	0
1106	0	0	0	0	0	N	0	0
1107	0	0	0	0	0	N	0	0
1108	0	0	0	0	0	N	0	0
1109	0	0	0	0	0	N	0	0
1110	0	0	0	0	0	N	0	0
1111	0	0	0	0	0	N	0	0
1112	0	0	0	0	0	N	0	0
n	12	12	12	12	12	12	12	12

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	10	0
1102	4	0
1103	6	0
1104	5	0
1105	5	0
1106	10	0
1107	9	0
1108	6	0
1109	9	0
1110	8	0
1111	5	0
1112	6	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2101	0	0	0	0	N	0	0	
2102	0	0	0	0	N	0	0	
2103	0	0	0	0	N	0	0	
2104	0	0	0	0	N	0	0	
2106	0	0	0	0	N	0	0	
2107	0	0	0	0	N	0	0	
2109	0	0	0	0	N	0	0	
2110	0	0	0	0	N	0	0	
2111	0	0	0	0	N	0	0	
2112	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.2105,2108: Not copulated

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	10	0
2102	10	0
2103	8	0
2104	8	0
2106	8	0
2107	8	0
2109	4	0
2110	12	0
2111	10	0
2112	6	0
n	10	10
Mean	8	0
S.D.	2	0

Animal No.2105,2108: Not copulated

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 1	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3101	0	0	0	0	N	0	0	
3102	0	0	0	0	N	0	0	
3103	0	0	0	0	N	0	0	
3104	0	0	0	0	N	0	1	
3105	0	0	0	0	N	0	0	
3106	0	0	0	0	N	0	0	
3107	0	0	0	0	N	0	0	
3108	0	0	0	0	N	0	0	
3110	0	0	0	0	N	0	0	
3111	0	0	0	0	N	0	0	
3112	0	0	0	0	N	0	0	
n	11	11	11	11	11	11	11	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.3109: Not copulated

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	7	0
3102	8	0
3103	5	0
3104	7	0
3105	6	0
3106	6	0
3107	6	0
3108	5	0
3110	7	0
3111	6	0
3112	6	0
n	11	11
Mean	6	0
S.D.	1	0

Animal No.3109: Not copulated

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0		Sex : Female	Day : 1	Dose : crotonic acid 500 mg/kg				
Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
4101	0	0	0	0	0	N	0	0
4102	0	0	0	0	0	N	0	0
4103	0	0	0	0	0	N	0	0
4104	0	0	0	0	0	N	0	0
4105	0	0	0	0	0	N	0	0
4106	0	0	0	0	0	N	0	0
4107	0	0	0	0	0	N	0	0
4108	0	0	0	0	0	N	0	0
4109	0	0	0	0	0	N	0	0
4110	0	0	0	0	0	N	0	0
4111	0	0	0	0	0	N	0	0
4112	0	0	0	0	0	N	0	0
n	12	12	12	12	12	12	12	12

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	6	0
4102	7	0
4103	9	0
4104	7	0
4105	4	0
4106	9	0
4107	7	0
4108	6	0
4109	8	0
4110	6	0
4111	3	0
4112	5	0
n	12	12
Mean	6	0
S.D.	2	0

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0		Sex : Female		Day : 7		Dose : crotonic acid 0 mg/kg		
Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
1101	0	0	0	0	0	N	0	0
1102	0	0	0	0	0	N	0	0
1103	0	0	0	0	0	N	0	0
1104	0	0	0	0	0	N	0	0
1105	0	0	0	0	0	N	0	0
1106	0	0	0	0	0	N	0	0
1107	0	0	0	0	0	N	0	0
1108	0	0	0	0	0	N	0	0
1109	0	0	0	0	0	N	0	0
1110	0	0	0	0	0	N	0	0
1111	0	0	0	0	0	N	0	0
1112	0	0	0	0	0	N	0	0
n	12	12	12	12	12	12	12	12

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	7	0
1102	3	0
1103	7	0
1104	6	0
1105	6	0
1106	10	0
1107	7	0
1108	5	0
1109	9	0
1110	9	0
1111	5	0
1112	8	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 7	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2101	0	0	0	0	N	0	0	
2102	0	0	0	0	N	0	0	
2103	0	0	0	0	N	0	0	
2104	0	0	0	0	N	0	0	
2106	0	0	0	0	N	0	0	
2107	0	0	0	0	N	0	0	
2109	0	0	0	0	N	0	0	
2110	0	0	0	0	N	0	0	
2111	0	0	0	0	N	0	0	
2112	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.2105,2108: Not copulated

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	7	0
2102	9	0
2103	7	0
2104	7	0
2106	9	0
2107	9	0
2109	5	0
2110	7	0
2111	8	0
2112	7	0
n	10	10
Mean	8	0
S.D.	1	0

Animal No.2105,2108: Not copulated

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 7	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3101	0	0	0	0	N	0	0	
3102	0	0	0	0	N	0	0	
3103	0	0	0	0	N	0	0	
3104	0	0	0	0	N	0	0	
3105	0	0	0	0	N	0	0	
3106	0	0	0	0	N	0	0	
3107	0	0	0	0	N	0	0	
3108	0	0	0	0	N	0	0	
3110	0	0	0	0	N	0	0	
3111	0	0	0	0	N	0	0	
3112	0	0	0	0	N	0	0	
n	11	11	11	11	11	11	11	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.3109: Not copulated

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	8	0
3102	6	0
3103	7	0
3104	6	0
3105	10	0
3106	6	0
3107	6	0
3108	6	0
3110	4	0
3111	7	0
3112	6	0
n	11	11
Mean	7	0
S.D.	2	0

Animal No.3109: Not copulated

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0		Sex : Female	Day : 7	Dose : crotonic acid 500 mg/kg				
Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
4101	0	0	0	0	0	N	0	0
4102	0	0	0	0	0	N	0	0
4103	0	0	0	0	0	N	0	0
4104	0	0	0	0	0	N	0	0
4105	0	0	0	0	0	N	0	0
4106	0	0	0	0	0	N	0	0
4107	0	0	0	0	0	N	0	0
4108	0	0	0	0	0	N	0	0
4109	0	0	0	0	0	N	0	0
4110	0	0	0	0	0	N	0	0
4111	0	0	0	0	0	N	0	0
4112	0	0	0	0	0	N	0	0
n	12	12	12	12	12	12	12	12

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	10	0
4102	5	0
4103	9	0
4104	7	0
4105	5	0
4106	7	0
4107	8	0
4108	3	0
4109	11	0
4110	10	0
4111	6	0
4112	8	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0		Sex : Female	Day : 14	Dose : crotonic acid 0 mg/kg				
Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
1101	0	0	0	0	0	N	0	0
1102	0	0	0	0	0	N	0	0
1103	0	0	0	0	0	N	0	0
1104	0	0	0	0	0	N	0	0
1105	0	0	0	0	0	N	0	0
1106	0	0	0	0	0	N	0	0
1107	0	0	0	0	0	N	0	0
1108	0	0	0	0	0	N	0	0
1109	0	0	0	0	0	N	0	0
1110	0	0	0	0	0	N	0	0
1111	0	0	0	0	0	N	0	0
1112	0	0	0	0	0	N	0	0
n	12	12	12	12	12	12	12	12

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	6	0
1102	3	0
1103	7	0
1104	6	0
1105	6	0
1106	5	0
1107	7	0
1108	5	0
1109	7	0
1110	6	0
1111	7	0
1112	8	0
n	12	12
Mean	6	0
S.D.	1	0

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2101	0	0	0	0	N	0	0	
2102	0	0	0	0	N	0	0	
2103	0	0	0	0	N	0	0	
2104	0	0	0	0	N	0	0	
2106	0	0	0	0	N	0	0	
2107	0	0	0	0	N	0	0	
2109	0	0	0	0	N	0	0	
2110	0	0	0	0	N	0	0	
2111	0	0	0	0	N	0	0	
2112	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.2105,2108: Not copulated

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	9	0
2102	6	0
2103	7	0
2104	7	0
2106	9	0
2107	6	0
2109	3	0
2110	9	0
2111	7	0
2112	8	0
n	10	10
Mean	7	0
S.D.	2	0

Animal No.2105,2108: Not copulated

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3101	0	0	0	0	N	0	0	
3102	0	0	0	0	N	0	0	
3103	0	0	0	0	N	0	0	
3104	0	0	0	0	N	0	0	
3105	0	0	0	0	N	0	0	
3106	0	0	0	0	N	0	0	
3107	0	0	0	0	N	0	0	
3108	0	0	0	0	N	0	0	
3110	0	0	0	0	N	0	0	
3111	0	0	0	0	N	0	0	
3112	0	0	0	0	N	0	0	
n	11	11	11	11	11	11	11	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.3109: Not copulated

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	5	0
3102	7	0
3103	6	0
3104	7	0
3105	6	0
3106	5	0
3107	5	0
3108	8	0
3110	4	0
3111	7	0
3112	9	0
n	11	11
Mean	6	0
S.D.	1	0

Animal No.3109: Not copulated

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 14	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4101	0	0	0	0	N	0	0	
4102	0	0	0	0	N	0	0	
4103	0	0	0	0	N	0	0	
4104	0	0	0	0	N	0	0	
4105	0	0	0	0	N	0	0	
4106	0	0	0	0	N	0	0	
4107	0	0	0	0	N	0	0	
4108	0	0	0	0	N	0	0	
4109	0	0	0	0	N	0	0	
4110	0	0	0	0	N	0	0	
4111	0	0	0	0	N	0	0	
4112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	5	0
4102	6	0
4103	6	0
4104	6	0
4105	5	0
4106	6	0
4107	5	0
4108	8	0
4109	7	0
4110	4	0
4111	4	0
4112	5	0
n	12	12
Mean	6	0
S.D.	1	0

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1101	0	0	0	0	N	0	0	
1102	0	0	0	0	N	0	0	
1103	0	0	0	0	N	0	0	
1104	0	0	0	0	N	0	0	
1105	0	0	0	0	N	0	0	
1106	0	0	0	0	N	0	0	
1107	0	0	0	0	N	0	0	
1108	0	0	0	0	N	0	0	
1109	0	0	0	0	N	0	0	
1110	0	0	0	0	N	0	0	
1111	0	0	0	0	N	0	0	
1112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	3	0
1102	2	0
1103	6	0
1104	3	0
1105	6	0
1106	3	0
1107	5	0
1108	6	0
1109	4	0
1110	3	0
1111	6	0
1112	4	0
n	12	12
Mean	4	0
S.D.	1	0

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2101	0	0	0	0	N	0	0	
2102	0	0	0	0	N	0	0	
2103	0	0	0	0	N	0	0	
2104	0	0	0	0	N	0	0	
2106	0	0	0	0	N	0	0	
2107	0	0	0	0	N	0	0	
2109	0	0	0	0	N	0	0	
2110	0	0	0	0	N	0	0	
2111	0	0	0	0	N	0	0	
2112	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.2105,2108: Not copulated

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	7	0
2102	4	0
2103	5	0
2104	7	0
2106	6	0
2107	6	0
2109	1	0
2110	5	0
2111	3	0
2112	4	0
n	10	10
Mean	5	0
S.D.	2	0

Animal No.2105,2108: Not copulated

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3101	0	0	0	0	N	0	0	
3102	0	0	0	0	N	0	0	
3103	0	0	0	0	N	0	0	
3104	0	0	0	0	N	0	0	
3105	0	0	0	0	N	0	0	
3106	0	0	0	0	N	0	0	
3107	0	0	0	0	N	0	0	
3108	0	0	0	0	N	0	0	
3110	0	0	0	0	N	0	0	
3111	0	0	0	0	N	0	0	
3112	0	0	0	0	N	0	0	
n	11	11	11	11	11	11	11	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.3109: Not copulated

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	4	0
3102	5	0
3103	1	0
3104	5	0
3105	3	0
3106	3	0
3107	3	0
3108	4	0
3110	3	0
3111	3	0
3112	3	0
n	11	11
Mean	3	0
S.D.	1	0

Animal No.3109: Not copulated

Open field observation		Period : F0 gestation		Species : Rat				
Generation : F0	Sex : Female	Day : 20	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4101	0	0	0	0	N	0	0	
4102	0	0	0	0	N	0	0	
4103	0	0	0	0	N	0	0	
4104	0	0	0	0	N	0	0	
4105	0	0	0	0	N	0	0	
4106	0	0	0	0	N	0	0	
4107	0	0	0	0	N	0	0	
4108	0	0	0	0	N	0	0	
4109	0	0	0	0	N	0	0	
4110	0	0	0	0	N	0	0	
4111	0	0	0	0	N	0	0	
4112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	5	0
4102	4	0
4103	4	0
4104	6	0
4105	5	0
4106	5	0
4107	6	0
4108	4	0
4109	7	0
4110	3	0
4111	6	0
4112	7	0
n	12	12
Mean	5	0
S.D.	1	0

Open field observation		Period : F0 lactation		Species : Rat				
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1101	0	0	0	0	N	0	0	
1102	0	0	0	0	N	0	0	
1103	0	0	0	0	N	0	0	
1104	0	0	0	0	N	0	0	
1105	0	0	0	0	N	0	0	
1106	0	0	0	0	N	0	0	
1107	0	0	0	0	N	0	0	
1108	0	0	0	0	N	0	0	
1109	0	0	0	0	N	0	0	
1110	0	0	0	0	N	0	0	
1111	0	0	0	0	N	0	0	
1112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	5	0
1102	5	0
1103	8	0
1104	4	0
1105	6	0
1106	5	0
1107	2	0
1108	5	0
1109	7	0
1110	4	0
1111	2	0
1112	7	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 lactation		Species : Rat				
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 50 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
2101	0	0	0	0	N	0	0	
2102	0	0	0	0	N	0	0	
2103	0	0	0	0	N	0	0	
2104	0	0	0	0	N	0	0	
2106	0	0	0	0	N	0	0	
2107	0	0	0	0	N	0	0	
2109	0	0	0	0	N	0	0	
2110	0	0	0	0	N	0	0	
2111	0	0	0	0	N	0	0	
2112	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.2105,2108: Not copulated

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Dose : crotonic acid 50 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	9	0
2102	5	0
2103	8	0
2104	6	0
2106	7	0
2107	6	0
2109	4	0
2110	4	0
2111	3	0
2112	6	0
n	10	10
Mean	6	0
S.D.	2	0

Animal No.2105,2108: Not copulated

Open field observation		Period : F0 lactation		Species : Rat				
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 150 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
3101	0	0	0	0	N	0	0	
3102	0	0	0	0	N	0	0	
3103	0	0	0	0	N	0	0	
3104	0	0	0	0	N	0	0	
3105	0	0	0	0	N	0	0	
3106	0	0	0	0	N	0	0	
3107	0	0	0	0	N	0	0	
3108	0	0	0	0	N	0	0	
3110	0	0	0	0	N	0	0	
3111	0	0	0	0	N	0	0	
3112	0	0	0	0	N	0	0	
n	11	11	11	11	11	11	11	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Animal No.3109: Not copulated

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Dose : crotonic acid 150 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	5	0
3102	6	0
3103	6	0
3104	6	0
3105	7	0
3106	4	0
3107	5	0
3108	5	0
3110	5	0
3111	6	0
3112	5	0
n	11	11
Mean	5	0
S.D.	1	0

Animal No.3109: Not copulated

Open field observation		Period : F0 lactation		Species : Rat				
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
4101	0	0	0	0	N	0	0	
4102	0	0	0	0	N	0	0	
4103	0	0	0	0	N	0	0	
4104	0	0	0	0	N	0	0	
4105	0	0	0	0	N	0	0	
4106	0	0	0	0	N	0	0	
4107	0	0	0	0	N	0	0	
4108	0	0	0	0	N	0	0	
4109	0	0	0	0	N	0	0	
4110	0	0	0	0	N	0	0	
4111	0	0	0	0	N	0	0	
4112	0	0	0	0	N	0	0	
n	12	12	12	12	12	12	12	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	4	0
4102	4	0
4103	7	0
4104	10	0
4105	3	0
4106	4	0
4107	7	0
4108	7	0
4109	10	0
4110	5	0
4111	4	0
4112	5	0
n	12	12
Mean	6	0
S.D.	2	0

Animal No.	Open field observation			Period : Administration			Species : Rat		
	Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 0 mg/kg					
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
5101	0	0	0	0	0	N	0	0	
5102	0	0	0	0	0	N	0	0	
5103	0	0	0	0	0	N	0	0	
5104	0	0	0	0	0	N	0	0	
5105	0	0	0	0	0	N	0	0	
5106	0	0	0	0	0	N	0	0	
5107	0	0	0	0	0	N	0	0	
5108	0	0	0	0	0	N	0	0	
5109	0	0	0	0	0	N	0	0	
5110	0	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Administration

Generation : F0

Sex : Female

Week : 1

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	6	0
5102	4	0
5103	4	0
5104	7	0
5105	7	0
5106	8	0
5107	7	0
5108	6	0
5109	5	0
5110	6	0
n	10	10
Mean	6	0
S.D.	1	0

Open field observation		Period : Administration		Species : Rat				
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
6101	0	0	0	0	N	0	0	
6102	0	0	0	0	N	0	0	
6103	0	0	0	0	N	0	0	
6104	0	0	0	0	N	0	0	
6105	0	0	0	0	N	0	0	
6106	0	0	0	0	N	0	0	
6107	0	0	0	0	N	0	0	
6108	0	0	0	0	N	0	0	
6109	0	0	0	0	N	0	0	
6110	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation			Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg		
Rearing	Defecation count				
Animal No.					
6101	7	0			
6102	6	0			
6103	6	0			
6104	6	0			
6105	7	0			
6106	2	0			
6107	4	0			
6108	7	0			
6109	4	0			
6110	3	0			
n	10	10			
Mean	5	0			
S.D.	2	0			

Open field observation		Period : Administration		Species : Rat				
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
5101	0	0	0	0	N	0	0	
5102	0	0	0	0	N	0	0	
5103	0	0	0	0	N	0	0	
5104	0	0	0	0	N	0	0	
5105	0	0	0	0	N	0	0	
5106	0	0	0	0	N	0	0	
5107	0	0	0	0	N	0	0	
5108	0	0	0	0	N	0	0	
5109	0	0	0	0	N	0	0	
5110	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Administration

Generation : F0

Sex : Female

Week : 2

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	7	0
5102	6	0
5103	5	0
5104	6	0
5105	10	0
5106	7	0
5107	6	0
5108	5	0
5109	5	0
5110	8	0
n	10	10
Mean	7	0
S.D.	2	0

Animal No.	Open field observation			Period : Administration			Species : Rat		
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg					
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
6101	0	0	0	0	0	N	0	0	
6102	0	0	0	0	0	N	0	0	
6103	0	0	0	0	0	N	0	0	
6104	0	0	0	0	0	N	0	0	
6105	0	0	0	0	0	N	0	0	
6106	0	0	0	0	0	N	0	0	
6107	0	0	0	0	0	N	0	0	
6108	0	0	0	0	0	N	0	0	
6109	0	0	0	0	0	N	0	0	
6110	0	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation		Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg	
Rearing	Defecation count			
Animal No.				
6101	5	0		
6102	6	0		
6103	9	0		
6104	5	0		
6105	5	0		
6106	2	0		
6107	4	0		
6108	6	0		
6109	4	0		
6110	3	0		
n	10	10		
Mean	5	0		
S.D.	2	0		

Open field observation		Period : Administration		Species : Rat				
Generation : F0	Sex : Female	Week : 3	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
5101	0	0	0	0	N	0	0	
5102	0	0	0	0	N	0	0	
5103	0	0	0	0	N	0	0	
5104	0	0	0	0	N	0	0	
5105	0	0	0	0	N	0	0	
5106	0	0	0	0	N	0	0	
5107	0	0	0	0	N	0	0	
5108	0	0	0	0	N	0	0	
5109	0	0	0	0	N	0	0	
5110	0	0	0	0	N	0	1	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Administration

Generation : F0

Sex : Female

Week : 3

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	9	0
5102	6	0
5103	7	0
5104	7	0
5105	13	0
5106	9	0
5107	5	0
5108	4	0
5109	4	0
5110	6	0
n	10	10
Mean	7	0
S.D.	3	0

Animal No.	Open field observation		Period : Administration		Species : Rat			
	Generation : F0	Sex : Female	Week : 3	Dose : crotonic acid 500 mg/kg	Arousal	Convulsion	Abnormal behavior	Urination
6101					0	0	0	0
6102					0	0	0	0
6103					0	0	0	0
6104					0	0	0	0
6105					0	0	0	0
6106					0	0	0	0
6107					0	0	0	0
6108					0	0	0	0
6109					0	0	0	0
6110					0	0	0	0
n	10	10	10	10	10	10	10	10

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation		Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 3	Dose : crotonic acid 500 mg/kg	
Rearing		Defecation count		
Animal No.				
6101	6	0		
6102	8	0		
6103	7	0		
6104	6	0		
6105	6	0		
6106	5	0		
6107	4	0		
6108	6	0		
6109	6	0		
6110	3	0		
n	10	10		
Mean	6	0		
S.D.	1	0		

Open field observation		Period : Administration		Species : Rat				
Generation : F0	Sex : Female	Week : 4	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
5101	0	0	0	0	N	0	0	
5102	0	0	0	0	N	0	0	
5103	0	0	0	0	N	0	0	
5104	0	0	0	0	N	0	0	
5105	0	0	0	0	N	0	0	
5106	0	0	0	0	N	0	0	
5107	0	0	0	0	N	0	0	
5108	0	0	0	0	N	0	0	
5109	0	0	0	0	N	0	0	
5110	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Administration

Generation : F0

Sex : Female

Week : 4

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	8	0
5102	5	0
5103	7	0
5104	10	0
5105	7	0
5106	9	0
5107	5	0
5108	6	0
5109	5	0
5110	7	0
n	10	10
Mean	7	0
S.D.	2	0

Open field observation		Period : Administration		Species : Rat				
Generation : F0	Sex : Female	Week : 4	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
6101	0	0	0	0	N	0	0	
6102	0	0	0	0	N	0	0	
6103	0	0	0	0	N	0	0	
6104	0	0	0	0	N	0	1	
6105	0	0	0	0	N	0	0	
6106	0	0	0	0	N	0	1	
6107	0	0	0	0	N	0	0	
6108	0	0	0	0	N	0	0	
6109	0	0	0	0	N	0	0	
6110	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation		Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 4	Dose : crotonic acid 500 mg/kg	
Rearing		Defecation count		
Animal No.				
6101	8	0		
6102	7	0		
6103	4	0		
6104	6	0		
6105	4	0		
6106	4	0		
6107	5	0		
6108	6	0		
6109	2	0		
6110	6	0		
n	10	10		
Mean	5	0		
S.D.	2	0		

Open field observation		Period : Administration		Species : Rat				
Generation : F0	Sex : Female	Week : 5	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
5101	0	0	0	0	N	0	0	
5102	0	0	0	0	N	0	0	
5103	0	0	0	0	N	0	0	
5104	0	0	0	0	N	0	1	
5105	0	0	0	0	N	0	0	
5106	0	0	0	0	N	0	0	
5107	0	0	0	0	N	0	0	
5108	0	0	0	0	N	0	0	
5109	0	0	0	0	N	0	0	
5110	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Administration

Generation : F0

Sex : Female

Week : 5

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	8	0
5102	5	0
5103	8	0
5104	4	0
5105	8	0
5106	6	0
5107	9	0
5108	7	0
5109	4	0
5110	4	0
n	10	10
Mean	6	0
S.D.	2	0

Open field observation		Period : Administration		Species : Rat				
Generation : F0	Sex : Female	Week : 5	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
6101	0	0	0	0	N	0	0	
6102	0	0	0	0	N	0	0	
6103	0	0	0	0	N	0	0	
6104	0	0	0	0	N	0	0	
6105	0	0	0	0	N	0	0	
6106	0	0	0	0	N	0	0	
6107	0	0	0	0	N	0	0	
6108	0	0	0	0	N	0	0	
6109	0	0	0	0	N	0	0	
6110	0	0	0	0	N	0	1	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Administration

Generation : F0

Sex : Female

Week : 5

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6101	4	0
6102	4	0
6103	8	0
6104	8	0
6105	5	0
6106	4	0
6107	5	0
6108	5	0
6109	5	0
6110	5	0
n	10	10
Mean	5	0
S.D.	1	0

Open field observation		Period : Administration		Species : Rat				
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
5101	0	0	0	0	N	0	0	
5102	0	0	0	0	N	0	0	
5103	0	0	0	0	N	0	0	
5104	0	0	0	0	N	0	1	
5105	0	0	0	0	N	0	0	
5106	0	0	0	0	N	0	0	
5107	0	0	0	0	N	0	0	
5108	0	0	0	0	N	0	0	
5109	0	0	0	0	N	0	0	
5110	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

	Open field observation			Period : Administration	
	Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 0 mg/kg	Species : Rat
	Rearing	Defecation count			
Animal No.					
5101	7	0			
5102	4	0			
5103	5	0			
5104	8	0			
5105	7	0			
5106	7	0			
5107	8	0			
5108	5	0			
5109	6	0			
5110	5	0			
n	10	10			
Mean	6	0			
S.D.	1	0			

Open field observation		Period : Administration		Species : Rat				
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 500 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
6101	0	0	0	0	N	0	0	
6102	0	0	0	0	N	0	0	
6103	0	0	0	0	N	0	0	
6104	0	0	0	0	N	0	0	
6105	0	0	0	0	N	0	0	
6106	0	0	0	0	N	0	0	
6107	0	0	0	0	N	0	0	
6108	0	0	0	0	N	0	0	
6109	0	0	0	0	N	0	0	
6110	0	0	0	0	N	0	0	
n	10	10	10	10	10	10	10	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation			Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 500 mg/kg		
Rearing		Defecation count			
Animal No.					
6101	6	0			
6102	6	0			
6103	6	0			
6104	6	0			
6105	6	0			
6106	5	0			
6107	6	0			
6108	4	0			
6109	4	0			
6110	3	0			
n	10	10			
Mean	5	0			
S.D.	1	0			

Open field observation		Period : Recovery		Species : Rat				
Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1008	0	0	0	0	N	0	0	
1009	0	0	0	0	N	0	0	
1010	0	0	0	0	N	0	1	
1011	0	0	0	0	N	0	0	
1012	0	0	0	0	N	0	0	
n	5	5	5	5	5	5	5	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation		Period : Recovery			
Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 0 mg/kg	Species : Rat	
	Rearing	Defecation count			
Animal No.					
1008	3	0			
1009	4	0			
1010	6	0			
1011	3	0			
1012	3	0			
n	5	5			
Mean	4	0			
S.D.	1	0			

Animal No.	Open field observation		Period : Recovery		Species : Rat			
	Generation : F0	Sex : Male	Week : 1	Dose : crotonic acid 500 mg/kg	Arousal	Convulsion	Abnormal behavior	Urination
4008	0	0	0	0	0	0	N	0
4009	0	0	0	0	0	0	N	1
4010	0	0	0	0	0	0	N	0
4011	0	0	0	0	0	0	N	0
4012	0	0	0	0	0	0	N	0
n	5	5	5	5	5	5	5	5

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Recovery

Generation : F0

Sex : Male

Week : 1

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4008	2	0
4009	4	0
4010	4	0
4011	3	0
4012	4	0
n	5	5
Mean	3	0
S.D.	1	0

Open field observation		Period : Recovery		Species : Rat				
Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 0 mg/kg					
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Animal No.								
1008	0	0	0	0	N	0	0	
1009	0	0	0	0	N	0	0	
1010	0	0	0	0	N	0	0	
1011	0	0	0	0	N	0	0	
1012	0	0	0	0	N	0	1	
n	5	5	5	5	5	5	5	

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1008	5	0
1009	8	0
1010	5	0
1011	5	0
1012	5	0
n	5	5
Mean	6	0
S.D.	1	0

Animal No.	Open field observation		Period : Recovery		Species : Rat			
	Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 500 mg/kg	Arousal	Convulsion	Abnormal behavior	Urination
4008	0	0	0	0	0	N	0	0
4009	0	0	0	0	0	N	0	0
4010	0	0	0	0	0	N	0	0
4011	0	0	0	0	0	N	0	1
4012	0	0	0	0	0	N	0	0
n	5	5	5	5	5	5	5	5

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation	Generation : F0	Sex : Male	Week : 2	Period : Recovery	Dose : crotonic acid 500 mg/kg	Species : Rat
	Rearing	Defecation count				
Animal No.						
4008	4	0				
4009	4	0				
4010	5	0				
4011	6	0				
4012	8	0				
n	5	5				
Mean	5	0				
S.D.	2	0				

Animal No.	Open field observation		Period : Recovery		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 0 mg/kg	Arousal	Convulsion	Abnormal behavior	Urination
5106	0	0	0	0	0	0	N	0
5107	0	0	0	0	0	0	N	0
5108	0	0	0	0	0	0	N	0
5109	0	0	0	0	0	0	N	0
5110	0	0	0	0	0	0	N	0
n	5	5	5	5	5	5	5	5

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Recovery

Generation : F0

Sex : Female

Week : 1

Dose : crotonic acid 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5106	8	0
5107	5	0
5108	5	0
5109	5	0
5110	7	0
n	5	5
Mean	6	0
S.D.	1	0

Animal No.	Open field observation		Period : Recovery		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : crotonic acid 500 mg/kg				
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
6106	0	0	0	0	0	N	0	0
6107	0	0	0	0	0	N	0	0
6108	0	0	0	0	0	N	0	0
6109	0	0	0	0	0	N	0	0
6110	0	0	0	0	0	N	0	0
n	5	5	5	5	5	5	5	5

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation		Period : Recovery			
Generation : F0		Sex : Female		Week : 1	
				Dose : crotonic acid 500 mg/kg	
				Species : Rat	
	Rearing	Defecation			
		count			
Animal No.					
6106	5	0			
6107	1	0			
6108	7	0			
6109	3	0			
6110	4	0			
n	5	5			
Mean	4	0			
S.D.	2	0			

Animal No.	Open field observation		Period : Recovery		Species : Rat			
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg	Arousal	Convulsion	Abnormal behavior	Urination
5106	0	0	0	0	0	N	0	0
5107	0	0	0	0	0	N	0	0
5108	0	0	0	0	0	N	0	0
5109	0	0	0	0	0	N	0	0
5110	0	0	0	0	0	N	0	0
n	5	5	5	5	5	5	5	5

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation		Period : Recovery			
Generation : F0		Sex : Female		Week : 2	
				Dose : crotonic acid 0 mg/kg	
				Species : Rat	
	Rearing	Defecation count			
Animal No.					
5106	8	0			
5107	9	0			
5108	5	0			
5109	3	0			
5110	7	0			
n	5	5			
Mean	6	0			
S.D.	2	0			

Animal No.	Open field observation							
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
6106	0	0	0	0	0	N	0	0
6107	0	0	0	0	0	N	0	0
6108	0	0	0	0	0	N	0	0
6109	0	0	0	0	0	N	0	0
6110	0	0	0	0	0	N	0	1
n	5	5	5	5	5	5	5	5

Arousal) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Nomal, 1: Increased alertness, 2: Markedly alert

Convulsion) 0: None, 1: Minor, 2: Moderate, 3: Severe

Abnormal behavior) 0: None, 1: Minor, 2: Moderate, 3: Severe

Stereotypy) 0: None, 1: Minor, 2: Moderate, 3: Severe

Gait) U: No/minimal location, 0: Nomal, 1: Slight, 2: Moderate, 3: Markedly

Posture) N: Normal, F: Flattened, H: Hunched

Grooming) 0: None, 1: Occasional bouts (up to four), 2: Numerous (more than four)

Urination) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Open field observation

Period : Recovery

Generation : F0

Sex : Female

Week : 2

Dose : crotonic acid 500 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6106	7	0
6107	5	0
6108	8	0
6109	2	0
6110	4	0
n	5	5
Mean	5	0
S.D.	2	0

Animal No.	Manipulative test		Period : F0 mating		Species : Rat
	Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 0 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
1008	0	0	0	0	P
1009	0	0	0	0	P
1010	0	0	0	0	P
1011	0	0	0	0	P
1012	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Aerial right- ing reflex	Landing foot splay mm
1008	0	45
1009	0	93
1010	0	94
1011	0	88
1012	0	115
n	5	5
Mean	0	87
S.D.	0	26

Aerial righting reflex) Total score

Animal No.	Manipulative test		Period : F0 mating		Species : Rat
	Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 50 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
2008	0	0	0	0	P
2009	0	0	0	0	P
2010	0	0	0	0	P
2011	0	0	0	0	P
2012	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 50 mg/kg	
Animal No.	Aerial right- ing reflex	Landing foot splay mm		
2008	0	91		
2009	0	80		
2010	0	100		
2011	0	77		
2012	0	75		
n	5	5		
Mean	0	85		
S.D.	0	11		
Aerial righting reflex) Total score				

Manipulative test		Period : F0 mating		Species : Rat	
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 150 mg/kg		
Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex	
Animal No.					
3008	0	0	0	P	
3009	0	0	0	P	
3010	0	0	0	P	
3011	0	0	0	P	
3012	0	0	0	P	
n	5	5	5	5	

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test		Period : F0 mating		Species : Rat
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 150 mg/kg	
Animal No.	Aerial right- ing reflex	Landing foot splay mm		
3008	0	65		
3009	0	63		
3010	0	76		
3011	0	77		
3012	0	78		
n	5	5		
Mean	0	72		
S.D.	0	7		
Aerial righting reflex) Total score				

Animal No.	Manipulative test		Period : F0 mating		Species : Rat
	Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 500 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
4008	0	0	0	0	P
4009	0	0	0	0	P
4010	0	0	0	0	P
4011	0	0	0	0	P
4012	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test

Generation : F0

Sex : Male

Week : 6

Period : F0 mating

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Aerial right- ing reflex	Landing foot splay mm
4008	0	106
4009	0	35
4010	0	110
4011	0	104
4012	0	50
n	5	5
Mean	0	81
S.D.	0	36

Aerial righting reflex) Total score

Manipulative test		Period : F0 lactation		Species : Rat	
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 0 mg/kg		
Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex	
Animal No.					
1101	0	0	0	P	
1104	0	0	0	P	
1105	0	0	0	P	
1107	0	0	0	P	
1108	0	0	0	P	
n	5	5	5	5	

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test

Generation : F0

Sex : Female

Day : 4

Period : F0 lactation

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Aerial right- ing reflex	Landing foot splay mm
1101	0	50
1104	0	60
1105	0	60
1107	0	59
1108	0	75
n	5	5
Mean	0	61
S.D.	0	9

Aerial righting reflex) Total score

Animal No.	Manipulative test		Period : F0 lactation		Species : Rat
	Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 50 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
2101	0	0	0	0	P
2102	0	0	0	0	P
2103	0	0	0	0	P
2107	0	0	0	0	P
2109	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Dose : crotonic acid 50 mg/kg

Species : Rat

Animal No.	Aerial right- ing reflex	Landing foot splay mm
2101	0	41
2102	0	85
2103	0	47
2107	0	45
2109	0	44
n	5	5
Mean	0	52
S.D.	0	18

Aerial righting reflex) Total score

Animal No.	Manipulative test		Period : F0 lactation		Species : Rat
	Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 150 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
3101	0	0	0	0	P
3103	0	0	0	0	P
3105	0	0	0	0	P
3107	0	0	0	0	P
3112	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test		Period : F0 lactation		Species : Rat
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 150 mg/kg	
Animal No.	Aerial right- ing reflex	Landing foot splay mm		
3101	0	71		
3103	0	92		
3105	0	69		
3107	0	67		
3112	0	61		
n	5	5		
Mean	0	72		
S.D.	0	12		
Aerial righting reflex) Total score				

Animal No.	Manipulative test		Period : F0 lactation		Species : Rat
	Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 500 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
4104	0	0	0	0	P
4105	0	0	0	0	P
4106	0	0	0	0	P
4109	0	0	0	0	P
4110	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test			Period : F0 lactation	Species : Rat
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 500 mg/kg	
Animal No.	Aerial right- ing reflex	Landing foot splay mm		
4104	0	49		
4105	0	48		
4106	0	51		
4109	0	57		
4110	0	57		
n	5	5		
Mean	0	52		
S.D.	0	4		
Aerial righting reflex) Total score				

Animal No.	Manipulative test		Period : Administration		Species : Rat
	Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 0 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
5106	0	0	0	0	P
5107	0	0	0	0	P
5108	0	0	0	0	P
5109	0	0	0	0	P
5110	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test			Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 0 mg/kg		
Animal No.	Aerial right- ing reflex	Landing foot splay mm			
5106	0	106			
5107	0	60			
5108	0	87			
5109	0	72			
5110	0	36			
n	5	5			
Mean	0	72			
S.D.	0	27			
Aerial righting reflex) Total score					

Animal No.	Manipulative test		Period : Administration		Species : Rat
	Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 500 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
6106	0	0	0	0	P
6107	0	0	0	0	P
6108	0	0	0	0	P
6109	0	0	0	0	P
6110	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test		Period : Administration		Species : Rat
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 500 mg/kg	
Animal No.	Aerial right- ing reflex	Landing foot splay mm		
6106	0	48		
6107	0	35		
6108	0	75		
6109	0	97		
6110	0	101		
n	5	5		
Mean	0	71		
S.D.	0	29		
Aerial righting reflex) Total score				

Animal No.	Manipulative test		Period : Recovery		Species : Rat
	Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 0 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
1008	0	0	0	0	P
1009	0	0	0	0	P
1010	0	0	0	0	P
1011	0	0	0	0	P
1012	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Aerial right- ing reflex	Landing foot splay mm
1008	0	56
1009	0	81
1010	0	77
1011	0	85
1012	0	95
n	5	5
Mean	0	79
S.D.	0	14

Aerial righting reflex) Total score

Animal No.	Manipulative test		Period : Recovery		Species : Rat
	Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 500 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
4008	0	0	0	0	P
4009	0	0	0	0	P
4010	0	0	0	0	P
4011	0	0	0	0	P
4012	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test			Period : Recovery	Species : Rat
Generation : F0	Sex : Male	Week : 2	Dose : crotonic acid 500 mg/kg	
Animal No.	Aerial right- ing reflex	Landing foot splay mm		
4008	0	79		
4009	0	41		
4010	0	74		
4011	0	102		
4012	0	81		
n	5	5		
Mean	0	75		
S.D.	0	22		
Aerial righting reflex) Total score				

Animal No.	Manipulative test		Period : Recovery		Species : Rat
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
5106	0	0	0	0	P
5107	0	0	0	0	P
5108	0	0	0	0	P
5109	0	0	0	0	P
5110	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupil size) N: Normal, M: Miosis, My: Mydriasis

Manipulative test		Period : Recovery		Species : Rat
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 0 mg/kg	
Animal No.	Aerial right- ing reflex	Landing foot splay mm		
5106	0	92		
5107	0	42		
5108	0	87		
5109	0	66		
5110	0	66		
n	5	5		
Mean	0	71		
S.D.	0	20		
Aerial righting reflex) Total score				

Animal No.	Manipulative test		Period : Recovery		Species : Rat
	Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg	
	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
6106	0	0	0	0	P
6107	0	0	0	0	P
6108	0	0	0	0	P
6109	0	0	0	0	P
6110	0	0	0	0	P
n	5	5	5	5	5

Auditory response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Approach response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Touch response) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction

Tail pinch response) -2: None, -1: Weak, 0: Normal, 1: Exaggerate

Pupillary reflex) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Manipulative test			Period : Recovery	Species : Rat
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg	
Animal No.	Aerial right- ing reflex	Landing foot splay mm		
6106	0	56		
6107	0	46		
6108	0	49		
6109	0	61		
6110	0	63		
n	5	5		
Mean	0	55		
S.D.	0	7		
Aerial righting reflex) Total score				

Grip strength			Period : F0 mating	Species : Rat
Generation : F0			Dose : crotonic acid 0 mg/kg	
Sex : Male			Week : 6	
Grip strength				
of fore limb				
of hind limb				
Animal No.	g	g		
1008	1745	1147		
1009	1520	1107		
1010	1979	1391		
1011	1877	1120		
1012	2103	1160		
n	5	5		
Mean	1845	1185		
S.D.	224	117		

Grip strength		Sex : Male		Week : 6	Period : F0 mating	Species : Rat
Generation : F0					Dose : crotonic acid 50 mg/kg	
	Grip strength of fore limb	Grip strength of hind limb				
Animal No.	g	g				
2008	1857	1364				
2009	1799	1038				
2010	1920	1161				
2011	1491	920				
2012	1902	1302				
n	5	5				
Mean	1794	1157				
S.D.	176	183				

Grip strength		Sex : Male		Week : 6	Period : F0 mating	Species : Rat
Generation : F0		Grip strength		Dose : crotonic acid 150 mg/kg		
	Grip strength of fore limb	Grip strength of hind limb				
Animal No.	g	g				
3008	1943	892				
3009	1859	1059				
3010	1900	1202				
3011	1814	967				
3012	1598	962				
n	5	5				
Mean	1823	1016				
S.D.	134	120				

Grip strength			Period : F0 mating	Species : Rat
Generation : F0			Dose : crotonic acid 500 mg/kg	
Sex : Male			Week : 6	
Animal No.	Grip strength of fore limb	Grip strength of hind limb		
	g	g		
4008	1865	1100		
4009	1468	672		
4010	1911	1211		
4011	1977	888		
4012	2101	1143		
n	5	5		
Mean	1864	1003		
S.D.	239	221		

Grip strength

Period : F0 lactation

Generation : F0

Sex : Female

Day : 4

Dose : crotonic acid 0 mg/kg

Species : Rat

	Grip strength of fore limb	Grip strength of hind limb
Animal No.	g	g
1101	1135	1083
1104	1449	823
1105	1148	812
1107	1562	947
1108	1703	1049
n	5	5
Mean	1399	943
S.D.	252	125

Grip strength		Sex : Female		Day : 4	Period : F0 lactation	Species : Rat
Generation : F0					Dose : crotonic acid 50 mg/kg	
	Grip strength of fore limb	Grip strength of hind limb				
Animal No.	g	g				
2101	908	570				
2102	1275	742				
2103	1220	733				
2107	1475	728				
2109	1240	677				
n	5	5				
Mean	1224	690				
S.D.	204	72				

Grip strength			Period : F0 lactation	Species : Rat
Generation : F0			Dose : crotonic acid 150 mg/kg	
Animal No.	Grip strength of fore limb	Grip strength of hind limb		
	g	g		
3101	1214	945		
3103	1417	1000		
3105	1279	792		
3107	1285	891		
3112	1190	848		
n	5	5		
Mean	1277	895		
S.D.	88	81		

Grip strength		Sex : Female		Day : 4	Period : F0 lactation	Species : Rat
Generation : F0					Dose : crotonic acid 500 mg/kg	
	Grip strength of fore limb	Grip strength of hind limb				
Animal No.	g	g				
4104	1292	916				
4105	1280	939				
4106	1246	672				
4109	1440	780				
4110	1363	877				
n	5	5				
Mean	1324	837				
S.D.	77	110				

Grip strength			Period : Administration	
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 0 mg/kg	Species : Rat
	Grip strength of fore limb	Grip strength of hind limb		
Animal No.	g	g		
5106	1709	757		
5107	1766	1100		
5108	1588	1110		
5109	1540	798		
5110	1376	669		
n	5	5		
Mean	1596	887		
S.D.	153	205		

Grip strength			Period : Administration	
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 500 mg/kg	Species : Rat
	Grip strength of fore limb	Grip strength of hind limb		
Animal No.	g	g		
6106	1376	811		
6107	1391	957		
6108	1490	745		
6109	1497	876		
6110	1602	956		
n	5	5		
Mean	1471	869		
S.D.	92	92		

Grip strength			Period : Recovery	Species : Rat
Generation : F0			Dose : crotonic acid 0 mg/kg	
Sex : Male			Week : 2	
Animal No.	Grip strength of fore limb	Grip strength of hind limb		
	g	g		
1008	1679	873		
1009	1816	845		
1010	2091	1322		
1011	1773	1343		
1012	1906	1105		
n	5	5		
Mean	1853	1098		
S.D.	156	237		

Grip strength		Sex : Male		Week : 2		Period : Recovery		Dose : crotonic acid 500 mg/kg		Species : Rat	
Generation : F0		Grip strength of fore limb		Grip strength of hind limb							
Animal No.		g		g							
4008		1649		492							
4009		1729		692							
4010		1706		1037							
4011		1981		987							
4012		1912		999							
n		5		5							
Mean		1795		841							
S.D.		143		239							

Grip strength		Sex : Female		Week : 2	Period : Recovery	Species : Rat
Generation : F0					Dose : crotonic acid 0 mg/kg	
	Grip strength of fore limb	Grip strength of hind limb				
Animal No.	g	g				
5106	1392	731				
5107	1526	854				
5108	1727	918				
5109	1439	771				
5110	1343	517				
n	5	5				
Mean	1485	758				
S.D.	151	153				

Grip strength			Period : Recovery		Species : Rat
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg		
	Grip strength of fore limb	Grip strength of hind limb			
Animal No.	g	g			
6106	1334	877			
6107	1294	785			
6108	1297	715			
6109	1354	767			
6110	1430	809			
n	5	5			
Mean	1342	791			
S.D.	55	59			

Motor activity		Sex : Male		Week : 6		Period : F0 mating		Species : Rat	
Generation : F0				Dose : crotonic acid 0 mg/kg					
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')		
Animal No.	Count	Count	Count	Count	Count	Count	Count		
1008	427	287	80	1	55	12	862		
1009	383	249	65	155	114	34	1000		
1010	450	218	170	150	30	6	1024		
1011	455	76	178	2	2	84	797		
1012	411	163	129	133	39	12	887		
n	5	5	5	5	5	5	5		
Mean	425	199	124	88	48	30	914		
S.D.	30	82	51	80	42	32	96		

Motor activity			Period : F0 mating				
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 50 mg/kg				Species : Rat
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Animal No.	Count	Count	Count	Count	Count	Count	Count
2008	467	308	141	79	2	58	1055
2009	521	254	170	258	141	95	1439
2010	382	97	8	147	1	19	654
2011	435	266	290	273	153	95	1512
2012	388	269	86	191	43	147	1124
n	5	5	5	5	5	5	5
Mean	439	239	139	190	68	83	1157
S.D.	58	82	105	80	74	48	343

Motor activity			Period : F0 mating				Species : Rat
Generation : F0	Sex : Male	Week : 6	Dose : crotonic acid 150 mg/kg				
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Animal No.	Count	Count	Count	Count	Count	Count	Count
3008	438	258	210	157	3	161	1227
3009	457	402	283	304	236	145	1827
3010	518	421	395	316	238	201	2089
3011	400	179	55	278	24	13	949
3012	501	367	237	267	35	14	1421
n	5	5	5	5	5	5	5
Mean	463	325	236	264	107	107	1503
S.D.	48	103	123	63	119	88	458

Motor activity		Sex : Male		Week : 6		Period : F0 mating		Species : Rat	
Generation : F0				Dose : crotonic acid 500 mg/kg					
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')		
Animal No.	Count	Count	Count	Count	Count	Count	Count		
4008	470	279	192	229	87	53	1310		
4009	422	72	8	267	33	83	885		
4010	385	206	3	18	12	211	835		
4011	527	401	285	188	82	0	1483		
4012	409	354	193	268	9	70	1303		
n	5	5	5	5	5	5	5		
Mean	443	262	136	194	45	83	1163		
S.D.	56	130	125	104	38	78	287		

Motor activity		Sex : Female		Day : 4		Period : F0 lactation		Species : Rat	
Generation : F0				Dose : crotonic acid 0 mg/kg				Total(0'-60')	
0'-10'		10'-20'		20'-30'		30'-40'		40'-50'	
50'-60'									
Animal No.	Count	Count	Count	Count	Count	Count	Count	Count	Count
1101	434	36	89	33	81	310	983		
1104	365	132	259	237	308	424	1725		
1105	232	31	2	202	55	6	528		
1107	371	191	140	161	6	55	924		
1108	352	105	36	44	8	168	713		
n	5	5	5	5	5	5	5		
Mean	351	99	105	135	92	193	975		
S.D.	74	67	101	93	125	174	457		

Animal No.	Motor activity Generation : F0	Sex : Female	Day : 4	Period : F0 lactation Dose : crotonic acid 50 mg/kg			Species : Rat
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
	Count	Count	Count	Count	Count	Count	Count
2101	458	269	146	28	7	8	916
2102	261	44	124	4	17	17	467
2103	358	402	81	35	14	11	901
2107	403	259	220	212	212	154	1460
2109	185	13	26	2	101	207	534
n	5	5	5	5	5	5	5
Mean	333	197	119	56	70	79	856
S.D.	110	165	73	88	88	94	395

Motor activity			Period : F0 lactation				
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 150 mg/kg				Species : Rat
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Animal No.	Count	Count	Count	Count	Count	Count	Count
3101	334	131	100	95	24	34	718
3103	322	209	198	115	191	230	1265
3105	453	375	197	198	288	241	1752
3107	373	323	292	178	239	207	1612
3112	377	129	13	47	10	21	597
n	5	5	5	5	5	5	5
Mean	372	233	160	127	150	147	1189
S.D.	51	112	107	62	127	110	518

Motor activity			Period : F0 lactation				
Generation : F0	Sex : Female	Day : 4	Dose : crotonic acid 500 mg/kg				Species : Rat
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Animal No.	Count	Count	Count	Count	Count	Count	Count
4104	259	70	4	20	22	12	387
4105	231	23	170	281	5	8	718
4106	235	160	133	8	29	205	770
4109	196	43	16	190	4	8	457
4110	207	56	53	8	112	0	436
n	5	5	5	5	5	5	5
Mean	226	70	75	101	34	47	554
S.D.	25	53	73	127	45	89	177

Motor activity			Period : Administration				
Generation : F0	Sex : Female	Week : 6	Dose : crotonic acid 0 mg/kg				Species : Rat
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Animal No.	Count	Count	Count	Count	Count	Count	Count
5106	516	445	263	225	337	26	1812
5107	455	467	376	336	246	242	2122
5108	356	345	341	304	218	223	1787
5109	468	360	128	294	5	0	1255
5110	427	352	210	74	43	28	1134
n	5	5	5	5	5	5	5
Mean	444	394	264	247	170	104	1622
S.D.	59	58	100	105	141	118	414

Motor activity		Period : Administration		Species : Rat			
Generation : F0		Dose : crotonic acid 500 mg/kg		Total(0'-60')			
Sex : Female		Week : 6					
0'-10'		10'-20'		20'-30'		30'-40'	
40'-50'		50'-60'					
Animal No.	Count	Count	Count	Count	Count	Count	Count
6106	504	395	404	231	229	194	1957
6107	411	183	84	2	147	294	1121
6108	457	344	294	388	355	294	2132
6109	402	385	313	291	255	301	1947
6110	430	314	59	28	98	121	1050
n	5	5	5	5	5	5	5
Mean	441	324	231	188	217	241	1641
S.D.	41	85	152	168	100	80	513

Motor activity		Sex : Male		Week : 2		Period : Recovery		Species : Rat	
Generation : F0				Dose : crotonic acid 0 mg/kg					
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')		
Animal No.	Count	Count	Count	Count	Count	Count	Count		
1008	431	155	216	97	237	66	1202		
1009	454	345	368	242	210	298	1917		
1010	364	238	312	200	214	269	1597		
1011	438	3	143	0	50	1	635		
1012	310	164	82	86	231	71	944		
n	5	5	5	5	5	5	5		
Mean	399	181	224	125	188	141	1259		
S.D.	61	125	118	96	78	133	510		

Animal No.	Motor activity Generation : F0	Sex : Male	Week : 2	Period : Recovery Dose : crotonic acid 500 mg/kg			Species : Rat
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
	Count	Count	Count	Count	Count	Count	Count
4008	490	417	228	339	610	165	2249
4009	411	148	288	262	312	97	1518
4010	304	283	173	168	281	55	1264
4011	447	365	304	197	235	117	1665
4012	445	346	284	300	266	378	2019
n	5	5	5	5	5	5	5
Mean	419	312	255	253	341	162	1743
S.D.	70	103	54	71	153	127	393

Animal No.	Motor activity	Sex : Female	Week : 2	Period : Recovery			Species : Rat
	Generation : F0			Dose : crotonic acid 0 mg/kg			
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
	Count	Count	Count	Count	Count	Count	Count
5106	411	412	348	289	94	14	1568
5107	484	450	353	337	341	319	2284
5108	362	298	278	154	102	9	1203
5109	425	94	140	141	17	69	886
5110	382	290	198	162	20	104	1156
n	5	5	5	5	5	5	5
Mean	413	309	263	217	115	103	1419
S.D.	47	139	93	90	133	127	541

Motor activity			Period : Recovery				
Generation : F0	Sex : Female	Week : 2	Dose : crotonic acid 500 mg/kg				Species : Rat
	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Animal No.	Count	Count	Count	Count	Count	Count	Count
6106	439	333	192	224	1	4	1193
6107	478	218	124	2	21	13	856
6108	449	373	289	246	274	214	1845
6109	372	352	407	207	189	249	1776
6110	306	139	1	2	0	200	648
n	5	5	5	5	5	5	5
Mean	409	283	203	136	97	136	1264
S.D.	69	100	155	123	127	118	536

Animal No.	Body weight Sex : Male /Day							Body weight gain	Unit : g	Species : Rat
	1	8	15	22	29	36	42			
1001	444	469	499	523	546	574	574	130		
1002	416	438	461	472	491	515	526	110		
1003	413	441	466	475	493	515	518	105		
1004	413	450	480	504	530	550	560	147		
1005	406	444	484	507	545	565	576	170		
1006	414	425	438	443	460	477	484	70		
1007	410	442	469	494	512	530	547	137		
1008	394	424	449	459	472	506	510	116		
1009	385	402	420	426	440	470	470	85		
1010	402	417	438	453	468	487	495	93		
1011	428	457	481	485	509	523	528	100		
1012	395	417	426	445	455	474	477	82		
n	12	12	12	12	12	12	12	12		
Mean	410	436	459	474	493	516	522	112		
S.D.	16	19	25	30	36	35	37	29		

Animal No.	Body weight Sex : Male /Day							Body weight gain	Unit : g	Species : Rat
	1	8	15	22	29	36	42			
2001	400	435	455	473	490	511	522	122		
2002	408	433	450	466	476	495	501	93		
2003	403	431	454	482	505	527	532	129		
2004	428	463	495	505	538	559	578	150		
2005	408	440	466	488	511	511	522	114		
2006	424	448	470	478	501	508	523	99		
2007	406	436	460	468	483	501	516	110		
2008	418	438	449	456	476	498	516	98		
2009	401	433	460	474	492	520	529	128		
2010	413	441	466	483	511	541	532	119		
2011	390	412	426	445	460	481	493	103		
2012	413	446	461	474	499	508	525	112		
n	12	12	12	12	12	12	12	12		
Mean	409	438	459	474	495	513	524	115		
S.D.	11	12	16	15	21	21	21	16		

Animal No.	Body weight Sex : Male /Day							Body weight gain	Unit : g	Species : Rat
	1	8	15	22	29	36	42			
3001	393	427	453	463	471	492	505	112		
3002	425	449	466	477	488	508	515	90		
3003	413	429	448	453	471	487	503	90		
3004	403	424	440	432	448	467	487	84		
3005	412	433	461	467	476	492	486	74		
3006	391	425	443	460	493	511	509	118		
3007	425	444	465	486	483	523	522	97		
3008	427	451	474	491	519	535	542	115		
3009	419	451	473	482	500	537	554	135		
3010	414	448	460	466	478	504	514	100		
3011	391	411	431	427	439	464	470	79		
3012	413	440	454	472	484	521	537	124		
n	12	12	12	12	12	12	12	12		
Mean	411	436	456	465	479	503	512	102		
S.D.	13	13	13	20	21	24	25	19		

Animal No.	Body weight Sex : Male /Day							Body weight gain	Unit : g	Species : Rat
	1	8	15	22	29	36	42			
4001	407	426	437	433	450	478	487	80		
4002	416	442	465	473	485	502	515	99		
4003	429	466	495	500	522	546	553	124		
4004	383	391	406	419	437	456	464	81		
4005	411	424	439	455	472	467	474	63		
4006	402	419	429	438	452	473	476	74		
4007	393	412	423	424	448	463	471	78		
4008	398	422	441	456	468	484	482	84		
4009	424	447	464	481	499	515	525	101		
4010	427	453	468	479	499	518	513	86		
4011	413	432	452	475	490	503	502	89		
4012	409	408	417	433	445	453	455	46		
n	12	12	12	12	12	12	12	12		
Mean	409	429	445	456	472	488	493	84		
S.D.	14	21	25	26	27	29	29	20		

Body weight				Period : F0 before mating Day 1-15	Unit : g	Species : Rat	
Sex : Female				Dose : crotonic acid 0 mg/kg			
Animal No.	/Day						Body weight gain
	1	8	15				
1101	252	279	283	31			
1102	245	255	257	12			
1103	246	255	258	12			
1104	250	252	265	15			
1105	250	272	275	25			
1106	259	265	271	12			
1107	255	265	282	27			
1108	250	271	276	26			
1109	263	269	276	13			
1110	256	265	268	12			
1111	241	255	256	15			
1112	267	278	285	18			
n	12	12	12	12			
Mean	253	265	271	18			
S.D.	8	9	10	7			

Body weight
Sex : FemalePeriod : F0 before mating Day 1-15
Dose : crotonic acid 50 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	15	
2101	246	254	256	10
2102	258	262	271	13
2103	259	273	287	28
2104	266	266	282	16
2105	254	261	261	7
2106	259	266	259	0
2107	258	276	284	26
2108	256	270	270	14
2109	250	252	267	17
2110	247	266	265	18
2111	239	253	264	25
2112	271	312	304	33
n	12	12	12	12
Mean	255	268	273	17
S.D.	9	16	14	9

Body weight				Period : F0 before mating Day 1-15	Unit : g	Species : Rat
Sex : Female				Dose : crotonic acid 150 mg/kg		
Animal No.	/Day	Body weight				
	1	8	15	gain		
3101	247	259	259	12		
3102	243	247	260	17		
3103	254	268	273	19		
3104	269	284	293	24		
3105	249	263	263	14		
3106	260	270	273	13		
3107	252	256	263	11		
3108	263	274	279	16		
3109	248	258	258	10		
3110	259	257	261	2		
3111	232	289	283	51		
3112	264	279	289	25		
n	12	12	12	12		
Mean	253	267	271	18		
S.D.	10	13	12	12		

Body weight				Period : F0 before mating Day 1-15	Unit : g	Species : Rat
Sex : Female				Dose : crotonic acid 500 mg/kg		
Animal No.	/Day	Body weight				
	1	8	15	gain		
4101	247	268	275	28		
4102	241	258	267	26		
4103	248	261	264	16		
4104	255	278	290	35		
4105	262	254	268	6		
4106	246	250	260	14		
4107	258	264	276	18		
4108	247	255	192	-55		
4109	270	270	284	14		
4110	252	257	265	13		
4111	234	255	257	23		
4112	240	250	258	18		
n	12	12	12	12		
Mean	250	260	263	13		
S.D.	10	9	25	23		

	Body weight				Period : F0 gestation Day 0-25	
	Sex : Female				Dose : crotonic acid 0 mg/kg	Unit : g
	/Day				Species : Rat	
Animal No.	0	7	14	20	Body weight gain	
1101	287	331	374	459	172	
1102	279	311	349	443	164	
1103	262	307	336	404	142	
1104	269	313	343	429	160	
1105	284	317	358	449	165	
1106	271	321	357	448	177	
1107	284	317	351	427	143	
1108	277	315	345	441	164	
1109	281	317	354	439	158	
1110	276	306	335	430	154	
1111	276	308	347	450	174	
1112	294	309	356	436	142	
n	12	12	12	12	12	
Mean	278	314	350	438	160	
S.D.	9	7	11	14	12	

Crotonic acid by oral administration in rats					Period : F0 gestation Day 0-25	Unit : g	Species : Rat
Body weight					Dose : crotonic acid 50 mg/kg		
Animal No.	/Day					Body weight gain	
	0	7	14	20			
2101	257	296	332	389	132		
2102	279	308	339	427	148		
2103	288	333	370	451	163		
2104	277	316	347	441	164		
2106	275	316	346	433	158		
2107	291	319	355	442	151		
2109	266	296	325	407	141		
2110	282	323	360	468	186		
2111	269	296	315	396	127		
2112	299	329	365	452	153		
n	10	10	10	10	10		
Mean	278	313	345	431	152		
S.D.	12	14	18	26	17		

Animal No.2105,2108: Not copulated

Animal No.	Body weight				Body weight gain	Unit : g	Species : Rat
	/Day						
	0	7	14	20			
3101	267	300	332	408	141		
3102	268	314	350	442	174		
3103	282	312	349	440	158		
3104	306	342	370	436	130		
3105	274	303	333	403	129		
3106	280	311	336	421	141		
3107	271	297	331	429	158		
3108	286	324	365	452	166		
3110	290	333	368	474	184		
3111	281	321	353	450	169		
3112	296	334	379	474	178		
n	11	11	11	11	11		
Mean	282	317	351	439	157		
S.D.	12	15	17	23	19		

Animal No.3109: Not copulated

	Body weight				Period : F0 gestation Day 0-25	
	Sex : Female				Dose : crotonic acid 500 mg/kg	Unit : g
					Species : Rat	
	Body weight					
Animal No.	0	7	14	20	gain	
4101	277	321	362	447	170	
4102	269	304	338	410	141	
4103	272	293	322	420	148	
4104	288	324	355	439	151	
4105	265	298	319	409	144	
4106	262	295	316	388	126	
4107	273	297	331	410	137	
4108	224	242	277	385	161	
4109	284	318	348	432	148	
4110	271	303	336	421	150	
4111	258	288	321	396	138	
4112	255	277	319	402	147	
n	12	12	12	12	12	
Mean	267	297	329	413	147	
S.D.	17	22	22	19	11	

Body weight
Sex : FemalePeriod : F0 lactation Day 0-5
Dose : crotonic acid 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		Body weight gain
	0	4	
1101	343	353	10
1102	328	343	15
1103	312	342	30
1104	312	338	26
1105	331	345	14
1106	348	353	5
1107	365	348	-17
1108	332	351	19
1109	339	348	9
1110	325	342	17
1111	350	348	-2
1112	338	358	20
n	12	12	12
Mean	335	347	12
S.D.	15	6	13

Body weight
Sex : FemalePeriod : F0 lactation Day 0-5
Dose : crotonic acid 50 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		Body weight gain
	0	4	
2101	337	318	-19
2102	354	341	-13
2103	346	369	23
2104	326	349	23
2106	347	341	-6
2107	335	358	23
2109	308	327	19
2110	342	343	1
2111	295	327	32
2112	338	355	17
n	10	10	10
Mean	333	343	10
S.D.	18	16	18

Animal No.2105,2108: Not copulated

Body weight
Sex : FemalePeriod : F0 lactation Day 0-5
Dose : crotonic acid 150 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		Body weight gain
	0	4	
3101	337	328	-9
3102	339	363	24
3103	318	346	28
3104	359	383	24
3105	332	342	10
3106	323	334	11
3107	339	333	-6
3108	329	371	42
3110	358	348	-10
3111	321	338	17
3112	381	351	-30
n	11	11	11
Mean	340	349	9
S.D.	19	17	21

Animal No.3109: Not copulated

Body weight
Sex : FemalePeriod : F0 lactation Day 0-5
Dose : crotonic acid 500 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		Body weight gain
	0	4	
4101	338	351	13
4102	332	343	11
4103	294	320	26
4104	351	350	-1
4105	306	326	20
4106	306	307	1
4107	307	331	24
4108	273	297	24
4109	324	329	5
4110	322	345	23
4111	324	335	11
4112	298	327	29
n	12	12	12
Mean	315	330	16
S.D.	21	17	10

	Body weight			Period : Administration					
	Sex : Female			Dose : crotonic acid 0 mg/kg				Unit : g	Species : Rat
	/Day							Body weight	
Animal No.	1	8	15	22	29	36	42	gain	
5101	252	271	279	283	296	307	298	46	
5102	258	272	271	296	280	285	309	51	
5103	247	261	275	274	280	294	294	47	
5104	267	278	281	297	307	310	320	53	
5105	261	278	294	292	307	318	314	53	
5106	246	263	280	284	295	307	304	58	
5107	241	258	266	274	283	292	292	51	
5108	252	270	280	282	284	295	299	47	
5109	236	254	252	268	261	268	270	34	
5110	260	269	273	283	294	298	301	41	
n	10	10	10	10	10	10	10	10	
Mean	252	267	275	283	289	297	300	48	
S.D.	10	8	11	10	14	14	14	7	

Crotonic acid by oral administration in rats				Period : Administration				Unit : g	Species : Rat
Body weight Sex : Female				Dose : crotonic acid 500 mg/kg					
Animal No.	/Day							Body weight	
	1	8	15	22	29	36	42	gain	
6101	271	276	283	296	300	308	308	37	
6102	269	272	278	294	294	295	299	30	
6103	258	253	272	287	291	287	303	45	
6104	260	252	263	275	277	250	280	20	
6105	248	252	262	269	282	280	283	35	
6106	246	262	265	269	273	285	284	38	
6107	246	265	266	273	274	289	293	47	
6108	257	268	282	292	292	312	339	82	
6109	251	259	262	269	273	284	280	29	
6110	247	251	282	276	267	284	290	43	
n	10	10	10	10	10	10	10	10	
Mean	255	261	272	280	282	287	296	41	
S.D.	9	9	9	11	11	17	18	17	

Body weight

Period : Recovery Day 1-15

Sex : Male

Dose : crotonic acid 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	14	
1008	513	531	540	27
1009	473	480	483	10
1010	504	506	512	8
1011	530	549	541	11
1012	484	497	504	20
n	5	5	5	5
Mean	501	513	516	15
S.D.	23	27	25	8

Body weight

Period : Recovery Day 1-15

Sex : Male

Dose : crotonic acid 500 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	14	
4008	485	396	365	-120
4009	524	546	552	28
4010	513	542	550	37
4011	501	525	529	28
4012	462	480	500	38
n	5	5	5	5
Mean	497	498	499	2
S.D.	24	63	78	68

Body weight
Sex : FemalePeriod : Recovery Day 1-15
Dose : crotonic acid 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	14	
5106	318	321	337	19
5107	298	305	306	8
5108	302	302	302	0
5109	277	275	275	-2
5110	298	310	310	12
n	5	5	5	5
Mean	299	303	306	7
S.D.	15	17	22	9

Body weight					Period : Recovery Day 1-15	Unit : g	Species : Rat
Sex : Female					Dose : crotonic acid 500 mg/kg		
Animal No.	/Day	Body weight					
	1	8	14	gain			
6106	290	288	296	6			
6107	298	300	304	6			
6108	343	330	324	-19			
6109	285	285	288	3			
6110	284	290	293	9			
n	5	5	5	5			
Mean	300	299	301	1			
S.D.	25	18	14	11			

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : crotonic acid 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day						Total food consumption
	2	8	15	30	36	42	
1001	21	22	23	21	25	24	136
1002	23	22	23	17	20	20	125
1003	23	22	24	18	22	17	126
1004	24	27	26	21	20	18	136
1005	24	26	27	19	25	25	146
1006	22	20	21	17	20	20	120
1007	23	25	23	20	23	25	139
1008	21	22	22	16	22	20	123
1009	23	22	17	17	22	20	121
1010	20	19	23	20	22	21	125
1011	24	26	27	24	26	22	149
1012	20	21	19	17	20	18	115
n	12	12	12	12	12	12	12
Mean	22	23	23	19	22	21	130
S.D.	1	3	3	2	2	3	11

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : crotonic acid 50 mg/kg

Unit : g

Species : Rat

Animal No.	/Day						Total food consumption
	2	8	15	30	36	42	
2001	25	27	23	22	19	23	139
2002	26	22	20	18	21	19	126
2003	21	22	22	17	21	19	122
2004	24	23	26	18	25	25	141
2005	24	24	23	20	18	21	130
2006	24	27	22	16	20	25	134
2007	21	22	23	16	20	20	122
2008	25	22	20	24	26	23	140
2009	23	25	25	20	23	24	140
2010	26	26	25	19	24	19	139
2011	22	24	23	20	26	22	137
2012	22	22	22	18	18	23	125
n	12	12	12	12	12	12	12
Mean	24	24	23	19	22	22	133
S.D.	2	2	2	2	3	2	7

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : crotonic acid 150 mg/kg

Unit : g

Species : Rat

Animal No.	/Day						Total food consumption
	2	8	15	30	36	42	
3001	24	23	26	18	20	20	131
3002	27	26	23	19	22	22	139
3003	19	19	20	16	16	18	108
3004	21	22	18	19	20	23	123
3005	26	20	23	18	19	17	123
3006	27	20	19	21	22	19	128
3007	24	24	26	22	26	21	143
3008	25	26	22	21	23	22	139
3009	24	23	23	27	27	24	148
3010	26	21	16	20	21	20	124
3011	24	24	21	19	21	19	128
3012	21	26	25	20	26	25	143
n	12	12	12	12	12	12	12
Mean	24	23	22	20	22	21	131
S.D.	3	2	3	3	3	2	11

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : crotonic acid 500 mg/kg

Unit : g

Species : Rat

Animal No.	/Day						Total food consumption
	2	8	15	30	36	42	
4001	25	24	19	18	21	21	128
4002	19	21	21	16	18	21	116
4003	26	24	25	19	22	22	138
4004	17	18	19	16	19	18	107
4005	17	20	20	19	18	18	112
4006	27	25	23	17	19	19	130
4007	21	21	18	16	18	18	112
4008	21	21	23	16	22	20	123
4009	24	25	20	19	22	19	129
4010	23	23	21	15	20	18	120
4011	23	22	20	19	22	21	127
4012	24	20	20	18	20	20	122
n	12	12	12	12	12	12	12
Mean	22	22	21	17	20	20	122
S.D.	3	2	2	1	2	1	9

Food consumption

Period : F0 before mating Day 1-15

Sex : Female

Dose : crotonic acid 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
1101	18	21	16	55
1102	11	19	13	43
1103	10	17	16	43
1104	19	15	17	51
1105	16	19	18	53
1106	17	14	19	50
1107	17	14	17	48
1108	14	18	17	49
1109	12	18	17	47
1110	11	16	15	42
1111	17	18	14	49
1112	18	22	17	57
n	12	12	12	12
Mean	15	18	16	49
S.D.	3	3	2	5

Food consumption

Period : F0 before mating Day 1-15

Sex : Female

Dose : crotonic acid 50 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
2101	11	17	17	45
2102	15	12	16	43
2103	10	19	17	46
2104	18	14	19	51
2105	16	19	16	51
2106	12	14	9	35
2107	16	17	18	51
2108	14	19	15	48
2109	14	11	15	40
2110	15	17	13	45
2111	14	16	13	43
2112	17	20	13	50
n	12	12	12	12
Mean	14	16	15	46
S.D.	2	3	3	5

Food consumption

Period : F0 before mating Day 1-15

Sex : Female

Dose : crotonic acid 150 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
3101	13	16	15	44
3102	15	13	18	46
3103	11	17	18	46
3104	14	20	18	52
3105	10	17	16	43
3106	13	19	18	50
3107	17	18	19	54
3108	19	20	17	56
3109	14	16	13	43
3110	16	16	13	45
3111	15	25	19	59
3112	17	20	21	58
n	12	12	12	12
Mean	15	18	17	50
S.D.	3	3	2	6

Food consumption

Period : F0 before mating Day 1-15

Sex : Female

Dose : crotonic acid 500 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
4101	16	17	16	49
4102	13	15	17	45
4103	11	17	15	43
4104	18	19	19	56
4105	20	14	18	52
4106	15	12	15	42
4107	13	12	16	41
4108	13	15	0	28
4109	14	15	17	46
4110	16	13	16	45
4111	15	19	13	47
4112	8	16	17	41
n	12	12	12	12
Mean	14	15	15	45
S.D.	3	2	5	7

Food consumption					Period : F0 gestation Day 0-25		Unit : g	Species : Rat
Sex : Female					Dose : crotonic acid 0 mg/kg			
Animal No.	/Day				Total food consumption			
	1	7	14	20				
1101	20	24	24	21	89			
1102	18	21	19	28	86			
1103	18	23	20	22	83			
1104	17	23	20	27	87			
1105	16	24	20	22	82			
1106	14	22	18	21	75			
1107	16	19	19	22	76			
1108	17	16	19	26	78			
1109	13	20	20	24	77			
1110	14	23	21	21	79			
1111	18	22	21	25	86			
1112	14	18	22	24	78			
n	12	12	12	12	12			
Mean	16	21	20	24	81			
S.D.	2	3	2	2	5			

Food consumption					Period : F0 gestation Day 0-25	Unit : g	Species : Rat
Sex : Female					Dose : crotonic acid 50 mg/kg		
Animal No.	/Day				Total food consumption		
	1	7	14	20			
2101	17	19	19	21	76		
2102	15	28	15	22	80		
2103	20	20	20	21	81		
2104	17	20	19	25	81		
2106	20	20	23	22	85		
2107	18	19	21	25	83		
2109	15	9	16	21	61		
2110	20	19	20	27	86		
2111	16	17	13	19	65		
2112	16	18	20	23	77		
n	10	10	10	10	10		
Mean	17	19	19	23	78		
S.D.	2	5	3	2	8		

Animal No.2105,2108: Not copulated

	Food consumption				Period : F0 gestation Day 0-25		Unit : g	Species : Rat
	Sex : Female				Dose : crotonic acid 150 mg/kg			
	/Day				Total food consumption			
Animal No.	1	7	14	20				
3101	19	19	24	22	84			
3102	13	22	19	26	80			
3103	11	20	22	22	75			
3104	20	23	24	22	89			
3105	16	18	20	20	74			
3106	15	18	16	24	73			
3107	20	20	23	23	86			
3108	18	22	20	21	81			
3110	18	24	23	26	91			
3111	15	23	20	22	80			
3112	18	22	22	25	87			
n	11	11	11	11	11			
Mean	17	21	21	23	82			
S.D.	3	2	2	2	6			

Animal No.3109: Not copulated

Food consumption					Period : F0 gestation Day 0-25	Unit : g	Species : Rat
Sex : Female					Dose : crotonic acid 500 mg/kg		
	/Day	Total food consumption					
Animal No.	1	7	14	20			
4101	17	21	20	23	81		
4102	14	23	19	22	78		
4103	14	16	14	18	62		
4104	15	19	19	23	76		
4105	15	15	17	17	64		
4106	14	18	14	20	66		
4107	8	15	20	23	66		
4108	11	17	16	28	72		
4109	15	20	18	21	74		
4110	14	18	17	20	69		
4111	15	18	24	26	83		
4112	19	14	20	25	78		
n	12	12	12	12	12		
Mean	14	18	18	22	72		
S.D.	3	3	3	3	7		

Food consumption

Period : F0 lactation Day 0-5

Sex : Female

Dose : crotonic acid 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		Total food consumption
	2	4	
1101	23	43	66
1102	39	45	84
1103	32	40	72
1104	26	48	74
1105	30	39	69
1106	20	43	63
1107	16	32	48
1108	27	42	69
1109	35	38	73
1110	34	43	77
1111	21	38	59
1112	28	34	62
n	12	12	12
Mean	28	40	68
S.D.	7	5	9

Food consumption

Period : F0 lactation Day 0-5

Sex : Female

Dose : crotonic acid 50 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		Total food consumption
	2	4	
2101	16	25	41
2102	28	41	69
2103	20	49	69
2104	34	37	71
2106	21	35	56
2107	23	45	68
2109	29	45	74
2110	29	39	68
2111	22	44	66
2112	34	37	71
n	10	10	10
Mean	26	40	65
S.D.	6	7	10

Animal No.2105,2108: Not copulated

Food consumption

Period : F0 lactation Day 0-5

Sex : Female

Dose : crotonic acid 150 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		Total food consumption
	2	4	
3101	19	39	58
3102	30	45	75
3103	32	39	71
3104	29	53	82
3105	28	33	61
3106	25	43	68
3107	21	47	68
3108	33	47	80
3110	24	34	58
3111	28	40	68
3112	11	33	44
n	11	11	11
Mean	25	41	67
S.D.	6	6	11

Animal No.3109: Not copulated

Food consumption

Period : F0 lactation Day 0-5

Sex : Female

Dose : crotonic acid 500 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		Total food consumption
	2	4	
4101	22	47	69
4102	22	34	56
4103	29	39	68
4104	22	38	60
4105	23	43	66
4106	21	39	60
4107	19	41	60
4108	28	38	66
4109	14	36	50
4110	34	41	75
4111	25	42	67
4112	30	51	81
n	12	12	12
Mean	24	41	65
S.D.	5	5	8

Food consumption		Period : Administration						Unit : g	Species : Rat
Sex : Female		Dose : crotonic acid 0 mg/kg							
Animal No.	/Day	Total food consumption							
	2	8	15	30	36	42			
5101	10	17	16	12	18	13	86		
5102	17	17	11	6	13	17	81		
5103	10	16	15	11	14	13	79		
5104	16	17	12	14	13	17	89		
5105	14	21	21	15	19	16	106		
5106	17	22	20	15	20	15	109		
5107	12	16	10	13	15	11	77		
5108	12	19	10	15	14	13	83		
5109	13	16	11	8	12	12	72		
5110	15	14	12	13	12	14	80		
n	10	10	10	10	10	10	10		
Mean	14	18	14	12	15	14	86		
S.D.	3	2	4	3	3	2	12		

Food consumption							Period : Administration	Unit : g	Species : Rat
Sex : Female							Dose : crotonic acid 500 mg/kg		
Animal No.	/Day						Total food consumption		
	2	8	15	30	36	42			
6101	15	17	18	13	14	15	92		
6102	19	18	19	18	14	15	103		
6103	17	14	16	16	12	14	89		
6104	13	10	15	11	0	14	63		
6105	12	18	16	10	12	10	78		
6106	14	16	16	9	17	13	85		
6107	16	16	18	14	15	14	93		
6108	17	14	19	18	17	17	102		
6109	12	15	15	11	12	11	76		
6110	15	18	20	14	17	16	100		
n	10	10	10	10	10	10	10		
Mean	15	16	17	13	13	14	88		
S.D.	2	3	2	3	5	2	13		

Food consumption

Period : Recovery Day 1-15

Sex : Male

Dose : crotonic acid 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	14	
1008	18	27	24	69
1009	18	25	23	66
1010	19	24	24	67
1011	25	31	25	81
1012	22	23	24	69
n	5	5	5	5
Mean	20	26	24	70
S.D.	3	3	1	6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Food consumption
Sex : Male
Period : Recovery Day 1-15
Dose : crotonic acid 500 mg/kg

Animal No.	/Day			Total food consumption	Unit : g	Species : Rat
	2	8	14			
4008	21	0	20	41		
4009	22	28	26	76		
4010	22	30	27	79		
4011	27	30	28	85		
4012	25	29	28	82		
n	5	5	5	5		
Mean	23	23	26	73		
S.D.	3	13	3	18		

Food consumption

Period : Recovery Day 1-15

Sex : Female

Dose : crotonic acid 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	14	
5106	21	19	22	62
5107	14	15	15	44
5108	15	16	14	45
5109	13	17	15	45
5110	17	20	17	54
n	5	5	5	5
Mean	16	17	17	50
S.D.	3	2	3	8

Food consumption

Period : Recovery Day 1-15

Sex : Female

Dose : crotonic acid 500 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	14	
6106	16	12	19	47
6107	17	19	18	54
6108	18	20	20	58
6109	16	15	15	46
6110	19	16	19	54
n	5	5	5	5
Mean	17	16	18	52
S.D.	1	3	2	5

Animal No.	Urinalysis								Species : Rat
	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color	
1008	>=9.0	2+	1+	-	-	1+	+/-	Y	
1009	>=9.0	+/-	1+	-	-	-	+/-	Y	
1010	7.0	1+	1+	-	-	-	+/-	Y	
1011	>=9.0	2+	1+	-	+/-	-	+/-	Y	
1012	8.0	1+	1+	-	+/-	-	+/-	Y	
n	5	5	5	5	5	5	5	5	

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Animal No.	Urinalysis								Species : Rat
	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color	
2008	7.0	2+	1+	1+	-	1+	+/-	Y	
2009	7.5	+/-	1+	-	-	-	+/-	Y	
2010	>=9.0	1+	1+	-	-	-	+/-	Y	
2011	>=9.0	2+	1+	-	-	-	+/-	Y	
2012	7.0	1+	1+	-	+/-	-	+/-	Y	
n	5	5	5	5	5	5	5	5	

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Animal No.	Urinalysis				Stage : Week 6 of administration				Species : Rat
	Sex : Male				Dose : crotonic acid 150 mg/kg				
	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color	
3008	6.5	1+	1+	-	-	-	+/-	Y	
3009	>=9.0	2+	2+	1+	-	1+	+/-	Y	
3010	8.0	1+	1+	-	-	-	+/-	Y	
3011	6.5	2+	1+	-	-	-	+/-	Y	
3012	>=9.0	1+	1+	-	+/-	-	+/-	Y	
n	5	5	5	5	5	5	5	5	

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Urinalysis
Sex : MaleStage : Week 6 of administration
Dose : crotonic acid 500 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color
Animal No.								
4008	6.5	1+	1+	-	-	1+	+/-	Y
4009	6.5	1+	1+	-	-	1+	+/-	Y
4010	7.0	2+	2+	-	-	1+	+/-	Y
4011	6.0	2+	+/-	-	+/-	-	+/-	Y
4012	6.5	1+	+/-	-	+/-	-	+/-	Y
n	5	5	5	5	5	5	5	5

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	RBC	WBC	Squamous epithelial cells	Small round epithelial cells	Cast	Crystal phosphate salts	Crystal calcium oxalate
1008	-	-	+/-	-	-	+/-	-
1009	-	-	+/-	-	-	+/-	-
1010	-	-	+/-	-	-	+/-	-
1011	-	-	+/-	-	-	+/-	-
1012	-	-	+/-	-	-	+/-	-
n	5	5	5	5	5	5	5

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis
Sex : MaleStage : Week 6 of administration
Dose : crotonic acid 50 mg/kg

Species : Rat

	RBC	WBC	Ep.SEC	Ep.SREC	Cast	Cr.PS	Cr.CO
Animal No.							
2008	-	-	+/-	-	-	+/-	-
2009	-	-	+/-	-	-	+/-	-
2010	-	-	+/-	-	-	+/-	-
2011	-	-	+/-	-	-	+/-	-
2012	-	-	+/-	-	-	-	-
n	5	5	5	5	5	5	5

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : crotonic acid 150 mg/kg

Species : Rat

	RBC	WBC	Ep.SEC	Ep.SREC	Cast	Cr.PS	Cr.CO
Animal No.							
3008	-	-	+/-	-	-	+/-	-
3009	-	-	+/-	-	-	+/-	-
3010	-	-	+/-	-	-	+/-	-
3011	-	-	+/-	-	-	-	-
3012	-	-	+/-	-	-	+/-	-
n	5	5	5	5	5	5	5

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : crotonic acid 500 mg/kg

Species : Rat

	RBC	WBC	Ep.SEC	Ep.SREC	Cast	Cr.PS	Cr.CO
Animal No.							
4008	-	-	+/-	-	-	+/-	-
4009	-	-	+/-	-	-	+/-	-
4010	-	-	+/-	-	-	+/-	-
4011	-	-	+/-	-	-	+/-	-
4012	-	-	+/-	-	-	-	-
n	5	5	5	5	5	5	5

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
1008	35	12.0	1996	1.5	4.0	1.9
1009	43	15.5	1110	1.0	2.7	1.4
1010	32	7.2	2426	1.0	2.7	1.4
1011	55	18.6	1342	1.5	3.9	2.2
1012	35	11.7	1746	1.6	3.2	1.9
n	5	5	5	5	5	5
Mean	40	13.0	1724	1.3	3.3	1.8
S.D.	9	4.3	522	0.3	0.6	0.4

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : crotonic acid 50 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
2008	47	10.9	1878	1.1	3.4	1.5
2009	50	22.5	1468	1.9	5.4	2.9
2010	40	16.5	1486	1.0	4.2	1.7
2011	33	10.4	2356	1.2	3.9	1.8
2012	45	8.8	2132	1.0	3.0	1.5
n	5	5	5	5	5	5
Mean	43	13.8	1864	1.2	4.0	1.9
S.D.	7	5.7	392	0.4	0.9	0.6

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : crotonic acid 150 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
3008	44	12.0	2100	1.2	4.2	2.2
3009	46	10.9	2072	1.2	3.9	1.8
3010	34	12.5	2348	1.8	4.9	2.7
3011	36	6.4	2590	1.0	2.7	1.3
3012	40	12.1	2040	1.4	4.2	2.0
n	5	5	5	5	5	5
Mean	40	10.8	2230	1.3	4.0	2.0
S.D.	5	2.5	235	0.3	0.8	0.5

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
4008	61	21.1	1042	0.9	3.1	1.6
4009	45	11.3	1368	1.0	2.2	1.4
4010	46	11.1	1466	1.0	2.5	1.5
4011	36	10.8	2034	1.0	3.1	1.8
4012	57	21.8	1120	1.0	3.7	1.8
n	5	5	5	5	5	5
Mean	49	15.2	1406	1.0	2.9	1.6
S.D.	10	5.7	392	0.0	0.6	0.2

Animal No.	Urinalysis								Species : Rat
	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color	
5106	>=9.0	+/-	-	-	-	-	+/-	Y	
5107	6.0	1+	-	-	-	-	+/-	Y	
5108	>=9.0	-	-	-	-	-	+/-	Y	
5109	6.5	1+	+/-	-	-	-	+/-	Y	
5110	7.5	+/-	+/-	-	-	-	+/-	Y	
n	5	5	5	5	5	5	5	5	

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Urinalysis

Stage : Week 6 of administration

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color
Animal No.								
6106	>=9.0	-	-	-	-	-	+/-	Y
6107	6.5	1+	+/-	-	-	-	+/-	Y
6108	7.5	-	-	-	-	-	+/-	Y
6109	>=9.0	+/-	+/-	-	-	-	+/-	Y
6110	6.0	-	-	-	-	-	+/-	Y
n	5	5	5	5	5	5	5	5

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Urinalysis					Stage : Week 6 of administration			Species : Rat
Sex : Female					Dose : crotonic acid 0 mg/kg			
Animal No.	RBC	WBC	Squamous epithelial cells	Small round epithelial cells	Cast	Crystal phosphate salts	Crystal calcium oxalate	
5106	-	-	+/-	-	-	+/-	-	
5107	-	-	+/-	-	-	-	-	
5108	-	-	+/-	-	-	+/-	-	
5109	-	-	+/-	-	-	+/-	-	
5110	-	-	+/-	-	-	+/-	-	
n	5	5	5	5	5	5	5	

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis

Stage : Week 6 of administration

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	RBC	WBC	Squamous epithelial cells	Small round epithelial cells	Cast	Crystal phosphate salts	Crystal calcium oxalate
6106	-	-	+/-	-	-	+/-	-
6107	-	-	+/-	-	-	+/-	-
6108	-	-	+/-	-	-	-	-
6109	-	-	+/-	-	-	+/-	-
6110	-	-	+/-	-	-	-	-
n	5	5	5	5	5	5	5

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis

Stage : Week 6 of administration

Sex : Female

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
5106	28	8.7	2366	1.2	3.2	1.7
5107	21	4.1	2798	0.7	1.6	0.8
5108	36	11.7	1250	1.0	2.1	1.1
5109	26	4.5	2610	0.5	1.9	0.8
5110	41	11.2	1440	1.1	2.5	1.4
n	5	5	5	5	5	5
Mean	30	8.0	2093	0.9	2.3	1.2
S.D.	8	3.6	703	0.3	0.6	0.4

Urinalysis

Stage : Week 6 of administration

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
6106	31	6.6	2462	0.8	2.7	1.3
6107	20	3.8	2462	0.5	1.3	0.4
6108	44	19.9	1166	1.8	3.6	2.2
6109	35	11.0	1572	1.4	2.9	1.6
6110	23	10.2	1504	1.2	2.2	1.3
n	5	5	5	5	5	5
Mean	31	10.3	1833	1.1	2.5	1.4
S.D.	10	6.1	594	0.5	0.9	0.7

Animal No.	Urinalysis								Species : Rat
	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color	
1008	>=9.0	1+	+/-	-	+/-	-	+/-	Y	
1009	8.5	-	-	-	+/-	-	+/-	Y	
1010	8.5	+/-	-	-	+/-	-	+/-	Y	
1011	>=9.0	1+	-	-	+/-	-	+/-	Y	
1012	>=9.0	+/-	-	-	+/-	-	+/-	Y	
n	5	5	5	5	5	5	5	5	

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Animal No.	Urinalysis								Species : Rat
	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color	
4008	6.0	1+	+/-	-	+/-	1+	+/-	Y	
4009	>=9.0	+/-	-	-	+/-	-	+/-	Y	
4010	>=9.0	1+	+/-	-	-	-	+/-	Y	
4011	7.5	2+	1+	-	-	-	+/-	Y	
4012	8.5	-	-	-	+/-	-	+/-	Y	
n	5	5	5	5	5	5	5	5	

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Urinalysis					Stage : Week 2 of recovery			Species : Rat
Sex : Male					Dose : crotonic acid 0 mg/kg			
Animal No.	RBC	WBC	Squamous epithelial cells	Small round epithelial cells	Cast	Crystal phosphate salts	Crystal calcium oxalate	
1008	-	-	+/-	-	-	+/-	-	
1009	-	-	+/-	-	-	+/-	-	
1010	-	-	+/-	-	-	+/-	-	
1011	-	-	+/-	-	-	+/-	-	
1012	-	-	+/-	-	-	+/-	-	
n	5	5	5	5	5	5	5	

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis		Stage : Week 2 of recovery		Dose : crotonic acid 500 mg/kg		Species : Rat	
Sex : Male							
Animal No.	RBC	WBC	Squamous epithelial cells	Small round epithelial cells	Cast	Crystal phosphate salts	Crystal calcium oxalate
4008	-	-	+/-	-	-	+/-	-
4009	-	-	+/-	-	-	+/-	-
4010	-	-	+/-	-	-	+/-	-
4011	-	-	+/-	-	-	+/-	-
4012	-	-	+/-	-	-	-	-
n	5	5	5	5	5	5	5

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis

Stage : Week 2 of recovery

Dose : crotonic acid 0 mg/kg

Sex : Male

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
1008	43	14.6	2082	1.5	5.1	2.5
1009	53	29.9	1302	2.1	5.4	2.9
1010	44	11.4	2414	1.2	4.7	2.0
1011	56	21.7	1640	2.3	5.3	3.2
1012	49	14.1	2078	1.7	4.8	2.3
n	5	5	5	5	5	5
Mean	49	18.3	1903	1.8	5.1	2.6
S.D.	6	7.5	434	0.4	0.3	0.5

Urinalysis

Stage : Week 2 of recovery

Sex : Male

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
4008	10	5.3	1740	0.0 a)	0.7	0.1 a)
4009	53	14.5	1616	1.8	3.4	2.3
4010	46	14.6	1800	1.4	4.2	2.1
4011	42	12.2	2356	1.5	4.3	2.3
4012	57	25.0	1754	2.0	6.9	3.1
n	5	5	5	5	5	5
Mean	42	14.3	1853	1.3	3.9	2.0
S.D.	19	7.1	289	0.8	2.2	1.1

a) Re-analyzed value

Animal No.	Urinalysis								Species : Rat
	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color	
5106	6.5	+/-	-	-	-	-	+/-	Y	
5107	6.5	-	-	-	-	-	+/-	Y	
5108	>=9.0	-	-	-	-	-	+/-	Y	
5109	8.0	-	-	-	-	-	+/-	Y	
5110	8.0	1+	+/-	1+	-	-	+/-	Y	
n	5	5	5	5	5	5	5	5	

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Urinalysis

Stage : Week 2 of recovery

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	Color
Animal No.								
6106	7.5	+/-	-	-	-	-	+/-	Y
6107	8.5	+/-	+/-	1+	-	-	+/-	Y
6108	7.0	-	-	-	-	-	+/-	Y
6109	7.5	-	+/-	-	-	-	+/-	Y
6110	>=9.0	-	+/-	-	-	-	+/-	Y
n	5	5	5	5	5	5	5	5

Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:≥300 mg/dL

Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL

Glucose) -:Negative , 1+:100 , 2+:250 , 3+:500 , 4+:≥1000 mg/dL

Occult Blood) -:Negative , +/-:0.015 , 1+:0.062 , 2+:0.135 , 3+:0.405 mg/dL

Bilirubin) -:Negative , 1+:0.8 , 2+:1.6 , 3+:3.2 mg/dL

Urobilinogen) +/-:0.1 - 1.0 , 1+:2.0 , 2+:4.0 , 3+:≥8.0 Ehrlich U/dL

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

Urinalysis					Stage : Week 2 of recovery			Species : Rat
Sex : Female					Dose : crotonic acid 0 mg/kg			
Animal No.	RBC	WBC	Squamous epithelial cells	Small round epithelial cells	Cast	Crystal phosphate salts	Crystal calcium oxalate	
5106	-	-	+/-	-	-	+/-	-	
5107	-	-	+/-	-	-	-	-	
5108	-	-	+/-	-	-	+/-	-	
5109	-	-	+/-	-	-	+/-	-	
5110	-	-	+/-	-	-	+/-	-	
n	5	5	5	5	5	5	5	

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis					Stage : Week 2 of recovery			Species : Rat
Sex : Female					Dose : crotonic acid 500 mg/kg			
	RBC	WBC	Squamous epithelial cells	Small round epithelial cells	Cast	Crystal phosphate salts	Crystal calcium oxalate	
Animal No.								
6106	-	-	+/-	-	-	+/-	-	
6107	-	-	+/-	-	-	+/-	-	
6108	-	-	+/-	-	-	+/-	-	
6109	-	-	+/-	-	-	+/-	-	
6110	-	-	+/-	-	-	+/-	-	
n	5	5	5	5	5	5	5	

RBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

WBC) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Squamous epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Small round epithelial cells) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Cast) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal phosphate salts) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Crystal calcium oxalate) -:Negative , +/-:Slight , 1+:Mild , 2+:Moderate , 3+:Severe

Urinalysis

Stage : Week 2 of recovery

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
5106	33	6.8	2690	1.0	2.7	1.5
5107	31	8.2	2214	1.1	2.9	1.5
5108	43	19.1	1226	1.5	3.6	2.0
5109	32	7.9	2190	0.9	2.7	1.4
5110	27	7.0	2638	1.0	2.8	1.2
n	5	5	5	5	5	5
Mean	33	9.8	2192	1.1	2.9	1.5
S.D.	6	5.2	587	0.2	0.4	0.3

Urinalysis

Stage : Week 2 of recovery

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h	Osmotic pressure mOsm/kg	U-Na mmol/24h	U-K mmol/24h	U-Cl mmol/24h
6106	28	6.5	2920	0.9	2.9	1.5
6107	27	6.3	2650	0.9	2.6	1.3
6108	26	6.4	1960	0.6	1.8	0.8
6109	39	10.1	1882	1.2	2.9	1.7
6110	40	12.4	1590	1.0	3.1	1.5
n	5	5	5	5	5	5
Mean	32	8.3	2200	0.9	2.7	1.4
S.D.	7	2.8	559	0.2	0.5	0.3

Hematology

Stage : End of administration

Dose : crotonic acid 0 mg/kg

Species : Rat

Sex : Male

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
1001	844	15.0	46.4	54.9	17.7	32.3	2.5	88.2	86.6	81.9	13.4
1002	870	15.0	45.1	51.8	17.3	33.4	2.0	99.1	84.7	77.7	18.7
1003	838	15.0	45.0	53.6	17.9	33.4	1.6	90.6	57.6	86.5	9.4
1004	863	14.8	44.8	51.9	17.2	33.1	1.2	83.8	50.7	78.8	16.8
1005	826	14.7	43.6	52.9	17.9	33.8	2.6	97.4	94.3	73.7	22.2
n	5	5	5	5	5	5	5	5	5	5	5
Mean	848	14.9	45.0	53.0	17.6	33.2	2.0	91.8	74.8	79.7	16.1
S.D.	18	0.1	1.0	1.3	0.3	0.6	0.6	6.4	19.3	4.8	4.9

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
1001	1.3	0.4	2.2	0.7	70.9	11.6	1.2	0.3	1.9	0.6	11.9
1002	1.5	0.4	1.3	0.4	65.8	15.8	1.3	0.3	1.1	0.4	11.5
1003	1.5	0.3	1.6	0.6	49.8	5.4	0.9	0.2	0.9	0.4	12.2
1004	2.1	0.3	1.6	0.4	40.0	8.5	1.0	0.2	0.8	0.2	13.0
1005	1.6	0.3	1.7	0.5	69.5	20.9	1.5	0.3	1.6	0.4	12.6
n	5	5	5	5	5	5	5	5	5	5	5
Mean	1.6	0.3	1.7	0.5	59.2	12.4	1.2	0.3	1.3	0.4	12.2
S.D.	0.3	0.1	0.3	0.1	13.6	6.1	0.2	0.1	0.5	0.1	0.6

	APTT	FIB
Animal No.	s	mg/dL
1001	16.3	255
1002	15.7	233
1003	17.7	260
1004	17.0	256
1005	17.8	258
n	5	5
Mean	16.9	252
S.D.	0.9	11

Hematology

Sex : Male

Stage : End of administration

Dose : crotonic acid 50 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
2001	827	14.3	42.5	51.4	17.3	33.5	2.0	95.6	90.9	84.1	12.7
2002	854	15.2	45.9	53.7	17.9	33.2	2.3	91.5	99.0	78.3	17.8
2003	807	15.1	45.8	56.8	18.7	32.9	2.1	94.6	89.9	73.8	23.4
2004	876	15.6	47.7	54.4	17.8	32.6	1.9	91.8	75.3	81.0	16.4
2005	856	14.9	44.5	52.0	17.4	33.5	1.9	91.7	70.8	80.4	16.5
n	5	5	5	5	5	5	5	5	5	5	5
Mean	844	15.0	45.3	53.7	17.8	33.1	2.0	93.0	85.2	79.5	17.4
S.D.	27	0.5	1.9	2.1	0.6	0.4	0.2	1.9	11.7	3.8	3.9

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
2001	1.1	0.3	1.4	0.4	76.4	11.6	1.0	0.3	1.3	0.4	12.4
2002	1.1	0.5	1.8	0.5	77.5	17.6	1.1	0.5	1.8	0.5	11.7
2003	1.1	0.3	1.2	0.2	66.3	21.1	0.9	0.2	1.1	0.2	12.9
2004	0.8	0.4	1.2	0.2	60.9	12.3	0.6	0.3	0.9	0.2	12.5
2005	0.9	0.3	1.4	0.5	56.9	11.7	0.6	0.2	1.0	0.4	12.7
n	5	5	5	5	5	5	5	5	5	5	5
Mean	1.0	0.4	1.4	0.4	67.6	14.9	0.8	0.3	1.2	0.3	12.4
S.D.	0.1	0.1	0.2	0.2	9.2	4.3	0.2	0.1	0.4	0.1	0.5

	APTT	FIB
Animal No.	s	mg/dL
2001	15.6	232
2002	17.4	242
2003	18.0	242
2004	15.8	275
2005	15.8	278
n	5	5
Mean	16.5	254
S.D.	1.1	21

Hematology

Stage : End of administration

Dose : crotonic acid 150 mg/kg

Species : Rat

Sex : Male

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
3001	869	15.2	45.3	52.2	17.4	33.4	1.8	89.1	68.4	83.5	13.1
3002	847	14.7	44.6	52.7	17.4	33.0	2.1	102.4	88.4	77.2	19.0
3003	912	15.8	47.1	51.6	17.3	33.5	1.5	88.0	101.6	79.8	14.6
3004	840	14.6	43.7	52.0	17.4	33.4	2.2	97.3	94.2	80.1	16.8
3005	865	15.0	44.9	51.9	17.4	33.5	1.6	99.5	70.8	74.3	23.5
n	5	5	5	5	5	5	5	5	5	5	5
Mean	867	15.1	45.1	52.1	17.4	33.4	1.8	95.3	84.7	79.0	17.4
S.D.	28	0.5	1.3	0.4	0.0	0.2	0.3	6.4	14.6	3.4	4.1

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
3001	1.0	0.3	1.5	0.6	57.1	9.0	0.7	0.2	1.0	0.4	12.5
3002	1.6	0.3	1.5	0.5	68.2	16.8	1.4	0.3	1.3	0.4	12.2
3003	1.7	0.5	2.1	1.3	81.1	14.8	1.7	0.5	2.2	1.3	12.0
3004	0.9	0.3	1.2	0.6	75.5	15.9	0.9	0.3	1.1	0.6	11.9
3005	0.6	0.3	1.0	0.3	52.7	16.6	0.4	0.2	0.7	0.2	16.9
n	5	5	5	5	5	5	5	5	5	5	5
Mean	1.2	0.3	1.5	0.7	66.9	14.6	1.0	0.3	1.3	0.6	13.1
S.D.	0.5	0.1	0.4	0.4	12.0	3.2	0.5	0.1	0.6	0.4	2.1

	APTT	FIB
Animal No.	s	mg/dL
3001	17.0	254
3002	14.3	296
3003	15.5	226
3004	17.0	237
3005	21.1	267
n	5	5
Mean	17.0	256
S.D.	2.6	27

Hematology

Sex : Male

Stage : End of administration

Dose : crotonic acid 500 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
4001	821	14.5	43.3	52.8	17.6	33.4	2.1	101.4	69.4	85.3	9.9
4002	873	15.2	46.8	53.6	17.5	32.6	2.5	100.8	84.1	79.0	17.4
4003	871	14.7	44.2	50.7	16.9	33.3	2.1	118.8	57.5	81.7	13.6
4004	868	15.2	46.4	53.4	17.5	32.8	2.7	92.7	89.0	73.8	21.5
4005	883	15.3	45.7	51.8	17.3	33.4	2.2	95.7	92.8	80.1	17.1
n	5	5	5	5	5	5	5	5	5	5	5
Mean	863	15.0	45.3	52.5	17.4	33.1	2.3	101.9	78.6	80.0	15.9
S.D.	24	0.4	1.5	1.2	0.3	0.4	0.3	10.1	14.7	4.2	4.4

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
4001	1.7	0.3	1.4	1.4	59.2	6.8	1.2	0.2	1.0	1.0	11.7
4002	1.0	0.4	1.4	0.8	66.5	14.6	0.8	0.4	1.2	0.7	12.7
4003	2.4	0.4	1.5	0.5	46.9	7.8	1.4	0.2	0.8	0.3	12.6
4004	1.3	0.6	1.9	0.8	65.6	19.2	1.2	0.5	1.7	0.7	11.6
4005	0.9	0.4	0.8	0.6	74.4	15.9	0.8	0.4	0.8	0.5	16.3
n	5	5	5	5	5	5	5	5	5	5	5
Mean	1.5	0.4	1.4	0.8	62.5	12.9	1.1	0.3	1.1	0.6	13.0
S.D.	0.6	0.1	0.4	0.3	10.3	5.4	0.3	0.1	0.4	0.3	1.9

	APTT	FIB
Animal No.	s	mg/dL
4001	16.7	226
4002	17.8	268
4003	19.0	227
4004	15.4	289
4005	19.6	205
n	5	5
Mean	17.7	243
S.D.	1.7	34

Hematology

Stage : Lactation day 5

Dose : crotonic acid 0 mg/kg

Species : Rat

Sex : Female

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
1101	711	12.8	39.1	55.0	17.9	32.6	6.8	120.3	94.7	67.0	28.5
1104	662	12.0	36.5	55.1	18.1	32.8	7.2	141.7	112.6	64.7	32.6
1105	665	13.0	38.4	57.7	19.5	33.8	5.5	122.5	123.4	66.7	31.0
1107	731	13.3	40.0	54.6	18.2	33.3	4.2	141.3	76.6	73.1	21.9
1108	769	13.7	41.3	53.7	17.8	33.2	5.0	112.8	79.5	55.9	40.4
n	5	5	5	5	5	5	5	5	5	5	5
Mean	708	13.0	39.1	55.2	18.3	33.1	5.7	127.7	97.4	65.5	30.9
S.D.	45	0.6	1.8	1.5	0.7	0.5	1.2	13.1	20.4	6.2	6.7

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
1101	0.5	0.5	3.1	0.4	63.4	27.0	0.5	0.5	2.9	0.4	12.2
1104	0.5	0.3	1.5	0.5	72.8	36.7	0.5	0.3	1.7	0.6	13.2
1105	0.5	0.3	0.8	0.7	82.3	38.2	0.6	0.4	1.0	0.9	12.9
1107	1.5	0.4	2.7	0.5	55.9	16.8	1.1	0.3	2.0	0.4	11.9
1108	0.8	0.3	2.0	0.7	44.5	32.1	0.6	0.3	1.6	0.5	14.0
n	5	5	5	5	5	5	5	5	5	5	5
Mean	0.8	0.4	2.0	0.6	63.8	30.2	0.7	0.4	1.8	0.6	12.8
S.D.	0.4	0.1	0.9	0.1	14.6	8.7	0.3	0.1	0.7	0.2	0.8

	APTT	FIB
Animal No.	s	mg/dL
1101	17.7	259
1104	16.8	300
1105	16.8	380
1107	16.1	247
1108	15.9	385
n	5	5
Mean	16.7	314
S.D.	0.7	65

Hematology

Stage : Lactation day 5

Dose : crotonic acid 50 mg/kg

Species : Rat

Sex : Female

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
2101	754	14.1	42.7	56.7	18.7	33.0	3.2	150.8	65.9	82.3	14.0
2102	728	13.8	41.8	57.4	18.9	32.9	7.7	149.6	75.1	55.8	39.8
2103	606	11.9	36.1	59.5	19.6	32.9	8.5	165.2	101.6	69.2	27.4
2107	740	13.4	40.8	55.1	18.1	32.9	4.6	129.1	149.4	57.9	38.3
2109	686	13.3	40.7	59.3	19.4	32.7	7.5	118.1	92.0	62.3	33.7
n	5	5	5	5	5	5	5	5	5	5	5
Mean	703	13.3	40.4	57.6	18.9	32.9	6.3	142.6	96.8	65.5	30.6
S.D.	60	0.8	2.5	1.8	0.6	0.1	2.3	18.8	32.6	10.7	10.5

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
2101	0.7	0.4	1.9	0.7	54.2	9.2	0.5	0.3	1.3	0.4	12.5
2102	1.1	0.2	2.7	0.4	41.9	29.9	0.8	0.2	2.0	0.3	13.0
2103	0.5	0.2	1.6	1.1	70.3	27.9	0.5	0.3	1.6	1.1	12.3
2107	0.9	0.4	2.0	0.4	86.5	57.2	1.3	0.6	3.0	0.7	13.0
2109	0.5	0.4	2.5	0.5	57.4	31.0	0.5	0.4	2.3	0.5	12.0
n	5	5	5	5	5	5	5	5	5	5	5
Mean	0.7	0.3	2.1	0.6	62.1	31.0	0.7	0.4	2.0	0.6	12.6
S.D.	0.3	0.1	0.5	0.3	17.0	17.1	0.3	0.2	0.7	0.3	0.4

	APTT	FIB
Animal No.	s	mg/dL
2101	19.6	234
2102	19.6	220
2103	16.6	388
2107	18.0	273
2109	13.8	419
n	5	5
Mean	17.5	307
S.D.	2.4	91

Hematology

Stage : Lactation day 5

Dose : crotonic acid 150 mg/kg

Species : Rat

Sex : Female

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
3101	691	12.9	38.4	55.6	18.7	33.7	3.9	138.0	72.9	69.0	27.4
3103	753	14.1	42.8	56.9	18.8	33.0	4.5	110.6	127.9	67.5	27.9
3105	691	13.2	39.4	57.1	19.1	33.5	6.3	118.6	88.6	62.2	32.6
3107	739	12.9	38.6	52.2	17.5	33.5	6.1	151.1	74.2	84.5	11.6
3112	715	13.5	40.6	56.9	18.9	33.2	5.8	137.1	164.2	68.7	27.6
n	5	5	5	5	5	5	5	5	5	5	5
Mean	718	13.3	40.0	55.7	18.6	33.4	5.3	131.1	105.6	70.4	25.4
S.D.	28	0.5	1.8	2.1	0.6	0.3	1.1	16.3	39.6	8.4	8.0

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
3101	0.8	0.2	2.2	0.5	50.3	20.0	0.6	0.1	1.6	0.4	14.0
3103	0.4	0.3	2.8	1.1	86.3	35.6	0.6	0.4	3.6	1.4	13.2
3105	0.7	0.3	3.7	0.5	55.1	28.9	0.6	0.3	3.2	0.4	11.3
3107	0.8	0.2	2.0	0.8	62.7	8.6	0.6	0.2	1.5	0.6	12.9
3112	0.7	0.4	1.7	0.8	112.8	45.4	1.2	0.7	2.8	1.3	12.5
n	5	5	5	5	5	5	5	5	5	5	5
Mean	0.7	0.3	2.5	0.7	73.4	27.7	0.7	0.3	2.5	0.8	12.8
S.D.	0.2	0.1	0.8	0.3	26.0	14.2	0.3	0.2	0.9	0.5	1.0

	APTT	FIB
Animal No.	s	mg/dL
3101	14.9	242
3103	17.1	308
3105	10.7	356
3107	12.8	379
3112	15.6	233
n	5	5
Mean	14.2	304
S.D.	2.5	66

Hematology

Stage : Lactation day 5

Dose : crotonic acid 500 mg/kg

Species : Rat

Sex : Female

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
4104	741	13.9	42.2	57.0	18.7	32.8	6.2	139.0	98.4	58.2	37.3
4105	748	13.9	42.4	56.6	18.6	32.8	6.1	139.6	110.0	71.9	23.9
4106	695	13.2	39.5	56.9	19.0	33.5	6.9	122.0	105.8	72.3	23.4
4109	731	13.1	39.8	54.4	17.9	32.9	4.3	154.7	99.3	73.5	20.7
4110	740	13.2	40.2	54.4	17.9	32.9	4.9	131.9	112.6	74.4	21.6
n	5	5	5	5	5	5	5	5	5	5	5
Mean	731	13.5	40.8	55.9	18.4	33.0	5.7	137.4	105.2	70.1	25.4
S.D.	21	0.4	1.4	1.3	0.5	0.3	1.1	12.0	6.3	6.7	6.8

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
4104	1.4	0.4	2.2	0.5	57.2	36.7	1.4	0.3	2.2	0.5	12.5
4105	0.6	0.3	2.1	1.1	79.1	26.3	0.7	0.4	2.3	1.2	12.6
4106	0.5	0.3	2.4	1.0	76.5	24.8	0.5	0.3	2.5	1.1	12.7
4109	0.7	0.4	3.9	0.8	72.9	20.5	0.7	0.4	3.9	0.8	13.4
4110	0.7	0.3	2.1	0.9	83.8	24.3	0.8	0.3	2.4	1.0	13.6
n	5	5	5	5	5	5	5	5	5	5	5
Mean	0.8	0.3	2.5	0.9	73.9	26.5	0.8	0.3	2.7	0.9	13.0
S.D.	0.4	0.1	0.8	0.2	10.1	6.1	0.3	0.1	0.7	0.3	0.5

	APTT	FIB
Animal No.	s	mg/dL
4104	17.3	271
4105	16.2	315
4106	16.7	244
4109	15.4	384
4110	18.4	269
n	5	5
Mean	16.8	297
S.D.	1.1	55

Hematology
Sex : FemaleStage : End of administration
Dose : crotonic acid 0 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
5101	738	14.5	40.9	55.5	19.7	35.5	1.5	100.6	65.6	80.3	14.8
5102	782	15.0	43.4	55.5	19.2	34.6	2.9	96.4	75.1	75.3	20.1
5103	774	15.1	42.3	54.7	19.5	35.6	1.7	97.9	48.3	83.1	11.8
5104	818	14.9	43.3	52.9	18.2	34.4	2.3	103.6	50.9	60.1	36.9
5105	802	14.9	43.2	53.8	18.6	34.5	1.6	85.0	45.9	78.9	17.9
n	5	5	5	5	5	5	5	5	5	5	5
Mean	783	14.9	42.6	54.5	19.0	34.9	2.0	96.7	57.2	75.5	20.3
S.D.	30	0.2	1.1	1.1	0.6	0.6	0.6	7.1	12.6	9.1	9.8

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
5101	1.8	0.5	1.7	0.9	52.7	9.7	1.2	0.3	1.1	0.6	12.2
5102	2.4	0.4	1.5	0.3	56.6	15.1	1.8	0.3	1.1	0.3	12.6
5103	1.9	0.3	2.5	0.4	40.1	5.7	0.9	0.2	1.2	0.2	12.3
5104	1.3	0.3	1.2	0.3	30.6	18.8	0.6	0.2	0.6	0.1	10.8
5105	1.3	0.1	1.1	0.6	36.2	8.2	0.6	0.1	0.5	0.3	12.6
n	5	5	5	5	5	5	5	5	5	5	5
Mean	1.7	0.3	1.6	0.5	43.2	11.5	1.0	0.2	0.9	0.3	12.1
S.D.	0.5	0.1	0.6	0.3	11.0	5.3	0.5	0.1	0.3	0.2	0.7

	APTT	FIB
Animal No.	s	mg/dL
5101	15.5	185
5102	16.2	251
5103	13.2	186
5104	13.3	219
5105	16.0	207
n	5	5
Mean	14.8	210
S.D.	1.5	27

Hematology
Sex : FemaleStage : End of administration
Dose : crotonic acid 500 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
6101	819	14.8	43.3	52.9	18.1	34.2	2.1	136.1	61.3	81.1	14.3
6102	871	15.7	46.2	53.1	18.0	33.9	2.2	116.9	71.9	84.3	12.1
6103	772	14.0	41.1	53.2	18.1	34.0	2.0	122.6	49.1	87.1	10.1
6104	865	15.6	46.6	53.8	18.0	33.4	2.5	126.4	64.3	85.2	11.5
6105	874	15.5	46.4	53.1	17.7	33.4	1.8	132.9	86.5	83.4	13.0
n	5	5	5	5	5	5	5	5	5	5	5
Mean	840	15.1	44.7	53.2	18.0	33.8	2.1	127.0	66.6	84.2	12.2
S.D.	44	0.7	2.4	0.3	0.2	0.4	0.3	7.7	13.8	2.2	1.6

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
6101	1.8	0.2	2.1	0.5	49.7	8.7	1.1	0.1	1.3	0.3	11.9
6102	0.9	0.4	1.7	0.6	60.7	8.7	0.7	0.3	1.2	0.4	11.0
6103	0.9	0.2	1.2	0.5	42.7	4.9	0.4	0.1	0.6	0.3	13.4
6104	1.0	0.3	1.3	0.6	54.8	7.4	0.7	0.2	0.8	0.4	12.4
6105	1.5	0.4	1.0	0.8	72.1	11.2	1.3	0.3	0.9	0.7	11.7
n	5	5	5	5	5	5	5	5	5	5	5
Mean	1.2	0.3	1.5	0.6	56.0	8.2	0.8	0.2	1.0	0.4	12.1
S.D.	0.4	0.1	0.4	0.1	11.2	2.3	0.4	0.1	0.3	0.2	0.9

	APTT	FIB
Animal No.	s	mg/dL
6101	16.9	194
6102	12.8	200
6103	17.1	186
6104	14.4	199
6105	12.8	223
n	5	5
Mean	14.8	200
S.D.	2.1	14

Hematology

Sex : Male

Stage : End of recovery

Dose : crotonic acid 0 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
1008	917	15.7	48.2	52.5	17.1	32.5	1.8	92.1	94.6	86.6	9.8
1009	888	15.8	47.8	53.9	17.8	33.0	1.8	96.2	66.1	80.6	14.5
1010	921	15.3	46.0	49.9	16.6	33.3	1.2	85.9	87.2	86.6	9.6
1011	816	14.3	42.7	52.3	17.6	33.6	1.6	81.7	76.4	83.1	12.2
1012	905	15.6	46.2	51.1	17.2	33.6	1.8	92.9	75.3	74.8	19.9
n	5	5	5	5	5	5	5	5	5	5	5
Mean	889	15.3	46.2	51.9	17.3	33.2	1.6	89.8	79.9	82.3	13.2
S.D.	43	0.6	2.2	1.5	0.5	0.5	0.3	5.8	11.1	4.9	4.2

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
1008	1.4	0.5	1.3	0.5	81.9	9.2	1.3	0.5	1.3	0.5	13.0
1009	1.7	0.5	2.3	0.4	53.3	9.6	1.1	0.3	1.5	0.3	12.5
1010	1.2	0.4	1.5	0.7	75.5	8.3	1.1	0.3	1.3	0.6	12.2
1011	1.2	0.2	2.5	0.8	63.5	9.3	0.9	0.2	1.9	0.6	13.2
1012	2.2	0.3	2.3	0.4	56.3	15.0	1.7	0.2	1.7	0.3	12.3
n	5	5	5	5	5	5	5	5	5	5	5
Mean	1.5	0.4	2.0	0.6	66.1	10.3	1.2	0.3	1.5	0.5	12.6
S.D.	0.4	0.1	0.5	0.2	12.3	2.7	0.3	0.1	0.3	0.2	0.4

	APTT	FIB
Animal No.	s	mg/dL
1008	20.9	248
1009	16.6	229
1010	14.5	233
1011	18.2	247
1012	16.2	216
n	5	5
Mean	17.3	235
S.D.	2.4	13

Hematology

Sex : Male

Stage : End of recovery

Dose : crotonic acid 500 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
4008	891	16.0	47.8	53.7	17.9	33.4	0.8	35.0	65.2	36.6	58.3
4009	961	17.5	51.0	53.1	18.3	34.4	1.4	99.7	106.6	88.3	7.8
4010	918	15.8	47.4	51.6	17.3	33.4	1.4	85.8	72.8	79.0	17.4
4011	848	15.2	45.7	53.9	17.9	33.2	1.6	105.3	84.1	85.5	10.7
4012	821	14.7	44.0	53.6	17.9	33.4	1.9	89.9	63.3	76.3	19.3
n	5	5	5	5	5	5	5	5	5	5	5
Mean	888	15.8	47.2	53.2	17.9	33.6	1.4	83.1	78.4	73.1	22.7
S.D.	56	1.1	2.6	0.9	0.4	0.5	0.4	28.0	17.8	21.0	20.5

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
4008	0.4	0.3	3.9	0.6	23.8	38.0	0.3	0.2	2.6	0.4	13.7
4009	1.3	0.6	1.1	0.8	94.2	8.4	1.4	0.7	1.2	0.8	13.0
4010	1.4	0.3	1.2	0.6	57.5	12.7	1.0	0.2	0.9	0.5	12.8
4011	1.1	0.3	1.5	0.9	71.9	9.0	0.9	0.2	1.3	0.8	13.4
4012	1.7	0.4	1.7	0.6	48.2	12.2	1.1	0.3	1.0	0.4	12.9
n	5	5	5	5	5	5	5	5	5	5	5
Mean	1.2	0.4	1.9	0.7	59.1	16.1	0.9	0.3	1.4	0.6	13.2
S.D.	0.5	0.1	1.2	0.1	26.3	12.4	0.4	0.2	0.7	0.2	0.4

	APTT	FIB
Animal No.	s	mg/dL
4008	15.3	258
4009	18.7	219
4010	20.9	230
4011	16.4	232
4012	16.2	266
n	5	5
Mean	17.5	241
S.D.	2.3	20

Hematology
Sex : FemaleStage : End of recovery
Dose : crotonic acid 0 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
5106	771	14.0	40.4	52.4	18.2	34.7	1.8	92.6	36.6	76.7	19.4
5107	756	14.6	41.4	54.8	19.3	35.2	1.9	109.5	107.3	71.5	23.2
5108	785	14.2	41.1	52.4	18.1	34.6	1.8	94.8	42.6	84.4	12.4
5109	776	14.6	40.7	52.5	18.8	35.8	2.7	109.3	44.0	77.8	17.2
5110	893	15.8	46.1	51.6	17.7	34.2	1.6	112.1	68.0	87.2	8.1
n	5	5	5	5	5	5	5	5	5	5	5
Mean	796	14.6	41.9	52.7	18.4	34.9	2.0	103.7	59.7	79.5	16.1
S.D.	55	0.7	2.4	1.2	0.6	0.6	0.4	9.2	29.2	6.3	5.9

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
5106	1.8	0.2	1.6	0.3	28.1	7.1	0.6	0.1	0.6	0.1	13.1
5107	2.2	0.4	2.1	0.6	76.7	24.9	2.4	0.5	2.2	0.6	12.7
5108	1.4	0.2	1.2	0.5	35.9	5.3	0.6	0.1	0.5	0.2	12.0
5109	2.4	0.4	1.9	0.4	34.2	7.6	1.0	0.2	0.8	0.2	12.9
5110	2.2	0.6	1.1	0.8	59.3	5.5	1.5	0.4	0.7	0.6	12.6
n	5	5	5	5	5	5	5	5	5	5	5
Mean	2.0	0.4	1.6	0.5	46.8	10.1	1.2	0.3	1.0	0.3	12.7
S.D.	0.4	0.2	0.4	0.2	20.5	8.3	0.8	0.2	0.7	0.2	0.4

	APTT	FIB
Animal No.	s	mg/dL
5106	14.5	192
5107	15.3	208
5108	15.0	230
5109	14.5	184
5110	16.7	192
n	5	5
Mean	15.2	201
S.D.	0.9	18

Hematology

Stage : End of recovery

Dose : crotonic acid 500 mg/kg

Species : Rat

Sex : Female

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
6106	796	14.9	44.7	56.2	18.7	33.3	2.5	94.2	62.8	74.3	21.6
6107	805	14.7	43.5	54.1	18.3	33.8	2.1	103.8	49.1	84.5	12.1
6108	814	15.5	44.8	55.1	19.0	34.5	1.2	94.2	66.1	82.4	11.9
6109	785	14.3	41.2	52.6	18.3	34.7	2.1	108.0	71.9	84.5	12.3
6110	869	15.2	44.2	50.8	17.4	34.3	1.7	98.0	49.8	83.5	10.0
n	5	5	5	5	5	5	5	5	5	5	5
Mean	814	14.9	43.7	53.8	18.3	34.1	1.9	99.6	59.9	81.8	13.6
S.D.	33	0.5	1.5	2.1	0.6	0.6	0.5	6.1	10.1	4.3	4.6

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
6106	1.1	0.4	1.9	0.7	46.7	13.6	0.7	0.3	1.2	0.4	12.8
6107	1.7	0.4	0.9	0.4	41.5	5.9	0.9	0.2	0.4	0.2	12.8
6108	1.9	0.7	2.0	1.1	54.4	7.9	1.3	0.4	1.3	0.7	13.3
6109	1.1	0.3	1.4	0.4	60.7	8.9	0.8	0.2	1.0	0.3	12.3
6110	3.3	0.3	2.0	0.9	41.6	5.0	1.6	0.2	1.0	0.5	12.7
n	5	5	5	5	5	5	5	5	5	5	5
Mean	1.8	0.4	1.6	0.7	49.0	8.3	1.1	0.3	1.0	0.4	12.8
S.D.	0.9	0.2	0.5	0.3	8.4	3.4	0.4	0.1	0.3	0.2	0.4

	APTT	FIB
Animal No.	s	mg/dL
6106	15.6	191
6107	15.7	173
6108	15.6	205
6109	13.2	191
6110	16.1	219
n	5	5
Mean	15.2	196
S.D.	1.2	17

Hematology
Sex : FemaleStage : Not copulated
Dose : crotonic acid 50 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
2105	802	14.4	43.1	53.8	17.9	33.3	2.0	96.6	77.9	84.7	11.5
2108	761	14.3	42.9	56.3	18.8	33.4	2.1	103.3	81.7	83.0	12.9
n	2	2	2	2	2	2	2	2	2	2	2
Mean	782	14.4	43.0	55.1	18.4	33.4	2.1	100.0	79.8	83.9	12.2
S.D.	29	0.1	0.1	1.8	0.6	0.1	0.1	4.7	2.7	1.2	1.0

	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
2105	0.9	0.4	2.0	0.5	66.0	8.9	0.7	0.3	1.6	0.4	12.6
2108	2.0	0.3	1.1	0.8	67.8	10.5	1.6	0.2	0.9	0.6	12.5
n	2	2	2	2	2	2	2	2	2	2	2
Mean	1.5	0.4	1.6	0.7	66.9	9.7	1.2	0.3	1.3	0.5	12.6
S.D.	0.8	0.1	0.6	0.2	1.3	1.1	0.6	0.1	0.5	0.1	0.1

	APTT	FIB
Animal No.	s	mg/dL
2105	15.6	216
2108	16.3	200
n	2	2
Mean	16.0	208
S.D.	0.5	11

Hematology
Sex : Female

Stage : Not copulated
Dose : crotonic acid 150 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RETIC	PLT	WBC	LYMP	NEUT
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁴ /μL	10 ² /μL	%	%
3109	805	14.5	42.7	53.1	18.0	33.8	2.4	95.3	87.5	79.9	15.8
n	1	1	1	1	1	1	1	1	1	1	1
Mean	805	14.5	42.7	53.1	18.0	33.8	2.4	95.3	87.5	79.9	15.8
S.D.											
	EOS	BASO	MONO	LUC	#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC	PT
Animal No.	%	%	%	%	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	s
3109	1.7	0.5	1.4	0.7	69.9	13.8	1.5	0.4	1.2	0.6	13.6
n	1	1	1	1	1	1	1	1	1	1	1
Mean	1.7	0.5	1.4	0.7	69.9	13.8	1.5	0.4	1.2	0.6	13.6
S.D.											
	APTT	FIB									
Animal No.	s	mg/dL									
3109	16.7	210									
n	1	1									
Mean	16.7	210									
S.D.											

Blood chemistry

Stage : End of administration

Dose : crotonic acid 0 mg/kg

Species : Rat

Sex : Male

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
1001	62	40	57	1	385	16.8	54	13	85	0.1	180
1002	70	64	55	1	505	14.1	68	30	101	0.1	132
1003	60	46	44	2	402	17.1	68	21	98	0.1	148
1004	73	41	38	1	369	8.8	45	30	77	0.1	181
1005	63	42	58	1	283	10.0	58	25	90	0.1	179
n	5	5	5	5	5	5	5	5	5	5	5
Mean	66	47	50	1	389	13.4	59	24	90	0.1	164
S.D.	6	10	9	0	79	3.8	10	7	10	0.0	23

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
1001	15	0.32	142	4.8	105	9.6	5.7	6.3	3.1	1.0
1002	18	0.22	142	4.6	106	9.6	5.7	5.5	3.0	1.2
1003	17	0.18	144	4.4	107	9.6	5.6	6.0	3.2	1.1
1004	14	0.28	144	4.7	107	9.7	6.4	5.7	3.2	1.3
1005	20	0.27	142	4.7	106	9.7	5.9	5.9	3.0	1.0
n	5	5	5	5	5	5	5	5	5	5
Mean	17	0.25	143	4.6	106	9.6	5.9	5.9	3.1	1.1
S.D.	2	0.05	1	0.2	1	0.1	0.3	0.3	0.1	0.1

Blood chemistry

Stage : End of administration

Dose : crotonic acid 50 mg/kg

Species : Rat

Sex : Male

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
2001	56	47	39	1	723	21.4	54	14	85	0.1	157
2002	67	52	55	1	380	16.6	61	33	102	0.1	153
2003	61	44	32	1	386	6.4	47	26	75	0.1	151
2004	52	53	68	1	455	14.2	70	49	105	0.1	141
2005	64	42	34	1	587	10.8	55	20	84	0.1	138
n	5	5	5	5	5	5	5	5	5	5	5
Mean	60	48	46	1	506	13.9	57	28	90	0.1	148
S.D.	6	5	15	0	147	5.7	9	14	13	0.0	8

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
2001	18	0.27	142	4.6	107	9.3	5.7	5.4	3.0	1.3
2002	19	0.21	143	4.5	108	9.8	6.1	5.9	3.2	1.2
2003	13	0.23	143	4.5	108	9.3	5.9	5.4	3.0	1.3
2004	15	0.21	145	4.6	107	10.1	6.2	6.1	3.2	1.1
2005	15	0.28	144	4.3	107	9.6	6.7	5.7	3.1	1.2
n	5	5	5	5	5	5	5	5	5	5
Mean	16	0.24	143	4.5	107	9.6	6.1	5.7	3.1	1.2
S.D.	2	0.03	1	0.1	1	0.3	0.4	0.3	0.1	0.1

Blood chemistry

Stage : End of administration

Dose : crotonic acid 150 mg/kg

Species : Rat

Sex : Male

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
3001	55	36	52	1	425	10.0	52	14	81	0.1	146
3002	62	46	46	1	640	11.5	62	38	101	0.1	158
3003	70	44	47	1	537	24.6	54	17	83	0.1	149
3004	53	37	38	1	391	14.8	50	15	84	0.1	149
3005	60	32	37	0	547	10.6	41	18	70	0.1	148
n	5	5	5	5	5	5	5	5	5	5	5
Mean	60	39	44	1	508	14.3	52	20	84	0.1	150
S.D.	7	6	6	0	100	6.0	8	10	11	0.0	5

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
3001	14	0.23	144	4.0	107	9.5	5.5	5.8	3.1	1.1
3002	16	0.25	144	4.1	108	9.7	5.3	5.7	3.1	1.2
3003	17	0.30	141	4.4	105	9.6	5.6	5.5	3.0	1.2
3004	19	0.23	142	4.3	105	9.8	6.0	6.1	3.1	1.0
3005	17	0.31	143	4.5	108	9.4	5.9	5.8	3.2	1.2
n	5	5	5	5	5	5	5	5	5	5
Mean	17	0.26	143	4.3	107	9.6	5.7	5.8	3.1	1.1
S.D.	2	0.04	1	0.2	2	0.2	0.3	0.2	0.1	0.1

Blood chemistry

Stage : End of administration

Dose : crotonic acid 500 mg/kg

Species : Rat

Sex : Male

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
4001	52	39	41	1	292	18.3	56	36	90	0.1	138
4002	61	47	51	1	441	17.5	55	33	89	0.1	147
4003	58	32	47	1	445	6.1	58	30	90	0.1	153
4004	67	47	48	1	512	16.6	73	41	112	0.1	118
4005	57	34	34	1	402	5.9	59	29	87	0.1	165
n	5	5	5	5	5	5	5	5	5	5	5
Mean	59	40	44	1	418	12.9	60	34	94	0.1	144
S.D.	6	7	7	0	81	6.3	7	5	10	0.0	18

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
4001	16	0.20	142	4.7	107	9.2	5.8	5.3	2.8	1.1
4002	14	0.25	144	4.6	106	9.7	5.8	5.6	3.1	1.2
4003	16	0.32	144	4.6	108	9.9	6.0	5.5	2.9	1.1
4004	15	0.25	143	4.6	107	9.5	6.2	5.5	3.0	1.2
4005	17	0.23	143	4.8	108	9.3	6.1	5.1	2.9	1.3
n	5	5	5	5	5	5	5	5	5	5
Mean	16	0.25	143	4.7	107	9.5	6.0	5.4	2.9	1.2
S.D.	1	0.04	1	0.1	1	0.3	0.2	0.2	0.1	0.1

Blood chemistry

Stage : Lactation day 5

Dose : crotonic acid 0 mg/kg

Species : Rat

Sex : Female

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
1101	66	67	36	1	194	25.1	45	63	104	0.1	115
1104	76	68	33	1	325	13.8	36	101	90	0.1	132
1105	83	61	35	1	228	22.4	56	85	116	0.1	128
1107	60	66	54	1	296	29.7	52	66	107	0.1	176
1108	95	65	36	1	504	17.8	51	27	110	0.1	112
n	5	5	5	5	5	5	5	5	5	5	5
Mean	76	65	39	1	309	21.8	48	68	105	0.1	133
S.D.	14	3	9	0	121	6.2	8	28	10	0.0	26

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
1101	27	0.27	141	4.6	106	10.8	8.5	6.1	3.5	1.3
1104	24	0.28	141	4.4	105	10.1	6.5	6.1	3.3	1.2
1105	24	0.23	141	4.4	106	10.6	5.8	6.3	3.4	1.2
1107	25	0.29	141	4.2	105	10.4	7.7	5.7	3.2	1.3
1108	21	0.26	142	4.6	109	10.4	6.2	6.3	3.5	1.3
n	5	5	5	5	5	5	5	5	5	5
Mean	24	0.27	141	4.4	106	10.5	6.9	6.1	3.4	1.3
S.D.	2	0.02	0	0.2	2	0.3	1.1	0.2	0.1	0.1

Blood chemistry

Stage : Lactation day 5

Dose : crotonic acid 50 mg/kg

Species : Rat

Sex : Female

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
2101	54	41	43	1	259	129.3	54	25	103	0.1	144
2102	70	60	38	1	276	10.0	52	90	117	0.0	133
2103	71	56	35	1	246	28.8	63	92	130	0.1	125
2107	80	77	50	2	279	8.5	55	52	108	0.1	142
2109	83	52	37	1	172	25.7	67	118	139	0.1	111
n	5	5	5	5	5	5	5	5	5	5	5
Mean	72	57	41	1	246	40.5	58	75	119	0.1	131
S.D.	11	13	6	0	44	50.5	6	37	15	0.0	14

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
2101	24	0.25	140	4.5	107	10.0	7.3	5.9	3.1	1.1
2102	25	0.24	142	4.5	105	10.9	7.7	6.6	3.5	1.1
2103	16	0.20	140	4.5	105	10.9	6.9	6.5	3.5	1.2
2107	20	0.26	141	4.6	106	9.7	6.8	5.8	3.2	1.2
2109	16	0.19	142	4.4	105	10.9	6.9	6.3	3.5	1.3
n	5	5	5	5	5	5	5	5	5	5
Mean	20	0.23	141	4.5	106	10.5	7.1	6.2	3.4	1.2
S.D.	4	0.03	1	0.1	1	0.6	0.4	0.4	0.2	0.1

Blood chemistry

Sex : Female

Stage : Lactation day 5

Dose : crotonic acid 150 mg/kg

Species : Rat

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
3101	66	57	32	1	356	27.9	58	144	137	0.1	155
3103	71	63	37	1	224	15.7	63	68	125	0.1	147
3105	72	82	41	1	552	16.7	64	112	136	0.1	139
3107	100	92	29	2	345	29.0	56	88	119	0.1	163
3112	131	51	74	1	146	9.0	43	60	94	0.1	133
n	5	5	5	5	5	5	5	5	5	5	5
Mean	88	69	43	1	325	19.7	57	94	122	0.1	147
S.D.	27	17	18	0	154	8.6	8	34	17	0.0	12

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
3101	22	0.25	141	4.7	108	9.9	5.9	5.9	3.4	1.4
3103	17	0.24	142	4.0	107	10.1	6.9	5.8	3.2	1.2
3105	24	0.28	142	4.0	107	10.2	6.2	5.7	3.0	1.1
3107	27	0.25	141	4.7	101	11.0	8.0	6.1	3.2	1.1
3112	12	0.21	141	4.3	105	10.3	8.5	6.2	3.3	1.1
n	5	5	5	5	5	5	5	5	5	5
Mean	20	0.25	141	4.3	106	10.3	7.1	5.9	3.2	1.2
S.D.	6	0.03	1	0.4	3	0.4	1.1	0.2	0.1	0.1

Blood chemistry

Stage : Lactation day 5

Dose : crotonic acid 500 mg/kg

Species : Rat

Sex : Female

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
4104	73	63	36	1	197	19.4	57	92	116	0.0	125
4105	64	57	24	2	182	11.1	49	86	109	0.1	118
4106	59	51	33	1	185	18.5	53	145	124	0.1	117
4109	89	75	61	1	202	22.7	53	105	124	0.1	112
4110	69	61	29	1	183	17.0	54	135	127	0.1	119
n	5	5	5	5	5	5	5	5	5	5	5
Mean	71	61	37	1	190	17.7	53	113	120	0.1	118
S.D.	11	9	14	0	9	4.3	3	26	7	0.0	5

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
4104	17	0.21	141	4.9	106	10.4	6.9	6.0	3.3	1.2
4105	25	0.23	142	4.0	107	10.7	6.2	6.0	3.3	1.2
4106	17	0.22	139	4.1	105	10.6	7.0	6.3	3.5	1.3
4109	23	0.22	138	4.8	104	10.3	6.6	6.1	3.3	1.2
4110	20	0.22	139	4.4	105	10.6	6.9	6.2	3.4	1.2
n	5	5	5	5	5	5	5	5	5	5
Mean	20	0.22	140	4.4	105	10.5	6.7	6.1	3.4	1.2
S.D.	4	0.01	2	0.4	1	0.2	0.3	0.1	0.1	0.0

Blood chemistry

Stage : End of administration

Dose : crotonic acid 0 mg/kg

Species : Rat

Sex : Female

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
5101	64	51	28	1	269	33.9	70	13	130	0.1	117
5102	62	56	31	1	341	108.3	56	18	103	0.1	135
5103	64	36	32	0	293	39.6	71	22	139	0.1	120
5104	49	26	32	1	165	12.6	71	15	148	0.1	148
5105	54	31	27	1	179	6.5	62	18	127	0.1	133
n	5	5	5	5	5	5	5	5	5	5	5
Mean	59	40	30	1	249	40.2	66	17	129	0.1	131
S.D.	7	13	2	0	75	40.5	7	3	17	0.0	13

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
5101	25	0.33	140	4.4	106	9.5	4.6	5.7	3.3	1.4
5102	19	0.30	139	3.6	106	9.9	4.4	6.0	3.4	1.3
5103	18	0.32	141	3.9	107	9.8	3.8	6.0	3.3	1.2
5104	14	0.27	142	3.4	108	10.0	3.6	6.8	3.9	1.3
5105	14	0.24	140	3.9	106	9.8	4.6	6.3	3.4	1.2
n	5	5	5	5	5	5	5	5	5	5
Mean	18	0.29	140	3.8	107	9.8	4.2	6.2	3.5	1.3
S.D.	5	0.04	1	0.4	1	0.2	0.5	0.4	0.3	0.1

Blood chemistry

Sex : Female

Stage : End of administration

Dose : crotonic acid 500 mg/kg

Species : Rat

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
6101	54	34	34	1	371	28.5	59	21	128	0.1	142
6102	52	39	39	1	160	14.1	51	29	119	0.1	138
6103	66	73	28	2	450	40.3	53	19	108	0.1	131
6104	51	26	44	1	174	21.2	51	17	111	0.1	117
6105	68	35	28	1	161	8.5	64	29	127	0.1	119
n	5	5	5	5	5	5	5	5	5	5	5
Mean	58	41	35	1	263	22.5	56	23	119	0.1	129
S.D.	8	18	7	0	137	12.5	6	6	9	0.0	11

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
6101	25	0.33	140	4.1	106	9.6	4.0	5.9	3.6	1.6
6102	15	0.26	144	3.8	111	10.0	3.1	5.9	3.5	1.5
6103	15	0.28	145	4.1	107	9.5	4.2	5.6	3.1	1.2
6104	22	0.34	143	4.3	107	9.9	4.6	6.1	3.4	1.3
6105	16	0.32	141	4.1	108	9.5	4.7	5.5	3.2	1.4
n	5	5	5	5	5	5	5	5	5	5
Mean	19	0.31	143	4.1	108	9.7	4.1	5.8	3.4	1.4
S.D.	5	0.03	2	0.2	2	0.2	0.6	0.2	0.2	0.2

Blood chemistry

Stage : End of recovery

Dose : crotonic acid 0 mg/kg

Species : Rat

Sex : Male

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
1008	52	37	35	1	261	9.2	52	83	94	0.1	166
1009	66	43	67	0	375	46.8	55	48	91	0.1	156
1010	61	40	39	1	339	8.6	43	32	73	0.1	161
1011	69	55	43	1	416	8.1	44	24	70	0.1	203
1012	64	49	44	1	363	6.1	52	40	86	0.1	126
n	5	5	5	5	5	5	5	5	5	5	5
Mean	62	45	46	1	351	15.8	49	45	83	0.1	162
S.D.	7	7	12	0	57	17.4	5	23	11	0.0	28

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
1008	15	0.22	140	5.0	103	9.5	5.1	6.2	3.3	1.1
1009	18	0.24	144	4.2	108	9.4	5.4	5.7	3.0	1.1
1010	18	0.20	142	4.9	105	9.0	5.3	5.7	2.9	1.0
1011	19	0.23	142	4.6	106	9.1	5.0	5.4	2.8	1.1
1012	18	0.22	142	4.7	106	9.3	5.1	5.7	2.9	1.0
n	5	5	5	5	5	5	5	5	5	5
Mean	18	0.22	142	4.7	106	9.3	5.2	5.7	3.0	1.1
S.D.	2	0.01	1	0.3	2	0.2	0.2	0.3	0.2	0.1

Blood chemistry

Stage : End of recovery

Dose : crotonic acid 500 mg/kg

Species : Rat

Sex : Male

	AST	ALT	LDH	γ-GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
4008	295	136	92	1	355	8.5	67	45	97	0.1	122
4009	66	52	57	1	377	22.9	61	53	95	0.1	150
4010	69	46	52	1	452	43.5	59	28	99	0.1	165
4011	67	50	41	1	314	8.5	32	34	63	0.1	170
4012	60	46	33	1	345	5.0	40	28	71	0.1	166
n	5	5	5	5	5	5	5	5	5	5	5
Mean	111	66	55	1	369	17.7	52	38	85	0.1	155
S.D.	103	39	23	0	52	16.0	15	11	17	0.0	20

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
4008	16	0.24	143	3.9	103	9.1	4.6	5.0	2.6	1.1
4009	18	0.21	143	4.6	105	9.6	5.2	6.2	3.1	1.0
4010	25	0.24	142	5.2	105	9.5	5.7	6.0	3.1	1.1
4011	20	0.26	142	4.6	107	9.6	5.0	5.6	3.0	1.2
4012	22	0.25	143	4.4	107	9.5	5.3	5.7	2.9	1.0
n	5	5	5	5	5	5	5	5	5	5
Mean	20	0.24	143	4.5	105	9.5	5.2	5.7	2.9	1.1
S.D.	3	0.02	1	0.5	2	0.2	0.4	0.5	0.2	0.1

Blood chemistry

Stage : End of recovery

Dose : crotonic acid 0 mg/kg

Species : Rat

Sex : Female

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
5106	57	35	35	2	366	9.2	42	25	93	0.1	180
5107	55	38	34	2	160	8.9	75	77	148	0.1	156
5108	61	31	41	1	187	17.6	67	17	132	0.1	172
5109	48	27	31	1	184	14.7	58	13	122	0.1	145
5110	49	29	33	0	180	11.8	50	17	103	0.1	110
n	5	5	5	5	5	5	5	5	5	5	5
Mean	54	32	35	1	215	12.4	58	30	120	0.1	153
S.D.	5	4	4	1	85	3.7	13	27	22	0.0	27

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
5106	19	0.24	139	4.6	107	9.9	4.5	6.2	3.4	1.2
5107	18	0.24	139	4.4	106	9.8	4.6	6.0	3.4	1.3
5108	20	0.29	140	4.2	107	9.9	5.2	6.2	3.5	1.3
5109	19	0.26	143	4.0	109	9.9	5.1	6.3	3.7	1.4
5110	18	0.30	142	4.1	108	9.7	4.4	6.4	3.4	1.1
n	5	5	5	5	5	5	5	5	5	5
Mean	19	0.27	141	4.3	107	9.8	4.8	6.2	3.5	1.3
S.D.	1	0.03	2	0.2	1	0.1	0.4	0.1	0.1	0.1

Blood chemistry

Sex : Female

Stage : End of recovery

Dose : crotonic acid 500 mg/kg

Species : Rat

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
6106	63	37	42	1	119	12.6	57	36	134	0.1	176
6107	76	34	45	1	283	8.6	46	15	96	0.1	150
6108	52	36	54	1	167	17.8	68	34	133	0.1	154
6109	60	42	42	1	247	53.8	53	27	119	0.1	131
6110	57	28	27	1	192	36.5	73	23	142	0.1	180
n	5	5	5	5	5	5	5	5	5	5	5
Mean	62	35	42	1	202	25.9	59	27	125	0.1	158
S.D.	9	5	10	0	65	18.9	11	9	18	0.0	20

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
6106	19	0.31	140	3.9	108	10.1	3.5	6.9	4.0	1.4
6107	18	0.27	142	4.2	108	9.1	5.0	5.9	3.2	1.2
6108	19	0.36	142	4.2	108	9.9	5.1	6.0	3.5	1.4
6109	16	0.23	142	4.8	109	9.7	4.9	6.3	3.5	1.3
6110	23	0.34	140	4.9	108	10.2	6.3	6.2	3.5	1.3
n	5	5	5	5	5	5	5	5	5	5
Mean	19	0.30	141	4.4	108	9.8	5.0	6.3	3.5	1.3
S.D.	3	0.05	1	0.4	0	0.4	1.0	0.4	0.3	0.1

Blood chemistry

Stage : Not copulated

Dose : crotonic acid 50 mg/kg

Species : Rat

Sex : Female

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
2105	52	34	34	1	222	20.1	64	34	124	0.1	164
2108	50	39	36	1	203	47.5	64	42	126	0.1	141
n	2	2	2	2	2	2	2	2	2	2	2
Mean	51	37	35	1	213	33.8	64	38	125	0.1	153
S.D.	1	4	1	0	13	19.4	0	6	1	0.0	16

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
2105	14	0.23	141	4.1	105	9.9	3.9	6.1	3.4	1.3
2108	17	0.24	141	3.7	106	10.3	4.8	6.0	3.6	1.5
n	2	2	2	2	2	2	2	2	2	2
Mean	16	0.24	141	3.9	106	10.1	4.4	6.1	3.5	1.4
S.D.	2	0.01	0	0.3	1	0.3	0.6	0.1	0.1	0.1

Blood chemistry
Sex : FemaleStage : Not copulated
Dose : crotonic acid 150 mg/kg

Species : Rat

	AST	ALT	LDH	γ -GTP	ALP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Animal No.	IU/L	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
3109	54	29	30	1	303	19.8	71	25	135	0.1	151
n	1	1	1	1	1	1	1	1	1	1	1
Mean	54	29	30	1	303	19.8	71	25	135	0.1	151
S.D.											

	BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB	A/G
Animal No.	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL	
3109	20	0.27	141	4.0	109	9.7	4.1	6.1	3.5	1.3
n	1	1	1	1	1	1	1	1	1	1
Mean	20	0.27	141	4.0	109	9.7	4.1	6.1	3.5	1.3
S.D.										

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
1001	558	2.11	0.38	14.2	2.5	5.0	0.9	6.6	1.2
1002	514	2.08	0.40	12.8	2.5	10.9	2.1	9.4	1.8
1003	504	2.17	0.43	15.9	3.2	13.9	2.8	17.6	3.5
1004	544	2.18	0.40	14.2	2.6	11.6	2.1	11.0	2.0
1005	557	2.11	0.38	11.1	2.0	9.6	1.7	8.6	1.5
1006	474	2.08	0.44	13.1	2.8	10.5	2.2	7.8	1.6
1007	527	2.15	0.41	13.2	2.5	10.5	2.0	12.0	2.3
n	7	7	7	7	7	7	7	7	7
Mean	525	2.13	0.41	13.5	2.6	10.3	2.0	10.4	2.0
S.D.	31	0.04	0.02	1.5	0.4	2.7	0.6	3.7	0.8

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
1001	11.6	2.1	227	41	1.81	0.32	15.75	2.82	0.99	0.18
1002	20.3	3.9	344	67	1.59	0.31	12.85	2.50	0.85	0.17
1003	31.5	6.3	319	63	1.36	0.27	12.81	2.54	0.68	0.13
1004	22.6	4.2	264	49	1.59	0.29	13.37	2.46	0.64	0.12
1005	18.2	3.3	285	51	1.47	0.26	13.74	2.47	0.74	0.13
1006	18.3	3.9	184	39	1.53	0.32	12.18	2.57	0.63	0.13
1007	22.5	4.3	272	52	1.54	0.29	14.81	2.81	0.81	0.15
n	7	7	7	7	7	7	7	7	7	7
Mean	20.7	4.0	271	52	1.56	0.29	13.64	2.60	0.76	0.14
S.D.	6.0	1.3	54	10	0.14	0.02	1.25	0.15	0.13	0.02

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
1001	1.64	0.29	1.96	0.35	3.60	0.65	29	5	33	6
1002	1.75	0.34	1.83	0.36	3.58	0.70	24	5	25	5
1003	1.73	0.34	1.68	0.33	3.41	0.68	27	5	20	4
1004	1.55	0.28	1.55	0.28	3.10	0.57	32	6	35	6
1005	1.59	0.29	1.60	0.29	3.19	0.57	34	6	37	7
1006	1.59	0.34	1.57	0.33	3.16	0.67	24	5	25	5
1007	1.70	0.32	1.75	0.33	3.45	0.65	31	6	35	7
n	7	7	7	7	7	7	7	7	7	7
Mean	1.65	0.31	1.71	0.32	3.36	0.64	29	5	30	6
S.D.	0.08	0.03	0.15	0.03	0.21	0.05	4	1	7	1

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Adrenal-RL		Testis-R		Testis-L		Testis-RL		Epididymis-R	
	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g
1001	62	11	1.84	0.33	1.79	0.32	3.63	0.65	724	130
1002	49	10	1.78	0.35	1.69	0.33	3.47	0.68	650	126
1003	47	9	1.73	0.34	1.72	0.34	3.45	0.68	619	123
1004	67	12	1.63	0.30	1.64	0.30	3.27	0.60	645	119
1005	71	13	1.56	0.28	1.58	0.28	3.14	0.56	623	112
1006	49	10	1.72	0.36	1.69	0.36	3.41	0.72	598	126
1007	66	13	1.52	0.29	1.50	0.28	3.02	0.57	582	110
n	7	7	7	7	7	7	7	7	7	7
Mean	59	11	1.68	0.32	1.66	0.32	3.34	0.64	634	121
S.D.	10	2	0.12	0.03	0.10	0.03	0.21	0.06	46	8

Animal No.	Epididymis-L		Epididymis-RL		Prostate		Seminalvesicle	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g
1001	643	115	1367	245	1.16	0.21	2.16	0.39
1002	650	126	1300	253	1.44	0.28	1.77	0.34
1003	618	123	1237	245	1.15	0.23	1.56	0.31
1004	587	108	1232	226	0.95	0.17	1.57	0.29
1005	622	112	1245	224	1.48	0.27	1.98	0.36
1006	598	126	1196	252	1.15	0.24	1.61	0.34
1007	547	104	1129	214	1.36	0.26	1.76	0.33
n	7	7	7	7	7	7	7	7
Mean	609	116	1244	237	1.24	0.24	1.77	0.34
S.D.	35	9	75	15	0.19	0.04	0.23	0.03

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 50 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
2001	508	2.03	0.40	11.5	2.3	8.9	1.8	8.6	1.7
2002	479	2.15	0.45	11.5	2.4	11.1	2.3	11.7	2.4
2003	516	2.09	0.41	15.0	2.9	13.2	2.6	7.8	1.5
2004	558	2.26	0.41	16.5	3.0	12.3	2.2	12.8	2.3
2005	507	2.02	0.40	13.3	2.6	13.6	2.7	13.0	2.6
2006	505	2.25	0.45	15.6	3.1	11.7	2.3	10.5	2.1
2007	498	2.08	0.42	11.7	2.3	11.8	2.4	10.8	2.2
2008	499	2.33	0.47	16.0	3.2	13.5	2.7	15.5	3.1
2009	512	2.07	0.40	12.4	2.4	12.0	2.3	13.5	2.6
2010	514	2.20	0.43	12.7	2.5	10.5	2.0	9.5	1.8
2011	479	2.23	0.47	10.3	2.2	11.7	2.4	10.0	2.1
2012	509	2.15	0.42	13.1	2.6	11.9	2.3	10.5	2.1
n	12	12	12	12	12	12	12	12	12
Mean	507	2.16	0.43	13.3	2.6	11.9	2.3	11.2	2.2
S.D.	20	0.10	0.03	2.0	0.3	1.3	0.3	2.2	0.4

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
2001	17.5	3.4	443	87	1.59	0.31	12.70	2.50	0.84	0.17
2002	22.8	4.8	321	67	1.54	0.32	11.93	2.49	0.79	0.16
2003	21.0	4.1	270	52	1.30	0.25	12.70	2.46	0.59	0.11
2004	25.1	4.5	362	65	1.73	0.31	16.57	2.97	0.92	0.16
2005	26.6	5.2	268	53	1.51	0.30	11.63	2.29	0.76	0.15
2006	22.2	4.4	377	75	1.42	0.28	13.67	2.71	0.85	0.17
2007	22.6	4.5	389	78	1.51	0.30	10.83	2.17	0.71	0.14
2008	29.0	5.8	254	51	1.43	0.29	12.53	2.51	0.54	0.11
2009	25.5	5.0	305	60	1.52	0.30	13.63	2.66	0.82	0.16
2010	20.0	3.9	370	72	1.59	0.31	14.06	2.74	0.66	0.13
2011	21.7	4.5	346	72	1.35	0.28	12.18	2.54	0.92	0.19
2012	22.4	4.4	265	52	1.43	0.28	14.46	2.84	0.64	0.13
n	12	12	12	12	12	12	12	12	12	12
Mean	23.0	4.5	331	65	1.49	0.29	13.07	2.57	0.75	0.15
S.D.	3.1	0.6	60	12	0.12	0.02	1.53	0.22	0.13	0.02

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 50 mg/kg

Species : Rat

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
2001	1.61	0.32	1.58	0.31	3.19	0.63	25	5	27	5
2002	1.48	0.31	1.59	0.33	3.07	0.64	36	8	39	8
2003	1.69	0.33	1.70	0.33	3.39	0.66	39	8	42	8
2004	1.85	0.33	1.89	0.34	3.74	0.67	32	6	34	6
2005	1.59	0.31	1.58	0.31	3.17	0.63	23	5	20	4
2006	1.67	0.33	1.82	0.36	3.49	0.69	23	5	24	5
2007	1.78	0.36	1.86	0.37	3.64	0.73	33	7	35	7
2008	1.53	0.31	1.60	0.32	3.13	0.63	30	6	35	7
2009	1.58	0.31	1.54	0.30	3.12	0.61	30	6	34	7
2010	1.69	0.33	1.69	0.33	3.38	0.66	29	6	31	6
2011	1.52	0.32	1.41	0.29	2.93	0.61	24	5	28	6
2012	1.64	0.32	1.71	0.34	3.35	0.66	31	6	34	7
n	12	12	12	12	12	12	12	12	12	12
Mean	1.64	0.32	1.66	0.33	3.30	0.65	30	6	32	6
S.D.	0.11	0.01	0.14	0.02	0.24	0.03	5	1	6	1

Animal No.	Adrenal-RL		Testis-R		Testis-L		Testis-RL		Epididymis-R	
	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g
2001	52	10	1.71	0.34	1.65	0.32	3.36	0.66	675	133
2002	75	16	1.59	0.33	1.62	0.34	3.21	0.67	606	127
2003	81	16	1.63	0.32	1.64	0.32	3.27	0.63	676	131
2004	66	12	1.84	0.33	1.79	0.32	3.63	0.65	692	124
2005	43	8	1.61	0.32	1.62	0.32	3.23	0.64	620	122
2006	47	9	1.84	0.36	1.88	0.37	3.72	0.74	650	129
2007	68	14	1.62	0.33	1.62	0.33	3.24	0.65	683	137
2008	65	13	1.68	0.34	1.69	0.34	3.37	0.68	691	138
2009	64	13	1.63	0.32	1.64	0.32	3.27	0.64	579	113
2010	60	12	1.74	0.34	1.81	0.35	3.55	0.69	659	128
2011	52	11	1.69	0.35	1.68	0.35	3.37	0.70	658	137
2012	65	13	1.56	0.31	1.58	0.31	3.14	0.62	591	116
n	12	12	12	12	12	12	12	12	12	12
Mean	62	12	1.68	0.33	1.69	0.33	3.36	0.66	648	128
S.D.	11	2	0.09	0.01	0.09	0.02	0.18	0.03	40	8

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 50 mg/kg

Species : Rat

Animal No.	Epididymis-L		Epididymis-RL		Prostate		Seminalvesicle	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g
2001	672	132	1347	265	1.30	0.26	1.75	0.34
2002	638	133	1244	260	0.97	0.20	2.01	0.42
2003	697	135	1373	266	1.48	0.29	2.28	0.44
2004	689	123	1381	247	1.40	0.25	1.81	0.32
2005	571	113	1191	235	1.31	0.26	1.64	0.32
2006	685	136	1335	264	1.34	0.27	1.42	0.28
2007	619	124	1302	261	1.09	0.22	1.50	0.30
2008	704	141	1395	280	1.33	0.27	1.72	0.34
2009	592	116	1171	229	1.20	0.23	1.45	0.28
2010	726	141	1385	269	1.34	0.26	1.91	0.37
2011	618	129	1276	266	1.10	0.23	1.35	0.28
2012	594	117	1185	233	1.32	0.26	1.76	0.35
n	12	12	12	12	12	12	12	12
Mean	650	128	1299	256	1.27	0.25	1.72	0.34
S.D.	51	10	84	16	0.15	0.03	0.27	0.05

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 150 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
3001	490	2.06	0.42	13.6	2.8	10.4	2.1	9.3	1.9
3002	504	2.11	0.42	13.3	2.6	9.6	1.9	11.3	2.2
3003	483	2.09	0.43	13.9	2.9	9.7	2.0	11.4	2.4
3004	471	2.10	0.45	11.7	2.5	11.5	2.4	10.5	2.2
3005	472	2.02	0.43	12.0	2.5	11.1	2.4	10.4	2.2
3006	491	2.05	0.42	12.7	2.6	12.4	2.5	12.1	2.5
3007	505	2.09	0.41	11.9	2.4	11.3	2.2	10.4	2.1
3008	532	2.25	0.42	13.3	2.5	13.4	2.5	13.3	2.5
3009	537	2.30	0.43	14.4	2.7	12.7	2.4	11.4	2.1
3010	501	2.16	0.43	12.6	2.5	13.0	2.6	11.3	2.3
3011	457	2.33	0.51	13.8	3.0	10.9	2.4	12.8	2.8
3012	515	2.01	0.39	12.9	2.5	13.1	2.5	11.6	2.3
n	12	12	12	12	12	12	12	12	12
Mean	497	2.13	0.43	13.0	2.6	11.6	2.3	11.3	2.3
S.D.	24	0.11	0.03	0.9	0.2	1.3	0.2	1.1	0.2

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
3001	19.7	4.0	196	40	1.40	0.29	13.01	2.66	0.83	0.17
3002	20.9	4.1	199	39	1.47	0.29	13.40	2.66	0.70	0.14
3003	21.1	4.4	246	51	1.41	0.29	10.69	2.21	0.92	0.19
3004	22.0	4.7	263	56	1.40	0.30	13.84	2.94	0.71	0.15
3005	21.5	4.6	330	70	1.50	0.32	12.56	2.66	0.60	0.13
3006	24.5	5.0	264	54	1.36	0.28	12.02	2.45	0.58	0.12
3007	21.7	4.3	293	58	1.64	0.32	13.88	2.75	0.84	0.17
3008	26.7	5.0	464	87	1.38	0.26	12.98	2.44	0.57	0.11
3009	24.1	4.5	325	61	1.50	0.28	14.10	2.63	0.57	0.11
3010	24.3	4.9	324	65	1.36	0.27	11.86	2.37	0.80	0.16
3011	23.7	5.2	212	46	1.39	0.30	11.60	2.54	0.58	0.13
3012	24.7	4.8	256	50	1.41	0.27	13.36	2.59	0.69	0.13
n	12	12	12	12	12	12	12	12	12	12
Mean	22.9	4.6	281	56	1.44	0.29	12.78	2.58	0.70	0.14
S.D.	2.0	0.4	74	13	0.08	0.02	1.05	0.19	0.12	0.03

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 150 mg/kg

Species : Rat

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
3001	1.56	0.32	1.57	0.32	3.13	0.64	23	5	22	4
3002	1.57	0.31	1.68	0.33	3.25	0.64	25	5	29	6
3003	1.31	0.27	1.46	0.30	2.77	0.57	22	5	26	5
3004	1.52	0.32	1.50	0.32	3.02	0.64	36	8	35	7
3005	1.41	0.30	1.37	0.29	2.78	0.59	31	7	33	7
3006	1.77	0.36	1.82	0.37	3.59	0.73	30	6	30	6
3007	1.68	0.33	1.74	0.34	3.42	0.68	31	6	31	6
3008	1.52	0.29	1.61	0.30	3.13	0.59	27	5	28	5
3009	1.77	0.33	1.77	0.33	3.54	0.66	34	6	36	7
3010	1.51	0.30	1.62	0.32	3.13	0.62	29	6	32	6
3011	1.67	0.37	1.55	0.34	3.22	0.70	27	6	31	7
3012	1.67	0.32	1.69	0.33	3.36	0.65	24	5	26	5
n	12	12	12	12	12	12	12	12	12	12
Mean	1.58	0.32	1.62	0.32	3.20	0.64	28	6	30	6
S.D.	0.14	0.03	0.13	0.02	0.26	0.05	4	1	4	1

Animal No.	Adrenal-RL		Testis-R		Testis-L		Testis-RL		Epididymis-R	
	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g
3001	45	9	1.61	0.33	1.56	0.32	3.17	0.65	632	129
3002	54	11	1.70	0.34	1.64	0.33	3.34	0.66	652	129
3003	48	10	1.60	0.33	1.61	0.33	3.21	0.66	629	130
3004	71	15	1.53	0.32	1.55	0.33	3.08	0.65	608	129
3005	64	14	1.48	0.31	1.56	0.33	3.04	0.64	692	147
3006	60	12	1.57	0.32	1.59	0.32	3.16	0.64	602	123
3007	62	12	1.76	0.35	1.74	0.34	3.50	0.69	654	130
3008	55	10	1.51	0.28	1.54	0.29	3.05	0.57	549	103
3009	70	13	1.52	0.28	1.55	0.29	3.07	0.57	549	102
3010	61	12	1.86	0.37	1.83	0.37	3.69	0.74	685	137
3011	58	13	1.86	0.41	1.83	0.40	3.69	0.81	712	156
3012	50	10	1.50	0.29	1.51	0.29	3.01	0.58	582	113
n	12	12	12	12	12	12	12	12	12	12
Mean	58	12	1.63	0.33	1.63	0.33	3.25	0.66	629	127
S.D.	8	2	0.14	0.04	0.11	0.03	0.25	0.07	53	16

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 150 mg/kg

Species : Rat

Animal No.	Epididymis-L		Epididymis-RL		Prostate		Seminalvesicle	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g
3001	607	124	1239	253	1.12	0.23	1.80	0.37
3002	623	124	1275	253	1.29	0.26	1.77	0.35
3003	628	130	1257	260	1.14	0.24	1.91	0.40
3004	591	125	1199	255	1.12	0.24	1.58	0.34
3005	651	138	1343	285	0.98	0.21	2.28	0.48
3006	598	122	1200	244	1.58	0.32	2.03	0.41
3007	657	130	1311	260	1.45	0.29	1.89	0.37
3008	567	107	1116	210	0.75	0.14	1.22	0.23
3009	583	109	1132	211	1.36	0.25	1.42	0.26
3010	744	149	1429	285	1.27	0.25	2.15	0.43
3011	673	147	1385	303	1.72	0.38	1.80	0.39
3012	588	114	1170	227	1.21	0.23	1.62	0.31
n	12	12	12	12	12	12	12	12
Mean	626	127	1255	254	1.25	0.25	1.79	0.36
S.D.	49	13	98	29	0.26	0.06	0.30	0.07

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
4001	469	2.10	0.45	12.2	2.6	8.5	1.8	9.3	2.0
4002	496	2.11	0.43	16.4	3.3	12.0	2.4	13.6	2.7
4003	542	2.21	0.41	14.1	2.6	10.6	2.0	8.6	1.6
4004	451	1.97	0.44	13.0	2.9	12.4	2.7	9.5	2.1
4005	456	2.10	0.46	12.5	2.7	14.7	3.2	13.2	2.9
4006	466	2.28	0.49	13.5	2.9	9.6	2.1	10.5	2.3
4007	457	2.12	0.46	10.7	2.3	11.4	2.5	9.5	2.1
n	7	7	7	7	7	7	7	7	7
Mean	477	2.13	0.45	13.2	2.8	11.3	2.4	10.6	2.2
S.D.	32	0.10	0.03	1.8	0.3	2.0	0.5	2.0	0.4

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
4001	17.8	3.8	297	63	1.48	0.32	12.76	2.72	0.83	0.18
4002	25.6	5.2	195	39	1.40	0.28	12.91	2.60	0.75	0.15
4003	19.2	3.5	246	45	1.31	0.24	14.62	2.70	0.64	0.12
4004	21.9	4.9	282	63	1.22	0.27	12.46	2.76	0.76	0.17
4005	27.9	6.1	175	38	1.24	0.27	12.44	2.73	0.81	0.18
4006	20.1	4.3	328	70	1.43	0.31	12.09	2.59	0.64	0.14
4007	20.9	4.6	273	60	1.25	0.27	11.09	2.43	0.62	0.14
n	7	7	7	7	7	7	7	7	7	7
Mean	21.9	4.6	257	54	1.33	0.28	12.62	2.65	0.72	0.15
S.D.	3.6	0.9	55	13	0.10	0.03	1.06	0.12	0.09	0.02

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
4001	1.65	0.35	1.72	0.37	3.37	0.72	27	6	32	7
4002	1.65	0.33	1.78	0.36	3.43	0.69	25	5	29	6
4003	1.63	0.30	1.62	0.30	3.25	0.60	32	6	37	7
4004	1.47	0.33	1.68	0.37	3.15	0.70	26	6	30	7
4005	1.59	0.35	1.52	0.33	3.11	0.68	33	7	35	8
4006	1.73	0.37	1.74	0.37	3.47	0.74	25	5	25	5
4007	1.39	0.30	1.37	0.30	2.76	0.60	24	5	25	5
n	7	7	7	7	7	7	7	7	7	7
Mean	1.59	0.33	1.63	0.34	3.22	0.68	27	6	30	6
S.D.	0.12	0.03	0.14	0.03	0.24	0.06	4	1	5	1

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Adrenal-RL		Testis-R		Testis-L		Testis-RL		Epididymis-R	
	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g
4001	59	13	1.53	0.33	1.67	0.36	3.20	0.68	581	124
4002	54	11	1.77	0.36	1.80	0.36	3.57	0.72	596	120
4003	69	13	1.46	0.27	1.50	0.28	2.96	0.55	668	123
4004	56	12	1.59	0.35	1.57	0.35	3.16	0.70	615	136
4005	68	15	1.47	0.32	1.56	0.34	3.03	0.66	552	121
4006	50	11	1.76	0.38	1.77	0.38	3.53	0.76	645	138
4007	49	11	1.53	0.33	1.56	0.34	3.09	0.68	584	128
n	7	7	7	7	7	7	7	7	7	7
Mean	58	12	1.59	0.33	1.63	0.34	3.22	0.68	606	127
S.D.	8	1	0.13	0.04	0.12	0.03	0.24	0.07	40	7

Animal No.	Epididymis-L		Epididymis-RL		Prostate		Seminalvesicle	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g
4001	614	131	1195	255	1.06	0.23	1.48	0.32
4002	590	119	1186	239	1.07	0.22	1.65	0.33
4003	691	127	1359	251	1.46	0.27	1.90	0.35
4004	652	145	1267	281	1.16	0.26	1.73	0.38
4005	597	131	1149	252	1.02	0.22	1.78	0.39
4006	634	136	1279	274	1.09	0.23	2.46	0.53
4007	541	118	1125	246	1.09	0.24	1.68	0.37
n	7	7	7	7	7	7	7	7
Mean	617	130	1223	257	1.14	0.24	1.81	0.38
S.D.	48	9	82	15	0.15	0.02	0.31	0.07

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : Lactation day 5

Sex : Female

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Pituitary		Thyroid-R		Thyroid-L	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
1101	331	1.98	0.60	22.9	6.9	6.0	1.8	6.7	2.0
1102	329	1.95	0.59	14.8	4.5	6.4	1.9	6.4	1.9
1103	321	1.78	0.55	17.5	5.5	8.4	2.6	11.3	3.5
1104	324	2.05	0.63	14.8	4.6	7.3	2.3	8.7	2.7
1105	319	1.93	0.61	19.3	6.1	11.4	3.6	6.2	1.9
1106	330	1.94	0.59	23.8	7.2	7.7	2.3	5.9	1.8
1107	321	1.96	0.61	16.1	5.0	7.1	2.2	5.7	1.8
1108	325	2.13	0.66	15.5	4.8	11.4	3.5	11.1	3.4
1109	326	1.98	0.61	23.5	7.2	10.5	3.2	8.4	2.6
1110	320	1.97	0.62	17.2	5.4	11.5	3.6	6.8	2.1
1111	328	2.02	0.62	16.6	5.1	6.2	1.9	7.6	2.3
1112	344	1.93	0.56	19.2	5.6	7.8	2.3	9.4	2.7
n	12	12	12	12	12	12	12	12	12
Mean	327	1.97	0.60	18.4	5.7	8.5	2.6	7.9	2.4
S.D.	7	0.08	0.03	3.3	1.0	2.1	0.7	1.9	0.6

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
1101	12.7	3.8	237	72	1.07	0.32	11.31	3.42	0.62	0.19
1102	12.8	3.9	266	81	0.92	0.28	11.63	3.53	0.70	0.21
1103	19.7	6.1	184	57	0.94	0.29	10.03	3.12	0.56	0.17
1104	16.0	4.9	202	62	0.98	0.30	11.76	3.63	0.59	0.18
1105	17.6	5.5	176	55	1.02	0.32	10.26	3.22	0.78	0.24
1106	13.6	4.1	246	75	1.17	0.35	11.50	3.48	0.92	0.28
1107	12.8	4.0	190	59	1.11	0.35	10.60	3.30	0.56	0.17
1108	22.5	6.9	175	54	1.05	0.32	9.52	2.93	0.55	0.17
1109	18.9	5.8	182	56	1.10	0.34	11.46	3.52	0.60	0.18
1110	18.3	5.7	198	62	0.98	0.31	11.24	3.51	0.49	0.15
1111	13.8	4.2	175	53	0.98	0.30	10.80	3.29	0.61	0.19
1112	17.2	5.0	289	84	1.09	0.32	11.70	3.40	0.76	0.22
n	12	12	12	12	12	12	12	12	12	12
Mean	16.3	5.0	210	64	1.03	0.32	10.98	3.36	0.65	0.20
S.D.	3.2	1.0	39	11	0.08	0.02	0.74	0.20	0.12	0.04

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : Lactation day 5

Sex : Female

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
1101	1.20	0.36	1.20	0.36	2.40	0.73	43	13	47	14
1102	1.10	0.33	1.10	0.33	2.20	0.67	37	11	42	13
1103	1.24	0.39	1.26	0.39	2.50	0.78	33	10	35	11
1104	1.02	0.31	0.97	0.30	1.99	0.61	51	16	52	16
1105	1.12	0.35	1.11	0.35	2.23	0.70	33	10	36	11
1106	1.27	0.38	1.29	0.39	2.56	0.78	32	10	32	10
1107	1.06	0.33	1.15	0.36	2.21	0.69	35	11	41	13
1108	1.02	0.31	1.06	0.33	2.08	0.64	30	9	35	11
1109	1.11	0.34	1.13	0.35	2.24	0.69	39	12	40	12
1110	1.16	0.36	1.13	0.35	2.29	0.72	36	11	37	12
1111	1.07	0.33	1.07	0.33	2.14	0.65	32	10	34	10
1112	1.30	0.38	1.25	0.36	2.55	0.74	28	8	32	9
n	12	12	12	12	12	12	12	12	12	12
Mean	1.14	0.35	1.14	0.35	2.28	0.70	36	11	39	12
S.D.	0.10	0.03	0.09	0.03	0.18	0.05	6	2	6	2

Animal No.	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
1101	90	27	53.9	16.3	66.6	20.1	120.5	36.4	736	222
1102	79	24	56.6	17.2	55.8	17.0	112.4	34.2	826	251
1103	68	21	46.4	14.5	50.3	15.7	96.7	30.1	574	179
1104	103	32	50.1	15.5	57.4	17.7	107.5	33.2	706	218
1105	69	22	62.5	19.6	52.6	16.5	115.1	36.1	670	210
1106	64	19	65.2	19.8	71.7	21.7	136.9	41.5	1073	325
1107	76	24	60.2	18.8	53.6	16.7	113.8	35.5	788	245
1108	65	20	58.2	17.9	49.8	15.3	108.0	33.2	747	230
1109	79	24	44.9	13.8	48.2	14.8	93.1	28.6	628	193
1110	73	23	48.7	15.2	49.6	15.5	98.3	30.7	802	251
1111	66	20	44.2	13.5	46.7	14.2	90.9	27.7	722	220
1112	60	17	51.8	15.1	38.5	11.2	90.3	26.3	617	179
n	12	12	12	12	12	12	12	12	12	12
Mean	74	23	53.6	16.4	53.4	16.4	107.0	32.8	741	227
S.D.	12	4	7.0	2.2	8.9	2.7	13.9	4.3	130	40

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : Lactation day 5

Sex : Female

Dose : crotonic acid 50 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Pituitary		Thyroid-R		Thyroid-L	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
2101	301	2.22	0.74	15.8	5.2	6.6	2.2	11.3	3.8
2102	322	1.92	0.60	18.9	5.9	10.5	3.3	10.6	3.3
2103	325	1.88	0.58	21.4	6.6	9.0	2.8	8.1	2.5
2104	331	2.06	0.62	20.0	6.0	10.5	3.2	11.3	3.4
2106	323	1.82	0.56	14.7	4.6	6.7	2.1	7.3	2.3
2107	332	1.86	0.56	16.3	4.9	9.6	2.9	7.3	2.2
2109	301	1.95	0.65	14.5	4.8	8.7	2.9	10.5	3.5
2110	332	2.09	0.63	18.4	5.5	5.7	1.7	6.9	2.1
2111	296	1.99	0.67	14.1	4.8	9.5	3.2	6.7	2.3
2112	344	1.93	0.56	20.8	6.0	8.3	2.4	6.5	1.9
n	10	10	10	10	10	10	10	10	10
Mean	321	1.97	0.62	17.5	5.4	8.5	2.7	8.7	2.7
S.D.	16	0.12	0.06	2.7	0.7	1.7	0.5	2.0	0.7

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
2101	17.9	5.9	222	74	1.10	0.37	9.67	3.21	0.49	0.16
2102	21.1	6.6	144	45	0.97	0.30	11.17	3.47	0.69	0.21
2103	17.1	5.3	247	76	1.04	0.32	10.63	3.27	0.73	0.22
2104	21.8	6.6	262	79	1.14	0.34	10.49	3.17	0.64	0.19
2106	14.0	4.3	187	58	0.97	0.30	10.54	3.26	0.71	0.22
2107	16.9	5.1	160	48	1.15	0.35	11.19	3.37	0.61	0.18
2109	19.2	6.4	310	103	0.97	0.32	10.18	3.38	0.69	0.23
2110	12.6	3.8	171	52	1.11	0.33	10.58	3.19	0.69	0.21
2111	16.2	5.5	178	60	1.00	0.34	10.47	3.54	0.66	0.22
2112	14.8	4.3	255	74	1.00	0.29	10.91	3.17	0.69	0.20
n	10	10	10	10	10	10	10	10	10	10
Mean	17.2	5.4	214	67	1.05	0.33	10.58	3.30	0.66	0.20
S.D.	3.0	1.0	54	18	0.07	0.03	0.45	0.13	0.07	0.02

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : Lactation day 5

Sex : Female

Dose : crotonic acid 50 mg/kg

Species : Rat

	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
Animal No.	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
2101	1.09	0.36	1.13	0.38	2.22	0.74	29	10	33	11
2102	1.04	0.32	1.02	0.32	2.06	0.64	38	12	36	11
2103	1.02	0.31	1.10	0.34	2.12	0.65	37	11	41	13
2104	1.16	0.35	1.13	0.34	2.29	0.69	34	10	39	12
2106	1.26	0.39	1.19	0.37	2.45	0.76	41	13	37	11
2107	1.24	0.37	1.23	0.37	2.47	0.74	42	13	38	11
2109	0.96	0.32	1.00	0.33	1.96	0.65	28	9	34	11
2110	1.14	0.34	1.07	0.32	2.21	0.67	43	13	45	14
2111	1.17	0.40	1.06	0.36	2.23	0.75	31	10	34	11
2112	1.12	0.33	1.10	0.32	2.22	0.65	35	10	34	10
n	10	10	10	10	10	10	10	10	10	10
Mean	1.12	0.35	1.10	0.35	2.22	0.69	36	11	37	12
S.D.	0.10	0.03	0.07	0.02	0.16	0.05	5	2	4	1

	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
Animal No.	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
2101	62	21	57.3	19.0	44.4	14.8	101.7	33.8	576	191
2102	74	23	53.8	16.7	53.1	16.5	106.9	33.2	693	215
2103	78	24	48.6	15.0	47.5	14.6	96.1	29.6	732	225
2104	73	22	56.3	17.0	54.3	16.4	110.6	33.4	662	200
2106	78	24	45.9	14.2	40.8	12.6	86.7	26.8	951	294
2107	80	24	50.6	15.2	37.4	11.3	88.0	26.5	893	269
2109	62	21	52.9	17.6	45.3	15.0	98.2	32.6	692	230
2110	88	27	57.9	17.4	55.4	16.7	113.3	34.1	860	259
2111	65	22	50.5	17.1	41.8	14.1	92.3	31.2	627	212
2112	69	20	47.5	13.8	49.1	14.3	96.6	28.1	825	240
n	10	10	10	10	10	10	10	10	10	10
Mean	73	23	52.1	16.3	46.9	14.6	99.0	30.9	751	234
S.D.	8	2	4.2	1.7	6.1	1.7	9.1	3.0	124	32

AB : Absolute weight, RE : Relative weight by body weight

Animal No. 2105,2108: Not copulated

Organ weight

Stage : Lactation day 5

Sex : Female

Dose : crotonic acid 150 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Pituitary		Thyroid-R		Thyroid-L	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
3101	313	1.91	0.61	15.4	4.9	7.1	2.3	5.0	1.6
3102	341	1.79	0.52	16.9	5.0	9.3	2.7	8.0	2.3
3103	329	1.89	0.57	17.3	5.3	7.7	2.3	8.8	2.7
3104	363	1.96	0.54	14.4	4.0	5.8	1.6	6.5	1.8
3105	324	2.13	0.66	21.0	6.5	8.4	2.6	6.3	1.9
3106	314	2.10	0.67	21.0	6.7	6.6	2.1	6.9	2.2
3107	312	1.87	0.60	17.7	5.7	6.8	2.2	7.2	2.3
3108	340	2.00	0.59	15.6	4.6	8.5	2.5	9.8	2.9
3110	333	1.92	0.58	16.6	5.0	6.1	1.8	8.4	2.5
3111	324	2.04	0.63	20.9	6.5	8.1	2.5	7.5	2.3
3112	328	1.92	0.59	20.3	6.2	9.3	2.8	6.1	1.9
n	11	11	11	11	11	11	11	11	11
Mean	329	1.96	0.60	17.9	5.5	7.6	2.3	7.3	2.2
S.D.	15	0.10	0.05	2.5	0.9	1.2	0.4	1.4	0.4

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
3101	12.1	3.9	243	78	1.41	0.45	9.64	3.08	0.58	0.19
3102	17.3	5.1	300	88	1.06	0.31	10.83	3.18	0.61	0.18
3103	16.5	5.0	204	62	1.06	0.32	10.56	3.21	0.63	0.19
3104	12.3	3.4	177	49	1.06	0.29	10.92	3.01	0.81	0.22
3105	14.7	4.5	246	76	0.99	0.31	10.58	3.27	0.69	0.21
3106	13.5	4.3	218	69	1.18	0.38	11.15	3.55	0.74	0.24
3107	14.0	4.5	146	47	1.04	0.33	11.92	3.82	0.63	0.20
3108	18.3	5.4	251	74	1.09	0.32	11.57	3.40	0.65	0.19
3110	14.5	4.4	194	58	1.07	0.32	11.03	3.31	0.64	0.19
3111	15.6	4.8	177	55	1.07	0.33	10.84	3.35	0.71	0.22
3112	15.4	4.7	252	77	1.08	0.33	10.08	3.07	0.66	0.20
n	11	11	11	11	11	11	11	11	11	11
Mean	14.9	4.5	219	67	1.10	0.34	10.83	3.30	0.67	0.20
S.D.	2.0	0.6	44	13	0.11	0.04	0.63	0.24	0.07	0.02

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : Lactation day 5

Sex : Female

Dose : crotonic acid 150 mg/kg

Species : Rat

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
3101	0.95	0.30	1.00	0.32	1.95	0.62	29	9	34	11
3102	1.11	0.33	1.09	0.32	2.20	0.65	34	10	30	9
3103	1.18	0.36	1.10	0.33	2.28	0.69	45	14	50	15
3104	1.23	0.34	1.16	0.32	2.39	0.66	41	11	45	12
3105	1.19	0.37	1.19	0.37	2.38	0.73	37	11	41	13
3106	1.21	0.39	1.25	0.40	2.46	0.78	39	12	45	14
3107	1.07	0.34	1.09	0.35	2.16	0.69	38	12	37	12
3108	1.23	0.36	1.18	0.35	2.41	0.71	40	12	38	11
3110	1.10	0.33	1.15	0.35	2.25	0.68	36	11	37	11
3111	1.28	0.40	1.24	0.38	2.52	0.78	37	11	44	14
3112	1.15	0.35	1.08	0.33	2.23	0.68	46	14	45	14
n	11	11	11	11	11	11	11	11	11	11
Mean	1.15	0.35	1.14	0.35	2.29	0.70	38	12	41	12
S.D.	0.09	0.03	0.08	0.03	0.16	0.05	5	2	6	2

Animal No.	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
3101	63	20	49.2	15.7	45.2	14.4	94.4	30.2	791	253
3102	64	19	62.2	18.2	56.8	16.7	119.0	34.9	724	212
3103	95	29	48.5	14.7	50.7	15.4	99.2	30.2	647	197
3104	86	24	49.0	13.5	59.1	16.3	108.1	29.8	885	244
3105	78	24	42.3	13.1	53.5	16.5	95.8	29.6	678	209
3106	84	27	52.5	16.7	51.2	16.3	103.7	33.0	942	300
3107	75	24	57.9	18.6	49.3	15.8	107.2	34.4	881	282
3108	78	23	53.5	15.7	43.7	12.9	97.2	28.6	670	197
3110	73	22	55.7	16.7	43.2	13.0	98.9	29.7	917	275
3111	81	25	48.3	14.9	57.3	17.7	105.6	32.6	804	248
3112	91	28	58.3	17.8	56.4	17.2	114.7	35.0	886	270
n	11	11	11	11	11	11	11	11	11	11
Mean	79	24	52.5	16.0	51.5	15.7	104.0	31.6	802	244
S.D.	10	3	5.7	1.8	5.7	1.6	7.9	2.4	108	36

AB : Absolute weight, RE : Relative weight by body weight

Animal No. 3109: Not copulated

Organ weight

Stage : Lactation day 5

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Pituitary		Thyroid-R		Thyroid-L	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
4101	336	2.02	0.60	21.9	6.5	10.1	3.0	8.8	2.6
4102	320	2.00	0.63	17.1	5.3	10.2	3.2	8.0	2.5
4103	310	2.01	0.65	16.6	5.4	7.0	2.3	9.3	3.0
4104	320	1.94	0.61	22.1	6.9	9.3	2.9	5.4	1.7
4105	296	1.93	0.65	15.0	5.1	8.4	2.8	10.5	3.5
4106	292	1.95	0.67	21.6	7.4	9.3	3.2	9.0	3.1
4107	309	1.96	0.63	14.0	4.5	8.5	2.8	8.8	2.8
4108	287	1.95	0.68	25.7	9.0	7.9	2.8	5.0	1.7
4109	305	1.94	0.64	15.4	5.0	8.5	2.8	8.4	2.8
4110	324	1.96	0.60	18.9	5.8	9.7	3.0	5.5	1.7
4111	307	1.93	0.63	14.9	4.9	6.1	2.0	4.3	1.4
4112	306	1.91	0.62	16.8	5.5	6.6	2.2	7.2	2.4
n	12	12	12	12	12	12	12	12	12
Mean	309	1.96	0.63	18.3	5.9	8.5	2.8	7.5	2.4
S.D.	14	0.03	0.03	3.7	1.3	1.4	0.4	2.0	0.7

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
4101	18.9	5.6	201	60	1.19	0.35	9.97	2.97	0.67	0.20
4102	18.2	5.7	137	43	1.08	0.34	10.58	3.31	0.69	0.22
4103	16.3	5.3	197	64	0.95	0.31	10.98	3.54	0.70	0.23
4104	14.7	4.6	208	65	1.05	0.33	10.66	3.33	0.65	0.20
4105	18.9	6.4	211	71	0.97	0.33	9.44	3.19	0.53	0.18
4106	18.3	6.3	135	46	0.94	0.32	9.66	3.31	0.53	0.18
4107	17.3	5.6	218	71	0.90	0.29	9.99	3.23	0.62	0.20
4108	12.9	4.5	108	38	0.91	0.32	9.41	3.28	0.58	0.20
4109	16.9	5.5	129	42	1.08	0.35	9.03	2.96	0.47	0.15
4110	15.2	4.7	254	78	1.07	0.33	10.31	3.18	0.63	0.19
4111	10.4	3.4	184	60	1.07	0.35	10.81	3.52	0.75	0.24
4112	13.8	4.5	186	61	1.04	0.34	10.49	3.43	0.60	0.20
n	12	12	12	12	12	12	12	12	12	12
Mean	16.0	5.2	181	58	1.02	0.33	10.11	3.27	0.62	0.20
S.D.	2.7	0.9	44	13	0.09	0.02	0.62	0.18	0.08	0.02

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : Lactation day 5

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
4101	1.13	0.34	1.13	0.34	2.26	0.67	44	13	53	16
4102	1.13	0.35	1.16	0.36	2.29	0.72	41	13	43	13
4103	1.17	0.38	1.09	0.35	2.26	0.73	31	10	34	11
4104	1.04	0.33	1.05	0.33	2.09	0.65	45	14	47	15
4105	1.03	0.35	1.00	0.34	2.03	0.69	39	13	43	15
4106	0.96	0.33	0.93	0.32	1.89	0.65	37	13	37	13
4107	1.14	0.37	1.06	0.34	2.20	0.71	33	11	34	11
4108	1.12	0.39	1.11	0.39	2.23	0.78	34	12	37	13
4109	1.09	0.36	1.04	0.34	2.13	0.70	40	13	43	14
4110	1.04	0.32	1.04	0.32	2.08	0.64	36	11	39	12
4111	1.12	0.36	1.15	0.37	2.27	0.74	33	11	37	12
4112	1.10	0.36	1.07	0.35	2.17	0.71	37	12	36	12
n	12	12	12	12	12	12	12	12	12	12
Mean	1.09	0.35	1.07	0.35	2.16	0.70	38	12	40	13
S.D.	0.06	0.02	0.07	0.02	0.12	0.04	4	1	6	2

Animal No.	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
4101	97	29	62.0	18.5	46.4	13.8	108.4	32.3	773	230
4102	84	26	49.9	15.6	48.1	15.0	98.0	30.6	710	222
4103	65	21	50.6	16.3	60.0	19.4	110.6	35.7	660	213
4104	92	29	64.7	20.2	58.7	18.3	123.4	38.6	905	283
4105	82	28	48.2	16.3	48.6	16.4	96.8	32.7	628	212
4106	74	25	58.2	19.9	53.8	18.4	112.0	38.4	706	242
4107	67	22	43.5	14.1	52.3	16.9	95.8	31.0	706	228
4108	71	25	42.6	14.8	44.1	15.4	86.7	30.2	732	255
4109	83	27	64.8	21.2	51.3	16.8	116.1	38.1	688	226
4110	75	23	53.2	16.4	31.0	9.6	84.2	26.0	811	250
4111	70	23	50.0	16.3	51.1	16.6	101.1	32.9	704	229
4112	73	24	48.0	15.7	50.9	16.6	98.9	32.3	644	210
n	12	12	12	12	12	12	12	12	12	12
Mean	78	25	53.0	17.1	49.7	16.1	102.7	33.2	722	233
S.D.	10	3	7.7	2.3	7.5	2.6	11.7	3.8	77	21

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Female

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
5101	296	1.93	0.65	14.7	5.0	7.6	2.6	6.6	2.2
5102	296	1.96	0.66	19.2	6.5	8.3	2.8	9.6	3.2
5103	288	1.88	0.65	15.4	5.3	8.5	3.0	6.1	2.1
5104	302	2.05	0.68	18.9	6.3	12.0	4.0	9.0	3.0
5105	298	1.89	0.63	16.1	5.4	10.5	3.5	8.1	2.7
n	5	5	5	5	5	5	5	5	5
Mean	296	1.94	0.65	16.9	5.7	9.4	3.2	7.9	2.6
S.D.	5	0.07	0.02	2.1	0.7	1.8	0.6	1.5	0.5

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
5101	14.2	4.8	285	96	0.92	0.31	7.77	2.63	0.66	0.22
5102	17.9	6.0	240	81	1.02	0.34	8.42	2.84	0.65	0.22
5103	14.6	5.1	234	81	0.84	0.29	6.25	2.17	0.46	0.16
5104	21.0	7.0	239	79	0.91	0.30	7.60	2.52	0.54	0.18
5105	18.6	6.2	318	107	0.91	0.31	7.74	2.60	0.41	0.14
n	5	5	5	5	5	5	5	5	5	5
Mean	17.3	5.8	263	89	0.92	0.31	7.56	2.55	0.54	0.18
S.D.	2.9	0.9	37	12	0.06	0.02	0.80	0.24	0.11	0.04

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
5101	0.91	0.31	0.92	0.31	1.83	0.62	35	12	38	13
5102	1.02	0.34	0.95	0.32	1.97	0.67	38	13	41	14
5103	0.88	0.31	0.83	0.29	1.71	0.59	29	10	33	11
5104	0.90	0.30	0.91	0.30	1.81	0.60	37	12	32	11
5105	0.94	0.32	0.93	0.31	1.87	0.63	31	10	30	10
n	5	5	5	5	5	5	5	5	5	5
Mean	0.93	0.32	0.91	0.31	1.84	0.62	34	11	35	12
S.D.	0.05	0.02	0.05	0.01	0.09	0.03	4	1	5	2

AB : Absolute weight, RE : Relative weight by body weight

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats
Organ weight
Sex : Female

Animal No.	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
	AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
	mg	mg/100g	mg	mg/100g	mg	mg/100g	mg	mg/100g	mg	mg/100g
5101	73	25	42.4	14.3	41.3	14.0	83.7	28.3	461	156
5102	79	27	41.1	13.9	43.9	14.8	85.0	28.7	407	138
5103	62	22	33.8	11.7	34.7	12.0	68.5	23.8	403	140
5104	69	23	38.1	12.6	43.9	14.5	82.0	27.2	595	197
5105	61	20	35.0	11.7	32.3	10.8	67.3	22.6	550	185
n	5	5	5	5	5	5	5	5	5	5
Mean	69	23	38.1	12.8	39.2	13.2	77.3	26.1	483	163
S.D.	8	3	3.7	1.2	5.4	1.7	8.7	2.8	86	27

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
6101	296	1.90	0.64	24.7	8.3	7.6	2.6	8.6	2.9
6102	277	1.97	0.71	13.7	4.9	7.3	2.6	6.8	2.5
6103	295	2.04	0.69	15.6	5.3	8.8	3.0	9.2	3.1
6104	256	1.89	0.74	16.7	6.5	9.3	3.6	8.5	3.3
6105	272	1.98	0.73	13.4	4.9	8.3	3.1	8.6	3.2
n	5	5	5	5	5	5	5	5	5
Mean	279	1.96	0.70	16.8	6.0	8.3	3.0	8.3	3.0
S.D.	17	0.06	0.04	4.6	1.5	0.8	0.4	0.9	0.3

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
6101	16.2	5.5	296	100	1.00	0.34	7.83	2.65	0.48	0.16
6102	14.1	5.1	274	99	0.80	0.29	6.92	2.50	0.35	0.13
6103	18.0	6.1	234	79	0.91	0.31	7.19	2.44	0.52	0.18
6104	17.8	7.0	330	129	0.85	0.33	6.18	2.41	0.53	0.21
6105	16.9	6.2	311	114	0.82	0.30	6.67	2.45	0.50	0.18
n	5	5	5	5	5	5	5	5	5	5
Mean	16.6	6.0	289	104	0.88	0.31	6.96	2.49	0.48	0.17
S.D.	1.6	0.7	37	19	0.08	0.02	0.61	0.10	0.07	0.03

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
6101	0.98	0.33	1.03	0.35	2.01	0.68	35	12	37	13
6102	0.94	0.34	0.93	0.34	1.87	0.68	35	13	41	15
6103	0.99	0.34	1.00	0.34	1.99	0.67	37	13	37	13
6104	0.83	0.32	0.94	0.37	1.77	0.69	30	12	34	13
6105	0.76	0.28	0.80	0.29	1.56	0.57	31	11	34	13
n	5	5	5	5	5	5	5	5	5	5
Mean	0.90	0.32	0.94	0.34	1.84	0.66	34	12	37	13
S.D.	0.10	0.02	0.09	0.03	0.18	0.05	3	1	3	1

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
6101	72	24	51.0	17.2	42.5	14.4	93.5	31.6	646	218
6102	76	27	32.4	11.7	42.8	15.5	75.2	27.1	832	300
6103	74	25	43.8	14.8	45.5	15.4	89.3	30.3	893	303
6104	64	25	41.0	16.0	41.8	16.3	82.8	32.3	454	177
6105	65	24	46.9	17.2	46.0	16.9	92.9	34.2	372	137
n	5	5	5	5	5	5	5	5	5	5
Mean	70	25	43.0	15.4	43.7	15.7	86.7	31.1	639	227
S.D.	5	1	7.0	2.3	1.9	1.0	7.7	2.6	228	74

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Male

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
1008	514	2.10	0.41	13.0	2.5	10.5	2.0	12.9	2.5
1009	467	2.06	0.44	9.8	2.1	13.6	2.9	11.0	2.4
1010	493	2.14	0.43	13.7	2.8	10.1	2.0	6.7	1.4
1011	528	2.37	0.45	20.4	3.9	15.6	3.0	15.1	2.9
1012	490	2.14	0.44	12.9	2.6	7.7	1.6	11.3	2.3
n	5	5	5	5	5	5	5	5	5
Mean	498	2.16	0.43	14.0	2.8	11.5	2.3	11.4	2.3
S.D.	23	0.12	0.02	3.9	0.7	3.1	0.6	3.1	0.6

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
1008	23.4	4.6	174	34	1.50	0.29	13.93	2.71	0.69	0.13
1009	24.6	5.3	274	59	1.36	0.29	11.39	2.44	0.64	0.14
1010	16.8	3.4	293	59	1.41	0.29	11.38	2.31	0.76	0.15
1011	30.7	5.8	155	29	1.71	0.32	13.29	2.52	0.77	0.15
1012	19.0	3.9	304	62	1.31	0.27	10.76	2.20	0.72	0.15
n	5	5	5	5	5	5	5	5	5	5
Mean	22.9	4.6	240	49	1.46	0.29	12.15	2.44	0.72	0.14
S.D.	5.4	1.0	70	16	0.16	0.02	1.38	0.20	0.05	0.01

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
1008	1.59	0.31	1.68	0.33	3.27	0.64	27	5	29	6
1009	1.34	0.29	1.47	0.31	2.81	0.60	25	5	25	5
1010	1.70	0.34	1.74	0.35	3.44	0.70	26	5	29	6
1011	2.15	0.41	2.36	0.45	4.51	0.85	27	5	28	5
1012	1.50	0.31	1.63	0.33	3.13	0.64	27	6	22	4
n	5	5	5	5	5	5	5	5	5	5
Mean	1.66	0.33	1.78	0.35	3.43	0.69	26	5	27	5
S.D.	0.31	0.05	0.34	0.06	0.65	0.10	1	0	3	1

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Male

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Adrenal-RL		Testis-R		Testis-L		Testis-RL		Epididymis-R	
	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g
1008	56	11	1.60	0.31	1.59	0.31	3.19	0.62	728	142
1009	50	11	1.80	0.39	1.83	0.39	3.63	0.78	731	157
1010	55	11	1.71	0.35	1.67	0.34	3.38	0.69	742	151
1011	55	10	1.75	0.33	1.72	0.33	3.47	0.66	715	135
1012	49	10	1.71	0.35	1.71	0.35	3.42	0.70	803	164
n	5	5	5	5	5	5	5	5	5	5
Mean	53	11	1.71	0.35	1.70	0.34	3.42	0.69	744	150
S.D.	3	1	0.07	0.03	0.09	0.03	0.16	0.06	34	12

Animal No.	Epididymis-L		Epididymis-RL		Prostate		Seminalvesicle	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g
1008	690	134	1418	276	1.12	0.22	1.87	0.36
1009	751	161	1482	317	1.34	0.29	1.83	0.39
1010	732	148	1474	299	1.32	0.27	1.81	0.37
1011	675	128	1390	263	1.53	0.29	2.07	0.39
1012	837	171	1640	335	1.25	0.26	2.22	0.45
n	5	5	5	5	5	5	5	5
Mean	737	148	1481	298	1.31	0.27	1.96	0.39
S.D.	64	18	97	29	0.15	0.03	0.18	0.03

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Male

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
4008	346	2.14	0.62	10.1	2.9	9.9	2.9	9.8	2.8
4009	525	2.08	0.40	13.6	2.6	10.9	2.1	7.0	1.3
4010	535	2.09	0.39	13.5	2.5	15.0	2.8	10.1	1.9
4011	511	2.21	0.43	13.4	2.6	14.5	2.8	12.2	2.4
4012	484	2.15	0.44	14.5	3.0	12.8	2.6	12.4	2.6
n	5	5	5	5	5	5	5	5	5
Mean	480	2.13	0.46	13.0	2.7	12.6	2.6	10.3	2.2
S.D.	77	0.05	0.09	1.7	0.2	2.2	0.3	2.2	0.6

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
4008	19.7	5.7	61	18	1.30	0.38	8.09	2.34	0.29	0.08
4009	17.9	3.4	262	50	1.49	0.28	11.96	2.28	0.71	0.14
4010	25.1	4.7	122	23	1.49	0.28	11.91	2.23	0.59	0.11
4011	26.7	5.2	339	66	1.49	0.29	12.51	2.45	0.76	0.15
4012	25.2	5.2	231	48	1.54	0.32	12.47	2.58	0.68	0.14
n	5	5	5	5	5	5	5	5	5	5
Mean	22.9	4.8	203	41	1.46	0.31	11.39	2.38	0.61	0.12
S.D.	3.9	0.9	111	20	0.09	0.04	1.86	0.14	0.19	0.03

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
4008	1.20	0.35	1.19	0.34	2.39	0.69	39	11	42	12
4009	1.84	0.35	1.89	0.36	3.73	0.71	28	5	26	5
4010	1.59	0.30	1.59	0.30	3.18	0.59	22	4	21	4
4011	1.68	0.33	1.78	0.35	3.46	0.68	36	7	36	7
4012	1.60	0.33	1.68	0.35	3.28	0.68	27	6	29	6
n	5	5	5	5	5	5	5	5	5	5
Mean	1.58	0.33	1.63	0.34	3.21	0.67	30	7	31	7
S.D.	0.24	0.02	0.27	0.02	0.50	0.05	7	3	8	3

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Male

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Adrenal-RL		Testis-R		Testis-L		Testis-RL		Epididymis-R	
	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g
4008	81	23	1.43	0.41	1.46	0.42	2.89	0.84	396	114
4009	54	10	1.72	0.33	1.79	0.34	3.51	0.67	639	122
4010	43	8	1.77	0.33	1.78	0.33	3.55	0.66	731	137
4011	72	14	1.58	0.31	1.53	0.30	3.11	0.61	639	125
4012	56	12	1.63	0.34	1.63	0.34	3.26	0.67	659	136
n	5	5	5	5	5	5	5	5	5	5
Mean	61	13	1.63	0.34	1.64	0.35	3.26	0.69	613	127
S.D.	15	6	0.13	0.04	0.15	0.04	0.28	0.09	127	10

Animal No.	Epididymis-L		Epididymis-RL		Prostate		Seminalvesicle	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g
4008	433	125	829	240	0.58	0.17	0.48	0.14
4009	640	122	1279	244	1.25	0.24	1.57	0.30
4010	708	132	1439	269	1.69	0.32	1.94	0.36
4011	610	119	1249	244	1.27	0.25	1.53	0.30
4012	642	133	1301	269	1.25	0.26	1.07	0.22
n	5	5	5	5	5	5	5	5
Mean	607	126	1219	253	1.21	0.25	1.32	0.26
S.D.	103	6	230	15	0.40	0.05	0.56	0.09

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Female

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
5106	321	2.00	0.62	13.8	4.3	7.3	2.3	7.9	2.5
5107	297	1.91	0.64	19.3	6.5	7.8	2.6	9.2	3.1
5108	287	2.05	0.71	17.5	6.1	9.0	3.1	10.4	3.6
5109	264	1.97	0.75	18.8	7.1	5.9	2.2	6.6	2.5
5110	296	1.87	0.63	10.5	3.5	11.3	3.8	7.5	2.5
n	5	5	5	5	5	5	5	5	5
Mean	293	1.96	0.67	16.0	5.5	8.3	2.8	8.3	2.8
S.D.	21	0.07	0.06	3.7	1.5	2.0	0.7	1.5	0.5

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
5106	15.2	4.7	183	57	0.96	0.30	7.84	2.44	0.53	0.17
5107	17.0	5.7	346	116	0.92	0.31	7.05	2.37	0.56	0.19
5108	19.4	6.8	221	77	0.91	0.32	7.23	2.52	0.52	0.18
5109	12.5	4.7	230	87	0.87	0.33	6.30	2.39	0.47	0.18
5110	18.8	6.4	202	68	0.85	0.29	6.92	2.34	0.51	0.17
n	5	5	5	5	5	5	5	5	5	5
Mean	16.6	5.7	236	81	0.90	0.31	7.07	2.41	0.52	0.18
S.D.	2.8	1.0	64	22	0.04	0.02	0.56	0.07	0.03	0.01

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
5106	1.15	0.36	1.19	0.37	2.34	0.73	38	12	42	13
5107	0.89	0.30	0.81	0.27	1.70	0.57	30	10	30	10
5108	0.94	0.33	0.97	0.34	1.91	0.67	33	11	35	12
5109	0.92	0.35	0.93	0.35	1.85	0.70	30	11	31	12
5110	0.99	0.33	0.94	0.32	1.93	0.65	30	10	31	10
n	5	5	5	5	5	5	5	5	5	5
Mean	0.98	0.33	0.97	0.33	1.95	0.66	32	11	34	11
S.D.	0.10	0.02	0.14	0.04	0.24	0.06	3	1	5	1

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Female

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
5106	80	25	57.6	17.9	63.8	19.9	121.4	37.8	861	268
5107	60	20	27.3	9.2	31.2	10.5	58.5	19.7	763	257
5108	68	24	48.5	16.9	39.1	13.6	87.6	30.5	766	267
5109	61	23	35.6	13.5	39.6	15.0	75.2	28.5	900	341
5110	61	21	48.6	16.4	44.4	15.0	93.0	31.4	540	182
n	5	5	5	5	5	5	5	5	5	5
Mean	66	23	43.5	14.8	43.6	14.8	87.1	29.6	766	263
S.D.	8	2	12.0	3.5	12.2	3.4	23.3	6.5	140	56

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
6106	280	1.95	0.70	16.7	6.0	12.5	4.5	11.6	4.1
6107	292	1.99	0.68	15.1	5.2	5.9	2.0	7.1	2.4
6108	318	1.98	0.62	16.8	5.3	9.7	3.1	8.2	2.6
6109	278	2.08	0.75	15.5	5.6	7.8	2.8	6.8	2.4
6110	279	1.94	0.70	18.9	6.8	10.2	3.7	8.0	2.9
n	5	5	5	5	5	5	5	5	5
Mean	289	1.99	0.69	16.6	5.8	9.2	3.2	8.3	2.9
S.D.	17	0.06	0.05	1.5	0.6	2.5	0.9	1.9	0.7

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
6106	24.1	8.6	230	82	0.94	0.34	7.15	2.55	0.55	0.20
6107	13.0	4.5	359	123	1.01	0.35	7.00	2.40	0.53	0.18
6108	17.9	5.6	238	75	1.09	0.34	7.84	2.47	0.68	0.21
6109	14.6	5.3	245	88	1.02	0.37	6.42	2.31	0.47	0.17
6110	18.2	6.5	282	101	0.94	0.34	7.45	2.67	0.49	0.18
n	5	5	5	5	5	5	5	5	5	5
Mean	17.6	6.1	271	94	1.00	0.35	7.17	2.48	0.54	0.19
S.D.	4.3	1.6	53	19	0.06	0.01	0.53	0.14	0.08	0.02

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
6106	0.97	0.35	0.96	0.34	1.93	0.69	34	12	35	13
6107	0.99	0.34	0.95	0.33	1.94	0.66	41	14	42	14
6108	0.95	0.30	1.05	0.33	2.00	0.63	38	12	36	11
6109	0.98	0.35	0.91	0.33	1.89	0.68	23	8	25	9
6110	0.90	0.32	0.94	0.34	1.84	0.66	34	12	37	13
n	5	5	5	5	5	5	5	5	5	5
Mean	0.96	0.33	0.96	0.33	1.92	0.66	34	12	35	12
S.D.	0.04	0.02	0.05	0.01	0.06	0.02	7	2	6	2

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
6106	69	25	54.2	19.4	54.7	19.5	108.9	38.9	698	249
6107	83	28	49.0	16.8	61.7	21.1	110.7	37.9	951	326
6108	74	23	42.3	13.3	50.6	15.9	92.9	29.2	467	147
6109	48	17	26.6	9.6	33.5	12.1	60.1	21.6	646	232
6110	71	25	40.1	14.4	47.3	17.0	87.4	31.3	506	181
n	5	5	5	5	5	5	5	5	5	5
Mean	69	24	42.4	14.7	49.6	17.1	92.0	31.8	654	227
S.D.	13	4	10.5	3.7	10.5	3.5	20.5	7.0	192	69

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : Non copulated

Sex : Female

Dose : crotonic acid 50 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
2105	296	1.99	0.67	14.1	4.8	8.9	3.0	8.4	2.8
2108	318	1.88	0.59	13.6	4.3	7.1	2.2	7.7	2.4
n	2	2	2	2	2	2	2	2	2
Mean	307	1.94	0.63	13.9	4.6	8.0	2.6	8.1	2.6
S.D.	16	0.08	0.06	0.4	0.4	1.3	0.6	0.5	0.3

Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g
2105	17.3	5.8	210	71	0.90	0.30	8.12	2.74	0.50	0.17
2108	14.8	4.7	312	98	1.29	0.41	8.81	2.77	0.53	0.17
n	2	2	2	2	2	2	2	2	2	2
Mean	16.1	5.3	261	85	1.10	0.36	8.47	2.76	0.52	0.17
S.D.	1.8	0.8	72	19	0.28	0.08	0.49	0.02	0.02	0.00

Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
2105	0.97	0.33	0.98	0.33	1.95	0.66	30	10	31	10
2108	1.17	0.37	1.19	0.37	2.36	0.74	29	9	30	9
n	2	2	2	2	2	2	2	2	2	2
Mean	1.07	0.35	1.09	0.35	2.16	0.70	30	10	31	10
S.D.	0.14	0.03	0.15	0.03	0.29	0.06	1	1	1	1

Animal No.	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB mg	RE mg/100g
2105	61	21	54.7	18.5	37.1	12.5	91.8	31.0	707	239
2108	59	19	50.1	15.8	44.5	14.0	94.6	29.7	593	186
n	2	2	2	2	2	2	2	2	2	2
Mean	60	20	52.4	17.2	40.8	13.3	93.2	30.4	650	213
S.D.	1	1	3.3	1.9	5.2	1.1	2.0	0.9	81	37

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : Non copulated

Sex : Female

Dose : crotonic acid 150 mg/kg

Species : Rat

Sex: Female	Body weight	Brain		Pituitary		Thyroid-R		Thyroid-L		
		AB	RE	AB	RE	AB	RE	AB	RE	
Animal No.	g	g	g/100g	mg	mg/100g	mg	mg/100g	mg	mg/100g	
3109	284	2.04	0.72	18.9	6.7	9.2	3.2	4.1	1.4	
n	1	1	1	1	1	1	1	1	1	
Mean	284	2.04	0.72	18.9	6.7	9.2	3.2	4.1	1.4	
S.D.										
Animal No.	Thyroid-RL		Thymus		Heart		Liver		Spleen	
	AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
	mg	mg/100g	mg	mg/100g	g	g/100g	g	g/100g	g	g/100g
3109	13.3	4.7	267	94	0.90	0.32	8.00	2.82	0.49	0.17
n	1	1	1	1	1	1	1	1	1	1
Mean	13.3	4.7	267	94	0.90	0.32	8.00	2.82	0.49	0.17
S.D.										
Animal No.	Kidney-R		Kidney-L		Kidney-RL		Adrenal-R		Adrenal-L	
	AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g	mg	mg/100g
3109	0.98	0.35	1.04	0.37	2.02	0.71	38	13	38	13
n	1	1	1	1	1	1	1	1	1	1
Mean	0.98	0.35	1.04	0.37	2.02	0.71	38	13	38	13
S.D.										
Animal No.	Adrenal-RL		Ovary-R		Ovary-L		Ovary-RL		Uterus	
	AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
	mg	mg/100g	mg	mg/100g	mg	mg/100g	mg	mg/100g	mg	mg/100g
3109	76	27	36.4	12.8	38.3	13.5	74.7	26.3	596	210
n	1	1	1	1	1	1	1	1	1	1
Mean	76	27	36.4	12.8	38.3	13.5	74.7	26.3	596	210
S.D.										

AB : Absolute weight, RE : Relative weight by body weight

Appendix 9-1(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1001 Male 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine, cecum Cell infiltration, mucosal: minimal, mononuclear

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch)
Intestine, colon, Intestine, rectum, Kidney, Lymph node, mesenteric
Lymph node, submandibular, Liver, Lung(bronchus), Mammary gland, inguinal
Parathyroid, Pancreas, Pituitary, Prostate, Salivary gland, submandibular
Sciatic nerve, Spleen, Stomach, Skeletal muscle, femoral
Seminal vesicle(coagulating gland), Spinal cord, thoracic, Testis, Thymus, Trachea
Thyroid, Urinary bladder

Appendix 9-2(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1002 Male 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Testis Atrophy,seminiferous tubular: minimal, bilateral

Thyroid Cyst,ultimobranchial: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus)
Mammary gland,inguinal, Parathyroid, Pancreas, Pituitary, Prostate
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Thymus, Trachea, Urinary bladder

Appendix 9-3(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1003 Male 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Urinary cast,hyaline: minimal

Lung(bronchus) Aggregation,alveolar macrophage: minimal

Pituitary Cyst,pars distalis: minimal

Prostate Cell infiltration,interstitial: minimal, mononuclear

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Mammary gland,inguinal, Parathyroid, Pancreas
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-4(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1004 Male 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Prostate Cell infiltration,interstitial: mild, mononuclear

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-5(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1005 Male 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Heart Cell infiltration: minimal, focal, mononuclear

Kidney Basophilia,tubular: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Parathyroid, Pancreas, Pituitary, Prostate, Salivary gland,submandibular
Sciatic nerve, Spleen, Stomach, Skeletal muscle,femoral
Seminal vesicle(coagulating gland), Spinal cord,thoracic, Testis, Thymus, Trachea
Thyroid, Urinary bladder

Appendix 9-6(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1006 Male 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-7(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1007 Male 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-8(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1008 Male 0 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-9(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1009 Male 0 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-10(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1010 Male 0 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-11(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1011 Male 0 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-12(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1012 Male 0 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-13(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2001 Male 50 mg/kg Day 43 End of administration

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present
1x2mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion/Ulcer, glandular stomach: minimal
fundus

Study No. : R-1169

Appendix 9-14(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2002 Male 50 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-15(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2003 Male 50 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-16(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2004 Male 50 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-17(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2005 Male 50 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Parathyroid, Pancreas, Pituitary, Prostate
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Study No. : R-1169

Appendix 9-18(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2006 Male 50 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-19(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2007 Male 50 mg/kg Day 43 End of administration

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present
5x1mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-20(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2008 Male 50 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Basophilia,tubular: minimal

Prostate Cell infiltration,interstitial: minimal, mononuclear

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Seminal vesicle(coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-21(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2009 Male 50 mg/kg Day 43 End of administration

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present
1x5mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-22(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2010 Male 50 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-23(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2011 Male 50 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-24(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2012 Male 50 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-25(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3001 Male 150 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, forestomach: minimal with hyperkeratosis

Appendix 9-26(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3002 Male 150 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, forestomach: minimal with hyperkeratosis

Appendix 9-27(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3003 Male 150 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-28(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3004 Male 150 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, forestomach: minimal with hyperkeratosis

Appendix 9-29(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3005 Male 150 mg/kg Day 43 End of administration

Gross pathology:

Kidney Dilatation, pelvic: mild, right

Other tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-30(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3006 Male 150 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-31(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3007 Male 150 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-32(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3008 Male 150 mg/kg Day 43 End of administration

Gross pathology:

Seminal vesicle(coagulating gland) Small: mild, right

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-33(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3009 Male 150 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine,cecum Cell infiltration,mucosal: minimal, mononuclear

Liver Microgranuloma: minimal

Prostate Cell infiltration,interstitial: minimal, mononuclear

Stomach Hyperplasia,squamous,forestomach: minimal
with hyperkeratosis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Lung(bronchus), Mammary gland,inguinal, Parathyroid
Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve, Spleen
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-34(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3010 Male 150 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-35(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3011 Male 150 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-36(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3012 Male 150 mg/kg Day 43 End of administration

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present
1x1mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-37(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4001 Male 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Heart Cell infiltration: minimal, focal, mononuclear

Stomach Hyperplasia,squamous,forestomach: moderate, diffuse with hyperkeratosis

Thyroid Cyst,ultimobranchial: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Parathyroid, Pancreas, Pituitary, Prostate
Salivary gland,submandibular, Sciatic nerve, Spleen, Skeletal muscle,femoral
Seminal vesicle(coagulating gland), Spinal cord,thoracic, Testis, Thymus, Trachea
Urinary bladder

Appendix 9-38(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4002 Male 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Urinary cast,hyaline: minimal

Stomach Hyperplasia,squamous,forestomach: moderate, diffuse with hyperkeratosis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Parathyroid, Pancreas, Pituitary, Prostate, Salivary gland,submandibular
Sciatic nerve, Spleen, Skeletal muscle,femoral, Seminal vesicle(coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-39(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4003 Male 500 mg/kg Day 43 End of administration

Gross pathology:

Stomach Thickening, wall, forestomach: mild

Other tissues Not remarkable

Histopathology:

Heart Cell infiltration: minimal, focal, mononuclear

Stomach Hyperplasia, squamous, forestomach: moderate, diffuse with hyperkeratosis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch)
Intestine, cecum, Intestine, colon, Intestine, rectum, Kidney
Lymph node, mesenteric, Lymph node, submandibular, Liver, Lung(bronchus)
Mammary gland, inguinal, Parathyroid, Pancreas, Pituitary, Prostate
Salivary gland, submandibular, Sciatic nerve, Spleen, Skeletal muscle, femoral
Seminal vesicle(coagulating gland), Spinal cord, thoracic, Testis, Thymus, Trachea
Thyroid, Urinary bladder

Appendix 9-40(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4004 Male 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Spleen Aggregation,macrophage: mild

Stomach Hyperplasia,squamous,forestomach: mild, diffuse with hyperkeratosis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Parathyroid, Pancreas, Pituitary, Prostate
Salivary gland,submandibular, Sciatic nerve, Skeletal muscle,femoral
Seminal vesicle(coagulating gland), Spinal cord,thoracic, Testis, Thymus, Trachea
Thyroid, Urinary bladder

Appendix 9-41(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4005 Male 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Urinary cast,hyaline: minimal

Prostate Cell infiltration,interstitial: mild, mononuclear

Stomach Erosion/Ulcer,glandular stomach: minimal
pylorus
Hyperplasia,squamous,forestomach: mild, diffuse
with hyperkeratosis and bulla in stratum corneum

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Skeletal muscle,femoral, Seminal vesicle(coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-42(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4006 Male 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-43(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4007 Male 500 mg/kg Day 43 End of administration

Gross pathology:

Kidney	Focus,white: 1 present, left 3x5mm
Stomach	Thickening,wall,forestomach: mild
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-44(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4008 Male 500 mg/kg Day 57 End of recovery

Gross pathology:

Seminal vesicle(coagulating gland) Small: mild, bilateral

Thymus Small: mild

Other tissues Not remarkable

Histopathology:

Stomach Hyperplasia,squamous,forestomach: mild, diffuse with hyperkeratosis

Appendix 9-45(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4009 Male 500 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, forestomach: mild, diffuse with hyperkeratosis

Appendix 9-46(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4010 Male 500 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-47(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4011 Male 500 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-48(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4012 Male 500 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-49(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1101 Female 0 mg/kg Day 43 End of administration,Dams

Gross pathology:

Stomach Focus,dark red,glandular stomach: 3 present
2x1mm,1x1mm,1x1mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion/Ulcer,glandular stomach: mild
fundus

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Skeletal muscle,femoral
Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-50(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1102 Female 0 mg/kg Day 46 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-51(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1103 Female 0 mg/kg Day 45 End of administration, Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-52(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1104 Female 0 mg/kg Day 44 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Thyroid Cyst,ultimobranhial: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Urinary bladder
Uterus, Vagina

Appendix 9-53(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1105 Female 0 mg/kg Day 43 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Thyroid Cyst,ultimobranchial: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Urinary bladder
Uterus, Vagina

Appendix 9-54 (1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1106 Female 0 mg/kg Day 49 End of administration, Dams

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present
2x1mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-55(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1107 Female 0 mg/kg Day 42 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Lung(bronchus) Aggregation,alveolar macrophage: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Mammary gland,inguinal, Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-56(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1108 Female 0 mg/kg Day 44 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-57(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1109 Female 0 mg/kg Day 45 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-58(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1110 Female 0 mg/kg Day 45 End of administration,Dams

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present
1x1mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-59(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1111 Female 0 mg/kg Day 45 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-60(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 1112 Female 0 mg/kg Day 46 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-61(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2101 Female 50 mg/kg Day 42 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-62(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2102 Female 50 mg/kg Day 43 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-63(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2103 Female 50 mg/kg Day 43 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-64(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2104 Female 50 mg/kg Day 45 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-65(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2105 Female 50 mg/kg Day 54 Undelivered

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-66(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2106 Female 50 mg/kg Day 45 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-67(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2107 Female 50 mg/kg Day 44 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-68(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2108 Female 50 mg/kg Day 54 Undelivered

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-69(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2109 Female 50 mg/kg Day 43 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-70(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2110 Female 50 mg/kg Day 47 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-71(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2111 Female 50 mg/kg Day 46 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-72(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 2112 Female 50 mg/kg Day 45 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-73(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3101 Female 150 mg/kg Day 44 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-74(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3102 Female 150 mg/kg Day 46 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-75(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3103 Female 150 mg/kg Day 45 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-76(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3104 Female 150 mg/kg Day 46 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Study No. : R-1169

Appendix 9-77(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3105 Female 150 mg/kg Day 45 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-78(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3106 Female 150 mg/kg Day 45 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-79(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3107 Female 150 mg/kg Day 44 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-80(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3108 Female 150 mg/kg Day 46 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-81(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3109 Female 150 mg/kg Day 54 Undelivered

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, forestomach: minimal
with hyperkeratosis and bulla in stratum corneum

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch)
Intestine, cecum, Intestine, colon, Intestine, rectum, Kidney
Lymph node, mesenteric, Lymph node, submandibular, Liver, Lung(bronchus)
Mammary gland, inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland, submandibular, Sciatic nerve, Spleen, Skeletal muscle, femoral
Spinal cord, thoracic, Thymus, Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-82(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3110 Female 150 mg/kg Day 46 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-83(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3111 Female 150 mg/kg Day 45 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-84(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 3112 Female 150 mg/kg Day 43 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-85(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4101 Female 500 mg/kg Day 44 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-86(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4102 Female 500 mg/kg Day 44 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-87(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4103 Female 500 mg/kg Day 45 End of administration,Dams

Gross pathology:

Stomach Focus,raised,forestomach: 1 present
5x3x1mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-88(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4104 Female 500 mg/kg Day 43 End of administration,Dams

Gross pathology:

Stomach Focus,raised,forestomach: 1 present
5x10x3mm

Other tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Lung(bronchus) Aggregation,alveolar macrophage: minimal

Stomach Hyperplasia,squamous,forestomach: moderate, diffuse
with hyperkeratosis,bulla in stratum corneum and submucosal
edema

Thyroid Cyst,ultimobranchial: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Mammary gland,inguinal, Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Urinary bladder, Uterus, Vagina

Appendix 9-89(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4105 Female 500 mg/kg Day 43 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach	Erosion/Ulcer,glandular stomach: minimal pylorus Hyperplasia,squamous,forestomach: minimal with hyperkeratosis
Thyroid	Cyst,ultimobranchial: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Skeletal muscle,femoral
Spinal cord,thoracic, Thymus, Trachea, Urinary bladder, Uterus, Vagina

Appendix 9-90(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4106 Female 500 mg/kg Day 43 End of administration,Dams

Gross pathology:

Stomach Thickening,wall,forestomach: mild

Other tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Stomach Hyperplasia,squamous,forestomach: moderate, diffuse
with hyperkeratosis,bulla in stratum corneum and submucosal
edema

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Skeletal muscle,femoral
Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-91(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4107 Female 500 mg/kg Day 44 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-92(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4108 Female 500 mg/kg Day 46 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-93(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4109 Female 500 mg/kg Day 43 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia,squamous,forestomach: mild, diffuse with hyperkeratosis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Skeletal muscle,femoral
Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-94(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4110 Female 500 mg/kg Day 43 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Lung(bronchus) Aggregation,alveolar macrophage: minimal

Parathyroid No sample

Stomach Hyperplasia,squamous,forestomach: moderate, diffuse with hyperkeratosis

Thyroid Cyst,ultimobranchial: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Mammary gland,inguinal
Ovary, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve, Spleen
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Urinary bladder
Uterus, Vagina

Appendix 9-95(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4111 Female 500 mg/kg Day 44 End of administration,Dams

Gross pathology:

Stomach Focus,raised,forestomach: 1 present
10x10x1mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-96(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 4112 Female 500 mg/kg Day 44 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-97(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5101 Female 0 mg/kg Day 43 End of administration

Gross pathology:

Stomach Focus, dark red, glandular stomach: 1 present
2x3mm

Other tissues Not remarkable

Histopathology:

Kidney Basophilia, tubular: minimal

Stomach Erosion/Ulcer, glandular stomach: minimal
fundus

Thyroid Cyst, ultimobranchial: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch)
Intestine, cecum, Intestine, colon, Intestine, rectum, Lymph node, mesenteric
Lymph node, submandibular, Liver, Lung(bronchus), Mammary gland, inguinal, Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular, Sciatic nerve
Spleen, Skeletal muscle, femoral, Spinal cord, thoracic, Thymus, Trachea
Urinary bladder, Uterus, Vagina

Appendix 9-98(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5102 Female 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Pancreas Atrophy, acinar, focal: minimal

Skeletal muscle, femoral Cell infiltration, focal: minimal, mononuclear

Thyroid Cyst, ultimobranchial: minimal, bilateral

Vagina Mucification: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch)
Intestine, cecum, Intestine, colon, Intestine, rectum, Kidney
Lymph node, mesenteric, Lymph node, submandibular, Lung(bronchus)
Mammary gland, inguinal, Ovary, Parathyroid, Pituitary
Salivary gland, submandibular, Sciatic nerve, Spleen, Stomach
Spinal cord, thoracic, Thymus, Trachea, Urinary bladder, Uterus

Appendix 9-99(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5103 Female 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-100(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5104 Female 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-101(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5105 Female 0 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-102(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5106 Female 0 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Study No. : R-1169

Appendix 9-103(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5107 Female 0 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-104(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5108 Female 0 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-105(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5109 Female 0 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Appendix 9-106(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 5110 Female 0 mg/kg Day 57 End of recovery

Gross pathology:

Stomach Focus, dark red, glandular stomach: 2 present
1x1mm, 2x1mm

Other tissues Not remarkable

Histopathology:

Stomach Erosion/Ulcer, glandular stomach: mild
fundus

Appendix 9-107(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6101 Female 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia,squamous,forestomach: moderate, diffuse with hyperkeratosis and bulla in stratum corneum

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Skeletal muscle,femoral
Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-108(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6102 Female 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Parathyroid No sample

Stomach Hyperplasia,squamous,forestomach: moderate, diffuse with hyperkeratosis

Thyroid Cyst,ultimobranchial: minimal, bilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus)
Mammary gland,inguinal, Ovary, Pancreas, Pituitary, Salivary gland,submandibular
Sciatic nerve, Spleen, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus
Trachea, Urinary bladder, Uterus, Vagina

Appendix 9-109(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6103 Female 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Basophilia,tubular: minimal

Stomach Hyperplasia,squamous,forestomach: moderate, diffuse
with hyperkeratosis and bulla in stratum corneum

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal, Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-110(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6104 Female 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine, cecum Cell infiltration, mucosal: minimal, mononuclear

Stomach Hyperplasia, squamous, forestomach: mild, diffuse with hyperkeratosis and bulla in stratum corneum

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow, femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine, duodenum, Intestine, jejunum, Intestine, ileum(Peyer's patch)
Intestine, colon, Intestine, rectum, Kidney, Lymph node, mesenteric
Lymph node, submandibular, Liver, Lung(bronchus), Mammary gland, inguinal, Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland, submandibular, Sciatic nerve
Spleen, Skeletal muscle, femoral, Spinal cord, thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-111(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6105 Female 500 mg/kg Day 43 End of administration

Gross pathology:

All tissues Not remarkable

Histopathology:

Liver Microgranuloma: minimal

Stomach Hyperplasia,squamous,forestomach: mild, diffuse with hyperkeratosis

Thyroid Cyst,ultimobranchial: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus)
Mammary gland,inguinal, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Sciatic nerve, Spleen, Skeletal muscle,femoral
Spinal cord,thoracic, Thymus, Trachea, Urinary bladder, Uterus, Vagina

Appendix 9-112(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6106 Female 500 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, forestomach: mild, diffuse with hyperkeratosis

Appendix 9-113(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6107 Female 500 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, forestomach: mild, diffuse with hyperkeratosis

Appendix 9-114(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6108 Female 500 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Hyperplasia, squamous, forestomach: mild, diffuse with hyperkeratosis

Appendix 9-115(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6109 Female 500 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Study No. : R-1169

Appendix 9-116(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of crotonic acid by oral administration in rats

Individual gross and histopathological findings

Animal No. 6110 Female 500 mg/kg Day 57 End of recovery

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Stomach

Animal No.	/Before mating (day)													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1101	E	M	D	P	E	E	M	D	P	E	E	M	D	P
1102	D	P	E	M	D	P	E	M	D	P	E	M	D	P
1103	P	E	M	D	P	E	M	D	P	E	M	D	P	E
1104	M	D	P	E	M	D	P	E	M	D	P	E	M	D
1105	E	M	D	P	E	E	M	D	P	E	E	M	D	P
1106	M	D	P	E	M	D	P	E	E	M	D	P	E	M
1107	M	D	P	E	M	D	P	E	M	D	P	E	M	D
1108	E	M	D	P	E	M	D	P	E	M	D	P	E	M
1109	P	E	M	D	P	E	M	D	P	E	M	D	P	E
1110	P	E	M	D	P	E	M	D	P	E	M	D	P	E
1111	D	P	E	M	D	P	E	M	D	P	E	M	D	P
1112	D	P	E	M	D	P	E	M	D	P	E	M	D	P

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

Estrus cycles and copulation

Generation : F0

Dose : crotonic acid 0 mg/kg

Species : Rat

Generation : F0		Dose : crotonic acid 0 mg/kg				Species : Rat	
Animal No.	/Before mating (day)	Length of estrous cycle			Mean	Number of estrus	Animal with abnormal estrous cycle
		(days)					
1101	E	4	5	5	4.7	4	-
1102	E	4	4	4	4.0	4	-
1103	M	4	4	4	4.0	4	-
1104	D	4	4		4.0	3	-
1105	E	4	5	5	4.7	4	-
1106	D	4	5		4.5	3	-
1107	P	4	4		4.0	3	-
1108	D	4	4	4	4.0	4	-
1109	M	4	4	4	4.0	4	-
1110	M	4	4	4	4.0	4	-
1111	E	4	4	4	4.0	4	-
1112	E	4	4	4	4.0	4	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

+ : Animal with abnormal estrous cycle, - : Animal with normal and regular cycle

Animal No.	/Before mating (day)													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2101	P	E	M	D	P	E	M	D	P	E	E	M	D	D
2102	M	D	P	E	M	D	P	E	M	D	P	E	M	D
2103	E	E	M	D	P	E	E	M	D	D	P	E	M	D
2104	M	D	P	E	M	D	P	E	M	D	P	E	M	D
2105	D	P	E	M	D	P	E	M	D	P	E	M	D	P
2106	D	P	E	M	D	P	E	M	D	P	E	M	D	P
2107	E	M	D	P	E	M	D	P	E	M	D	P	E	M
2108	D	P	E	M	D	P	E	M	D	P	E	M	D	P
2109	M	D	P	E	M	D	P	E	M	D	P	E	M	D
2110	M	D	D	P	E	M	D	D	P	E	M	D	D	P
2111	D	P	E	M	D	P	E	M	D	P	E	M	D	P
2112	D	D	D	D	D	D	D	D	D	D	D	D	P	E

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

Estrus cycles and copulation

Generation : F0

Dose : crotonic acid 50 mg/kg

Species : Rat

Generation : F0		Dose : crotonic acid 50 mg/kg			Species : Rat			
Animal No.	/Before mating (day)	Length of estrous cycle			Mean	Number of estrus	Animal with abnormal estrous cycle	
	15	(days)						
2101	P		4	4	4.0	3	-	
2102	P		4	4	4.0	3	-	
2103	D		5	6	5.5	3	+	
2104	D		4	4	4.0	3	-	
2105	E		4	4	4	4.0	4	-
2106	E		4	4	4	4.0	4	-
2107	D		4	4	4	4.0	4	-
2108	E		4	4	4	4.0	4	-
2109	P		4	4		4.0	3	-
2110	E		5	5		5.0	3	-
2111	E		4	4	4	4.0	4	-
2112	M					1	+	

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

+ : Animal with abnormal estrous cycle, - : Animal with normal and regular cycle

Animal No.	/Before mating (day)													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3101	P	E	M	D	P	E	M	D	P	E	M	D	P	E
3102	D	P	E	E	M	D	D	P	E	M	D	D	P	E
3103	P	E	M	D	P	E	M	D	P	E	M	D	P	E
3104	D	P	E	M	D	P	E	M	D	P	E	M	D	P
3105	P	E	M	D	P	E	M	D	P	E	M	D	P	E
3106	M	D	D	P	E	E	M	D	P	E	M	D	P	E
3107	P	E	M	D	P	E	M	D	P	E	M	D	P	E
3108	D	P	E	M	D	P	E	M	D	P	E	M	D	P
3109	D	P	E	M	D	P	E	M	D	P	E	M	D	P
3110	D	P	E	M	D	P	E	M	D	P	E	M	D	P
3111	E	M	D	D	D	D	D	D	D	D	D	D	P	E
3112	E	M	D	P	E	M	D	P	E	M	D	P	E	M

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

Estrus cycles and copulation

Generation : F0

Dose : crotonic acid 150 mg/kg

Species : Rat

Animal No.	/Before mating (day)	Length of estrous cycle			Mean	Number of estrus	Animal with abnormal estrous cycle
		(days)					
3101	M	4	4	4	4.0	4	-
3102	M	6	5		5.5	3	+
3103	M	4	4	4	4.0	4	-
3104	E	4	4	4	4.0	4	-
3105	M	4	4	4	4.0	4	-
3106	M	5	4		4.5	3	-
3107	M	4	4	4	4.0	4	-
3108	E	4	4	4	4.0	4	-
3109	E	4	4	4	4.0	4	-
3110	E	4	4	4	4.0	4	-
3111	M	13			13.0	2	+
3112	D	4	4	4	4.0	4	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

+ : Animal with abnormal estrous cycle, - : Animal with normal and regular cycle

Animal No.	/Before mating (day)													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4101	E	M	D	P	E	M	D	P	E	M	D	P	E	M
4102	E	M	D	P	E	M	D	P	E	M	D	P	E	M
4103	P	E	M	D	P	E	M	D	P	E	M	D	P	E
4104	E	M	D	P	E	M	D	P	E	M	D	P	E	M
4105	M	D	P	E	M	D	P	E	M	D	P	E	M	D
4106	M	D	P	E	M	D	P	E	M	D	P	E	M	D
4107	D	P	E	M	D	P	E	M	D	D	P	E	E	M
4108	E	M	D	P	E	M	D	P	E	M	D	D	D	D
4109	M	D	P	E	M	D	P	E	M	D	P	E	M	D
4110	M	D	P	E	M	D	P	E	M	D	P	E	M	D
4111	E	M	D	P	E	M	D	P	E	M	D	P	E	M
4112	P	E	M	D	D	P	E	M	D	D	P	E	M	D

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

Estrus cycles and copulation

Generation : F0

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Before mating (day)	Length of estrous cycle			Mean	Number of estrus	Animal with abnormal estrous cycle	
	15	(days)						
4101	D		4	4	4	4.0	4	-
4102	D		4	4	4	4.0	4	-
4103	M		4	4	4	4.0	4	-
4104	D		4	4	4	4.0	4	-
4105	P		4	4		4.0	3	-
4106	P		4	4		4.0	3	-
4107	D		4	5		4.5	3	-
4108	D		4	4		4.0	3	+
4109	P		4	4		4.0	3	-
4110	P		4	4		4.0	3	-
4111	D		4	4	4	4.0	4	-
4112	D		5	5		5.0	3	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

+ : Animal with abnormal estrous cycle, - : Animal with normal and regular cycle

Reproductive performance

Generation : F0

Sex : Male

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving a)	1st mating		
		Paired animal	Copulation b)	Fertility c)
1001	1	1101	+	+
1002	4	1102	+	+
1003	3	1103	+	+
1004	2	1104	+	+
1005	1	1105	+	+
1006	7	1106	+	+
1007	1	1107	+	+
1008	2	1108	+	+
1009	3	1109	+	+
1010	3	1110	+	+
1011	4	1111	+	+
1012	4	1112	+	+
n	12		12	12
Mean	2.9			
S.D.	1.7			
No. of positives			12	12
%			100.0 d)	100.0 e)

a)-: Not copulation

b)+: Copulation, -: Not copulation

c)+: Pregnant, -: Non-pregnant

d): (Number of copulated animals / Number of mated animals)×100

e): (Number of males which impregnated females / Number of copulated males)×100

Reproductive performance

Generation : F0

Sex : Male

Dose : crotonic acid 50 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving a)	1st mating		
		Paired animal	Copulation b)	Fertility c)
2001	1	2101	+	+
2002	1	2102	+	+
2003	1	2103	+	+
2004	2	2104	+	+
2005	-	2105	-	-
2006	4	2106	+	+
2007	2	2107	+	+
2008	-	2108	-	-
2009	1	2109	+	+
2010	4	2110	+	+
2011	4	2111	+	+
2012	3	2112	+	+
n	10		12	10
Mean	2.3			
S.D.	1.3			
No. of positives			10	10
%			83.3 d)	100.0 e)

a)-: Not copulation

b)+: Copulation, -: Not copulation

c)+: Pregnant, -: Non-pregnant

d): (Number of copulated animals / Number of mated animals)×100

e): (Number of males which impregnated females / Number of copulated males)×100

Animal No.	Elapsed day of conceiving a)	1st mating		
		Paired animal	Copulation b)	Fertility c)
3001	3	3101	+	+
3002	4	3102	+	+
3003	3	3103	+	+
3004	4	3104	+	+
3005	3	3105	+	+
3006	3	3106	+	+
3007	3	3107	+	+
3008	4	3108	+	+
3009	-	3109	-	
3010	4	3110	+	+
3011	3	3111	+	+
3012	2	3112	+	+
n	11		12	11
Mean	3.3			
S.D.	0.6			
No. of positives			11	11
%			91.7 d)	100.0 e)

a)-: Not copulation

b)+: Copulation, -: Not copulation

c)+: Pregnant, -: Non-pregnant

d): (Number of copulated animals / Number of mated animals)×100

e): (Number of males which impregnated females / Number of copulated males)×100

Reproductive performance

Generation : F0

Sex : Male

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving a)	1st mating		
		Paired animal	Copulation b)	Fertility c)
4001	2	4101	+	+
4002	2	4102	+	+
4003	3	4103	+	+
4004	2	4104	+	+
4005	1	4105	+	+
4006	1	4106	+	+
4007	2	4107	+	+
4008	4	4108	+	+
4009	1	4109	+	+
4010	1	4110	+	+
4011	2	4111	+	+
4012	2	4112	+	+
n	12		12	12
Mean	1.9			
S.D.	0.9			
No. of positives			12	12
%			100.0 d)	100.0 e)

a)-: Not copulation

b)+: Copulation, -: Not copulation

c)+: Pregnant, -: Non-pregnant

d): (Number of copulated animals / Number of mated animals)×100

e): (Number of males which impregnated females / Number of copulated males)×100

Reproductive performance

Generation : F0

Sex : Female

Dose : crotonic acid 0 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving a)	1st mating		
		Paired animal	Copulation b)	Fertility c)
1101	1	1001	+	+
1102	4	1002	+	+
1103	3	1003	+	+
1104	2	1004	+	+
1105	1	1005	+	+
1106	7	1006	+	+
1107	1	1007	+	+
1108	2	1008	+	+
1109	3	1009	+	+
1110	3	1010	+	+
1111	4	1011	+	+
1112	4	1012	+	+
n	12		12	12
Mean	2.9			
S.D.	1.7			
No. of positives			12	12
%			100.0 d)	100.0 e)

a)-: Not copulation

b)+: Copulation, -: Not copulation

c)+: Pregnant, -: Non-pregnant

d): (Number of copulated animals / Number of mated animals)×100

e): (Number of pregnant females / Number of copulated females)×100

Reproductive performance

Generation : F0

Sex : Female

Dose : crotonic acid 50 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving a)	1st mating		
		Paired animal	Copulation b)	Fertility c)
2101	1	2001	+	+
2102	1	2002	+	+
2103	1	2003	+	+
2104	2	2004	+	+
2105	-	2005	-	-
2106	4	2006	+	+
2107	2	2007	+	+
2108	-	2008	-	-
2109	1	2009	+	+
2110	4	2010	+	+
2111	4	2011	+	+
2112	3	2012	+	+
n	10		12	10
Mean	2.3			
S.D.	1.3			
No. of positives			10	10
%			83.3 d)	100.0 e)

a)-: Not copulation

b)+: Copulation, -: Not copulation

c)+: Pregnant, -: Non-pregnant

d): (Number of copulated animals / Number of mated animals)×100

e): (Number of pregnant females / Number of copulated females)×100

Reproductive performance

Generation : F0

Sex : Female

Dose : crotonic acid 150 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving a)	1st mating		
		Paired animal	Copulation b)	Fertility c)
3101	3	3001	+	+
3102	4	3002	+	+
3103	3	3003	+	+
3104	4	3004	+	+
3105	3	3005	+	+
3106	3	3006	+	+
3107	3	3007	+	+
3108	4	3008	+	+
3109	-	3009	-	
3110	4	3010	+	+
3111	3	3011	+	+
3112	2	3012	+	+
n	11		12	11
Mean	3.3			
S.D.	0.6			
No. of positives			11	11
%			91.7 d)	100.0 e)

a)-: Not copulation

b)+: Copulation, -: Not copulation

c)+: Pregnant, -: Non-pregnant

d): (Number of copulated animals / Number of mated animals)×100

e): (Number of pregnant females / Number of copulated females)×100

Reproductive performance

Generation : F0

Sex : Female

Dose : crotonic acid 500 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving a)	1st mating		
		Paired animal	Copulation b)	Fertility c)
4101	2	4001	+	+
4102	2	4002	+	+
4103	3	4003	+	+
4104	2	4004	+	+
4105	1	4005	+	+
4106	1	4006	+	+
4107	2	4007	+	+
4108	4	4008	+	+
4109	1	4009	+	+
4110	1	4010	+	+
4111	2	4011	+	+
4112	2	4012	+	+
n	12		12	12
Mean	1.9			
S.D.	0.9			
No. of positives			12	12
%			100.0 d)	100.0 e)

a)-: Not copulation

b)+: Copulation, -: Not copulation

c)+: Pregnant, -: Non-pregnant

d): (Number of copulated animals / Number of mated animals)×100

e): (Number of pregnant females / Number of copulated females)×100

Delivery data

Generation : F0

Dose : crotonic acid 0 mg/kg

Species : Rat

Dam No.	Gestation period (day)	Number of corpora lutea	Number of implan- tation	Preimplan- tation loss (%) a)	Implantation index (%) b)	Delivery index (%) c)	Live birth index (%) d)	Number of offspring	Number of live newborns			Number of dead newborns			
									M	F	Total	M	F	U	Total
1101	22	19(10/9)	19(10/9)	0.0	100.0	89.5	100.0	17	9	8	17	0	0	0	0
1102	22	17(11/6)	17(11/6)	0.0	100.0	100.0	100.0	17	8	9	17	0	0	0	0
1103	22	14(7/7)	13(6/7)	7.1	92.9	100.0	100.0	13	5	8	13	0	0	0	0
1104	22	16(4/12)	16(4/12)	0.0	100.0	100.0	100.0	16	6	10	16	0	0	0	0
1105	22	17(9/8)	17(9/8)	0.0	100.0	100.0	100.0	17	7	10	17	0	0	0	0
1106	22.5	17(7/10)	16(6/10)	5.9	94.1	100.0	100.0	16	10	6	16	0	0	0	0
1107	21.5	15(8/7)	14(8/6)	6.7	93.3	100.0	100.0	14	6	8	14	0	0	0	0
1108	22	16(9/7)	16(9/7)	0.0	100.0	87.5	100.0	14	9	5	14	0	0	0	0
1109	22	14(4/10)	14(4/10)	0.0	100.0	100.0	100.0	14	7	7	14	0	0	0	0
1110	22	16(8/8)	16(8/8)	0.0	100.0	100.0	100.0	16	11	5	16	0	0	0	0
1111	21.5	16(6/10)	16(6/10)	0.0	100.0	100.0	100.0	16	7	9	16	0	0	0	0
1112	22	16(9/7)	15(9/6)	6.3	93.8	86.7	100.0	13	9	4	13	0	0	0	0
n	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	22.0	16.1	15.8	2.2	97.8	97.0	100.0	15.3	7.8	7.4	15.3	0.0	0.0	0.0	0.0
S.D.	0.3	1.4	1.6	3.2	3.2	5.5	0.0	1.5	1.8	2.0	1.5	0.0	0.0	0.0	0.0

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

a): [(Number of corpora lutea - Number of implantation) / Number of corpora lutea]×100

b): (Number of implantation / Number of corpora lutea)×100

c): (Number of delivered pups / Number of implantation)×100

d): (Number of live borns / Number of delivered pups)×100

Delivery data

Generation : F0

Dose : crotonic acid 50 mg/kg

Species : Rat

Dam No.	Gestation period (day)	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a)	Implantation index (%) b)	Delivery index (%) c)	Live birth index (%) d)	Number of offspring	Number of live newborns			Number of dead newborns			
									M	F	Total	M	F	U	Total
2101	21.5	14(9/5)	14(9/5)	0.0	100.0	64.3	100.0	9	2	7	9	0	0	0	0
2102	22	15(8/7)	15(8/7)	0.0	100.0	93.3	100.0	14	6	8	14	0	0	0	0
2103	22.5	15(8/7)	15(8/7)	0.0	100.0	93.3	100.0	14	7	7	14	0	0	0	0
2104	23	16(10/6)	16(10/6)	0.0	100.0	93.8	100.0	15	9	6	15	0	0	0	0
2106	21.5	16(10/6)	16(10/6)	0.0	100.0	100.0	100.0	16	9	7	16	0	0	0	0
2107	22	15(6/9)	15(6/9)	0.0	100.0	93.3	100.0	14	7	7	14	0	0	0	0
2109	22	15(7/8)	14(7/7)	6.7	93.3	92.9	100.0	13	6	7	13	0	0	0	0
2110	23	17(9/8)	17(9/8)	0.0	100.0	94.1	93.8	16	9	6	15	1	0	0	1
2111	22	18(6/12)	18(6/12)	0.0	100.0	83.3	100.0	15	10	5	15	0	0	0	0
2112	22	15(7/8)	15(7/8)	0.0	100.0	100.0	93.3	15	6	8	14	0	1	0	1
n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	22.2	15.6	15.5	0.7	99.3	90.8	98.7	14.1	7.1	6.8	13.9	0.1	0.1	0.0	0.2
S.D.	0.5	1.2	1.3	2.1	2.1	10.4	2.7	2.0	2.3	0.9	1.9	0.3	0.3	0.0	0.4

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

Animal No.2105,2108: Not copulated

a): [(Number of corpora lutea - Number of implantation) / Number of corpora lutea]×100

b): (Number of implantation / Number of corpora lutea)×100

c): (Number of delivered pups / Number of implantation)×100

d): (Number of live borns / Number of delivered pups)×100

Delivery data

Generation : F0

Dose : crotonic acid 150 mg/kg

Species : Rat

Dam No.	Gestation period (day)	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a)	Implantation index (%) b)	Delivery index (%) c)	Live birth index (%) d)	Number of offspring	Number of live newborns			Number of dead newborns			
									M	F	Total	M	F	U	Total
3101	21.5	16(8/8)	15(7/8)	6.3	93.8	86.7	100.0	13	7	6	13	0	0	0	0
3102	22	19(7/12)	18(7/11)	5.3	94.7	83.3	100.0	15	4	11	15	0	0	0	0
3103	22	17(9/8)	17(9/8)	0.0	100.0	100.0	100.0	17	6	11	17	0	0	0	0
3104	22	17(6/11)	10(6/4)	41.2	58.8	100.0	100.0	10	7	3	10	0	0	0	0
3105	22	13(8/5)	13(8/5)	0.0	100.0	100.0	100.0	13	9	4	13	0	0	0	0
3106	22.5	16(8/8)	16(8/8)	0.0	100.0	100.0	100.0	16	8	8	16	0	0	0	0
3107	21.5	16(10/6)	16(10/6)	0.0	100.0	100.0	100.0	16	12	4	16	0	0	0	0
3108	22	20(8/12)	17(7/10)	15.0	85.0	94.1	100.0	16	10	6	16	0	0	0	0
3110	22.5	17(11/6)	17(11/6)	0.0	100.0	100.0	100.0	17	10	7	17	0	0	0	0
3111	22	17(7/10)	17(7/10)	0.0	100.0	100.0	100.0	17	6	11	17	0	0	0	0
3112	21.5	18(10/8)	18(10/8)	0.0	100.0	100.0	100.0	18	8	10	18	0	0	0	0
n	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	22.0	16.9	15.8	6.2	93.8	96.7	100.0	15.3	7.9	7.4	15.3	0.0	0.0	0.0	0.0
S.D.	0.4	1.8	2.4	12.5	12.5	6.1	0.0	2.4	2.3	3.0	2.4	0.0	0.0	0.0	0.0

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

Animal No.3109: Not copulated

a): [(Number of corpora lutea - Number of implantation) / Number of corpora lutea]×100

b): (Number of implantation / Number of corpora lutea)×100

c): (Number of delivered pups / Number of implantation)×100

d): (Number of live borns / Number of delivered pups)×100

Delivery data

Generation : F0

Dose : crotonic acid 500 mg/kg

Species : Rat

Dam No.	Gestation period (day)	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a)	Implantation index (%) b)	Delivery index (%) c)	Live birth index (%) d)	Number of offspring	Number of live newborns			Number of dead newborns			
									M	F	Total	M	F	U	Total
4101	22.5	15(8/7)	15(8/7)	0.0	100.0	100.0	93.3	15	11	3	14	0	1	0	1
4102	22	14(7/7)	14(7/7)	0.0	100.0	78.6	100.0	11	4	7	11	0	0	0	0
4103	22	16(11/5)	16(11/5)	0.0	100.0	100.0	100.0	16	10	6	16	0	0	0	0
4104	21.5	16(10/6)	15(9/6)	6.3	93.8	100.0	100.0	15	6	9	15	0	0	0	0
4105	22	15(8/7)	15(8/7)	0.0	100.0	93.3	100.0	14	6	8	14	0	0	0	0
4106	22.5	16(9/7)	16(9/7)	0.0	100.0	87.5	92.9	14	4	9	13	0	1	0	1
4107	22	15(8/7)	15(8/7)	0.0	100.0	100.0	100.0	15	8	7	15	0	0	0	0
4108	22	15(10/5)	15(10/5)	0.0	100.0	100.0	100.0	15	5	10	15	0	0	0	0
4109	22	17(8/9)	15(8/7)	11.8	88.2	93.3	100.0	14	6	8	14	0	0	0	0
4110	22	15(10/5)	15(10/5)	0.0	100.0	93.3	92.9	14	4	9	13	0	1	0	1
4111	22.5	14(5/9)	14(5/9)	0.0	100.0	100.0	100.0	14	6	8	14	0	0	0	0
4112	22	16(10/6)	16(10/6)	0.0	100.0	100.0	100.0	16	9	7	16	0	0	0	0
n	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	22.1	15.3	15.1	1.5	98.5	95.5	98.3	14.4	6.6	7.6	14.2	0.0	0.3	0.0	0.3
S.D.	0.3	0.9	0.7	3.7	3.7	6.8	3.2	1.3	2.4	1.8	1.4	0.0	0.5	0.0	0.5

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

a): [(Number of corpora lutea - Number of implantation) / Number of corpora lutea]×100

b): (Number of implantation / Number of corpora lutea)×100

c): (Number of delivered pups / Number of implantation)×100

d): (Number of live borns / Number of delivered pups)×100

Dam No.	Number of offspring examined	/Findings	Number of offspring with any anomaly (%)a)
1101	17	No anomaly	0 (0.0)
1102	17	No anomaly	0 (0.0)
1103	13	No anomaly	0 (0.0)
1104	16	No anomaly	0 (0.0)
1105	17	No anomaly	0 (0.0)
1106	16	No anomaly	0 (0.0)
1107	14	No anomaly	0 (0.0)
1108	14	No anomaly	0 (0.0)
1109	14	No anomaly	0 (0.0)
1110	16	No anomaly	0 (0.0)
1111	16	No anomaly	0 (0.0)
1112	13	No anomaly	0 (0.0)
Total	183		0
n	12		12
Mean			(0.0)
S.D.			(0.0)

Mean : Average of incidence (%)

a) : (Number of offspring with any anomaly / Number of offspring) x 100

Dam No.	Number of offspring examined	/Findings	Number of offspring with any anomaly (%)a)
2101	9	No anomaly	0 (0.0)
2102	14	No anomaly	0 (0.0)
2103	14	No anomaly	0 (0.0)
2104	15	No anomaly	0 (0.0)
2106	16	No anomaly	0 (0.0)
2107	14	No anomaly	0 (0.0)
2109	13	No anomaly	0 (0.0)
2110	16	No anomaly	0 (0.0)
2111	15	No anomaly	0 (0.0)
2112	15	No anomaly	0 (0.0)
Total	141		0
n	10		10
Mean			(0.0)
S.D.			(0.0)

Mean : Average of incidence (%)

a) : (Number of offspring with any anomaly / Number of offspring) x 100

Animal No. 2105 : Not copulated

Animal No. 2108 : Not copulated

Dam No.	Number of offspring examined	/Findings	Number of offspring with any anomaly (%)a)
3101	13	No anomaly	0 (0.0)
3102	15	No anomaly	0 (0.0)
3103	17	No anomaly	0 (0.0)
3104	10	No anomaly	0 (0.0)
3105	13	No anomaly	0 (0.0)
3106	16	No anomaly	0 (0.0)
3107	16	No anomaly	0 (0.0)
3108	16	No anomaly	0 (0.0)
3110	17	No anomaly	0 (0.0)
3111	17	No anomaly	0 (0.0)
3112	18	No anomaly	0 (0.0)
Total	168		0
n	11		11
Mean			(0.0)
S.D.			(0.0)

Mean : Average of incidence (%)

a) : (Number of offspring with any anomaly / Number of offspring) x 100

Animal No. 3109 : Not copulated

Dam No.	Number of offspring examined	/Findings	Number of offspring with any anomaly (%)a)
4101	15	No anomaly	0 (0.0)
4102	11	No anomaly	0 (0.0)
4103	16	No anomaly	0 (0.0)
4104	15	No anomaly	0 (0.0)
4105	14	No anomaly	0 (0.0)
4106	14	No anomaly	0 (0.0)
4107	15	No anomaly	0 (0.0)
4108	15	No anomaly	0 (0.0)
4109	14	No anomaly	0 (0.0)
4110	14	No anomaly	0 (0.0)
4111	14	No anomaly	0 (0.0)
4112	16	No anomaly	0 (0.0)
Total	173		0
n	12		12
Mean			(0.0)
S.D.			(0.0)

Mean : Average of incidence (%)

a) : (Number of offspring with any anomaly / Number of offspring) x 100

Dam No.	Number of offspring examined		/Findings
1101	17		No anomaly
1102	17		No anomaly
1103	13		No anomaly
1104	16		No anomaly
1105	17		No anomaly
1106	16		No anomaly
1107	14		No anomaly
1108	14		No anomaly
1109	14		No anomaly
1110	16		No anomaly
1111	15		No anomaly
1112	13		No anomaly
Total	182		
n	12		

Appendix 13 - 6

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

External examination of offspring

Unit : Number of anomalous offspring

Days after birth : 4

Generation : F0

Dose : crotonic acid 50 mg/kg

Species : Rat

Dam No.	Number of	
	offspring	/Findings
	examined	
2101	9	No anomaly
2102	14	No anomaly
2103	14	No anomaly
2104	15	No anomaly
2106	16	No anomaly
2107	14	No anomaly
2109	13	No anomaly
2110	15	No anomaly
2111	15	No anomaly
2112	14	No anomaly
Total	139	
n	10	

Animal No. 2105 : Not copulated

Animal No. 2108 : Not copulated

Appendix 13 - 7

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

External examination of offspring

Unit : Number of anomalous offspring

Days after birth : 4

Generation : F0

Dose : crotonic acid 150 mg/kg

Species : Rat

Dam No.	Number of offspring examined	/Findings
3101	13	No anomaly
3102	15	No anomaly
3103	16	No anomaly
3104	10	No anomaly
3105	13	No anomaly
3106	16	No anomaly
3107	16	No anomaly
3108	16	No anomaly
3110	17	No anomaly
3111	17	No anomaly
3112	16	No anomaly
Total	165	
n	11	

Animal No. 3109 : Not copulated

Appendix 13 - 8

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of
crotonic acid by oral administration in rats

Study No. : R-1169

External examination of offspring

Unit : Number of anomalous offspring

Days after birth : 4

Generation : F0

Dose : crotonic acid 500 mg/kg

Species : Rat

Dam No.	Number of offspring examined	/Findings
4101	14	No anomaly
4102	11	No anomaly
4103	15	No anomaly
4104	15	No anomaly
4105	14	No anomaly
4106	12	No anomaly
4107	15	No anomaly
4108	15	No anomaly
4109	14	No anomaly
4110	13	No anomaly
4111	14	No anomaly
4112	16	No anomaly
Total	168	
n	12	

Viability index and sex ratio of offspring on day 4 after birth

Generation : F0

Dose : crotonic acid 0 mg/kg

Species : Rat

Dam No.	Number of live offspring		Viability index (%)a)	Day 4		Sex ratio (%)b)
	Day 0	Day 4		Number of live offspring		
				Male	Female	
1101	17	17	100.0	9	8	
1102	17	17	100.0	8	9	
1103	13	13	100.0	5	8	
1104	16	16	100.0	6	10	
1105	17	17	100.0	7	10	
1106	16	16	100.0	10	6	
1107	14	14	100.0	6	8	
1108	14	14	100.0	9	5	
1109	14	14	100.0	7	7	
1110	16	16	100.0	11	5	
1111	16	15	93.8	6	9	
1112	13	13	100.0	9	4	
n	12	12	12			93/182
Mean	15.3	15.2	99.5			51.1
S.D.	1.5	1.5	1.8			

a) : (Number of live offspring on day 4 after birth / Number of live newborns) × 100

b) : (Number of live males on day 4 after birth / Number of live offspring on day 4 after birth) × 100

Viability index and sex ratio of offspring on day 4 after birth

Generation : F0

Dose : crotonic acid 50 mg/kg

Species : Rat

Dam No.	Number of live offspring		Viability index (%)a)	Day 4		Sex ratio (%)b)
	Day 0	Day 4		Male	Female	
2101	9	9	100.0	2	7	
2102	14	14	100.0	6	8	
2103	14	14	100.0	7	7	
2104	15	15	100.0	9	6	
2106	16	16	100.0	9	7	
2107	14	14	100.0	7	7	
2109	13	13	100.0	6	7	
2110	15	15	100.0	9	6	
2111	15	15	100.0	10	5	
2112	14	14	100.0	6	8	
n	10	10	10			71/139
Mean	13.9	13.9	100.0			51.1
S.D.	1.9	1.9	0.0			

a) : (Number of live offspring on day 4 after birth / Number of live newborns) × 100

b) : (Number of live males on day 4 after birth / Number of live offspring on day 4 after birth) × 100

Animal No. 2105 : Not copulated

Animal No. 2108 : Not copulated

Viability index and sex ratio of offspring on day 4 after birth

Generation : F0

Dose : crotonic acid 150 mg/kg

Species : Rat

Generation : F0			Dose : Citronic acid 150 mg/kg			Species : Rat
Dam No.	Number of live offspring		Viability index (%)a)	Day 4		Sex ratio (%)b)
	Day 0	Day 4		Number of live offspring		
				Male	Female	
3101	13	13	100.0	7	6	
3102	15	15	100.0	4	11	
3103	17	16	94.1	6	10	
3104	10	10	100.0	7	3	
3105	13	13	100.0	9	4	
3106	16	16	100.0	8	8	
3107	16	16	100.0	12	4	
3108	16	16	100.0	10	6	
3110	17	17	100.0	10	7	
3111	17	17	100.0	6	11	
3112	18	16	88.9	7	9	
n	11	11	11			86/165
Mean	15.3	15.0	98.5			52.1
S.D.	2.4	2.1	3.6			

a) : (Number of live offspring on day 4 after birth / Number of live newborns) × 100

b) : (Number of live males on day 4 after birth / Number of live offspring on day 4 after birth) × 100

Animal No. 3109 : Not copulated

Viability index and sex ratio of offspring on day 4 after birth

Generation : F0

Dose : crotonic acid 500 mg/kg

Species : Rat

Dam No.	Number of live offspring		Viability index (%)a	Day 4		Sex ratio (%)b
	Day 0	Day 4		Number of live offspring		
				Male	Female	
4101	14	14	100.0	11	3	
4102	11	11	100.0	4	7	
4103	16	15	93.8	9	6	
4104	15	15	100.0	6	9	
4105	14	14	100.0	6	8	
4106	13	12	92.3	4	8	
4107	15	15	100.0	8	7	
4108	15	15	100.0	5	10	
4109	14	14	100.0	6	8	
4110	13	13	100.0	4	9	
4111	14	14	100.0	6	8	
4112	16	16	100.0	9	7	
n	12	12	12			78/168
Mean	14.2	14.0	98.8			46.4
S.D.	1.4	1.4	2.7			

a) : (Number of live offspring on day 4 after birth / Number of live newborns) × 100

b) : (Number of live males on day 4 after birth / Number of live offspring on day 4 after birth) × 100

Body weight of offspring

Generation : F0

Dose : crotonic acid 0 mg/kg

Unit : g

Species : Rat

Dam No.	Sex	0 /Days after birth		4/Pre-culled	
		n	B.W.	n	B.W.
1101	Male	9	6.4	9	10.4
	Female	8	5.8	8	9.7
1102	Male	8	6.6	8	10.1
	Female	9	6.0	9	8.9
1103	Male	5	7.0	5	10.5
	Female	8	6.6	8	9.9
1104	Male	6	6.6	6	9.8
	Female	10	5.9	10	8.6
1105	Male	7	6.6	7	9.9
	Female	10	6.0	10	9.3
1106	Male	10	7.1	10	9.4
	Female	6	6.8	6	9.5
1107	Male	6	6.0	6	9.5
	Female	8	5.7	8	8.8
1108	Male	9	6.8	9	10.6
	Female	5	6.6	5	10.3
1109	Male	7	6.7	7	10.6
	Female	7	6.3	7	10.2
1110	Male	11	6.2	11	10.4
	Female	5	6.0	5	9.8
1111	Male	7	6.0	6	9.2
	Female	9	5.6	9	8.7
1112	Male	9	6.2	9	10.8
	Female	4	5.9	4	10.4
n	Male	94		93	
	Female	89		89	
Mean	Male		6.5		10.1
	Female		6.1		9.5
S.D.	Male		0.4		0.5
	Female		0.4		0.6

Body weight of offspring

Generation : F0

Dose : crotonic acid 50 mg/kg

Unit : g

Species : Rat

Dam No.	Sex	/Days after birth		4/Pre-culled	
		0			
		n	B.W.	n	B.W.
2101	Male	2	6.5	2	10.3
	Female	7	6.1	7	9.7
2102	Male	6	6.3	6	10.3
	Female	8	6.2	8	9.9
2103	Male	7	7.2	7	11.8
	Female	7	6.9	7	10.9
2104	Male	9	7.9	9	12.0
	Female	6	7.2	6	11.2
2106	Male	9	6.1	9	8.7
	Female	7	5.8	7	8.0
2107	Male	7	6.9	7	11.4
	Female	7	6.4	7	10.7
2109	Male	6	6.5	6	11.1
	Female	7	6.1	7	10.7
2110	Male	9	8.1	9	11.5
	Female	6	8.1	6	12.2
2111	Male	10	6.4	10	9.9
	Female	5	6.2	5	9.5
2112	Male	6	6.7	6	10.7
	Female	8	6.5	8	10.1
n	Male	71		71	
	Female	68		68	
Mean	Male		6.9		10.8
	Female		6.6		10.3
S.D.	Male		0.7		1.0
	Female		0.7		1.1

Animal No.2105,2108: Not copulated

Body weight of offspring

Generation : F0

Dose : crotonic acid 150 mg/kg

Unit : g

Species : Rat

Dam No.	Sex	/Days after birth		4/Pre-culled	
		0		n	B.W.
		n	B.W.	n	B.W.
3101	Male	7	6.2	7	10.0
	Female	6	5.5	6	9.4
3102	Male	4	6.5	4	11.4
	Female	11	6.1	11	10.6
3103	Male	6	6.4	6	10.0
	Female	11	6.2	10	10.1
3104	Male	7	7.1	7	12.9
	Female	3	6.8	3	12.6
3105	Male	9	6.8	9	10.5
	Female	4	6.6	4	10.6
3106	Male	8	6.3	8	9.1
	Female	8	6.3	8	9.6
3107	Male	12	6.2	12	8.4
	Female	4	5.8	4	7.6
3108	Male	10	6.7	10	10.9
	Female	6	6.5	6	10.4
3110	Male	10	6.9	10	10.1
	Female	7	6.4	7	9.8
3111	Male	6	6.7	6	9.8
	Female	11	6.3	11	9.2
3112	Male	8	6.0	7	9.6
	Female	10	5.3	9	8.8
n	Male	87		86	
	Female	81		79	
Mean	Male		6.5		10.2
	Female		6.2		9.9
S.D.	Male		0.3		1.2
	Female		0.5		1.3

Animal No.3109: Not copulated

Body weight of offspring

Generation : F0

Dose : crotonic acid 500 mg/kg

Unit : g

Species : Rat

Dam No.	Sex	0 /Days after birth		4/Pre-culled	
		n	B.W.	n	B.W.
4101	Male	11	7.3	11	11.1
	Female	3	6.9	3	10.6
4102	Male	4	7.2	4	12.0
	Female	7	6.8	7	11.1
4103	Male	10	6.5	9	10.0
	Female	6	6.2	6	9.6
4104	Male	6	6.2	6	9.2
	Female	9	5.8	9	8.7
4105	Male	6	6.9	6	10.5
	Female	8	6.5	8	10.1
4106	Male	4	6.8	4	10.2
	Female	9	6.1	8	9.3
4107	Male	8	6.6	8	10.4
	Female	7	6.3	7	10.2
4108	Male	5	6.5	5	9.4
	Female	10	6.2	10	9.1
4109	Male	6	7.1	6	10.8
	Female	8	6.7	8	10.7
4110	Male	4	6.3	4	10.1
	Female	9	6.0	9	9.4
4111	Male	6	7.1	6	11.7
	Female	8	6.4	8	10.2
4112	Male	9	6.3	9	10.0
	Female	7	5.9	7	9.8
n	Male	79		78	
	Female	91		90	
Mean	Male		6.7		10.5
	Female		6.3		9.9
S.D.	Male		0.4		0.8
	Female		0.4		0.7

Body weight gain of offspring

Generation : F0

Dose : crotonic acid 0 mg/kg

Base : Day 4 after birth

Unit : g

Species : Rat

Dam No.	Sex	/Days after birth /Before culling	
		n	0-4
1101	Male	9	4.0
	Female	8	3.9
1102	Male	8	3.5
	Female	9	2.9
1103	Male	5	3.5
	Female	8	3.3
1104	Male	6	3.2
	Female	10	2.7
1105	Male	7	3.3
	Female	10	3.3
1106	Male	10	2.3
	Female	6	2.7
1107	Male	6	3.5
	Female	8	3.1
1108	Male	9	3.8
	Female	5	3.7
1109	Male	7	3.9
	Female	7	3.9
1110	Male	11	4.2
	Female	5	3.8
1111	Male	6	3.2
	Female	9	3.1
1112	Male	9	4.6
	Female	4	4.5
n	Male	93	
	Female	89	
Mean	Male		3.6
	Female		3.4
S.D.	Male		0.6
	Female		0.6

Body weight gain of offspring

Generation : F0

Dose : crotonic acid 50 mg/kg

Base : Day 4 after birth

Unit : g

Species : Rat

Dam No.	Sex	/Days after birth /Before culling	
		n	0-4
2101	Male	2	3.8
	Female	7	3.6
2102	Male	6	4.0
	Female	8	3.7
2103	Male	7	4.6
	Female	7	4.0
2104	Male	9	4.1
	Female	6	4.0
2106	Male	9	2.6
	Female	7	2.2
2107	Male	7	4.5
	Female	7	4.3
2109	Male	6	4.6
	Female	7	4.6
2110	Male	9	3.4
	Female	6	4.1
2111	Male	10	3.5
	Female	5	3.3
2112	Male	6	4.0
	Female	8	3.6
n	Male	71	
	Female	68	
Mean	Male		3.9
	Female		3.7
S.D.	Male		0.6
	Female		0.7

Animal No.2105,2108: Not copulated

Body weight gain of offspring

Generation : F0

Dose : crotonic acid 150 mg/kg

Base : Day 4 after birth

Unit : g

Species : Rat

Dam No.	Sex	/Days after birth /Before culling	
		n	0-4
3101	Male	7	3.8
	Female	6	3.9
3102	Male	4	4.9
	Female	11	4.5
3103	Male	6	3.6
	Female	10	3.9
3104	Male	7	5.8
	Female	3	5.8
3105	Male	9	3.7
	Female	4	4.0
3106	Male	8	2.8
	Female	8	3.3
3107	Male	12	2.2
	Female	4	1.8
3108	Male	10	4.2
	Female	6	3.9
3110	Male	10	3.2
	Female	7	3.4
3111	Male	6	3.1
	Female	11	2.9
3112	Male	7	3.6
	Female	9	3.5
n	Male	86	
	Female	79	
Mean	Male		3.7
	Female		3.7
S.D.	Male		1.0
	Female		1.0

Animal No.3109: Not copulated

Body weight gain of offspring

Generation : F0

Dose : crotonic acid 500 mg/kg

Base : Day 4 after birth

Unit : g

Species : Rat

Dam No.	Sex	/Days after birth /Before culling	
		n	0-4
4101	Male	11	3.8
	Female	3	3.7
4102	Male	4	4.8
	Female	7	4.3
4103	Male	9	3.5
	Female	6	3.4
4104	Male	6	3.0
	Female	9	2.9
4105	Male	6	3.6
	Female	8	3.6
4106	Male	4	3.4
	Female	8	3.2
4107	Male	8	3.8
	Female	7	3.9
4108	Male	5	2.9
	Female	10	2.9
4109	Male	6	3.7
	Female	8	4.0
4110	Male	4	3.8
	Female	9	3.4
4111	Male	6	4.6
	Female	8	3.8
4112	Male	9	3.7
	Female	7	3.9
n	Male	78	
	Female	90	
Mean	Male		3.7
	Female		3.6
S.D.	Male		0.5
	Female		0.4

Dam No.	Number of offspring examined	/Findings
1101	0	
1102	0	
1103	0	
1104	0	
1105	0	
1106	0	
1107	0	
1108	0	
1109	0	
1110	0	
1111	1	No anomaly
1112	0	
Total	1	
n	12	

External examination of dead offspring

Unit : Number of anomalous offspring

Generation : F0

Dose : crotonic acid 50 mg/kg

Species : Rat

Dam No.	Number of offspring examined		/Findings
2101	0		
2102	0		
2103	0		
2104	0		
2106	0		
2107	0		
2109	0		
2110	0		
2111	0		
2112	0		
Total	0		
n	10		

Animal No. 2105 : Not copulated

Animal No. 2108 : Not copulated

Dam No.	Number of offspring examined	/Findings
3101	0	
3102	0	
3103	1	No anomaly
3104	0	
3105	0	
3106	0	
3107	0	
3108	0	
3110	0	
3111	0	
3112	2	No anomaly
Total	3	
n	11	

Animal No. 3109 : Not copulated

Dam No.	Number of offspring examined	/Findings
4101	0	
4102	0	
4103	1	No anomaly
4104	0	
4105	0	
4106	1	No anomaly
4107	0	
4108	0	
4109	0	
4110	0	
4111	0	
4112	0	
Total	2	
n	12	

信頼性保証書 (1/3)

試験番号 : R-1169

試験表題 : クロトン酸のラットを用いた
経口投与による反復投与毒性・生殖発生毒性併合試験

本試験は以下に示す基準を遵守して実施されたことを保証致します。

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

なお、調査は下記の通り実施致しました。

2016 年 3 月 28 日

株式会社ボゾリサーチセンター
信頼性保証部門

試験における調査

項 目	担当者	調 査 日	試験責任者及び 運営管理者への 報告日
試験計画書		2015 年 9 月 17 日	2015 年 9 月 17 日
作業予定表・ コンピュータプロトコール		2015 年 9 月 30 日	2015 年 10 月 1 日
改善確認		2015 年 10 月 6 日	2015 年 10 月 6 日
調製・保存（被験物質）		2015 年 10 月 8 日	2015 年 10 月 8 日
投与液の濃度及び均一性確認		2015 年 10 月 8 日	2015 年 10 月 9 日
群分け		2015 年 10 月 12 日	2015 年 10 月 13 日

信頼性保証書 (2/3)

項 目	担当者	調 査 日	試験責任者及び 運営管理者への 報告日
体重・摂餌量測定・投与・ 一般状態の観察・腔垢検査		2015 年 10 月 13 日	2015 年 10 月 13 日
詳細な一般状態の観察		2015 年 10 月 15 日	2015 年 10 月 16 日
交配		2015 年 10 月 28 日	2015 年 10 月 28 日
尿検査 (尿量・色調・定性・沈渣)		2015 年 11 月 17 日	2015 年 11 月 17 日
摂水量測定		2015 年 11 月 18 日	2015 年 11 月 18 日
分娩・哺育観察・体重測定		2015 年 11 月 18 日	2015 年 11 月 18 日
尿検査（電解質・浸透圧）		2015 年 11 月 19 日	2015 年 11 月 20 日
機能検査・握力測定・ 自発運動量測定		2015 年 11 月 19 日	2015 年 11 月 19 日
採血・剖検		2015 年 11 月 23 日	2015 年 11 月 24 日
血液学検査（血液凝固検査）		2015 年 11 月 24 日	2015 年 11 月 24 日
病理組織学検査（切り出し）		2015 年 12 月 1 日	2015 年 12 月 1 日
被験物質の安定性		2015 年 12 月 16 日	2015 年 12 月 16 日
図・表・付表		2016 年 2 月 23 日	
		2016 年 2 月 24 日	
		2016 年 2 月 25 日	2016 年 2 月 26 日
改善確認		2016 年 2 月 29 日	2016 年 3 月 1 日
測定レポート（投与液の濃度及 び均一性確認、被験物質の安定 性：案）		2016 年 2 月 29 日	2016 年 3 月 1 日
最終報告書草案		2016 年 2 月 25 日	
		2016 年 2 月 26 日	
		2016 年 2 月 29 日	2016 年 3 月 1 日
測定レポート（投与液の濃度及 び均一性確認、被験物質の安定 性）		2016 年 3 月 1 日	2016 年 3 月 1 日

信頼性保証書 (3/3)

項 目	担当者	調 査 日	試験責任者及び 運営管理者への 報告日
生データ（入荷～剖検・病理、 飼育関係、被験物質関係、 投与液の濃度及び均一性確認、 被験物質の安定性）		2016 年 3 月 18 日	
		2016 年 3 月 22 日	
		2016 年 3 月 23 日	
		2016 年 3 月 24 日	
		2016 年 3 月 25 日	2016 年 3 月 25 日
改善確認		2016 年 3 月 28 日	2016 年 3 月 28 日
最終報告書		2016 年 3 月 28 日	2016 年 3 月 28 日

プロセス調査

項 目	試験番号	担当者	調 査 日	試験責任者及び 運営管理者への 報告日
動物入荷	B-7907		2015 年 9 月 18 日	2015 年 9 月 18 日
検疫・馴化	B-7910		2015 年 8 月 17 日	2015 年 8 月 18 日
	B-7910		2015 年 8 月 22 日	2015 年 8 月 24 日
血液学検査・ 血液化学検査	B-7850		2015 年 10 月 6 日	2015 年 10 月 6 日
病理組織学検査	B-7837		2015 年 10 月 6 日	2015 年 10 月 6 日
（包埋・薄切・染色）	B-7837		2015 年 10 月 7 日	2015 年 10 月 7 日
	B-7837		2015 年 10 月 13 日	2015 年 10 月 13 日