

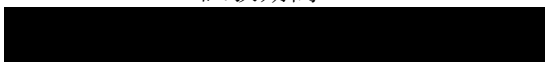


最 終 報 告 書

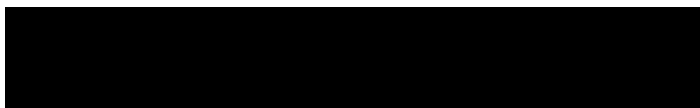
キナ抽出物：ラットを用いた経口投与による
反復投与毒性・生殖発生毒性併合試験

試験番号 

試験期間



試験施設



試験委託者

国立医薬品食品衛生研究所
安全性生物試験研究センター



試験受託者





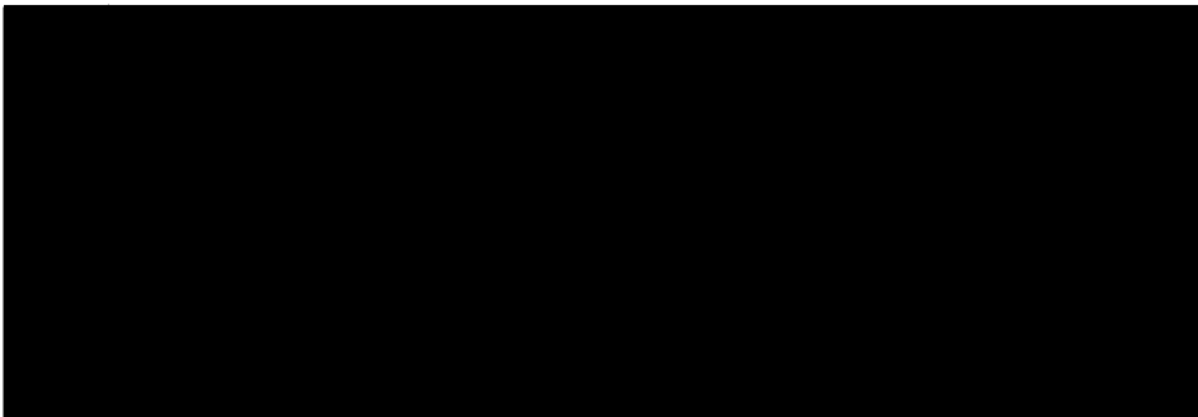
1. GLP 陳述書

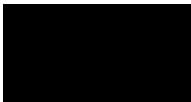
試験番号 : 

試験表題 : キナ抽出物：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

本試験は以下の GLP 基準を遵守して実施した。

- 「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)





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	規制に関する情報	8
3.4.1	GLP	8
3.4.2	毒性試験ガイドライン	8
3.4.3	動物の福祉	8
3.5	試験委託者	9
3.6	試験受託者	9
3.7	試験施設及び試験場所	9
3.7.1	試験施設	9
3.7.2	試験場所	9
3.8	試験責任者	9
3.9	試験担当者	9
3.10	試験日程	10
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	10
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	10
3.13	資料保存	10
3.14	試験責任者の署名	12
4.	要約	13
4.1	反復投与毒性	13
4.2	生殖発生毒性	13
5.	緒言	14
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	媒体及び被験液の調製	15
6.2.1	媒体の調製	15
6.2.2	被験液の調製	15
6.2.2.1	調製方法	15
6.2.2.2	調製頻度	15



6.2.2.3	保存条件	15
6.2.2.4	安定性	15
6.2.3	被験物質のろ過及び投与液の濃度分析	15
6.2.3.1	被験物質のろ過	16
6.2.3.2	投与液の濃度分析	16
6.3	試験系及び系統の選択理由	17
6.4	試験動物及び群分け	17
6.5	飼育条件	18
6.6	飼料、床敷及び飲料水中の混入物質	19
6.7	動物の識別	19
6.8	投与経路、投与期間、投与回数及び回復期間とそれらの選択理由	19
6.9	投与方法	20
6.10	投与量及び群構成	20
6.11	投与量の設定根拠	20
6.12	検査及び方法	21
6.12.1	一般状態の観察	21
6.12.2	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
6.12.2.1	詳細な一般状態の観察	22
6.12.2.2	機能検査	22
6.12.2.3	握力測定	22
6.12.2.4	自発運動量測定	22
6.12.3	体重測定	22
6.12.4	摂餌量測定	23
6.12.5	腔垢検査	23
6.12.6	交配	23
6.13	分娩及び哺育観察	23
6.13.1	母動物の観察	23
6.13.2	出生児の観察	24
6.14	臨床検査	25
6.14.1	尿検査	25
6.14.2	臨床検査のための採血	25
6.14.2.1	血液学検査	26
6.14.2.2	凝固系検査	27
6.14.2.3	血液化学検査	27
6.15	ホルモン測定	27
6.15.1	血清試料の採取、測定対象、保存及び送付	27
6.15.2	T4 測定	28
6.16	病理学検査	29



6.16.1	剖検	29
6.16.2	器官重量測定	29
6.16.3	病理組織学検査	29
7.	データ採取に使用したコンピュータシステム	31
8.	パラメータの算出	31
9.	統計解析	32
10.	試験結果	33
10.1	一般状態	33
10.2	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	33
10.2.1	詳細な一般状態の観察	33
10.2.1.1	ケージ内観察	33
10.2.1.2	手に持ったの観察	33
10.2.1.3	オープンフィールド内観察	33
10.2.2	機能検査	34
10.2.3	握力	34
10.2.4	自発運動量	34
10.3	体重	35
10.4	摂餌量	35
10.5	尿検査（摂水量測定を含む）	35
10.6	血液学検査	36
10.7	凝固系検査	36
10.8	血液化学検査	37
10.9	血中 T4 濃度測定	37
10.10	器官重量	37
10.11	剖検所見	38
10.12	病理組織学検査	38
10.13	性周期	38
10.14	交配成績	38
10.15	分娩成績並びに分娩及び哺育状態	38
10.16	出生児の Anogenital Distance (AGD)	39
10.17	出生児の生存性	39
10.18	出生児の性比	39
10.19	出生児の体重	39
10.20	死亡児の肉眼観察所見	39
10.21	雄新生児の乳頭/乳輪数	39
10.22	出生児の生後 13 日剖検所見	39
10.23	出生児の器官重量	40
11.	考察及び結論	40



11.1	反復投与毒性	40
11.2	生殖発生毒性	40
12.	参考文献	41

添付資料

Attachment 1	被験物質分析証明書	42
Attachment 2	既存添加物の原体サンプル情報	43
Attachment 3	被験物質のろ過作業及び投与液の濃度分析報告書 ..	46
Attachment 4	ホルモン測定報告書	71
Attachment 5	Historical Control Data in the Test Facility	88

図

Fig. 1~5	自発運動量	89
Fig. 6~8	体重	94
Fig. 9~11	摂餌量	97

表

Table 1-1~1-9	一般状態	100
Table 2-1~2-24	ホームケージ内観察	109
Table 2-25~2-86	手に持ったの観察	133
Table 2-87~2-158	オープンフィールド内観察	195
Table 2-159~2-165	機能検査	267
Table 2-166~2-170	握力	274
Table 2-171~2-175	自発運動量	279
Table 3-1~3-7	体重	284
Table 4-1~4-9	摂餌量	291
Table 5-1~5-18	尿検査	300
Table 6-1~6-5	血液学検査	318
Table 7-1~7-5	凝固系検査	323
Table 8-1~8-5	血液化学検査	328
Table 9-1~9-8	器官重量	333
Table 10-1~10-5	剖検所見	341
Table 11-1~11-15	病理組織学検査	346
Table 12	性周期	361
Table 13-1、13-2	交配成績	362
Table 14	分娩成績	364
Table 15	出産児の外表観察	365
Table 16	出生児の Anogenital Distance (AGD)	366



Table 17	出生児の生存性	367
Table 18	出生児の性比	368
Table 19-1、19-2	出生児の体重	369
Table 20	死亡児の肉眼観察所見	371
Table 21	雄新生児の乳頭/乳輪数	372
Table 22	出生児の生後 13 日剖検所見	373
Table 23-1、23-2	出生児の器官重量	374

個体別表

Appendix 1-1~1-28	一般状態	376
Appendix 2-1~2-76	ホームケージ内観察	404
Appendix 2-77~2-152	手に持ったの観察	480
Appendix 2-153~2-304	オープンフィールド内観察	556
Appendix 2-305~2-318	機能検査	708
Appendix 2-319~2-332	握力	722
Appendix 2-333~2-346	自発運動量	736
Appendix 3-1~3-22	体重	750
Appendix 4-1~4-28	摂餌量	772
Appendix 5-1~5-30	尿検査	800
Appendix 6-1~6-14	血液学検査	830
Appendix 7-1~7-14	凝固系検査	844
Appendix 8-1~8-14	血液化学検査	858
Appendix 9-1~9-24	器官重量	872
Appendix 10-1~10-116	剖検所見及び病理組織学検査	896
Appendix 11-1~11-8	性周期	1012
Appendix 12-1~12-8	交配成績	1020
Appendix 13-1~13-4	分娩成績	1028
Appendix 14-1~14-4	出産児の外表観察	1032
Appendix 15-1~15-4	出生児の Anogenital Distance (AGD)	1036
Appendix 16-1~16-4	出生児の生存性	1040
Appendix 17-1~17-4	出生児の性比	1044
Appendix 18-1~18-8	出生児の体重	1048
Appendix 19-1~19-4	死亡児の肉眼観察所見	1056
Appendix 20-1~20-4	雄新生児の乳頭/乳輪数	1060
Appendix 21-1~21-4	出生児の生後 13 日剖検所見	1064
Appendix 22-1~22-8	出生児の器官重量	1068

信頼性保証書	1076

3. 試験実施概要

3.1 試験番号

3.2 試験表題

キナ抽出物：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

3.3 試験目的

キナ抽出物（既存添加物、CAS No. 68990-12-5、苦味料等）をラットに一定期間反復投与したときに発現する一般毒性及び生殖発生毒性を明らかにし、有害影響の認められない用量を求めることを含む安全性に関する情報を得ることを目的とした。

3.4 規制に関する情報

3.4.1 GLP

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

3.4.2 毒性試験ガイドライン

- 「新規化学物質等に係る試験の方法について：哺乳類を用いる反復投与毒性・生殖発生毒性併合試験」
（平成 23 年 3 月 31 日付け薬食発 0331 第 7 号厚生労働省医薬食品局長、平成 23・03・29 製局第 5 号経済産業省製造産業局長、環保企発第 110331009 号環境省総合環境政策局長連名通知）（最終改正：令和 2 年 11 月 5 日）

3.4.3 動物の福祉

- 「動物の愛護及び管理に関する法律」
（昭和 48 年 10 月 1 日法律第 105 号）
- 「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」
（平成 18 年 4 月 28 日環境省告示第 88 号）
- 「動物実験の適正な実施に向けたガイドライン」
（日本学術会議 平成 18 年 6 月 1 日）
- 「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について」
（平成 18 年 6 月 1 日科発第 0601001 号）

本試験は動物実験委員会 (IACUC) の承認を受けて実施した（承認番号 G210323）。

また、試験施設は Assessment and Accreditation of Laboratory Animal Care (AAALAC) International の完全認証施設である。

3.5 試験委託者

国立医薬品食品衛生研究所
安全性生物試験研究センター

3.6 試験受託者

3.7 試験施設及び試験場所

3.7.1 試験施設

3.7.2 試験場所

3.8 試験責任者

3.9 試験担当者

被験物質管理責任者 :
試験主担当者 :
臨床検査責任者 :
病理検査責任者 :
被験物質のろ過作業及び投与液の濃度分析責任者（試験主任者 1）*
:
ホルモン測定責任者（試験主任者 2）**
:

3.10 試験日程

試験開始日 :
被験物質入手日 :
動物入荷日 :
実験開始日（投与開始日） :
交配開始日 :
分娩開始日 :
投与終了剖検日 :
回復開始日 :
母動物剖検開始日 :
回復終了剖検日 :
動物試験終了日 :
実験完了日（病理組織学検査終了日） :
試験終了日 :

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

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

3.13 資料保存

試験計画書（試験計画書変更書を含む）原本、記録文書、生データ、報告書類（最終報告書の原本を含む）及び標本（被験物質保存試料を含む）は に保存する。ただし、臨床検査後の残余生体試料（尿、血漿、血清）及び腔垢標本については、試験終了後に廃棄する。また、固定した死産児及び死亡児については、出生率、生後 4 及び 13 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、廃棄した。なお、資料の保存期間は試験終了後 5 年間とする。

被験物質のろ過作業及び投与液の濃度分析に関する作業計画書原本、生データ等の試験関係資料及び作業報告書原本は に保存する。なお、その期間は作業報告書作成後 5 年間とする。

ホルモン測定に関するホルモン測定計画書原本、生データ等の試験関係資料及びホ

ルモン測定報告書原本は

に保存する。なお、その期間はホルモン測定報告書作成後 5 年間とする。

試験施設と各試験場所における保存期間終了後の資料の取扱いについては国立医薬品食品衛生研究所とで協議し、その処置を決定する。



3.14 試験責任者の署名



4. 要約

キナ抽出物を注射用水に溶解させ、100、300 及び 1000 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、雌には交配を行わない非交配群として媒体対照群及び 1000 mg/kg 群に各 10 匹を追加）の雄には交配前 14 日間に加え交配期間を通して剖検前日まで（42 日間）、交配群雌には交配前 14 日間に加え交配期間及び妊娠期間を通して授乳 13 日まで（50~55 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、媒体対照群及び 1000 mg/kg 群の一部の動物（雄 5 匹と非交配群雌 5 匹）については、42 日間投与した後 14 日間の回復期間を設け、毒性変化の可逆性を検討した。なお、媒体対照群には媒体である注射用水を投与した。

検査項目は一般状態、詳細な一般状態観察、機能検査、握力、自発運動量、体重、摂餌量、尿検査（摂水量測定を含む）、血清中ホルモン(T4)、血液学検査、凝固系検査、血液化学検査、剖検、器官重量及び病理組織学検査とした。

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ず、一般状態、詳細な一般状態観察、機能検査、握力、自発運動量、体重、尿検査（摂水量測定を含む）、血液学検査、凝固系検査、血液化学検査、血清中ホルモン(T4)、器官重量及び剖検並びに病理組織学検査には、被験物質投与の影響は認められなかった。

4.2 生殖発生毒性

雌雄動物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、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。また、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、生後の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、本試験条件下では、本被験物質の反復投与毒性に対する無影響量及び無毒性量は、雌雄ともにいずれも 1000 mg/kg と判断した。また、生殖発生毒性に対する無影響量及び無毒性量は、いずれも親動物及び児動物ともに 1000 mg/kg と判断した。

5. 緒言

国立医薬品食品衛生研究所 安全性生物試験研究センター の委託により、キナ抽出物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。

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

以下の情報は、非 GLP 下で実施された分析結果に基づくものであるが、データの信頼性は試験委託者が保証していることを確認している（Attachment 1 及び 2）。

供給者	: 国立医薬品食品衛生研究所
提供事業者	:
製造元	:
名称	: キナ抽出物
英名	: Cinchona Bark Extract
由来・製法	: アカキナの樹皮をエタノールで抽出し、濾過した後、エバポレーターで濃縮して得られた抽出液の濃縮物
CAS 番号	: 68990-12-5
ロット番号	: 143072
入手量	: 1 kg×4 本（1 本は N-R114 で使用）
成分含量	: 総アルカロイド量 5.45% 固形分 70.5%
キニーネ含有量	: 0.4094% ¹⁾
性状	: 赤~暗褐色の粘性を有する液体
安定性	: 保存条件下で安定
使用期限	: オリジナル容器に密封状態で出荷後 24 ヶ月
製造日	:
有効期限	:
保存条件	: 室温（許容範囲：1°C~30°C、実測値は許容範囲内であった）、遮光
取扱い上の注意	: 作業場の換気を十分に行い、マスク、保護眼鏡、保護手袋等の適切な保護具を着用し、直接の接触を防ぐ。取り扱い後は、手、顔等を良く洗い、うがいをする。
保存場所	: 被験物質保存室及び被験物質調製室
保存試料	: 被験物質約 1 g を保存試料として保存した。
残余品の処理	: 使用後の残余は全て試験委託者に返却した。

6.1.2 媒体

名称 : 注射用水
規格 : 日本薬局方
メーカー : 株式会社大塚製薬工場
ロット番号 :
保存条件 : 室温
保存場所 : 被験物質調製室

6.2 媒体及び被験液の調製

6.2.1 媒体の調製

注射用水をそのまま用いた。媒体対照群の投与に用いる媒体は、被験物質を取り扱う前に 1 日必要量を褐色ガラス瓶に分注し、被験液と同じ条件で保存した。

6.2.2 被験液の調製

6.2.2.1 調製方法

高用量群液 (100 mg/mL 液) の調製に必要な被験物質濾過原液 (6.2.3.1 項参照) を秤取し、乳鉢に入れ、適量の媒体を加えて乳棒を用いて混合・溶解した。溶解液をメスシリンダーに移し、媒体を加えて 100 mg/mL 液とした。中及び低用量群液 (30 及び 10 mg/mL 液) は 100 mg/mL 液を段階希釈して調製した。被験液は投与用に 1 日必要分ずつ褐色ガラス瓶に分注した。

6.2.2.2 調製頻度

最大 7 日分を一括して調製し、調製後 9 日以内に使用した。

6.2.2.3 保存条件

冷蔵保存した (許容範囲 : 2°C~8°C、実測値は許容範囲内であった)。

6.2.2.4 安定性

において、キナ抽出物 (ロット番号) の 10 及び 100 mg/mL 溶液 (媒体 : 注射用水) は遮光瓶 (気密容器) で冷蔵 9 日間保存後、更に室温 24 時間保存後の安定性が確認されている (非 GLP 試験)²⁾。

6.2.3 被験物質のろ過及び投与液の濃度分析

試験委託者から受領した被験物質を に送付 (として 送付済み) し、 で濾過したものを被験物質濾過原液として提供を受けた。また、初回投与及び雄の最終投与に使用する各濃度の被験液について濃度を測定した。なお、当試験に使用した被験物質濾過原液の安定性は、同ロット品について投与期間終了後に で実施された安定性分析結果 (非 GLP 試験) から確

認められた（詳細は Attachment 3 参照）。

1) 作業番号（試験場所番号）

2) 作業表題

「キナ抽出物：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」における被験物質のろ過作業及び投与液の濃度分析

3) 作業・操作

上記測定に関する操作手順は試験場所 1 の SOP に従って行った。

4) 作業報告書

試験場所 1 において作業報告書を作成した。試験責任者は作業報告書の写しを入手し、当試験（ ）の最終報告書に添付した。またその内容を当試験の最終報告書に反映させた。

6.2.3.1 被験物質のろ過

被験物質容器を約 40°C に加温したお湯に浸し、60 分間加温（この時、適宜転倒混和を行った）して、均一にした。融解した被験物質について、メッシュ（サンプルパック：栄研化学株式会社、型式：KA1000）を用いて濾過したもの（濾過分画）を被験物質濾過原液として取り扱った^{3) 4)}。この濾過分画について、マグネチックスターラーによる攪拌操作を行い、必要量を分取して遮光保存した。分取された被験物質濾過原液は室温条件下で宅配便を使用して試験場所 1 から受領した（ ）（詳細は Attachment 3 参照）。

6.2.3.2 投与液の濃度分析

初回投与及び雄の最終投与に使用した各濃度の被験液（上、中、下層から各約 10 mL 採取）について にて高速液体クロマトグラフ（HPLC）法により濃度測定を実施した。初回投与に使用した被験液については、投与開始前に分析を行った。その結果、各濃度液におけるキニーネを指標とした濃度の表示値に対する割合は 86.1%~99.7%^{注)}、各層の濃度の平均値に対す割合は 93.0%~105.7%であり、いずれも許容範囲（濃度：キニーネを指標とした表示値に対して 100.0%± 15.0%、均一性；各層の濃度が平均値に対して 100.0%± 15.0%）を満たしたことから、被験液の調製に問題はなかったと判断した（詳細は Attachment 3 参照）。なお、本測定法は にて実施したバリデーション試験で確立された方法である（ ）²⁾。

注) 雄の最終投与用として、 に調製した投与液を分析したところ、30 mg/mL 液の濃度が設定濃度の 82.9%となり、基準（設定濃度の±15%）をみたさなかったことから、本投与液は投与に使用せず廃棄した。改めて に再調製し、再分析を実施した。再分析の結果、投与液濃度は基準をみたしたことから、再分析の結果を採用し、 に調製した投与液を雄の最終投与に使用した。

6.3 試験系及び系統の選択理由

毒性試験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。ラットは医薬品などの安全性試験に広く用いられており、この試験に使用される系統のラットは特性がよく知られ、背景資料が豊富であることから選択した。

6.4 試験動物及び群分け

動物種	: ラット (SPF)
系統	: Sprague-Dawley [CrI:CD(SD)]
供給源	: 日本チャールス・リバー株式会社、厚木飼育センター
入荷時週齢	: 7 週齢
購入匹数	: 雄 56 匹、雌 82 匹
検疫・馴化期間	: 22 日間
投与開始時週齢	: 10 週齢
供試動物数	: 雄 48 匹、雌 68 匹
検疫・馴化期間中の観察	: 全動物について、体重測定 (5 回: 馴化 1、3、10、17 日及び 22 日 [群分け日])、生死並びに体外表、栄養状態、姿勢、行動及び排泄物などの一般状態の観察 (1 回/日) を実施した。詳細な一般状態の観察 (詳細は 6.12.2 項参照) を検疫終了後、群分けまでの期間に実施した (1 回)。更に、雄は検疫期間終了後、群分け前までに陰囊内の精巣の触診 (1 回) 及び陰茎亀頭の観察 (1 回) を実施し、雌は検疫期間終了後、群分け前まで膣垢を採取して性周期を調べた (詳細は 6.12.5 項参照)。
供試動物の選択	: 検疫・馴化期間中の一般状態、詳細な一般状態の観察、入荷日から群分け日までの体重推移に加え雌は性周期 (馴化 6~19 日の 14 日間) に異常が無く、雄は性成熟に達している (精巣下降及び陰茎亀頭包皮分離がみられる) ことを条件とし、健康と考えられる動物を選択した。
群分け	: 上記に示した手順で選択した動物のうち、体重増加 (検疫初回の体重~群分け時の体重) が順調な動物を群分け当日 (投与開始前日) の体重に基づいて、各群の平均体重ができるだけ均等となるように群分けを行った。動物の割付けはコンピュータを用いたブロック・ランダム化により行った (ブロック配置により必要な群を構成し、試験群及び群内の個体番号を無作為に割当てた)。
投与開始時体重範囲	: 雄は 379 g~456 g (平均値: 418 g)、雌は 226 g~284 g (平均値: 252 g) であり、雌雄それぞれ平均体重の



± 20%以内であった。

余剰動物の処置

： 供試動物の選択条件を満たして余剰となった雌 12 匹は交配予備動物（無処置動物）として継続飼育し、交配群動物の交配が終了した後 [REDACTED] に試験から除外した。その他の残余動物の雄 8 匹、雌 2 匹は、群分け後の [REDACTED] に試験から除外した。なお、試験から除外された動物は、動物管理部門に移管した。

6.5 飼育条件

飼育室番号

： [REDACTED]。検疫・馴化期間は性ごと（雄：[REDACTED]、雌：[REDACTED]）に収容し、群分け後は各群を 2 分割して収容した（表 1 参照）。

表 1. 飼育室の動物振り分け表（群分け後）

飼育室番号	[REDACTED]		[REDACTED]	
性	雄	雌	雄	雌
動物番号	1001~1007	1101~1107	1008~1012	1108~1112
	2001~2007	2101~2107	2008~2012	2108~2112
	3001~3007	3101~3107	3008~3012	3108~3112
	4001~4007	4101~4107	4008~4012	4108~4112
		5101~5105		5106~5110
		6101~6105		6106~6110

温度

： 23°C ± 3°C

相対湿度

： 50% ± 20%

換気回数

： 1 時間 10~15 回

照明

： 1 日 12 時間（07:00~19:00）

ケージ

： 床敷（コンフィネスト、株式会社ファルマ、ロット番号 [REDACTED]）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）

収容匹数

： 入荷から群分けまで；同性 2 匹/ケージ
群分け以降；雌雄とも 1 匹/ケージ
交尾成立雌；授乳 13 日まで 1 腹/ケージ

飼料

： 固型飼料 CRF-1（γ 線滅菌、オリエンタル酵母工業株式会社、ロット番号 [REDACTED]）をステンレス製給餌器に入れて自由に摂取させた。

飲料水

： 御殿場市営水道水を自動給水装置により自由に摂取させた。

環境エンリッチメント

： 動物実験委員会の指針に従って、適切な環境エンリッチメントを与えた。

6.6 飼料、床敷及び飲料水中の混入物質

下記の混入物質に関する分析報告書の結果が基準内であることを確認した。

- 飼料の分析報告書（ユーロフィン・フード・テストイング株式会社、供試全ロット）
- 床敷の分析報告書（一般財団法人日本食品分析センター、供試全ロット）
- 水道法に準拠した水質の分析報告書（芝浦セムテック株式会社、年 4 回）

6.7 動物の識別

小動物用耳標	：	番号が刻印された小動物用耳標を入荷時に装着し、実験期間を通じてこの番号を個体識別の基本とした。
動物番号	：	群分け後は、試験群、性及び群内の個体が区別できるよう、4桁の数字を割り当てた（表2及び表3の群構成参照）。出生児については生後13日の体重測定時に、母動物番号に続けて性別を示すアルファベット（雄はM、雌はF）、同腹内番号を示す2桁の出生児番号を体重測定順に割付け、油性インクで尾に付した記号で識別した。
ケージラベル	：	群分け後、各飼育ケージには投与量（群）ごとに色分けしたケージラベルを添付し、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。ケージラベルの裏には試験番号、性別及び耳標番号のみを表示し、詳細な一般状態の観察、機能検査あるいは握力測定時には、ケージラベルを裏返して観察者への投与量の情報を制限した。

6.8 投与経路、投与期間、投与回数及び回復期間とそれらの選択理由

毒性試験ガイドラインに従い、投与経路は、経口投与を選択した。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（7日/週）とした。交配群の雄及び非交配群の雌に設定した回復動物の回復期間は、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のに適切と考えられる14日間とし、この間休薬させた。

各群の投与期間は以下の通りとした。

交配群（雄）	：	交配前14日間及び交配開始日から28日間
交配群（雌）	：	交配前14日間及び交配開始日から授乳13日まで
非交配群（雌のみ）	：	交配群の投与開始日から42日間

6.9 投与方法

投与方法は、げっ歯類の経口投与において一般的な強制経口投与とした。

投与容量は 10 mL/kg とし、フレキシブル胃ゾンデを用いて被験液を胃内に強制経口投与した（概ね午前中）。ただし、投与時に分娩途中であった場合、分娩の終了を待って投与を行った。媒体対照群には媒体（注射用水）を同様に投与した。動物ごとの投与液量（表示単位：0.1 mL）は直近の体重を基準に算出した。

6.10 投与量及び群構成

投与量は、交配群は 100、300 及び 1000 mg/kg の 3 用量とし、媒体対照群を加えた 4 群構成とした。また、非交配群は 1000 mg/kg の 1 用量とし、媒体対照群を加えた 2 群構成とした。1 群当たりの動物数は、交配群では各群で雌雄各 12 匹とし、このうち雄の媒体対照群及び高用量群の各 5 匹を回復動物とした。非交配群では各群で雌 10 匹とし、このうち各群の 5 匹を回復動物とした。群構成を表 2 及び表 3 に示す。

表 2. 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
媒体対照	0	0	10	7	1001-1007	5	1008-1012
低用量	100	10	10	12	2001-2012		
中用量	300	30	10	12	3001-3012		
高用量	1000	100	10	7	4001-4007	5	4008-4012

表 3. 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
媒体対照	0	0	10	12	1101-1112	5	5101-5105	5	5106-5110
低用量	100	10	10	12	2101-2112				
中用量	300	30	10	12	3101-3112				
高用量	1000	100	10	12	4101-4112	5	6101-6105	5	6106-6110

6.11 投与量の設定根拠

で実施した妊娠ラットを用いた経口投与による反復投与毒性・生殖発生毒性併合用量設定予備試験（、投与量：500 及び 1000 mg/kg、5 匹/群/雌）において、雌ラットに妊娠 9 日から分娩を経て授乳 4 日まで約 17 日間にわたり経口投与した結果、いずれの群においても死亡はみられず、1000 mg/kg においても、母動物の一般状態、体重、摂餌量、分娩・哺育状態、血液学検査、血液化学検査及び剖検並びに出生児の外表、生存性及び体重に明らかな毒性兆候を示唆する変化はみられなかった。これらのことから、本試験の高用量群を、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）〕

に示されている最高投与限度用量である 1000 mg/kg に設定し、中用量群以下を公比約 3 で除して 300 及び 100 mg/kg に設定した。

6.12 検査及び方法

試験日の起算に関しては以下の通りとした。

投与開始日	: 投与 1 日 (Day of dosing 1、Day 1)
投与 1 日から 7 日	: 投与 1 週 (Week of dosing 1、Week 1)
回復開始日 (投与 42 日の翌日)	
	: 回復 1 日 (Day 1 of recovery)
回復 1 日から 7 日	: 回復 1 週 (Week 1 of recovery)
交尾成立日	: 妊娠 0 日 (Gestation Day 0)
分娩終了日 (出産日)	: 授乳 0 日 (Lactation Day 0)
出生日	: 生後 0 日 (Postnatal Day 0)

6.12.1 一般状態の観察

全動物について、投与期間中 (交配群雌の妊娠及び授乳期間を含む) は毎日 3 回 (投与前、投与直後及び投与 1~4 時間後、ただし、詳細な一般状態の観察実施日は投与前と投与直後の 2 回/日)、回復期間中は毎日 1 回 (午前 ; 07:00~12:30)、剖検日は 1 回 (剖検のための動物搬出前)、それぞれ生死並びに身体の外観、排泄物 (尿、糞)、栄養状態、姿勢及び行動などの一般状態における異常の有無をケージサイドから観察した。また、動物を手にとっての観察を投与 1 週は投与開始日とその翌日の最低 2 回行い、投与 2 週以降は詳細な一般状態の観察 (6.12.2 参照) と兼ねて行った。

6.12.2 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、全動物について行った (投与期間中は検査当日の投与後 1~4 時間の間に開始)。雄及び非交配群雌は投与期間中及び回復期間中毎週 1 回、交配群雌は交配前投与期間中毎週 1 回、妊娠期間中及び授乳期間中は指定された日 (交尾動物は妊娠 1、7、14 及び 20 日、分娩動物は授乳 6 及び 13 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、交配群雌は各群の分娩順で動物番号が若い順に 5 匹^{注)}、非交配群雌の群内番号 6~10 番) について行った。投与期間中は交配群雌では授乳 13 日 (投与 50~52 日) に、その他は投与期間終了週 (投与 38 日) に、回復期間中は媒体対照群及び高用量群の雌雄について回復期間終了週 (回復 10 日) に行った。

詳細な一般状態の観察及び機能検査については実測値あるいはスコア化した評点法を用いた。また、投与及び回復期間中の観察、検査及び測定は、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、動物をランダムに配置した状態で行った。ただし、自発運動量の測定はブラインド化しないで行った。

注) : 交配群雌の検査対象動物を表 4 に示した。

表 4. 機能検査、握力測定及び自発運動量測定を実施した交配群雌動物

試験群	動物番号
媒体対照群	1102、1105、1106、1109、1110
低用量群	2103、2105、2107、2109、2111
中用量群	3101、3102、3104、3106、3109
高用量群	4103、4105、4106、4108、4111

6.12.2.1 詳細な一般状態の観察

1) ケージ内観察

姿勢、痙攣、異常行動

2) 手に持つての観察と症状の評価

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

3) オープンフィールド内観察

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）

6.12.2.2 機能検査

詳細な一般状態観察に続いて、聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射、空中正向反射を検査した。

6.12.2.3 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。

6.12.2.4 自発運動量測定

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。

6.12.3 体重測定

雄及び非交配群雌は投与 1、8、15、22、29、36 及び 42 日に、回復動物は更に回復 1、8 及び 14 日に、交配群雌は投与 1、8 及び 15 日、妊娠 0、7、14 及び 20 日、授乳 0、4、7 及び 13 日、並びに全動物について剖検日に体重を測定した。また、投与期間中の体重増加量（雄及び非交配群雌：投与 1 日から投与 42 日、交配群雌：投与 1 日から投与 15 日、妊娠 0 日から妊娠 20 日及び授乳 0 日から授乳 13 日）及び回復期間中の体重増加量（回復 1 日から回復 14 日）を算出した。分娩が午後となった母動物の授乳 0 日の体重は午後に、剖検日は前日から約 16 時間絶食させた後、相対器官重量

算出用に搬出前に、その他は午前中（投与期間中は投与前）に測定した。交配期間中の雌の体重は評価の対象としないため、帳票には反映させなかった。

6.12.4 摂餌量測定

雄及び非交配群雌は投与 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、4、7 及び 13 日にそれぞれ残餌量を測定し、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。また、各期間の総摂餌量（雄及び非交配群雌：投与 1 日から投与 15 日及び回復 1 日から回復 14 日、交配群雌：投与 1 日から投与 15 日、妊娠 0 日から妊娠 20 日及び授乳 0 日から授乳 13 日）を算出した。給餌量/残餌量の測定は測定日の午前中（投与期間中は投与前）に行った。

6.12.5 腔垢検査

交配群雌の全動物について、投与開始日から交尾成立まで毎日（午前）並びに剖検日に腔垢を採取して、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、交配期間中は腔垢内の精子の有無も調べた。交配前投与期間中の観察結果から発情回数及び発情期から次の発情期までの日数（性周期）、観察雌動物数に対する性周期異常を示した動物数の割合を求めた。

非交配群雌については、剖検日に腔垢を採取し、腔垢像を上記同様に分類した。

交配期間中の腔垢観察は交尾確認を目的とすること、剖検日の腔垢観察は雌の生殖器の病理組織との相関関係の確認を目的とすることから、腔垢像の分類結果については、帳票には反映させなかった。

6.12.6 交配

交配前投与期間終了後、交配群の同投与群内の個体番号が同じ雌雄を 1:1 で終夜同居させ、翌朝、腔内に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 5 日間であった。

6.13 分娩及び哺育観察

6.13.1 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）、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（妊娠 0 日）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（妊娠 22 日の 12:00 までに分娩終了したものは、22.0 日とし、以後、17:00 までに分娩終了したものは、22.5 日とした）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 13 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 14 日に 6.16 項に記す検査を行った。

6.13.2 出生児の観察

生後 0 日に出生児数及び死産児（含む死亡児）数を数え、これらを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の有無を肉眼的に観察し、性別を判定した。出生児は体重を個体別に測定し、更にスライドゲージを用いて、肛門縁から生殖突起の付け根までの距離（AGD; anogenital distance、肛門生殖突起間距離）を測定（0.1 mm 単位）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。

出生日から生後 13 日まで毎日 1 回、母動物の一般状態観察時に死亡児及び異常行動の有無を確認した。死亡児は異常の有無を肉眼により観察した後、ブアン液で固定して保存した。生存児は生後 0、4、7 及び 13 日に体重を個体別に測定し、各腹単位で雌雄別に平均値を算出した。また、体重増加量（生後 0 日から生後 4 日、生後 4 日から生後 7 日及び生後 4 日から生後 13 日）を算出した。生後 4 日の性別の確認及び体重測定後、1 腹当たりの哺育児数を 8 匹（可能な限り雌雄 4 匹ずつ）となるように調整した。除外された出生児のうち各群分娩順の 5 腹について、腹ごとに生後 4 日除外児を無作為に選び、イソフルラン吸入麻酔下に開腹し、腹大動脈から血液（目標：合計約 0.6 mL）を無処理のサンプルチューブに注射筒を用いて採取した。血液は遠心分離（3,000 rpm、約 1,600×g、10 分間）して血清を得た。血清は、腹ごとにプールした後（約 0.2 mL）、ポリプロピレン容器に移し試験場所 2 への送付に備え-80°C の冷凍庫（許容範囲：-70°C 以下）に保存した。採血した児は、残りの除外された出生児とともにイソフルラン吸入麻酔下で腹大動脈からの放血により安楽死させた後、廃棄した。

生後 13 日に全生存児の性別を確認し、雄児について乳頭/乳輪数を調べ、記録した。両性の児が存在する腹については、分娩の早い順に 5 腹を選択し、各腹から無作為に雌雄各 1 匹を選び、イソフルラン吸入麻酔下に開腹し注射筒を用いて腹大動脈から採血した（目標：合計約 2.0 mL）。採取した血液は無処理のサンプルチューブに移して遠心分離（3,000 rpm、約 1,600×g、10 分間）し、血清を得た。血清は腹ごとにプールした後、ポリプロピレン容器に分注（約 0.3 mL×3 本）し、それぞれをカラーペンで赤、青、緑に色分けして、試験場所 2 への送付時まで-80°C の冷凍庫（許容範囲：-70°C 以下）に保存した。採血した児は、残りの生存児とともにイソフルラン吸入麻酔下で腹大動脈からの放血により安楽死させ、外部生殖器の発達程度に注意を払い、体外表、胸腔内及び腹腔内の主要器官・組織を肉眼的に観察した。各腹の出生児雌雄各 1 匹（出生児番号：M01 及び F01）については甲状腺を摘出してリン酸緩衝 10%ホルマリン液で固定し、重量を測定後、同固定液に保存した。甲状腺重量（絶対重量）は左右一緒に測定し、剖検日の体重に対する相対重量を算出した。

6.14 臨床検査

6.14.1 尿検査

以下の動物を検査対象とした。

投与 6 週（投与 37~38 日）：雄及び非交配群雌の各群 5 匹（雄の群内番号 8~12 番、非交配群雌の群内番号 6~10 番）

回復 2 週（回復 9~10 日）：回復動物の全動物

採尿器をセットしたケージに動物を個別に収容し（投与 6 週検査では投与後に収容した）、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、表 5 に記載した項目及び方法により検査した。また、尿検査時には、前日からの 1 日当たりの摂水量（単位：mL/24h）を、給水瓶を用いて重量法で測定した（1 g = 1 mL とみなした）。

表 5. 尿検査の項目、測定法及び使用機器など

1) 4 時間尿についての検査	
検査項目	測定方法
pH	マルティステックス SG 試験紙 ^{a)}
タンパク質	マルティステックス SG 試験紙 ^{a)}
ケトン体	マルティステックス SG 試験紙 ^{a)}
グルコース	マルティステックス SG 試験紙 ^{a)}
潜血	マルティステックス SG 試験紙 ^{a)}
ビリルビン	マルティステックス SG 試験紙 ^{a)}
ウロビリノーゲン	マルティステックス SG 試験紙 ^{a)}
比重	マルティステックス SG 試験紙 ^{a)}
色調	肉眼観察
沈渣	鏡検法
尿量（4 時間量） ^{注)}	容量測定（単位：mL）
2) 20 時間尿についての検査	
検査項目	測定方法
尿量（20 時間量） ^{注)}	容量測定（単位：mL）
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.）	
注)：4 時間の尿量と 20 時間の尿量を合計して 24 時間の尿量（mL/24h）を算出した。	

6.14.2 臨床検査のための採血

投与終了及び回復終了の計画剖検時に、採血針を用いて以下の表 6 に従って各検査用として別々に採血した。全動物について剖検前日（最終投与日あるいは回復 14 日）から一夜（約 16~21 時間）絶食させた。採血は雄及び交配群雌並びに非交配群雌の各群 5 匹（動物番号が若い順、ただし、交配群雌は分娩順の 5 匹）の計画剖検動物から行った。

表 6. 臨床検査のための採血

	血液学検査	凝固系検査	血液化学検査	ホルモン測定
絶食	前日から一夜（約 16~21 時間）絶食			
麻酔	イソフルラン吸入			
採血部位	腹大動脈			
抗凝固剤	EDTA-2K	3.8%クエン酸ナトリウム	ヘパリンナトリウム	なし
採血量	約 1 mL	0.9 mL	約 3 mL	約 4 mL
採血容器	BD Vacutainer (Becton, Dickinson and Company)	クエン酸ナトリウム溶液加容器（血液/クエン酸溶液、9/1、v/v）	ベノジェクト II ヘパリンナトリウム、5 mL 採血用（テルモ株式会社）	ベノジェクト II オートセップ 6 mL 採血用（テルモ株式会社）
試料	全血	血漿	血漿	血清
遠心条件	遠心分離は行わない	3000 rpm、約 1600 ×g、10 分間	3000 rpm、約 1600 ×g、10 分間で得られた上清を同条件で更に 1 回	3000 rpm、約 1600 ×g、10 分間

6.14.2.1 血液学検査

得られた血液について表 7 に記載した項目を検査した。また、鏡検による確認に備え、全生存例について、May-Grünwald-Giemsa 染色法による血液塗抹標本を作製したが、鏡検は実施しなかった。

表 7. 血液学検査の項目、測定法及び使用機器など

検査項目	測定方法	単位
赤血球数(RBC)	フローサイトメトリー法 ^{a)}	10 ⁴ (E4)/μL
ヘモグロビン濃度(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)	RBC 及び MCV から算出 ^{a)}	%
平均赤血球容積(MCV)	フローサイトメトリー法 ^{a)}	fL
平均赤血球ヘモグロビン量(MCH)	RBC 及び HGB から算出 ^{a)}	pg
平均赤血球ヘモグロビン濃度(MCHC)	HGB 及び HCT から算出 ^{a)}	g/dL
赤血球容積分布幅(RDW)	赤血球容積ヒストグラムの標準偏差と MCV から算出 ^{a)}	%
網赤血球数(RETIC)	フローサイトメトリー法 ^{a)}	10 ⁹ (E9)/L
血小板数(PLT)	フローサイトメトリー法 ^{a)}	10 ⁴ (E4)/μL
白血球数(WBC)	フローサイトメトリー法 ^{a)}	10 ² (E2)/μL
白血球分類 ^注	フローサイトメトリー法 ^{a)}	10 ² (E2)/μL
使用測定機器		
a)：総合血液学検査装置 アドヴィア 2120i (Siemens Healthcare Diagnostics Inc.)		
注：リンパ球(LYMP)、好中球(NEUT)、好酸球(EOS)、好塩基球(BASO)、単球(MONO)及び大型非染色球(LUC)		

血液学検査の再測定

動物番号	測定項目	理由	採用
1003	全項目	血小板凝集の可能性	初回測定値
5102、5103	全項目	血小板凝集の可能性	再測定値
4103	γ-GTP	他の試料に比べ高値	再測定値

6.14.2.2 凝固系検査

得られた血漿について表 8 に記載した項目を検査した。

表 8. 凝固系検査の項目、測定法及び使用機器など

検査項目	測定方法	単位
プロトロンビン時間 (PT)	Coagulometric test ^{a)}	s
活性化部分トロンボプラスチン時間 (APTT)	Coagulometric test ^{a)}	s
フィブリノゲン量 (FIB)	Coagulometric test ^{a)}	mg/dL
使用測定機器		
a) : 血液凝固自動分析装置 ACL Elite Pro (Instrumentation Laboratory Corporation)		

6.14.2.3 血液化学検査

得られた血漿について表 9 に記載の項目を検査した。

表 9. 血液化学検査の項目、測定法及び使用機器など

検査項目	測定方法	単位
アスパラギン酸アミノトランスフェラーゼ(AST)	UV-rate 法 ^{a)}	IU/L
アラニンアミノトランスフェラーゼ(ALT)	UV-rate 法 ^{a)}	IU/L
アルカリホスファターゼ(ALP)	Bessey-Lowry 法 ^{a)}	IU/L
γ-グルタミルトランスぺプチダーゼ(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
総胆汁酸(TBA)	3α-ヒドロキシステロイドデヒドロゲナーゼ(3α-HSD)法 ^{a)}	μmol/L
総コレステロール(T-CHO)	CEH-COD-POD 法 ^{a)}	mg/dL
トリグリセライド(TG)	LPL-GK-GPO-POD 法 ^{a)}	mg/dL
リン脂質(PL)	PLD-ChOD-POD 法 ^{a)}	mg/dL
総ビリルビン(T-BIL)	ビリルビンオキシダーゼ法 ^{a)}	mg/dL
グルコース(GLU)	グルコースデヒドロゲナーゼ法 ^{a)}	mg/dL
尿素窒素(BUN)	Urease-LEDH 法 ^{a)}	mg/dL
クレアチニン(CRNN)	Creatininase-creatinase-sarcosine oxidase-POD 法 ^{a)}	mg/dL
ナトリウム(Na)	イオン選択電極法 ^{a)}	mmol/L
カリウム(K)	イオン選択電極法 ^{a)}	mmol/L
塩素(Cl)	イオン選択電極法 ^{a)}	mmol/L
カルシウム(Ca)	OCPC 法 ^{a)}	mg/dL
無機リン(P)	PNP-XOD-POD 法 ^{a)}	mg/dL
総タンパク質(TP)	Biuret 法 ^{a)}	g/dL
アルブミン(ALB)	BCG 法 ^{a)}	g/dL
使用測定機器		
a) : 臨床化学自動分析装置 TBA-120FR 形 (キヤノンメディカルシステムズ株式会社)		

6.15 ホルモン測定

6.15.1 血清試料の採取、測定対象、保存及び送付

1) 試料の分取と保存

6.14.2 項で得られた血清試料はサンプルチューブに分注 (約 0.5 mL×3 本) し、それぞれをカラーペンで赤、青、緑に色分けして、試験場所 2 への送付時まで

■

-80°C の冷凍庫（許容値：-70°C 以下）に保存した。容器には、試験番号、検査時期、検査項目、試料番号、採取年月日及びサンプル名を明記したラベルを貼付した。

2) 測定対象

6.14.2 項で得られた雄及び交配群雌並びに非交配群雌の血清及び 6.13.2 項で得られた生後 4 及び 13 日児動物の血清を T4 (thyroxine) 測定対象とした。なお、測定は雄及び生後 13 日の児動物の測定を優先して実施し、測定結果に被験物質投与の影響と推定される異常がみられなかったため、非交配群雌、授乳 14 日の母動物及び生後 4 日の児動物並びに回復動物については測定を行わなかった。3 本に分注した血清はそのうち 1 本（赤、青、緑の順に優先した）を測定し、残余の血清はホルモン測定用の予備として保存した。

3) 試料の送付

測定に供する血清は、凍結した状態でドライアイスと同梱させ、試験場所 2（試験主任者宛）に送付した。

送付試料数 : 110 サンプル
(交配群雄 30 サンプル×3 本、交配群雌 20 サンプル×3 本、非交配群雌 20 サンプル×3 本、生後 13 日の児動物 20 サンプル×3 本、生後 4 日の児動物 20 サンプル)

送付日 : ■
; 交配群雄（投与終了時）のサンプル
■
; 上記以外のサンプル

6.15.2 T4 測定

1) ホルモン測定番号

OT-210011

2) 分析方法

RIA method（詳細は Attachment 4 参照）

3) 測定項目

甲状腺ホルモン（T4）

4) 作業・操作

測定に関する操作手順は試験場所 2 の SOP に従った。

5) ホルモン測定報告書

試験場所 2 においてホルモン測定報告書が作成された。試験責任者はホルモン測定報告書の PDF ファイルを入手し、当試験（■）の最終報告書に添付した。また、その内容を当試験の最終報告書に反映させた。

6) 残余血清の処理

ホルモン測定終了後の残余血清は、ホルモン測定報告書作成後に試験責任者の指

示に基づいて試験場所 2 で廃棄する。

6.16 病理学検査

6.16.1 剖検

最終投与翌日及び回復期間終了日に、血液学検査、凝固系検査、血液化学検査及びホルモン測定のために採血した動物は採血後、その他の動物はイソフルラン吸入麻酔下で、腹大動脈からの放血により安楽死させ、外表及び全ての器官/組織を詳細に観察した。なお、母動物については剖検時に着床痕数を数えた。

6.16.2 器官重量測定

全動物について表 10 に示した器官の重量（絶対重量）を測定するとともに、剖検日の体重に対する相対重量を算出した。両側性の器官は左右一緒に測定した。

6.16.3 病理組織学検査

検査対象器官/組織を表 10 に示した。全動物について全検査対象器官/組織をリン酸緩衝 10%ホルマリン液で固定した。ただし、眼球及び視神経はリン酸緩衝 3%グルタルアルデヒド・2.5%ホルマリン液で固定、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%ホルマリン液で保存した。以降の検査は次の通りとした。

1) パラフィン包埋及びヘマトキシリン・エオジン（H・E）染色標本作製

以下に記載した動物の全検査対象器官/組織について標本作製した。

- － 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雄及び交配群雌並びに非交配群雌の各群 5 匹（動物番号が若い順、ただし、交配群雌は分娩順の 5 匹）

ただし、甲状腺に関しては、被験物質投与による変化が疑われなかったため（親動物に組織学変化及び甲状腺重量の変動はみられなかったため）、採血を実施しなかった雄及び交配群雌並びに雌雄の生後 13 日児動物（全母体の各腹雌雄各 1 例）については、標本作製を行わなかった。

2) 鏡検

以下の通り実施した。

非腫瘍病変のグレーディングは以下の通りとした。

著変無し（Not remarkable）

軽微（Minimal）

軽度（Mild）

中等度（Moderate）

高度（Severe）

<投与終了時剖検群>

媒体対照群及び高用量群

： 全検査対象器官/組織



中及び低用量群 : 高用量群において被験物質投与による変化が疑われなかったため、鏡検は行わなかった。

<回復終了時剖検群>

全群 : 全検査対象器官/組織

<計画剖検時に採血を実施しなかった雄及び交配群雌並びに生後 13 日児動物>

被験物質投与による変化が疑われなかったため、甲状腺の鏡検は行わなかった。

表 10. 病理学検査対象器官/組織

組 織	病理組織	重量測定
	HE	
脳（大脳、小脳、橋）	√	√ （脳として）
延髄	√	
脊髄（胸部）	√	
坐骨神経	√*	
視神経	√*	
眼球	√*	
ハーダー腺	（保存のみ・両側）	
下垂体	√	
甲状腺	√	√ （甲状腺として）
上皮小体	√*	
副腎	√	√
胸腺	√	√
脾臓	√	√
顎下リンパ節	√*	
腸間膜リンパ節	√	
パイエル板（回腸）	√	
心臓	√	√
胸大動脈	（保存のみ）	
気管	√	
肺（気管支を含む）	√	
舌	（保存のみ）	
食道	（保存のみ）	
胃	√	
十二指腸	√	
空腸	√	
回腸	√	
盲腸	√	
結腸	√	
直腸	√	
顎下腺	√*	
舌下腺	（保存のみ・両側）	
肝臓	√	√
脾臓	√	
腎臓	√	√
膀胱	√	
精巣/卵巣	√/√	√/√
精巣上体/子宮	√/√	√/√
前立腺/膣	√/√	√/

組 織	病理組織	重量測定
	HE	
精嚢（凝固腺含む）	√	√
乳腺（鼠径部）	√*	
胸骨	（保存のみ）	
大腿骨	√*	
胸骨骨髓	（保存のみ）	
大腿骨骨髓	√*	
大腿四頭筋	√*	
皮膚（鼠径部）	√*	
肉眼的異常部位	√	
肛門挙筋・球海綿体筋（LABC）	（重量測定のみ）	√
カウパー腺（COW）	（重量測定のみ）	√
陰茎亀頭（GP）	（重量測定のみ）	√
喉頭	（保存のみ）	
個体識別部（耳標を装着した耳介）	（保存のみ）	

各項目該当ある場合は√で示した。

*：両側を摘出し、片側を鏡検した（他の両側性器官は両側を鏡検）。

7. データ採取に使用したコンピュータシステム

- ・ MiTOX-BOZO システム（Version 9.3.1.1、三井 E&S システム技研株式会社）
- ・ PATHOS5 システム（Pathology Operating Systems Ltd.）

8. パラメータの算出

以下の式に従って各パラメータを算出した。

出生児の体重及び AGD については母動物ごと雌雄別に平均値を求めた。この際、AGD は生後 0 日の体重の三乗根で除して標準化（小数点以下第 1 位まで表示）した。雄生存児の乳頭/乳輪数は母動物（腹）ごとに平均値を求めた。空中正向反射は 3 回の動物ごとのトータルスコアを求めた。

1) 群ごとに算出したパラメータ

性周期異常率(%) = (性周期異常を示した動物数/観察雌動物数) × 100

交尾率(%) = (交尾動物数/同居動物数) × 100

(雌又は雄の)受胎率(%) = [妊娠した雌(又は雌を妊娠させた雄)の数/交尾した雌(又は交尾した雄)の数] × 100

出産率(%) = (生児出産雌数/妊娠雌数) × 100

異常児を有する母動物発現率(%) = (異常児を有する母動物数/母動物数) × 100

生後 0 日の性比(%) = (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

2) 母動物（腹）ごとに算出したパラメータ

妊娠期間(日) = 妊娠 0 日から分娩した日までの日数

分娩率(%) = (出産児数/着床痕数) × 100

出生率(%) = (出生児数/出産児数) × 100

外表異常率(%) = (外表異常児数/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

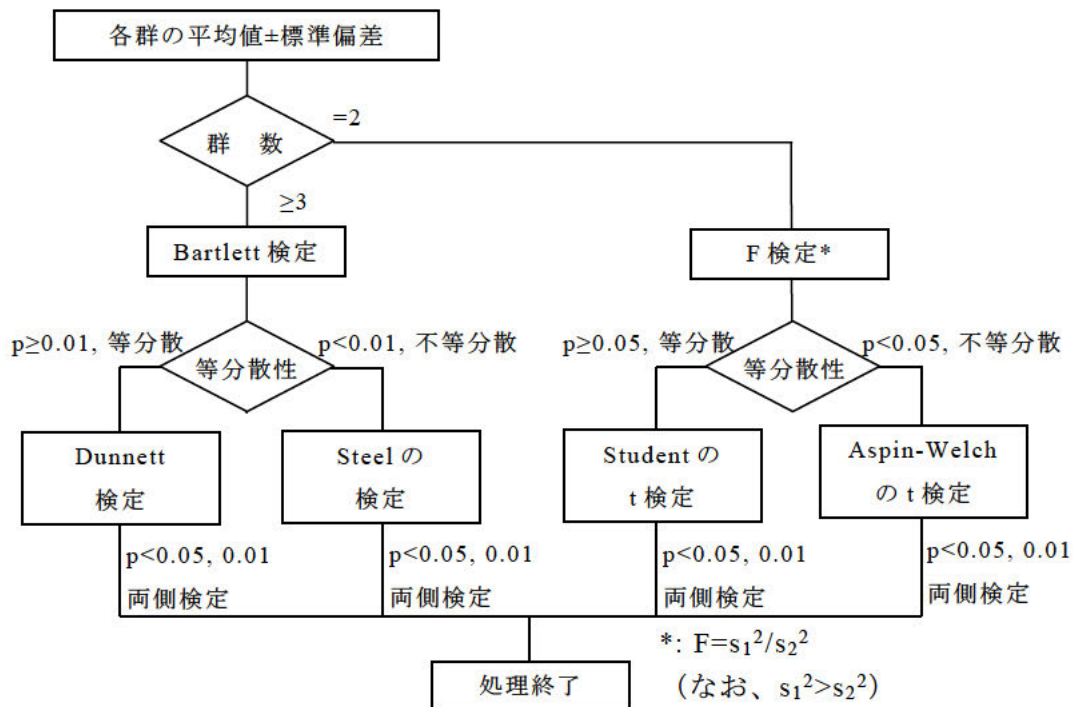
生後 13 日生存率(%) = (生後 13 日の生存児数/生後 4 日調整後の児数) × 100

9. 統計解析

媒体対照群と各被験物質投与群との間で検定を行った。解析には、SAS Release 9.1.3 (SAS Institute Inc.)を使用した。

- 1) 体重、体重増加量、摂餌量、総摂餌量、オープンフィールド内観察における排糞数と立ち上がり回数、握力及び自発運動量、尿検査の定量的項目及び摂水量、血液学検査、凝固系検査、血液化学検査及び器官重量（含、剖検時体重）、発情期発現回数、性周期（発情周期）、交尾までに要した日数、妊娠期間、着床数、出産児数、出生児数、死産児数、AGD、乳頭/乳輪数：

下記の模式図に従って検定した。



- 2) 分娩率、外表異常率、出生率、生存率：

群ごとに平均値及び標準偏差を求め、Wilcoxon の順位和検定を行った（有意水準 0.05 及び 0.01、両側）。なお、いずれの群にも外表異常児はみられなかったため、外表異常率について検定は行わなかった。

- 3) 性周期異常率、交尾率、雌雄の受胎率、出産率及び児の性比：

各群の性周期異常を示した動物数、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、雌雄児数に基づき、Fisher の直接確率計算法により検定を行った（有意水準 0.05 及び 0.01、両側）。なお、いずれの群にも外

表異常児はみられなかったため、異常児を有する母動物発現率について検定は行わなかった。

10. 試験結果

10.1 一般状態

結果を Table 1-1~1-9、Appendix 1-1~1-28 に示した。

1) 投与期間

雄及び非交配群雌では、投与期間を通じ、いずれの動物にも異常はみられなかった。

交配群雌では、交配前、妊娠及び授乳期の各投与期間を通じ、いずれの動物にも分娩/哺育状態を含め異常はみられなかった。

2) 回復期間

雌雄ともに、回復期間を通じ、いずれの動物にも異常は認められなかった。

10.2 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

10.2.1 詳細な一般状態の観察

10.2.1.1 ケージ内観察

結果を Table 2-1~2-24、Appendix 2-1~2-76 に示した。

1) 投与期間

雄、非交配群雌及び交配群雌の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

雌雄ともに、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。

10.2.1.2 手に持ったの観察

結果を Table 2-25~2-86、Appendix 2-77~2-152 に示した。

1) 投与期間

雄、非交配群雌及び交配群雌の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

雌雄ともに、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。

10.2.1.3 オープンフィールド内観察

結果を Table 2-87~2-158、Appendix 2-153~2-304 に示した。

1) 投与期間

雄、非交配群雌及び交配群雌の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。

雄の 100 mg/kg 群で投与 1 及び 2 週の立ち上がり回数に媒体対照群と比べ有意な高値、交配群雌の 300 mg/kg 群で妊娠 20 日及び授乳 6 日の立ち上がり回数に有意な低値が認められたが、いずれも用量に関連しない変化であり、偶発的な有意差と判断した。その他には、雌雄とも立ち上がり回数及び排糞の個数に媒体対照群と各被験物質投与群との間に差は認められなかった。

2) 回復期間

雌雄ともに、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。

雌雄ともに立ち上がり回数及び排糞の個数に媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

10.2.2 機能検査

結果を Table 2-159~2-165、Appendix 2-305~2-318 に示した。

1) 投与期間終了週検査

雄、交配群雌及び非交配群雌では、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) 回復期間終了週検査

雌雄ともに、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。

10.2.3 握力

結果を Table 2-166~2-170、Appendix 2-319~2-332 に示した。

1) 投与期間終了週測定

雄、非交配群雌及び交配群雌では、媒体対照群と各被験物質投与群との間に差は認められなかった。

2) 回復期間終了週測定

雌雄ともに、媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

10.2.4 自発運動量

結果を Fig. 1~5、Table 2-171~2-175、Appendix 2-333~2-346 に示した。

1) 投与期間終了週測定

雄、非交配群雌及び交配群雌では、媒体対照群と各被験物質投与群との間に差は認められなかった。

2) 回復期間終了週測定

雄では、媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

非交配群雌では 1000 mg/kg 群で媒体対照群と比べ測定開始後 50~60 分の運動量に有意な低値が認められたが、その他の測定時点及び総運動量に異常はみられず、また投与終了時にも異常はないことから、被験物質投与と関連しない偶発的な有意差と判断した。

10.3 体重

結果を Fig. 6~8、Table 3-1~3-7、Appendix 3-1~3-22 に示した。

1) 投与期間

雄では、投与期間を通じ、媒体対照群と各被験物質投与群との間に差は認められなかった。

交配群雌では、交配前、妊娠及び授乳期の各期間中媒体対照群と各被験物質投与群との間に差は認められなかった。なお、300 mg/kg 群で妊娠期間中の体重増加量に媒体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り、偶発的な有意差と判断した。

非交配群雌では、投与期間中及び体重増加量を含め媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

2) 回復期間

雌雄ともに、媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

10.4 摂餌量

結果を Fig. 9~11、Table 4-1~4-9、Appendix 4-1~4-28 に示した。

1) 投与期間

雄では、交配前投与期間及び総摂餌量を含め、媒体対照群と各被験物質投与群との間に差は認められなかった。

交配群雌では、交配前、妊娠及び授乳期間及び各期間中の総摂餌量を含め、媒体対照群と各被験物質投与群との間に差は認められなかった。

非交配群雌では、投与期間及び投与 1~15 日の総摂餌量を含め、媒体対照群と 1000 mg/kg 群との間に被験物質投与に関連すると考えられる差は認められなかった。なお、1000 mg/kg 群で投与 2 日に媒体対照群と比べ有意な低値が認められたが、一時的な変化であり、交配群雌の同用量群の同時点には差は認められないことから偶発的な有意差と判断した。

2) 回復期間

雌雄ともに、媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

10.5 尿検査（摂水量測定を含む）

結果を Table 5-1~5-18、Appendix 5-1~5-30 に示した。

1) 投与期間終了週検査

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、雌雄ともにいずれの検査項目においても媒体対照群と各被験物質投与群との間に差は認められなかった。

2) 回復期間終了時検査

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、雌雄ともにいずれの検査項目においても媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

10.6 血液学検査

結果を Table 6-1~6-5、Appendix 6-1~6-14 に示した。

1) 投与期間終了時検査

雄では、いずれの検査項目においても媒体対照群と各被験物質投与群との間に差は認められなかった。

交配群雌では、1000 mg/kg 群で媒体対照群と比べ網赤血球数 (RETIC) に有意な低値が認められたが、関連する赤血球系パラメータには異常はなく毒性学的意義はないと判断した。

非交配群雌では、1000 mg/kg 群で媒体対照群と比べ平均赤血球ヘモグロビン濃度 (MCHC) に有意な低値が認められたが、1000 mg/kg 群の個体別値はすべて媒体対照群の個体別値の範囲内に収まっており、媒体対照群との差も 2% と軽度であることから生理的変動範囲内の偶発的有意差と判断した。

2) 回復期間終了時検査

雌雄ともに、いずれの検査項目においても媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

10.7 凝固系検査

結果を Table 7-1~7-5、Appendix 7-1~7-14 に示した。

1) 投与期間終了時検査

雄では、いずれの検査項目においても媒体対照群と各被験物質投与群との間に差は認められなかった。

交配群雌では、いずれの検査項目においても媒体対照群と各被験物質投与群との間に差は認められなかった。

非交配群雌では、いずれの検査項目においても媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

2) 回復期間終了時検査

雌雄ともに、いずれの検査項目においても媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

10.8 血液化学検査

結果を Table 8-1~8-5、Appendix 8-1~8-14 に示した。

1) 投与期間終了時

雄では、いずれの検査項目においても媒体対照群と各被験物質投与群との間に差は認められなかった。

交配群雌では、いずれの検査項目においても媒体対照群と各被験物質投与群との間に差は認められなかった。

非交配群雌では、いずれの検査項目においても媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

2) 回復期間終了時

雄では、いずれの検査項目においても媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

雌では、1000 mg/kg 群で媒体対照群と比べクレアチニン(CRNN)に有意な低値が認められたが、病理組織学的検査では関連した変化は認められず、かつ低値であることから毒性学的意義はないと判断した。その他に、1000 mg/kg 群で媒体対照群と比べナトリウム(Na)に有意な低値が認められたが、試験施設の背景データ (Attachment 5) の範囲内であることから、生理的変動範囲内の変化で偶発的有意差と判断した。

10.9 血中 T4 濃度測定

結果をホルモン濃度測定報告書 (Attachment 4) に示した。

1) 投与期間終了時 (雄)

雄の T4 濃度は、媒体対照群と各被験物質群との間に差は認められなかった。

2) 生後 13 日齢児

生後 13 日齢児の T4 濃度は、媒体対照群と各被験物質群との間に差は認められなかった。

10.10 器官重量

結果を Table 9-1~9-8、Appendix 9-1~9-24 に示した。

1) 投与期間終了時

雄では、1000 mg/kg 群で媒体対照群と比べ前立腺の絶対及び相対重量に有意な高値が認められた。

交配群雌では、いずれの器官重量においても媒体対照群と各被験物質投与群との間に差は認められなかった。

非交配群雌では、1000 mg/kg 群で媒体対照群と比べ肝臓の絶対及び相対重量に有意な高値が認められたが、試験施設の背景データ (Attachment 5) の範囲内であることから、生理的変動範囲内の変化で偶発的有意差と判断した。

2) 回復期間終了時

雄では、いずれの器官重量においても媒体対照群と 1000 mg/kg 群との間に差は認められなかった。

雌では、1000 mg/kg 群で媒体対照群と比べ甲状腺の絶対及び相対重量に有意な高値が認められたが、試験施設の背景データ (Attachment 5) の範囲内であることから、生理的変動範囲内の変化で偶発的有意差と判断した。

10.11 剖検所見

結果を Table 10-1~10-5、Appendix 10-1~10-116 に示した。

1) 投与期間終了時

交配群雌雄及び非交配群雌のいずれの動物にも被験物質投与の影響と考えられる肉眼所見はみられなかった。

2) 回復期間終了時

雌雄のいずれの動物にも被験物質投与の影響と考えられる肉眼所見はみられなかった。

10.12 病理組織学検査

結果を Table 11-1~11-15、Appendix 10-1~10-116 に示した。

いずれの動物にも被験物質の影響と考えられる組織所見はみられなかった。

交配群及び非交配群において種々の組織変化が認められたが、その発現状況及び病理組織学的な性状より偶発性変化と判断した。

10.13 性周期

結果を Table 12、Appendix 11-1~11-8 に示した。

性周期異常率、発情期像発現回数及び平均性周期（発情周期）には、媒体対照群と各被験物質投与群との間に差は認められなかった。

10.14 交配成績

結果を Table 13-1 及び 13-2、Appendix 12-1~12-8 に示した。

全ての組み合わせは交配 5 日までに交尾が成立し、交尾までに要した日数、交尾率及び受胎率には、媒体対照群と各被験物質投与群との間に差は認められなかった。

10.15 分娩成績並びに分娩及び哺育状態

結果を Table 14、15、Appendix 13-1~13-4、14-1~14-4 に示した。

分娩成績では、妊娠期間、出産率、着床痕数、分娩率、出生率、出産児数、出生児数、性比（生後 0 日）及び死産児数に媒体対照群と各被験物質投与群との間で差は認められなかった。また、いずれの群にも外表異常児はみられなかった。

妊娠動物の分娩状態では、妊娠 21.5 から 23.0 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。

10.16 出生児の Anogenital Distance (AGD)

結果を Table 16、Appendix 15-1~15-4 に示した。

生後 0 日の AGD には、雌雄とも被験物質の影響は認められなかった。なお、100 mg/kg 群の雄児で媒体対照群比べ AGD に有意な高値が認められたが、用量に関連しない変化であり、体重の立方根で除した標準化値には差は認められないことから、被験物質と関連しない偶発的有意差と考えられた。

10.17 出生児の生存性

結果を Table 17、Appendix 16-1~16-4 に示した。

生後 4 及び 13 日の生存児数及び生存率には、媒体対照群と各被験物質投与群との間に差は認められなかった。

10.18 出生児の性比

結果を Table 18、Appendix 17-1~17-4 に示した。

生後 4 日の性比には、媒体対照群と各被験物質投与群との間に差は認められなかった。

10.19 出生児の体重

結果を Table 19-1 及び 19-2、Appendix 18-1~18-8 に示した。

雌雄出生児ともに、出生時、生後 4 日の調整前及び調整後、生後 7 及び 13 日の体重並びに生後 0~4、4~7 及び 4~13 日の間の体重増加量には、媒体対照群と各被験物質投与群との間に差は認められなかった。

10.20 死亡児の肉眼観察所見

結果を Table 20、Appendix 19-1~19-4 に示した。

いずれの死亡児にも肉眼的異常はみられなかった。

10.21 雄新生児の乳頭/乳輪数

結果を Table 21、Appendix 20-1~20-4 に示した。

雄新生児の乳頭/乳輪はいずれの動物にも認められなかった。

10.22 出生児の生後 13 日剖検所見

結果を Table 22、Appendix 21-1~21-4 に示した。

いずれの動物にも肉眼的異常はみられなかった。

10.23 出生児の器官重量

結果を Table 23-1 及び 23-2、Appendix 22-1~22-8 に示した。

雌雄ともに、甲状腺重量には媒体対照群と各被験物質投与群との間に差は認められなかった。

11. 考察及び結論

キナ抽出物の 0（媒体対照群：注射用水）、100、300 及び 1000 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 13 日まで（50~55 日間）、非交配群雌には 42 日間、それぞれ強制経口投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0 及び 1000 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。

11.1 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、詳細な一般状態観察、機能検査、握力、自発運動量、体重、摂餌量、尿検査（摂水量測定を含む）、血液学検査、凝固系検査、血液化学検査、血清中ホルモン(T4)、器官重量及び剖検並びに病理組織学検査には、被験物質投与の影響は認められなかった。

投与期間終了時において、雄の 1000 mg/kg 群で前立腺重量に高値が認められたが、病理組織学検査に異常がないことから、毒性学的意義はないと考えられた。回復期間終了時には上記変化は認められなかった。

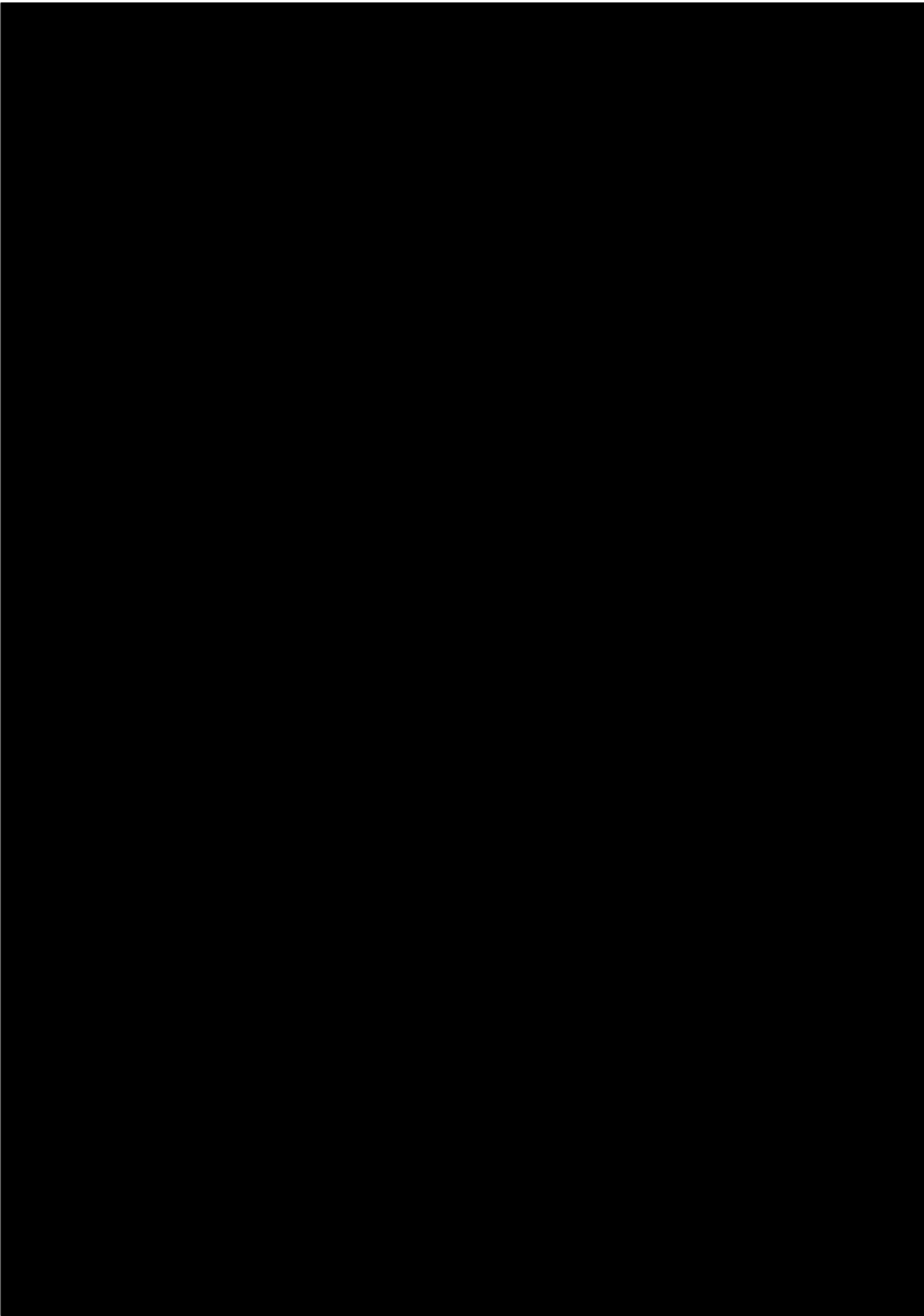
11.2 生殖発生毒性

雌雄動物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、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。また、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、生後の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、本試験条件下でキナ抽出物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変化は認められなかった。したがって、本被験物質の反復投与毒性に対する無影響量及び無毒性量は、雌雄ともいずれも 1000 mg/kg と判断した。また、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、母動物及び児動物のいずれも被験物質の影響が認められないことから、いずれも 1000 mg/kg と判断した。

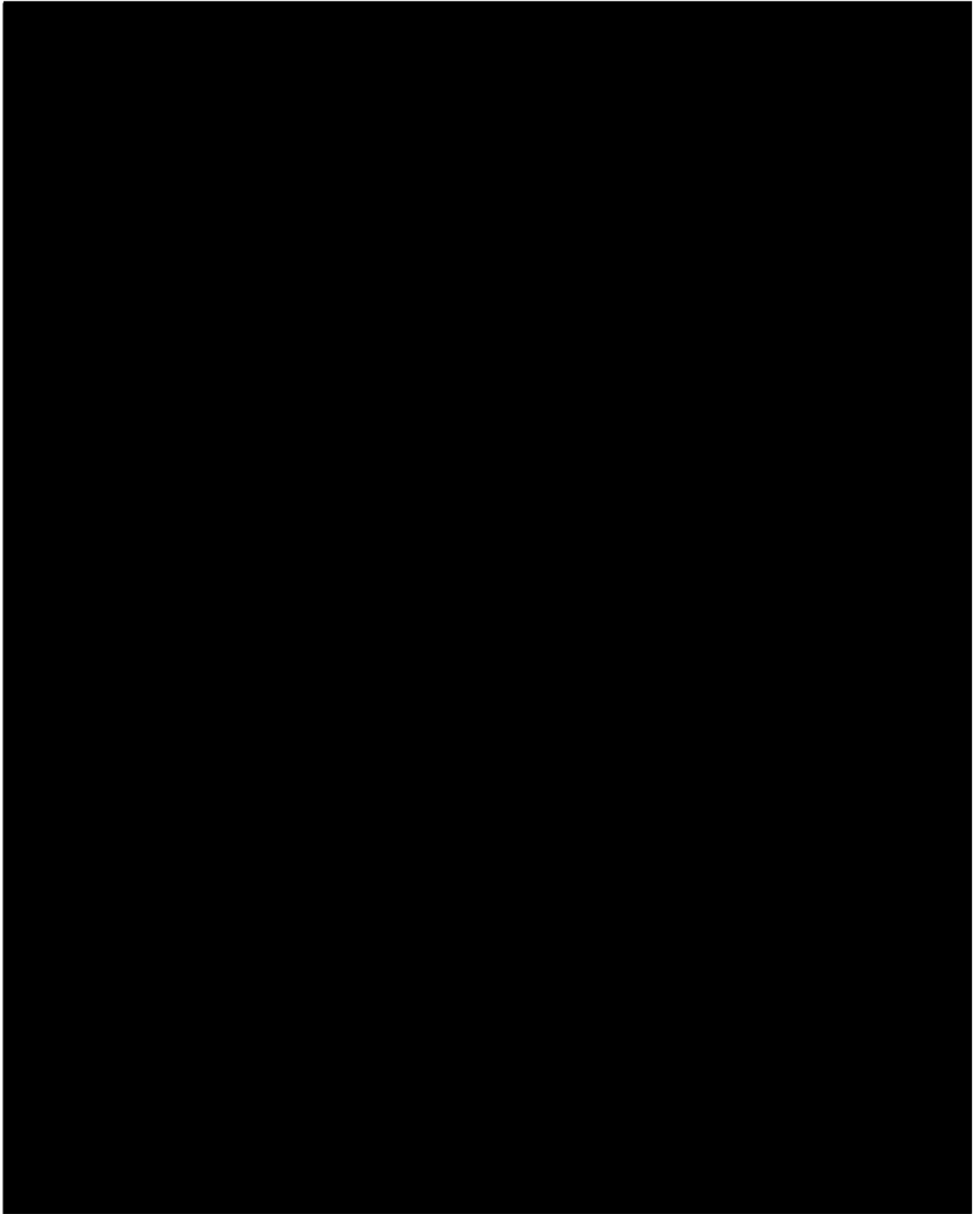
12. 参考文献

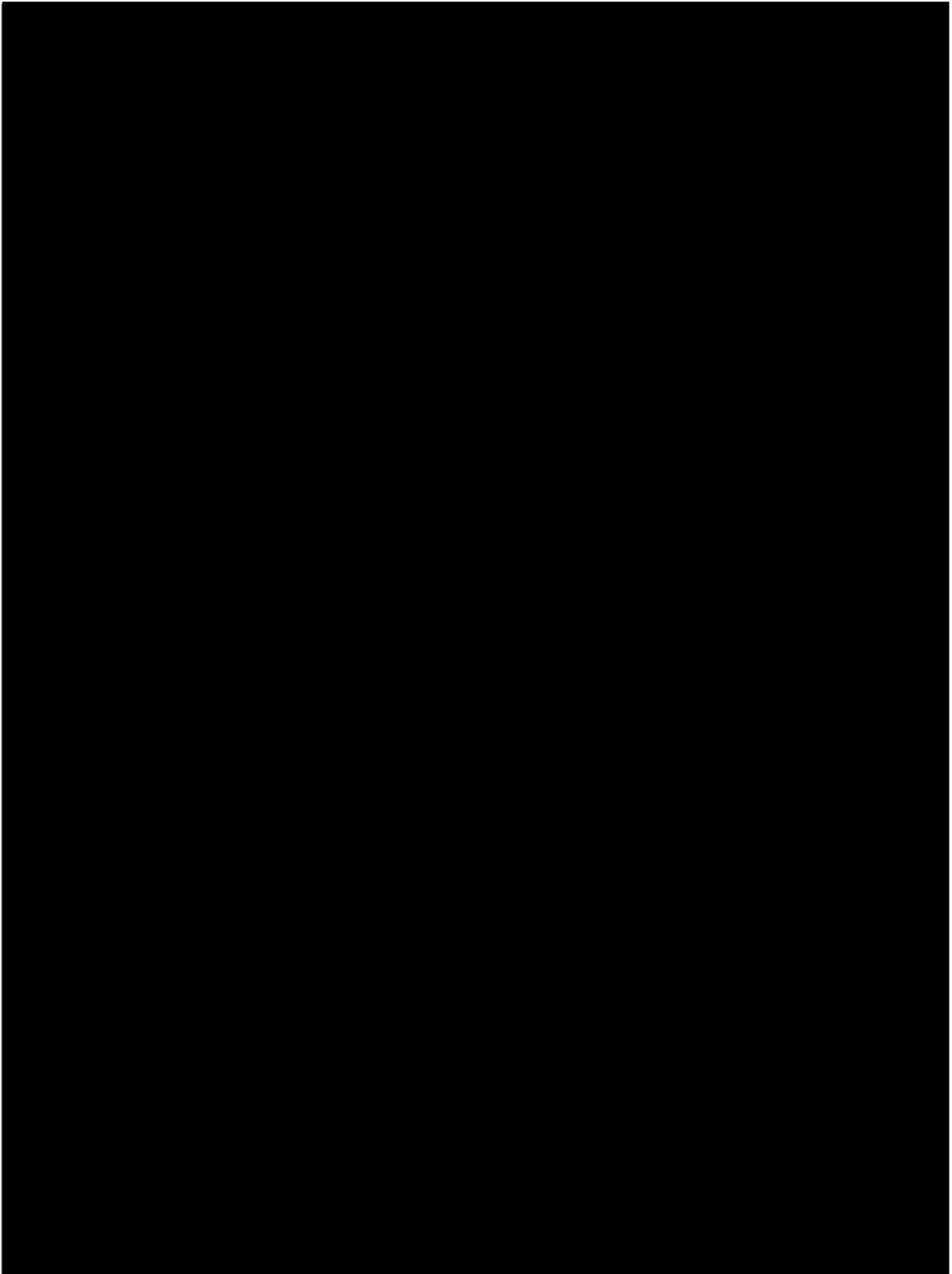
- 1) キナ抽出物中のキニーネ含量測定（加温融解ろ過処理したキナ抽出物中のキニーネ含量の測定） 最終報告書 [REDACTED]
- 2) 既存添加物の安全性に関する試験（キナ抽出物投与液の分析バリデーション及び安定性試験） 最終報告書 [REDACTED]
- 3) 既存添加物の安全性に関する試験（キナ抽出物のラットを用いた 90 日間反復経口投与毒性試験のための用量設定試験） [REDACTED]
- 4) キナ抽出物投与液のメッシュを用いたゾンデ追加検討試験 最終報告書 [REDACTED]

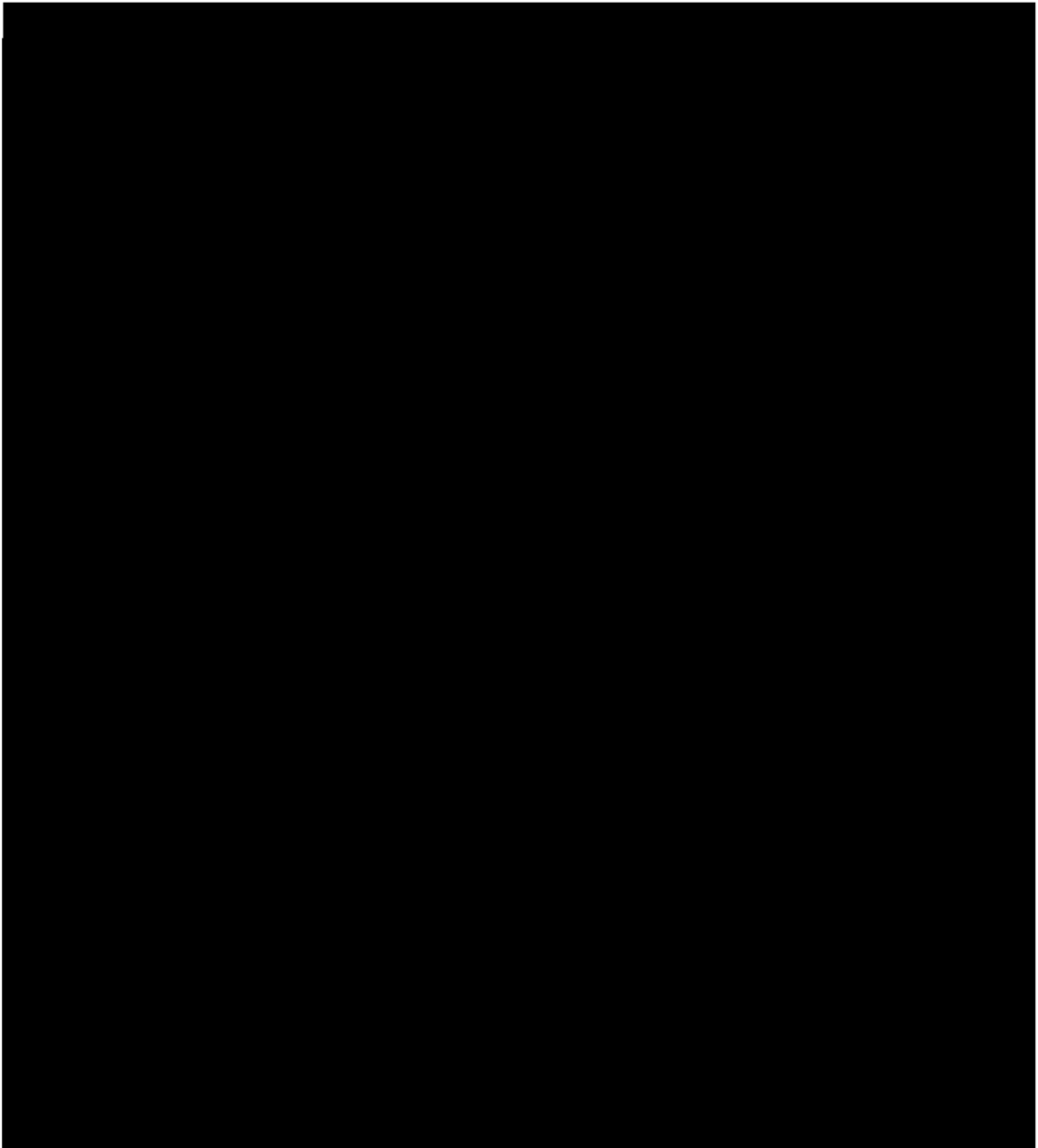




別添









作業報告書

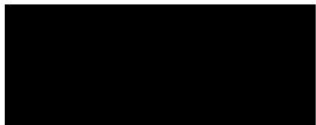
「キナ抽出物：ラットを用いた経口投与による反復投与毒性・
生殖発生毒性併合試験」における被験物質のろ過作業
及び投与液の濃度分析

作業番号： 



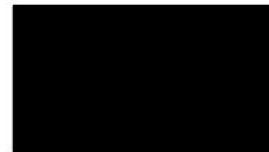
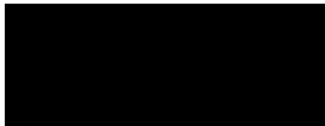
目次

目次.....	2
GLP 陳述書.....	4
作業情報.....	5
作業報告書の作成.....	7
試験主任者及び作業従事者.....	8
1 要約.....	9
2 緒言.....	9
3 被験物質.....	9
4 被験物質投与液分析法.....	10
4.1 均一性試験.....	10
4.2 濃度確認試験.....	11
4.3 測定試料.....	11
4.4 標準物質.....	11
4.5 試薬.....	12
4.6 使用機器.....	12
4.7 試薬溶液の調製.....	12
4.7.1 移動相.....	12
4.7.1.1 移動相 A.....	12
4.7.1.2 移動相 B.....	12
4.7.2 希釈液.....	12
4.7.2.1 希釈液 A.....	12
4.7.2.2 希釈液 B.....	13
4.8 分析用試料の調製.....	13
4.8.1 標準原液.....	13
4.8.2 検量線用標準溶液.....	13
4.8.3 QC 用試料.....	13
4.8.4 試料前処理法.....	13
4.9 測定条件.....	14
4.9.1 HPLC 条件.....	14
4.9.2 システム適合性.....	14



4.10 分析項目及び判定基準	14
4.10.1測定試料実測時の測定系の精度管理方法	14
4.10.2濃度の算出	15
4.11 計算式	15
4.12 データ処理方法	15
4.12.1数値の取り扱い	15
4.13 再測定	16
5 資料の保管	16
6 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	16
7 試験結果	16
7.1 均一性試験	16
7.2 濃度確認試験	16
7.3 分析における精度管理結果	17
8 結論	17
9 文献	17
10 総括表	18
Table 1: 被験物質投与液の均一性確認試験	19
Table 2: 被験物質投与液の濃度確認試験	20
Table 3: システム適合性データ	21
Table 4: 検量線データ	22
Table 5: QC サンプルデータ	23
11 信頼性保証書	24

最終頁 25



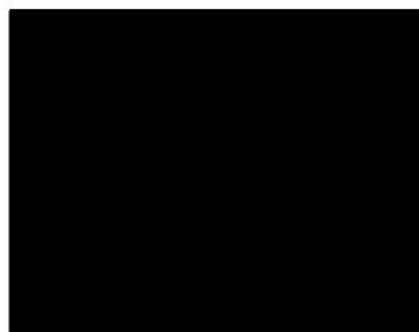
GLP 陳述書

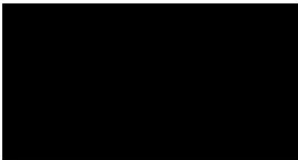
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併合試験」における被験物質のろ過作業及び投与液の濃度分析

作業番号 :



本試験は「新規化学物質等に係る試験を実施する試験施設に関する基準」（平成 23 年 3 月 31 日付け、薬食発 0331 第 8 号厚生労働省医薬食品局長、平成 23・03・29 製局第 6 号経済産業省製造産業局長、環保企発第 110331010 号環境省総合環境政策局長通知）に従って実施されたものです。





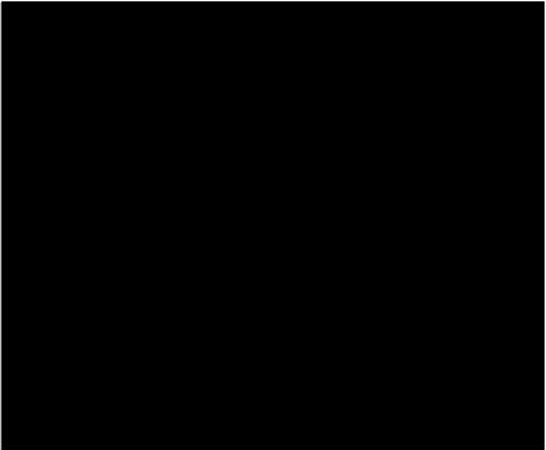
作業情報

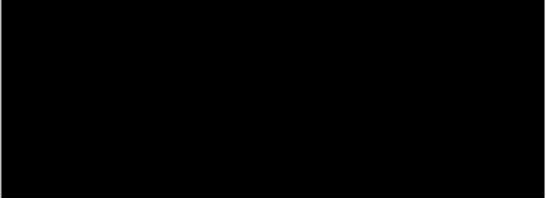
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作業番号 : 

作業目的 : 本作業は、複数場所試験として実施の「キナ抽出物：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」の一部として、被験物質のろ過作業及び投与液の濃度を確認することを目的とした。

適用 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 日付け、薬食発 0331 第 8 号厚生労働省医薬食品局長、平成 23・03・29 製局第 6 号経済産業省製造産業局長、環保企発第 110331010 号環境省総合環境政策局長通知）に従って実施した。

試験施設 : 

試験場所 : 

試験表題及び試験番号

試験表題 : キナ抽出物：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 : 



作業日程

作業開始日

:



作業終了日

:

試験場所終了日

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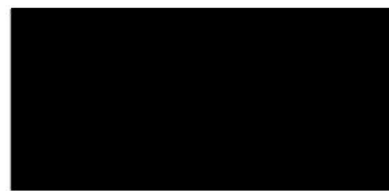


作業報告書の作成

作業表題 : 「キノ抽出物：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」における被験物質のろ過作業及び投与液の濃度分析

作業番号 : 

試験主任者 : 





試験主任者及び作業従事者

試験主任者 :

被験物質のろ過作業 :

分析担当者 :

集計処理 :

被験物質管理責任者 :



1 要約

複数場所試験として実施の「キナ抽出物：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」（[REDACTED]）の一部として、被験物質のろ過作業及び投与液の濃度を確認することを目的とした。

その結果、被験物質投与液の均一性及び濃度確認において、全ての基準を満たした。

また、被験物質のろ過作業に問題はみられず、被験物質投与液分析におけるシステム適合性、検量線及びQC用試料のいずれにおいても基準を満たし、測定系の信頼性が確認された。

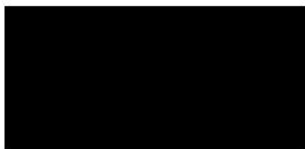
以上のことから、試験施設で調製された被験物質投与液（100、30 及び 10 mg/mL）は正確に調製されていることが確認された。

2 緒言

複数場所試験として実施の「キナ抽出物：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」の一部として、被験物質のろ過作業及び投与液の濃度を確認することを目的とした。

3 被験物質

名称	: キナ抽出物
英名	: Cinchona Bark Extract
CAS No.	: 68990-12-5
提供事業者	: [REDACTED]
供給源	: [REDACTED]
製造元	: [REDACTED]
ロット番号	: [REDACTED]
キニーネ含有量	: 0.4094% ¹⁾
外観及び性状	: 赤～暗褐色の粘性を有する液体
試験主任者入手日	: [REDACTED]
安定性	: 出荷後 24 ヶ月
保管条件	: 室温、遮光
保管場所	: [REDACTED]
使用期限	: [REDACTED]
保管温度	: 被験物質管理責任者管理：実測値 15.5～21.0°C [REDACTED] 試験主任者管理：実測値 13.5～20.5°C [REDACTED]
取り扱い上の注意	: マスク、手袋及び保護メガネなど適切な保護具を着用した。
分取方法	: 分取方法は参考文献 ^{2,3)} に記載の方法に従った。



被験物質容器を約 40℃ に加温したお湯に浸し、60 分間加温（この時、適宜転倒混和を行った）して、均一にした。融解した被験物質について、メッシュ（サンプルパック：栄研化学株式会社、型式：KA1000）を用いて濾過したもの（濾過画分）を被験物質として取り扱った。この濾過画分について、マグネチックスターラーによる攪拌操作を行い、必要量を分取して、DIMS 医科学研究所の被験物質室温保管庫に遮光保存した。分取した一部の被験物質について、試験施設における最終投与終了後、ろ過抽出物中のキニーネ含量測定（  に供した。

分取日から送付日までの保管温度

: 1 回目分取 15.5～20.0℃



2 回目分取 15.0～18.0℃



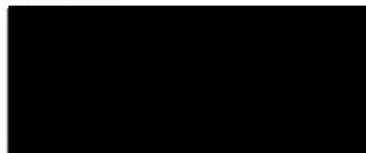
3 回目分取 15.5～20.0℃



送付先・送付条件

: 分取した被験物質は室温条件下で試験施設に送付した。

試験施設；



被験物質送付日

: 1 回目



2 回目



3 回目



4 被験物質投与液分析法

試験場所にて信頼性が確認された方法^{4,5)}を用いた。測定は以降に示す作業内容に従って実施した。

4.1 均一性試験

初回（分析日：）及び最終回調製時（分析日：）

に、各濃度調製投与液における被験物質の均一性について分析を行った。測定試料はマグネ

チェックスターラーにて撹拌させながら採取して、投与液中の被験物質濃度を測定し、均一性の程度を確認した。均一性の程度は、上層、中層及び下層の平均値の±15%で評価した。

4.2 濃度確認試験

初回（分析日： ）及び最終回調製時（分析日： ）の各濃度調製投与液について、投与液中の被験物質濃度を分析した。分析値は均一性試験の分析値の平均値をあて、設定濃度の±15%で評価した。

4.3 測定試料

測定試料（投与液）：100 mg/mL（高用量群）、30 mg/mL（中用量）及び10 mg/mL（低用量群）、各約10 mL（3本/濃度）

測定試料の授受：試験施設より、褐色ガラス瓶に分取された測定試料（投与液）を宅配便にて冷蔵条件下で移送された。
測定試料の容器に表示される情報（試験番号、被験物質名称、投与量、投与液濃度及び調製日）とサンプル数を確認した。

初回調製

測定試料移送日

測定試料受領日

最終調製

測定試料移送日

測定試料受領日

残サンプルの取り扱い：測定後の残余測定試料（投与液）は、各時期のデータ確定後に試験責任者及び試験主任者が協議し、廃棄した。

4.4 標準物質

名称：キニーネ

製造元：シグマアルドリッチ

供給源：

CAS No.：130-95-0

ロット番号：

純度：95.1%

外観及び性状：灰白色、粉末

試験主任者入手日：

保管条件：室温・遮光

保管場所：

保管温度：被験物質管理責任者管理：実測値 15.0～20.5°C

試験主任者管理：実測値 13.5～20.5℃

取り扱い上の注意：手袋、マスク、保護メガネを装着した。

4.5 試薬

塩酸：特級、富士フイルム和光純薬株式会社
ロット番号：[REDACTED]

メタノール：HPLC 用、富士フイルム和光純薬株式会社
ロット番号：[REDACTED]

リン酸二水素ナトリウム二水和物（分子量：156.01）
：特級、富士フイルム和光純薬株式会社
ロット番号：[REDACTED]

純水：Elix Essential 3（UV）を用いて製造した水

4.6 使用機器

名称	型式	製造業者
電子天秤	CPA225D	SARTORIUS K.K.
HPLC	LC-20 シリーズ	株式会社島津製作所
UV 検出器	SPD-20A	
データ処理システム	LabSolutions	
卓上型超音波洗浄器	VS-F100	アズワン株式会社
Elix Essential3（UV）	F1AB86324A	メルクミリポア
スターラー	HS-3E	井内盛栄堂

4.7 試薬溶液の調製

4.7.1 移動相

4.7.1.1 移動相 A

リン酸二水素ナトリウム二水和物（実測値：3.12000、3.12132 及び 3.12083 g）を純水に溶かし 1000 mL とし、超音波脱気したものを移動相 A（20 mM リン酸二水素ナトリウム）とした。

4.7.1.2 移動相 B

4.5 項に記載のメタノールを移動相 B とした。

4.7.2 希釈液

4.7.2.1 希釈液 A

塩酸とメタノールを 1：100（v/v）の割合で混合した液を希釈液 A とした。

4.7.2.2 希釈液 B

メタノールと純水を 1 : 1 (v/v) の割合で混合した液を希釈液 B とした。

4.8 分析用試料の調製

4.8.1 標準原液

標準物質約 25 mg (実測値 : 0.02633、0.02515 及び 0.02603 g) を精密に量り、メタノールを用いて正確に 100 mL とし、標準原液 (SS、約 250 µg/mL) とした。超音波処理は行わなかった。標準原液は用時調製とした。

4.8.2 検量線用標準溶液

次表に示すように希釈液を用いて正確に希釈し、検量線用標準溶液 (S1~S4) を調製した。なお、1 次希釈にはメタノール、2 次希釈には希釈液 B を用いた。測定には S1~S4 を用い、検量線用標準溶液は用時調製とした。

検量線用 標準溶液 No.	採取液	1 次希釈		2 次希釈		キニーネ 理論濃度 (µg/mL)
		採取量 (mL)	全量 (mL)	1 次希釈液 採取量 (mL)	全量 (mL)	
S4	SS	1	50	2.5	25	0.5
S3	S4 1 次希釈液	4	5	2.5	25	0.4
S2	S4 1 次希釈液	8	20	2.5	25	0.2
S1	S4 1 次希釈液	4	20	2.5	25	0.1

4.8.3 QC 用試料

次表に示すように希釈液を用いて正確に希釈し、QC 用試料 (QC1 及び QC2) を調製した。なお、1 次希釈にはメタノール、2 次希釈には希釈液 B を用いた。測定には QC1 及び QC2 を用い、QC 用試料は用時調製とした。

QC 用試料 No.	採取液	1 次希釈		2 次希釈		キニーネ 理論濃度 (µg/mL)
		採取量 (mL)	全量 (mL)	1 次希釈液 採取量 (mL)	全量 (mL)	
QC2	S4 1 次希釈液	4	5	2.5	25	0.4
QC1	S4 1 次希釈液	8	20	2.5	25	0.2

4.8.4 試料前処理法

次表に従い各被験物質投与液をスターラーにて攪拌しながら、メスピペットを用いて採取して (各 n=1) 正確に希釈後、孔径 0.45 µm のフィルター (メルクミリポア Millex-LCR、ロット番号 : R9CA01441 及び R9DA20388) でろ過し、測定用試料とした。なお、測定用試料は用時調製とし、それぞれ 1 次希釈には純水、2 次希釈には希釈液 A、3 次希釈には希釈液 B を用いた。2

次希釈後 15 分間超音波処理を行い、冷却して室温に戻した。体積減少がみられた場合は希釈液 A で再度全量とした。

投与液 (mg/mL)	1 次希釈		2 次希釈		3 次希釈		希釈 倍率	キナ抽出物 濃度 ($\mu\text{g/mL}$)
	採取量 (mL)	全量 (mL)	1 次希釈液 採取量 (mL)	全量 (mL)	2 次希釈液 採取量 (mL)	全量 (mL)		
10	-	-	1	10	2.5	25	100	100
30	-	-	1	30	2.5	25	300	100
100	1	10	1	10	2.5	25	1000	100

4.9 測定条件

4.9.1 HPLC 条件

カラム : Hydrosphere C18 [4.6 mm I.D.×150 mm、5 μm 、株式会社ワイエムシイ (ロット番号: 18050)]

移動相 : 移動相 A: 20mM リン酸二水素ナトリウムと移動相 B: メタノールを 65:35 の割合で送液した。

測定波長 : 235 nm

カラム温度 : 37°C

サンプラー : 15°C

流量 : 1.0 mL/min

試料注入量 : 10 μL

分析時間 : 25 min

4.9.2 システム適合性

システムの性能 : 検量線用標準溶液 (S3) 10 μL につき、上記の条件で操作するとき (システムの再現性で測定した 1 回目のクロマトグラムを用いた)、キニーネのピークの理論段数及びシンメトリー係数は、それぞれ 7000 段以上、2.0 以下。

システムの再現性 : 検量線用標準溶液 (S3) 10 μL につき、上記の条件で試験を 3 回繰り返すとき、キニーネのピーク面積値の相対標準偏差 (RSD) は 2.0% 以下。

4.10 分析項目及び判定基準

4.10.1 測定試料実測時の測定系の精度管理方法

試料を測定するときは、検量線用標準溶液 (S1~S4、各 $n=1$)、QC 用試料 (2 濃度、各 $n=1$)、測定試料 ($n=1$)、及び QC 用試料 (2 濃度、各 $n=1$) の順に測定し、測定法の信頼性を確認した。

判定基準 : QC 用試料の RE が $\pm 10.0\%$ 以内

4.10.2 濃度の算出

検量線用標準溶液（S1～S4、各 n=1）を分析法に従って測定し、得られたピーク面積値を用いて、最小二乗法による一次回帰直線式から検量線（ $Y = aX + b$ 、Y：ピーク面積値、X：濃度、重み付け：なし）を作成した。検量線の判定基準は、相関係数（r）が 0.995 以上、逆回帰値の真度（相対誤差：RE）が±10.0%以内とし、上記の判定基準を満たすとき、測定試料より得られたピーク面積値を検量線に当てはめ、濃度を算出した。希釈して測定した試料は、希釈試料の測定値に希釈倍数を乗じた値を用いた。

4.11 計算式

(1) 投与液濃度

$$\text{投与液（被験物質）濃度（mg/mL）} = \text{測定値（μg/mL）} / \text{被験物質中キニーネ含量（％）} \times 100 \times \text{希釈倍率} / 1000$$

(2) RE（％）

$$\text{検量線 RE（％）} = [(\text{逆回帰値} - \text{理論値}) / \text{理論値}] \times 100$$

(3) RSD（％）

$$\text{RSD（％）} = (\text{標準偏差} / \text{平均値}) \times 100$$

(4) 均一性（％）

$$\text{均一性（％）} = (\text{各層の濃度} / \text{上層、中層及び下層の投与液中濃度の平均値}) \times 100$$

(5) 検量線用標準溶液

$$\text{キニーネ濃度実測値（μg/mL）} = \text{標準物質秤取量（g）} \times \text{キニーネ純度（％）} \times \text{キニーネ濃度理論値（μg/mL）} / \text{標準物質秤取量理論値（g）} / 100$$

4.12 データ処理方法

データ処理装置でクロマトグラム、理論段数、シンメトリー係数、ピーク面積値、測定値、検量線（重み付け：なし）の相関係数（r）、検量線の傾き及び y 切片を算出した。

平均値、相対誤差（RE）、標準偏差（SD）、投与液中濃度及び相対標準偏差（RSD）は表計算ソフト Excel（Microsoft Excel）を使用した。なお、平均値の算出には四捨五入した表示値ではなく、個別値の算出桁数+2 桁（切り捨て）の数値を用いた。

4.12.1 数値の取り扱い

数値は（n+1）桁目を四捨五入して n 桁で表示した。

算出項目	単位	算出桁数
理論段数	段	整数
シンメトリー係数	-	小数点以下 1 桁
ピーク面積値	μAU・sec	整数
相関係数	-	小数点以下 3 桁
測定値	μg/mL	有効数字 4 桁

キニーネ理論濃度	μg/mL	小数点以下 5 桁
投与液濃度	mg/mL	小数点以下 2 桁
投与液濃度の平均値	mg/mL	個別値と同じ桁数
RE	%	小数点以下 1 桁
SD	-	平均値の桁数に合わせる
RSD	%	小数点以下 1 桁
均一性	%	小数点以下 1 桁

4.13 再測定

最終回調製時の被験物質投与液（ ）を分析したところ、30 mg/mL 投与液濃度が設定濃度の 82.9%となり、基準をみたさなかった（設定濃度の±15%）。試験責任者に連絡を入れ、試験責任者から再調製された 30 mg/mL 投与液の分析をするよう指示を受けた。再調製された投与液は（ ）に受領した。再分析の結果、投与液濃度は基準をみたしたことから、再分析の結果を採用した。

5 資料の保管

作業計画書（原本）、作業報告書（原本）、被験物質に関する記録、作業成績に関する記録、QAU の調査に関する記録、その他本試験に係る記録文書は、作業報告書提出後 5 年間、株式会社 DIMS 医科学研究所の資料保管室にて保管する。保管期間の満了後の措置については試験施設と協議の上決定する。

6 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

認められなかった。

7 試験結果

7.1 均一性試験

投与液中の被験物質の均一性試験の結果を Table 1 に示した。

初回調製時（ ）の 10、30 及び 100 mg/mL 投与液の均一性は 93.0～105.7%、最終回調製時（ ）の 10、30 及び 100 mg/mL 投与液の均一性は、98.6～102.5%の範囲であり、いずれも均一性確認の判定基準（±15%）を満たしたことから、被験物質投与液の均一性に問題はみられなかった

7.2 濃度確認試験

投与液中の被験物質の濃度確認試験の結果を Table 2 に示した。

初回調製時（ ）の 10、30 及び 100 mg/mL 投与液の濃度は、設定濃度の 86.1～89.2%、最終回調製時（ ）の 10、30 及び 100 mg/mL 投与液の

濃度は 91.6～99.7%であり、いずれも濃度確認の判定基準（±15%）を満たしており、正確に調製されていることが確認された。

7.3 分析における精度管理結果

システム適合性、検量線用標準溶液、QC 用試料の分析結果を Table 3～5 に示した。

キニーネのピークの理論段数及びシンメトリー係数、キニーネのピーク面積値の相対標準偏差（RSD）、検量線の相関係数（r）、逆回帰地の真度（相対誤差：RE）、QC 用試料の相対誤差（RE）のすべての結果は判定基準内であり、測定法の信頼性が確認された。

8 結論

複数場所試験として実施の「キナ抽出物：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：[REDACTED]）の一部として、被験物質のろ過作業及び投与液の濃度を確認することを目的とし、ろ過作業及び濃度分析を実施した。

その結果、試験施設で調製された投与液（100、30 及び 10 mg/mL）の均一性の程度は、上層、中層及び下層の平均値の±15%以内、濃度は設定濃度の±15%以内であり、正確に調製されていることが確認された。

また、被験物質のろ過作業に問題はみられず、投与液分析におけるシステム適合性、検量線及び QC 用試料のいずれにおいても基準を満たし、測定系の信頼性が確認された。

9 文献

- 1) キナ抽出物中のキニーネ含量測定（加温融解ろ過処理したキナ抽出物中のキニーネ含量の測定） 最終報告書 [REDACTED]
- 2) 既存添加物の安全性に関する試験（キナ抽出物のラットを用いた 90 日間反復経口投与毒性試験のための用量設定試験） 最終報告書 [REDACTED]
- 3) キナ抽出物投与液のメッシュを用いたゾンデ通過検討試験 最終報告書 [REDACTED]
- 4) 既存添加物の安全性に関する試験（キナ抽出物投与液の分析バリデーション及び安定性試験） 最終報告書 [REDACTED]
- 5) 既存添加物の安全性に関する試験（キナ抽出物投与液の分析バリデーション及び安定性試験） 最終報告書修正書 [REDACTED]



10 総括表

Table 1 Results for homogeneity

Test article	Date of analysis	Intended concentration (mg/mL)	Sampling point	Found concentration (mg/mL)	Homogeneity ^a (%)
Cinchona Bark Extract	December 21, 2021	10	Upper	8.79	99.4
			Middle	8.81	99.7
			Lower	8.92	100.9
			Mean	8.84	
		30	Upper	27.00	100.9
			Middle	26.61	99.4
			Lower	26.67	99.7
			Mean	26.76	
		100	Upper	87.23	101.3
			Middle	80.02	93.0
			Lower	90.99	105.7
			Mean	86.08	
	February 1, 2022	10	Upper	9.05	98.8
			Middle	9.03	98.6
			Lower	9.39	102.5
			Mean	9.16	
		100	Upper	94.33	102.3
			Middle	91.04	98.8
			Lower	91.13	98.9
			Mean	92.17	
	February 3, 2022	30 ^b	Upper	29.66	99.2
			Middle	29.93	100.1
			Lower	30.12	100.7
			Mean	29.90	

a : Homogeneity (%) = Found concentration / Mean found concentration x 100

b : Reanalysis was performed

Table 2 Results for content analyses

Test article	Date of analysis	Intended concentration (mg/mL)	Found concentration (mg/mL)	Ratio ^a (%)
Cinchona Bark Extract	December 21, 2021	10	8.84	88.4
		30	26.76	89.2
		100	86.08	86.1
	February 1, 2022	10	9.16	91.6
		100	92.17	92.2
	February 3, 2022	30 ^b	29.90	99.7

a : Ratio (%) = Found concentration / Intended concentration*100

b : Reanalysis was performed

Table 3 Data of system suitability

Test article	Date of analysis	Injection time	Quinine peak area (μ AU-sec)	Number of theoretical plates (plates)	Symmetry coefficient
Cinchona Bark Extract	December 21, 2021	1	22895	11373	1.1
		2	22891		
		3	22977		
		Mean	22921		
		SD	49		
		RSD (%)	0.2		
	February 1, 2022	1	20380	11372	1.1
		2	20244		
		3	20063		
		Mean	20229		
		SD	159		
		RSD (%)	0.8		
	February 3, 2022	1	22321	11350	1.0
		2	22174		
		3	21642		
		Mean	22046		
		SD	357		
		RSD (%)	1.6		

SD: Standard deviation

RSD: Relative standard deviation

Table 4 Data of calibration curve

Test article	Date of analysis	Measured quinine concentration (µg/mL)	Back calculated concentration (µg/mL)	RE (%)	Quinine peak area (µAU-sec)	Slope	Y intercept	Correlation coefficient (r)
Cinchona Bark Extract	December 21, 2021	0.10016	0.09971	-0.4	5488	58210.3	-315.888	1.000
		0.20032	0.20108	0.4	11389			
		0.40064	0.40019	-0.1	22979			
		0.50080	0.50095	0.0	28845			
	February 1, 2022	0.09567	0.09661	1.0	4778	55056.2	-541.158	1.000
		0.19134	0.19228	0.5	10045			
		0.38268	0.37610	-1.7	20165			
		0.47835	0.48305	1.0	26054			
	February 3, 2022	0.09902	0.09999	1.0	5671	57634.6	-92.0517	1.000
		0.19804	0.19590	-1.1	11198			
		0.39607	0.39861	0.6	22881			
		0.49509	0.49372	-0.3	28363			

RE: Relative error

Weighting factor : -

Table 5 Data of QC sample

Test article	Date of analysis	Quinine measured concentration in QC sample (µg/mL)	Calculated concentration (µg/mL)	RE (%)
Cinchona Bark Extract	December 21, 2021	0.20032	0.2007	0.2
			0.1991	-0.6
		0.40064	0.3985	-0.5
	February 1, 2022		0.3919	-2.2
		0.19134	0.1963	2.6
			0.1961	2.5
	February 3, 2022	0.38268	0.3815	-0.3
			0.3706	-3.2
		0.19804	0.1964	-0.8
			0.1933	-2.4
		0.39607	0.3974	0.3
			0.3904	-1.4

RE : Relative error



11 信賴性保證書

信頼性保証書

作業表題 「キナ抽出物：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」における被験物質のろ過作業及び投与液の濃度分析

作業番号 XXXXXXXXXX

本試験は適用 GLP 及び当施設の信頼性保証部門に関する標準操作手順書（SOP）に従って下記の調査を実施しました。その結果、試験計画書及び SOP に従って試験が適正に実施されており、作業報告書には試験をした方法、手順が正確に記載され、かつ試験の生データを正確に反映していることを認めます。

適用 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 日付け、薬食発 0331 第 8 号厚生労働省医薬食品局長、平成 23・03・29 製局第 6 号経済産業省製造産業局長、環保企発第 110331010 号環境省総合環境政策局長通知）

調査の内容	QAU 調査日	試験場所	試験施設
作業計画書			
被験物質に関する記録			
ろ過作業			
被験物質の送付			
測定試料の入手			
測定試料の分析			
帳票の確認			
記録類の確認			
記録類の再確認			
作業報告書草稿			
作業報告書			

試験場所：試験場所管理責任者及び試験主任者への報告日

試験施設：運営管理者、試験責任者及び主信頼性保証部門責任者への報告日



ホルモン測定報告書

「キナ抽出物：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 )」におけるホルモン測定





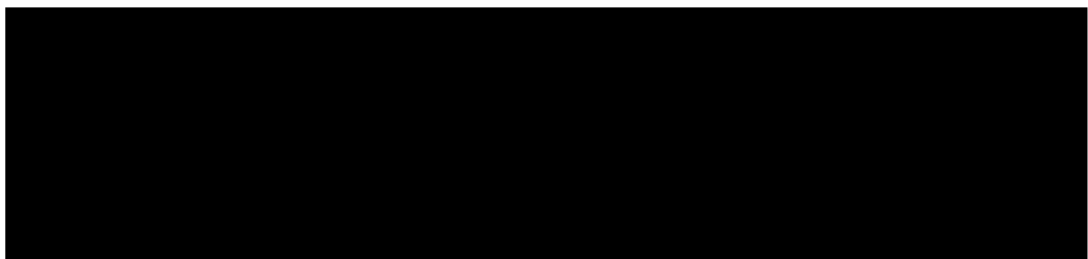
1. GLP 陳述書

ホルモン測定番号 : 

ホルモン測定表題 : 「キノ抽出物：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 ）」にお
けるホルモン測定

本作業は以下の GLP 基準を遵守して実施したものです。

- 「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）



2. 目次

1.	GLP 陳述書	2
2.	目次	3
3.	ホルモン測定実施概要	5
3.1	ホルモン測定番号	5
3.2	ホルモン測定表題	5
3.3	目的.....	5
3.4	遵守した基準	5
3.4.1	GLP	5
3.5	試験施設	5
3.6	試験場所.....	5
3.7	試験責任者.....	5
3.8	試験主任者.....	5
3.9	担当者	6
3.10	日程.....	6
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	6
3.12	資料の保存.....	6
3.13	試験主任者の署名	7
4.	要約	8
5.	試験構成	9
5.1	概要.....	9
5.2	試料.....	10
6.	材料及び方法.....	10
6.1	アッセイ方法	11
6.1.1	T4 測定.....	11
6.1.1.1	Cal-1/2 及び Cal-1/4 の調製	11
6.1.1.2	測定操作.....	11
6.2	データ解析.....	12
6.3	測定成立条件の評価	12
6.4	再測定	12
7.	統計解析	13
8.	結果及び考察.....	14
8.1	投与終了時雄動物（EOA）	14
8.2	生後 13 日児動物（PD13）	14
9.	結論	14



Tables

Table 1	Hormone concentrations in rat serum of EOA (Male)	15
Table 2	Hormone concentrations in rat serum of PD13 (Pups).....	15

信賴性保證書	16



3. ホルモン測定実施概要

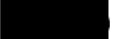
3.1 ホルモン測定番号



3.2 ホルモン測定表題

「キナ抽出物：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 ）」におけるホルモン測定

3.3 目的

「キナ抽出物：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 ）」において採取された血清中のホルモン濃度を測定することを目的とした。

3.4 遵守した基準

3.4.1 GLP

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

3.5 試験施設



3.6 試験場所



3.7 試験責任者



3.8 試験主任者



■■■■■

3.9 担当者

測定担当者 : ■■■■■

3.10 日程

試料受領日	■■■■■	■■■■■
測定日	■■■■■	■■■■■
ホルモン測定報告書作成日	■■■■■	■■■■■

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

該当事象はなかった。

3.12 資料の保存

以下のホルモン測定関係資料をファイルに綴じ込み、■■■■■
■■■■■の資料保存施設に保存する。その期間はホルモン測定報告書作成後 5
年間とする。期間終了後の取扱いについては、試験施設と■■■■■
■■■■■の間で協議し、その処置を決定する。

- 1) ホルモン測定計画書の原本
- 2) 試験計画書の写し
- 3) 試験計画書変更書の写し
- 4) 生データ及びその他の記録文書
- 5) ホルモン測定報告書の原本
- 6) 通信記録



3.13 試験主任者の署名





4. 要約

「キナ抽出物：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 ）」において採取された投与終了時雄動物（EOA）及び生後 13 日児動物（PD13）の血清中のホルモン（T4）濃度を測定した。

その結果、T4 濃度は媒体対照群と全ての投与群との間に有意差は認められなかった。



5. 試験構成

5.1 概要

試験番号  (キナ抽出物：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) の群構成を下表に示す。

群構成表（雄）

試験群	投与量 (mg/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
媒体対照	0	7	1001-1007	5	1008-1012
低用量	100	12	2001-2012		
中用量	300	12	3001-3012		
高用量	1000	7	4001-4007	5	4008-4012

群構成表（雌）

試験群	投与量 (mg/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
媒体対照	0	12	1101-1112	5	5101-5105	5	5106-5110
低用量	100	12	2101-2112				
中用量	300	12	3101-3112				
高用量	1000	12	4101-4112	5	6101-6105	5	6106-6110

5.2 試料

Text-Table 1

ホルモン 測定試料 (血清)	試験群	動物数	血清試料数			
			交配群		非交配群	
			投与終了 時割検群	回復終了 時割検群	投与終了 時割検群	回復終了 時割検群
測定対象	媒体対照	雄 10	5	5 ^{a)}	—	—
		雌 15	5 ^{a)}	—	5 ^{a)}	5 ^{a)}
	低用量	雄 5	5	—	—	—
		雌 5	5 ^{a)}	—	—	—
	中用量	雄 5	5	—	—	—
		雌 5	5 ^{a)}	—	—	—
	高用量	雄 10	5	5 ^{a)}	—	—
		雌 15	5 ^{a)}	—	5 ^{a)}	5 ^{a)}
	上記に加え、生後 4 日及び 13 日の児動物（交配群の各用量群の母動物から 5 腹ずつ、計 40 腹分）。					
	a)：本動物及び生後 4 日児動物は、試験責任者の判断により測定しなかった。					
受領チューブ数	雌雄：約 0.5 mL×3 本、児（生後 4 日）：約 0.2 mL×1 本、児（生後 13 日）：約 0.3 mL×3 本、合計 290 本					
試験施設での保存条件	-80℃ の冷凍庫（許容範囲：-70℃ 以下）、実測値は許容範囲内であった。					
輸送条件	ドライアイス同梱下で輸送された。					
識別	ラベルに明記された情報（試験番号、検査時期、検査項目、試料番号、試料名、色分け及び採取年月日）をもとに、試験場所で血清試料名を割り付けた。					
試験場所での保存条件	-80℃ の冷凍庫（許容範囲：-70℃ 以下）、実測値は許容範囲内であった。					
血清試料安定性（-70℃ 以下）	保存安定性：16 週間、繰返し凍結融解回数：3 回まで。測定は上記の条件内で実施した。					
残余の取扱い	測定後の残余の血清は、ホルモン測定報告書作成後に試験責任者の指示に基づいて試験場所で廃棄する。					

6. 材料及び方法

受領した試料（Text-Table 1）を用いて下記 6.1 に従い、ホルモン（T4）濃度を測定した。

測定方法及び測定キットに関する情報を下表（Text-Table 2、Text-Table 3）に示す。

Text-Table 2

ホルモン測定				
検査項目	測定方法	単位	表示桁数	測定範囲
T4	RIA 法	ng/mL	小数第 1 位	5.7 ~ 340.0 ng/mL
使用測定機器 ガンマカウンター (AccuFLEX γ 7010、日立)				

Text-Table 3

T4	
キット	: RIA-gnost®-T4 (Cisbio Bioassays)
保存条件	: 2~8°C (実測値は許容範囲内であった。)
Lot No. (使用期限)	: [REDACTED]
Calibrator (表示濃度)	: Cal-0、1 (22.6 ng/mL)、2 (49.0 ng/mL)、3 (100.0 ng/mL)、 4 (196.0 ng/mL)、5 (340.0 ng/mL)

6.1 アッセイ方法

6.1.1 T4 測定

6.1.1.1 Cal-1/2 及び Cal-1/4 の調製

Cal-1 と Cal-0 を 1 : 1 (60 μ L : 60 μ L) で混合し、Cal-1/2 (表示濃度 : 11.3 ng/mL) とした。さらに、Cal-1/2 と Cal-0 を 1 : 1 (30 μ L : 30 μ L) で混合し、Cal-1/4 (表示濃度 : 5.7 ng/mL) とした。調製当日を使用期限とした。

6.1.1.2 測定操作

- 1) 各試料 20 μ L を Ab チューブ (Antibody-coated tube) に加えた。
- 2) ^{125} I-T4 tracer (1 mL) を Ab チューブに添加し、ふたをして攪拌した。
- 3) ^{125} I-T4 tracer をプラスチックチューブ (丸底テストチューブ、WATSON) に加えたものを Total Count (TC) とした。
- 4) 23°C 設定のインキュベータ内で 45~55 分間 (実時間 : 50 分間) 振とうした。
- 5) Ab チューブ内の溶液をアスピレータで除去した。
- 6) ガンマカウンターでチューブの ^{125} I (60 秒間) の放射線計数率 (cpm) を測定した。

6.2 データ解析

Magellan Tracker ver. 7.0 ソフトウェア (Tecan) を用いて、放射線計数率 (cpm) から各試料の T4 濃度を算出した。

X 軸を濃度 (ng/mL、対数表示)、Y 軸を放射線計数率 (cpm) の測定値とし、表示濃度のプロットから検量線を作成した。

解析法、表示桁数を下表に示す。

検査項目	解析法	表示桁数	
		放射線計数率 (cpm)	測定濃度
T4	4 パラメーター Marquardt (重み付け: $1/Y^2$)	小数第 1 位	小数第 1 位

6.3 測定成立条件の評価

本測定は、以下の測定成立条件を全て満たしていたことから測定成立とした。計算は Microsoft office Excel で実施 (表示桁数で計算) した。

1) TC 及び Cal-0

- TC 及び Cal-0 の平均放射線計数率が Cal-1/4 の平均放射線計数率を超えている。
- 平均放射線計数率は以下の計算式から算出した (小数第 1 位まで表示)。

$$\text{平均放射線計数率 (cpm)} = \frac{\text{個別放射線計数率 (cpm) の和}}{2}$$

2) 標準試料

- duplicate での個別放射線計数率の差が 2 倍未満である。
- 測定濃度 (個別濃度の平均) の表示濃度に対する真度が Cal-1/4、Cal-5 で $100 \pm 25.0\%$ 以内、Cal-1/2~4 のうち 4 試料以上で $100 \pm 20.0\%$ 以内である。
- 真度 (%) は以下の計算式から算出した (小数第 1 位まで表示)。

$$\text{真度 (\%)} = \frac{\text{測定濃度}}{\text{表示濃度}} \times 100$$

3) QC

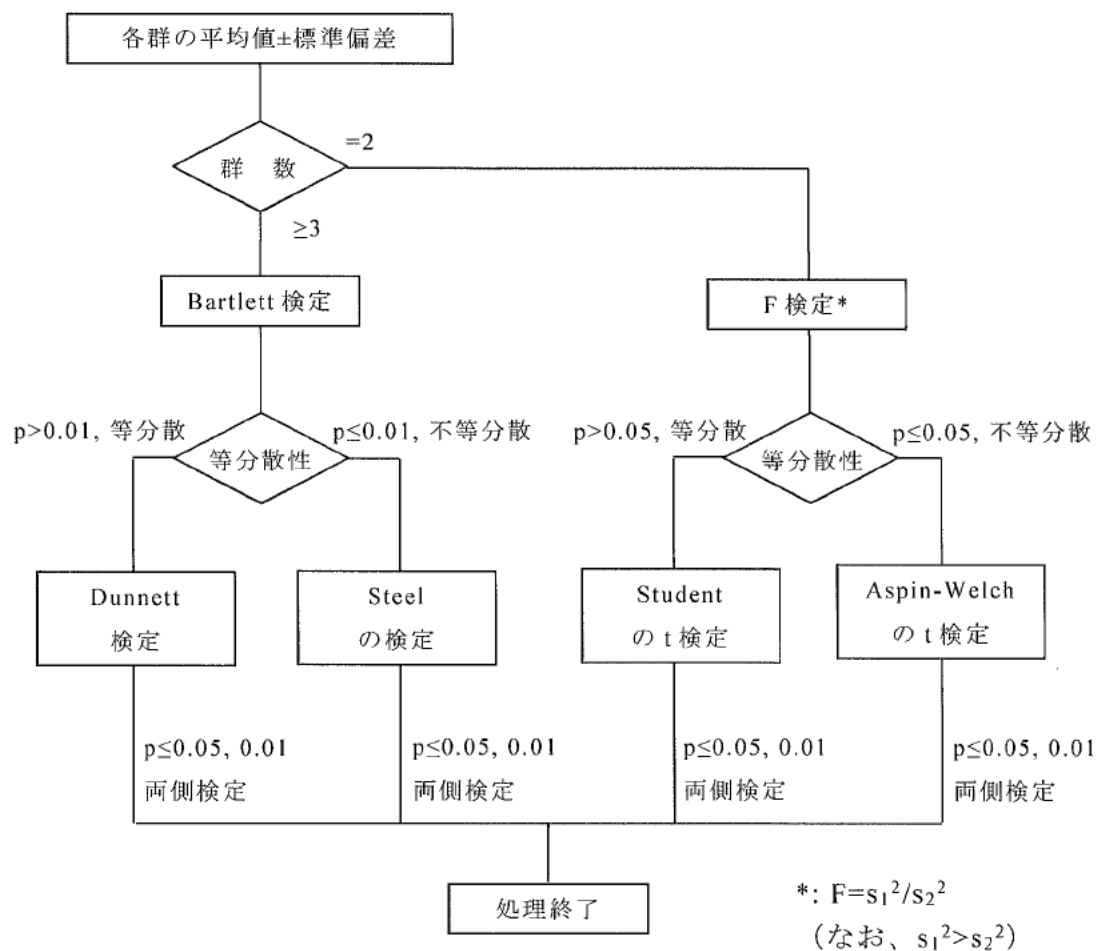
duplicate での個別放射線計数率の差が 2 倍未満で、かつ測定濃度 (個別濃度の平均) が表示濃度範囲内である。

6.4 再測定

再測定は実施しなかった。

7. 統計解析

検査項目について下記の模式図に示す方法に従って検定した。各群の平均値 (Mean) 及び標準偏差 (SD) の算出には、それぞれ Microsoft Office Excel における AVERAGE 関数及び STDEV 関数を用いた。解析には SAS Release 9.1.3 を使用した。





8. 結果及び考察

8.1 投与終了時雄動物（EOA）

T4 濃度測定の結果を Table 1 に示す。

T4 濃度は媒体対照群と全ての投与群との間に有意差は認められなかった。

8.2 生後 13 日児動物（PD13）

T4 濃度測定の結果を Table 2 に示す。

T4 濃度は媒体対照群と全ての投与群との間に有意差は認められなかった。

9. 結論

「キナ抽出物：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 ）」において採取された投与終了時雄動物（EOA）及び生後 13 日児動物（PD13）の血清中のホルモン（T4）濃度を測定した。

その結果、T4 濃度は媒体対照群と全ての投与群との間に有意差は認められなかった。

**Table 1** Hormone concentrations in rat serum of EOA (Male)

Animal No.	T4 (ng/mL)	Animal No.	T4 (ng/mL)	Animal No.	T4 (ng/mL)	Animal No.	T4 (ng/mL)
1001	38.3	2001	21.7	3001	30.8	4001	33.4
1002	31.5	2002	31.5	3002	26.1	4002	30.1
1003	37.6	2003	40.5	3003	39.1	4003	30.8
1004	35.7	2004	40.1	3004	29.0	4004	32.8
1005	34.1	2005	35.4	3005	29.9	4005	32.3
Mean	35.4	Mean	33.8	Mean	31.0	Mean	31.9
SD	2.7	SD	7.7	SD	4.9	SD	1.4
n	5	n	5	n	5	n	5

EOA: End of administration

No significant difference in any treated groups from vehicle control group.

Table 2 Hormone concentrations in rat serum of PD13 (Pups)

Animal No.	T4 (ng/mL)	Animal No.	T4 (ng/mL)	Animal No.	T4 (ng/mL)	Animal No.	T4 (ng/mL)
1102	48.3	2103	40.6	3101	39.6	4103	40.8
1105	37.3	2105	39.4	3102	43.7	4105	47.0
1106	35.7	2107	48.0	3104	33.0	4106	61.3
1109	31.6	2109	33.0	3106	47.6	4108	33.1
1110	37.5	2111	45.4	3109	48.6	4111	41.8
Mean	38.1	Mean	41.3	Mean	42.5	Mean	44.8
SD	6.2	SD	5.8	SD	6.4	SD	10.5
n	5	n	5	n	5	n	5

PD13: Postnatal day 13

Animal No.: Dam No. of pups

No significant difference in any treated groups from vehicle control group.



信頼性保証書（1/2）

ホルモン測定番号：

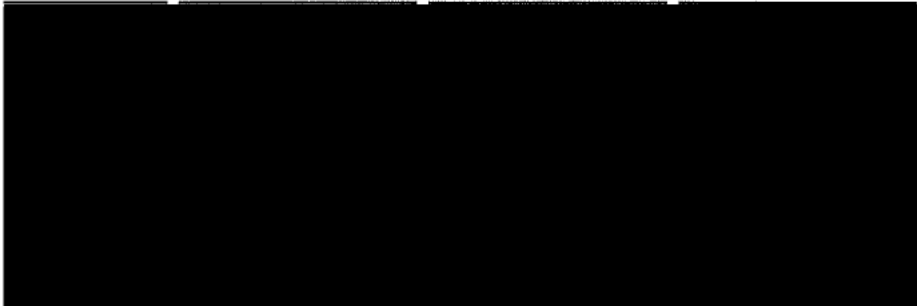


ホルモン測定表題：「キナ抽出物：ラットを用いた経口投与による反復投与毒性・生殖発生毒性併合試験（試験番号 ）」におけるホルモン測定

本測定は以下に示す基準に従っ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し、報告致しました。

調 査 項 目	調査担当者	調 査 日	試験主任者 及び試験場所 管理責任者 への報告日	試験責任者、 運営管理者及び 主信頼性保証 部門責任者 への報告日
ホルモン測定 計画書				
試料受領（雄動物）				
試料受領（雌雄及び 児動物）				
ホルモン測定				



信頼性保証書（2/2）

調 査 項 目	調査担当者	調 査 日	試験主任者 及び試験場所 管理責任者 への報告日	試験責任者、 運営管理者及び 主信頼性保証 部門責任者 への報告日
ホルモン測定 報告書草案、 生データ				
改善確認				
ホルモン測定 報告書				



Attachment 5

Historical Control Data in the Test Facility

([REDACTED])

Period covered: [REDACTED]

Animal species: Rat

Strain: CrI:CD(SD)

Study type: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Historical Control Data of Blood Chemistry

<u>Stage</u>	<u>Test Item</u>	<u>Sex</u>	<u>Week of age</u>	<u>Number of Studies</u>	<u>Min.</u>	<u>Max.</u>	<u>Mean $\pm$ 2 S.D.</u>
End of Recovery Period	Na (mmol/L)	Female	18	12	141	143	142.2 $\pm$ 1.2

Historical Control Data of Absolute Organ Weights

<u>Stage</u>	<u>Test Item</u>	<u>Sex</u>	<u>Week of age</u>	<u>Number of Studies</u>	<u>Min.</u>	<u>Max.</u>	<u>Mean $\pm$ 2 S.D.</u>
End of Dosing Period	Liver (g)	Female	16	12	6.70	8.88	7.50 $\pm$ 1.40
End of Recovery Period	Thyroid-RL (mg)	Female	18	12	14.7	19.7	16.3 $\pm$ 2.8

Historical Control Data of Relative Organ Weights

<u>Stage</u>	<u>Test Item</u>	<u>Sex</u>	<u>Week of age</u>	<u>Number of Studies</u>	<u>Min.</u>	<u>Max.</u>	<u>Mean $\pm$ 2 S.D.</u>
End of Dosing Period	Liver (g/100 gBW)	Female	16	12	2.40	2.78	2.59 $\pm$ 0.24
End of Recovery Period	Thyroid-RL (mg/100 gBW)	Female	18	12	5.0	6.4	5.5 $\pm$ 1.0

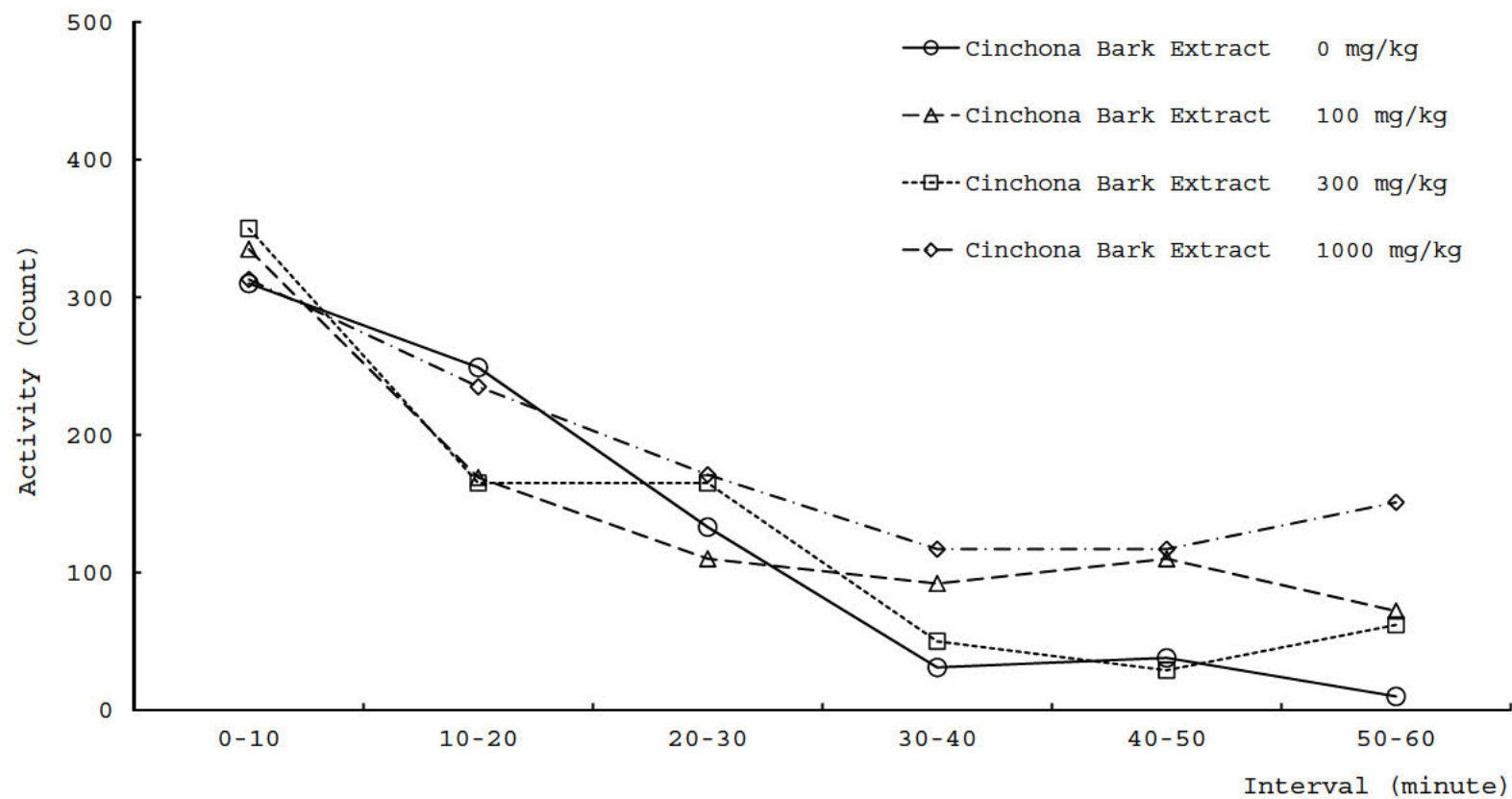


Fig.1 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Motor activity of male rats (Week 6 of administration)

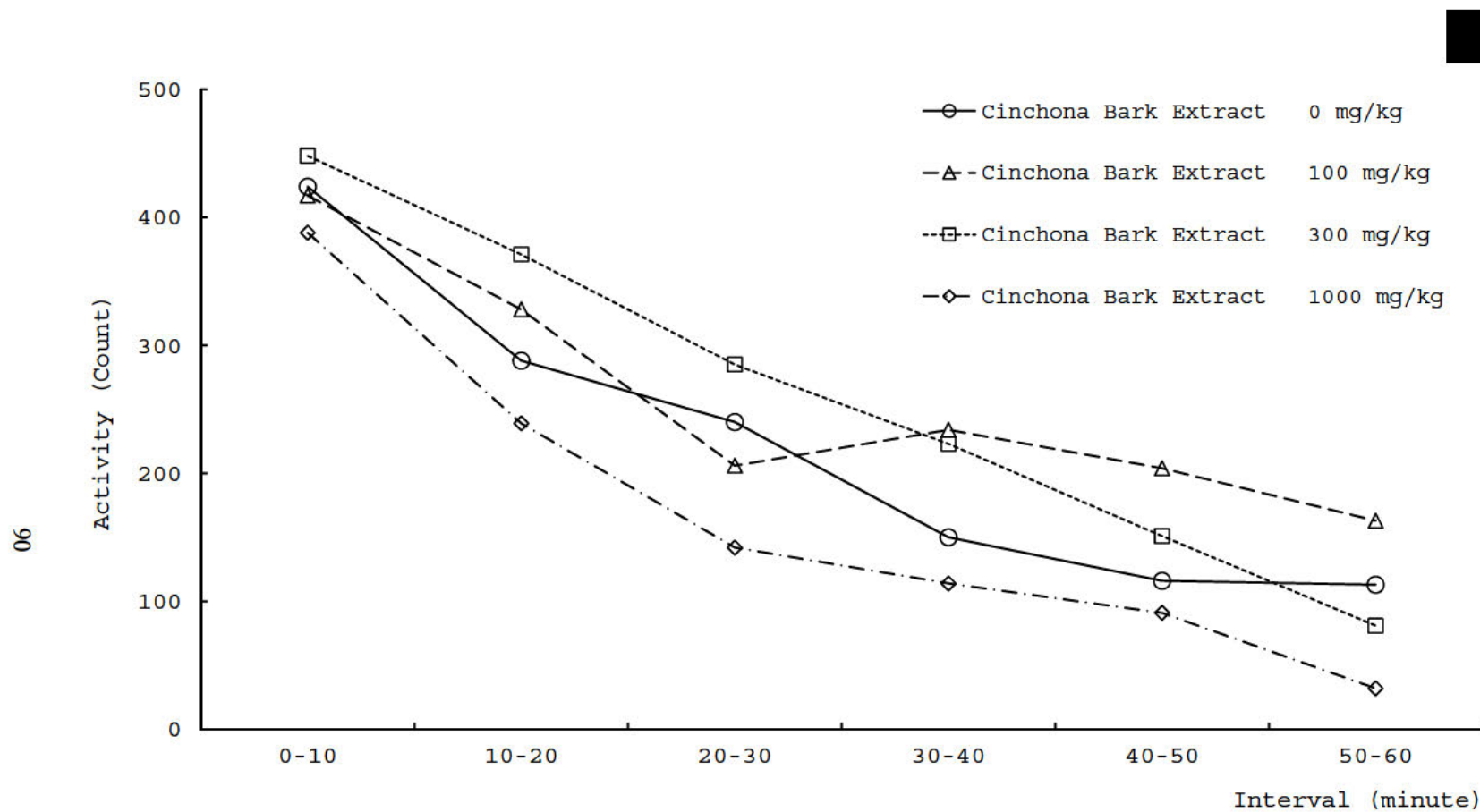


Fig.2 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Motor activity of female rats (Main group, Lactation Day13)

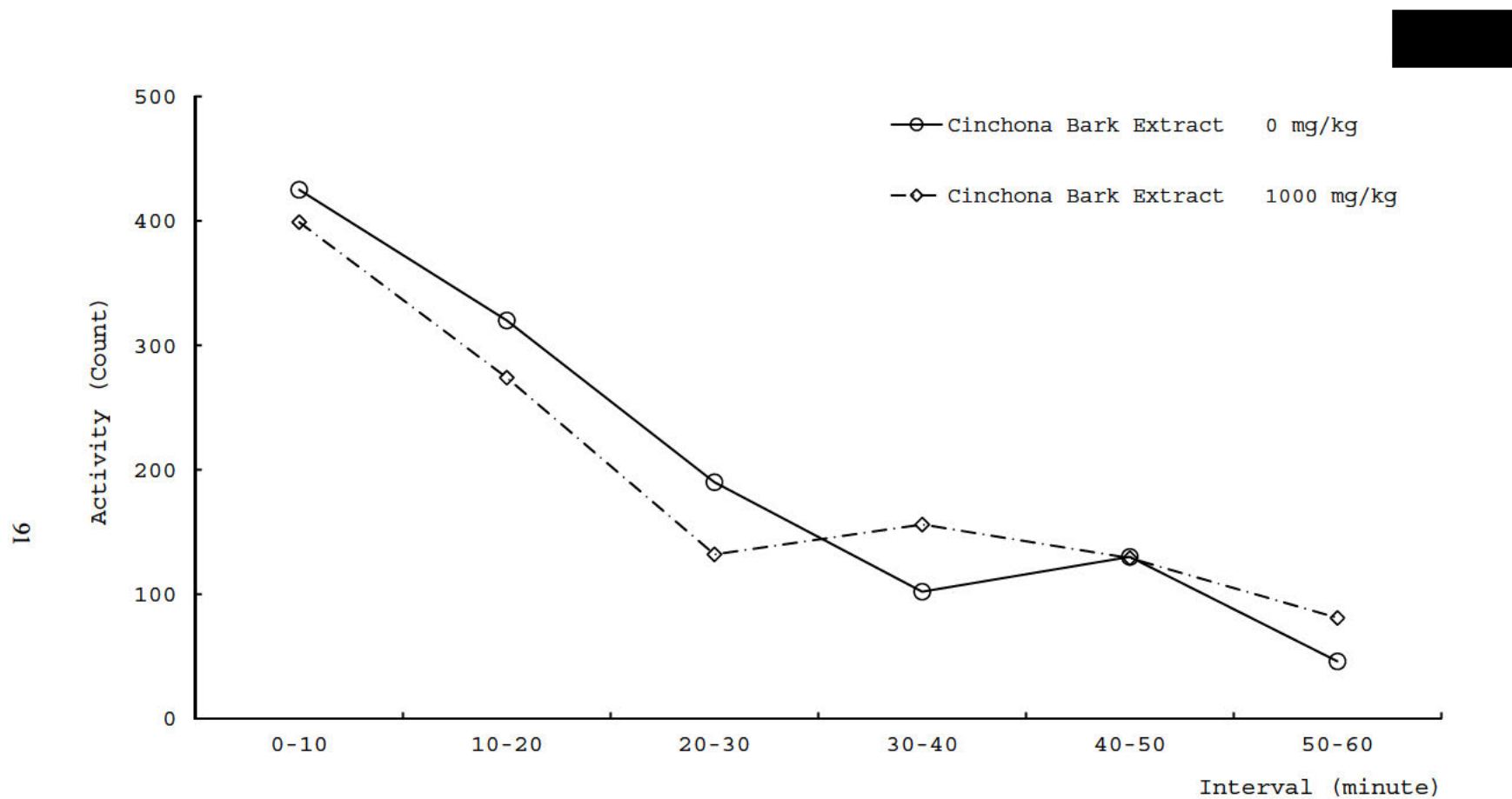


Fig.3 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Motor activity of female rats (Non-mating group, Week 6 of administration)



92

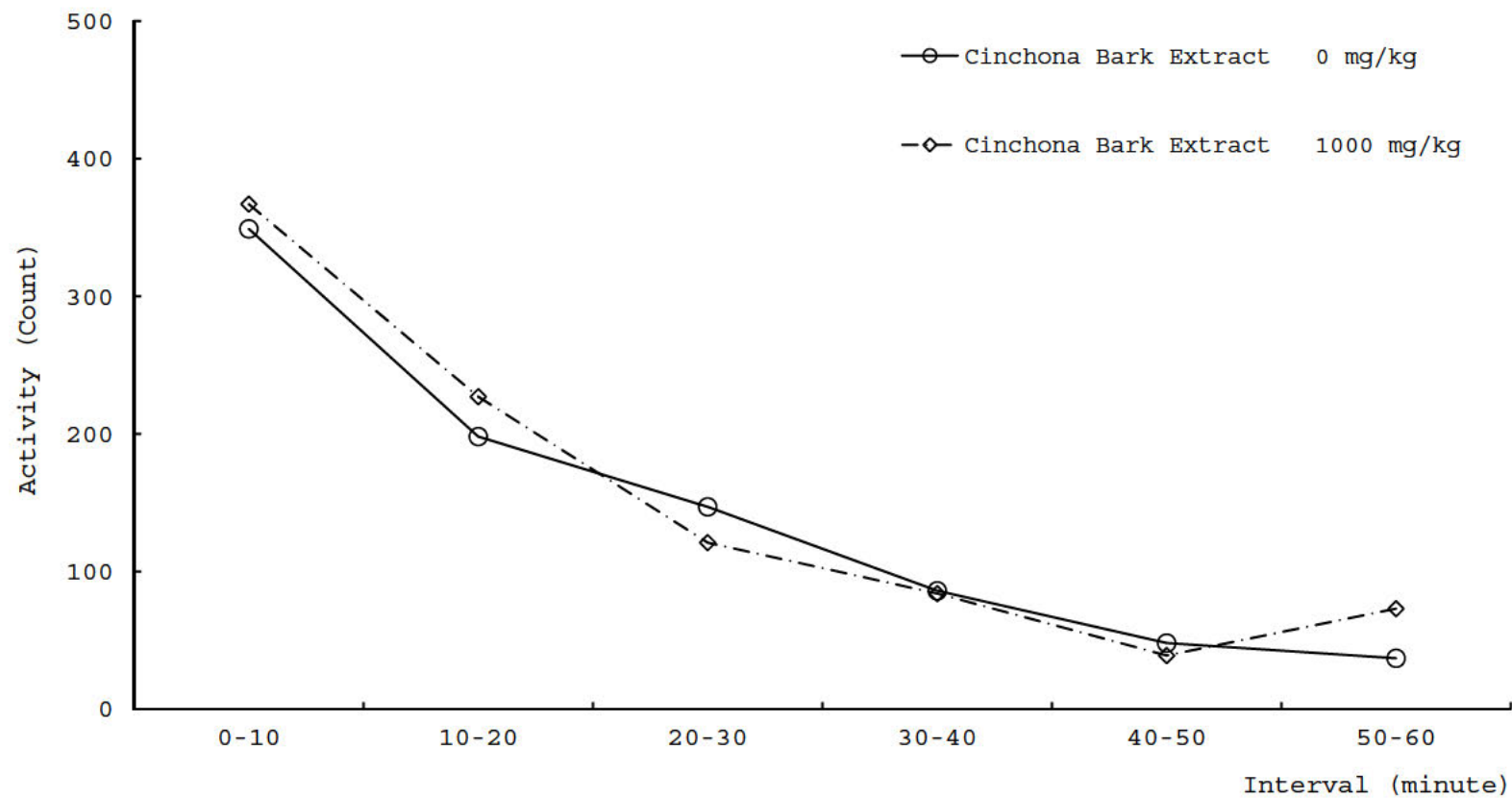


Fig.4 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Motor activity of male rats (Week 2 of recovery)

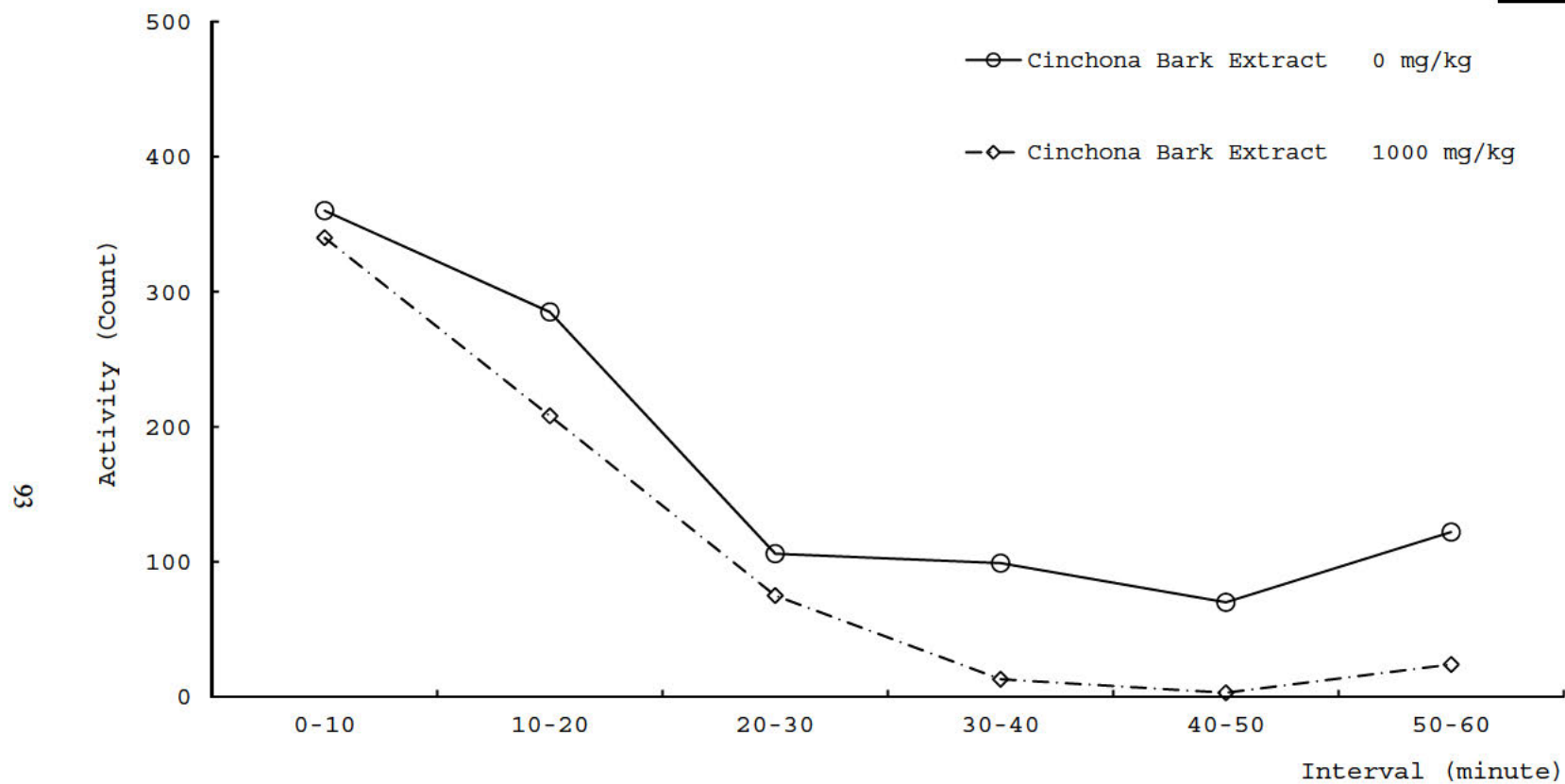


Fig.5 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Motor activity of female rats (Non-mating group, Week 2 of recovery)

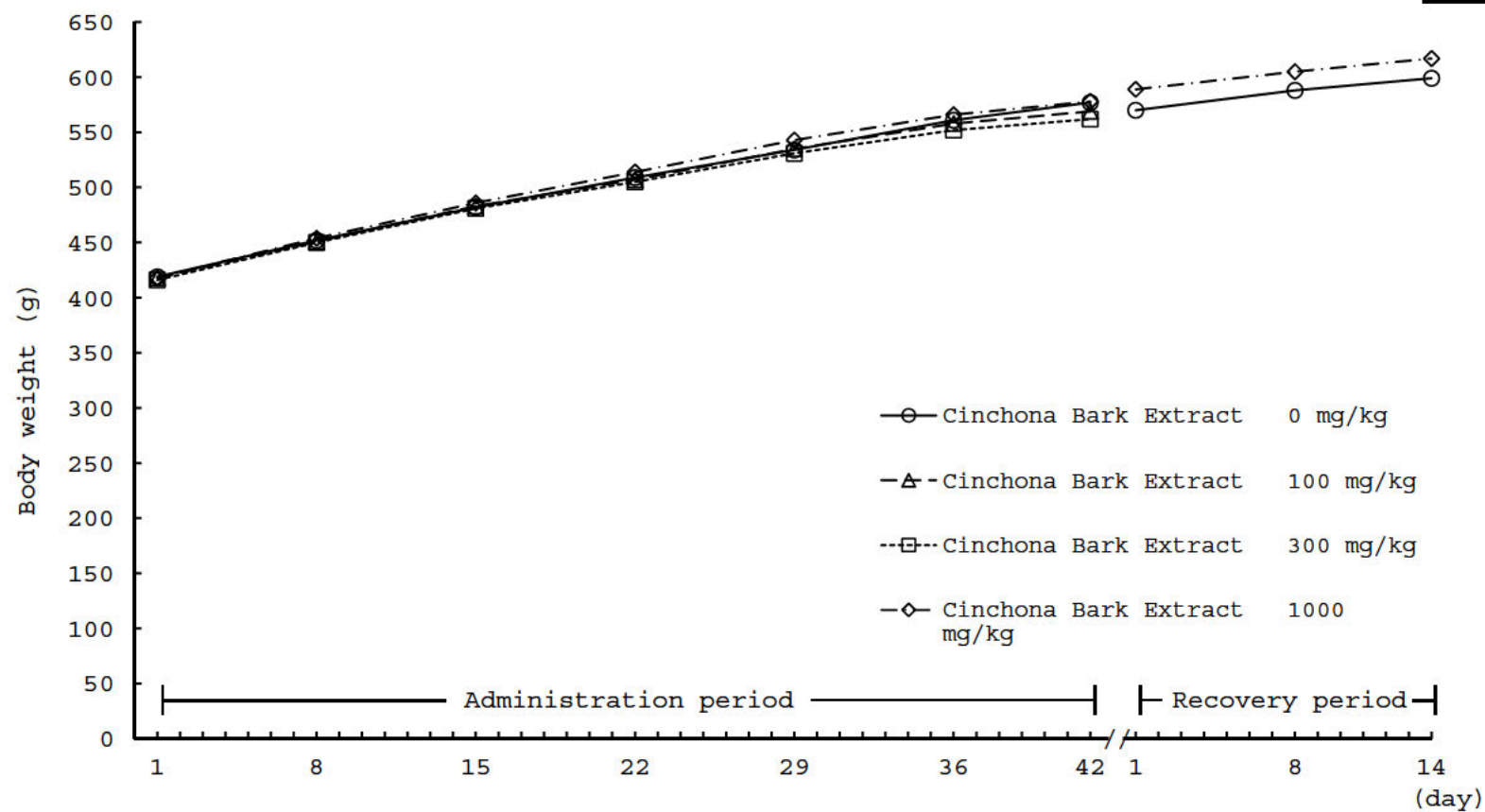


Fig.6 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Body weight of male rats

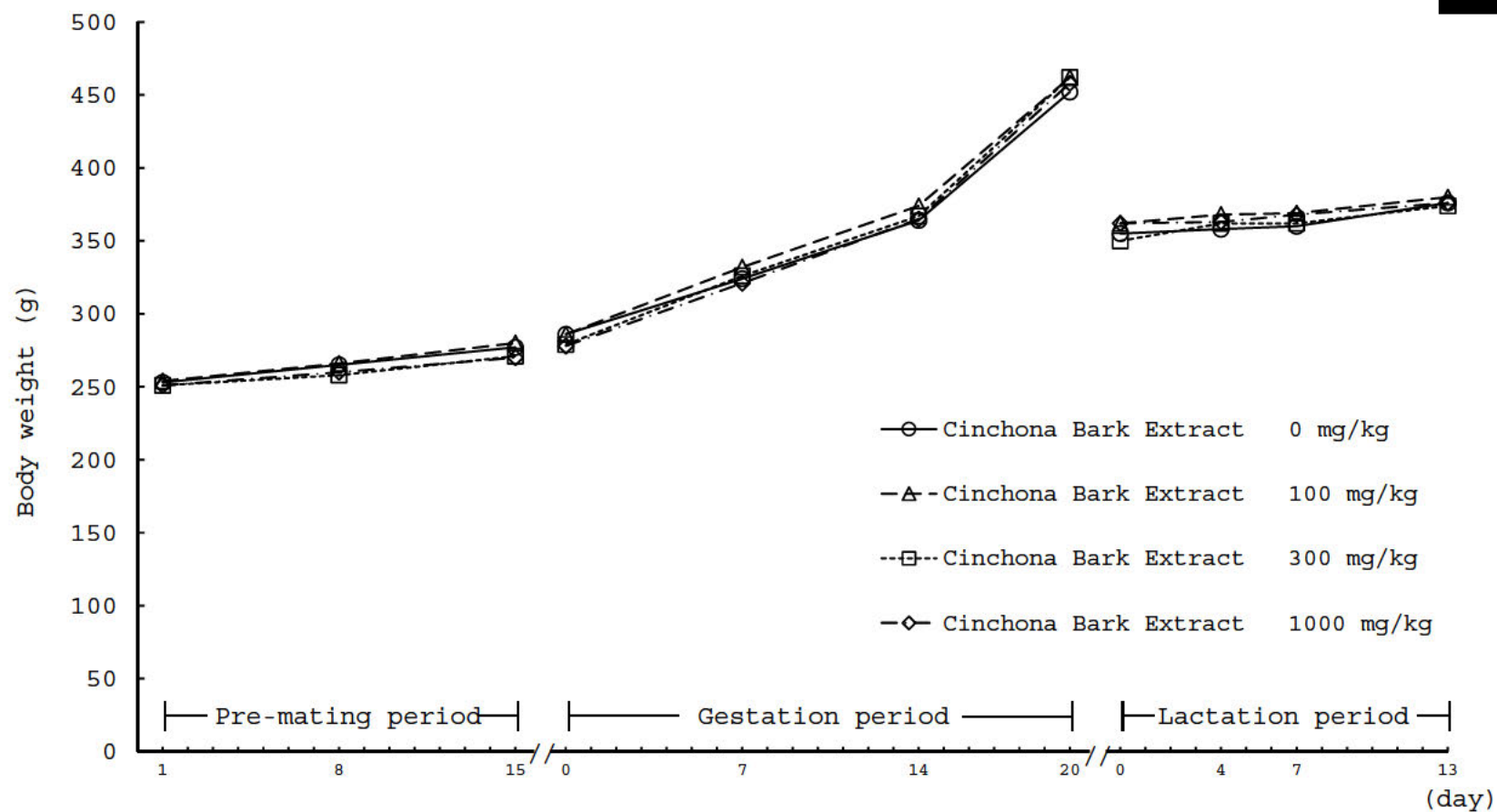


Fig.7 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Body weight of female rats (Main group)

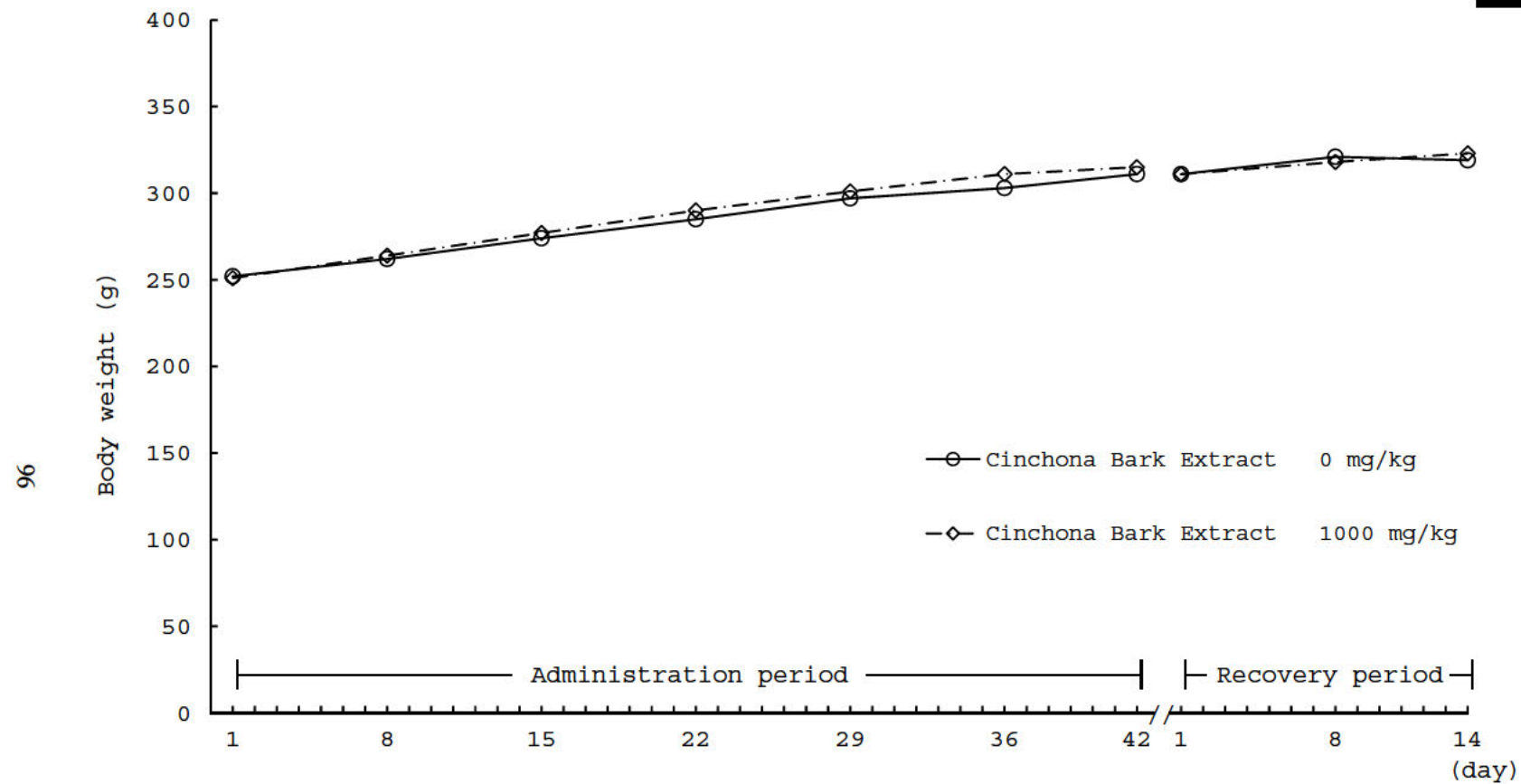


Fig.8 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Body weight of female rats (Non-mating group)

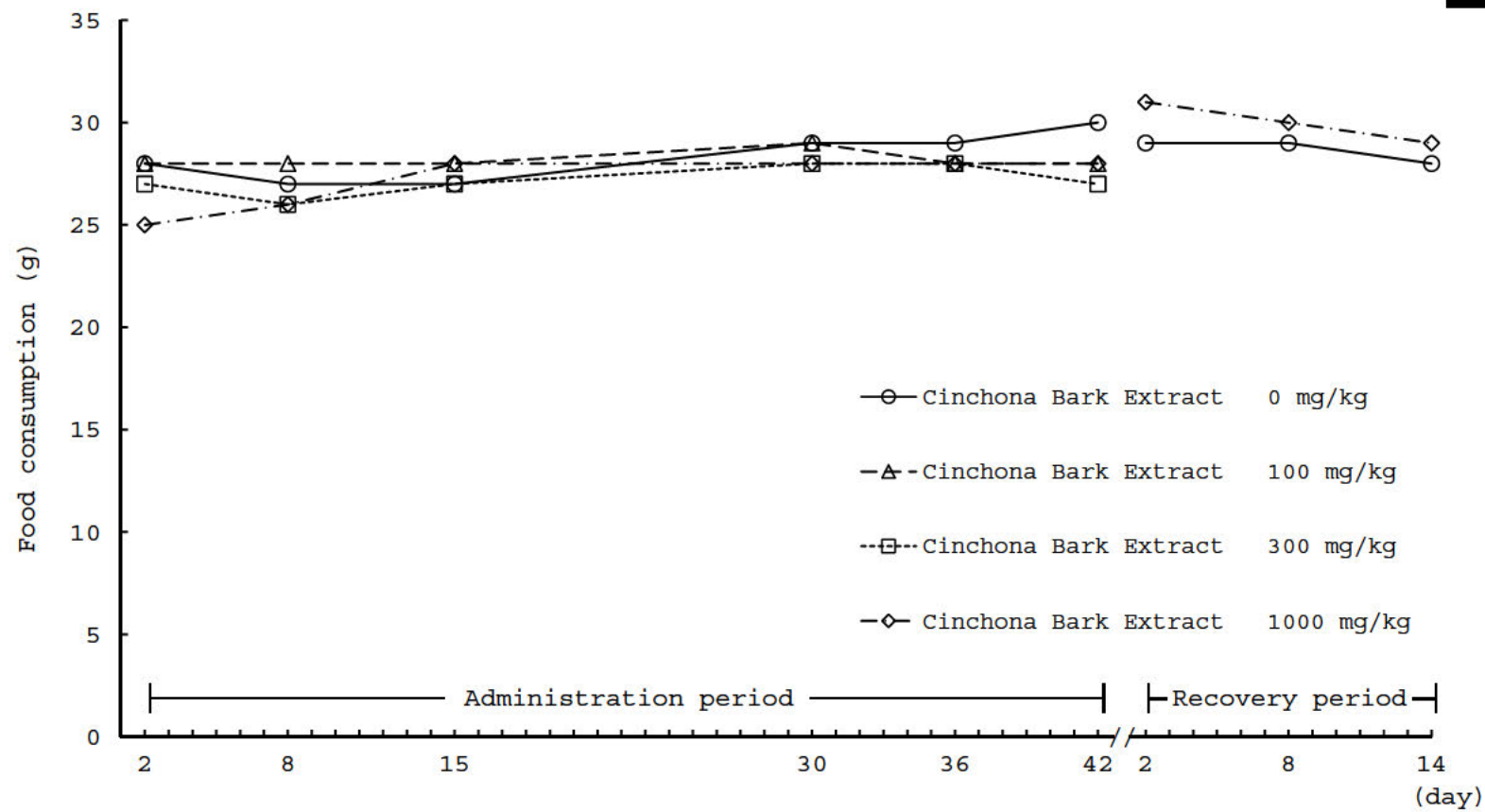


Fig.9 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Food consumption of male rats

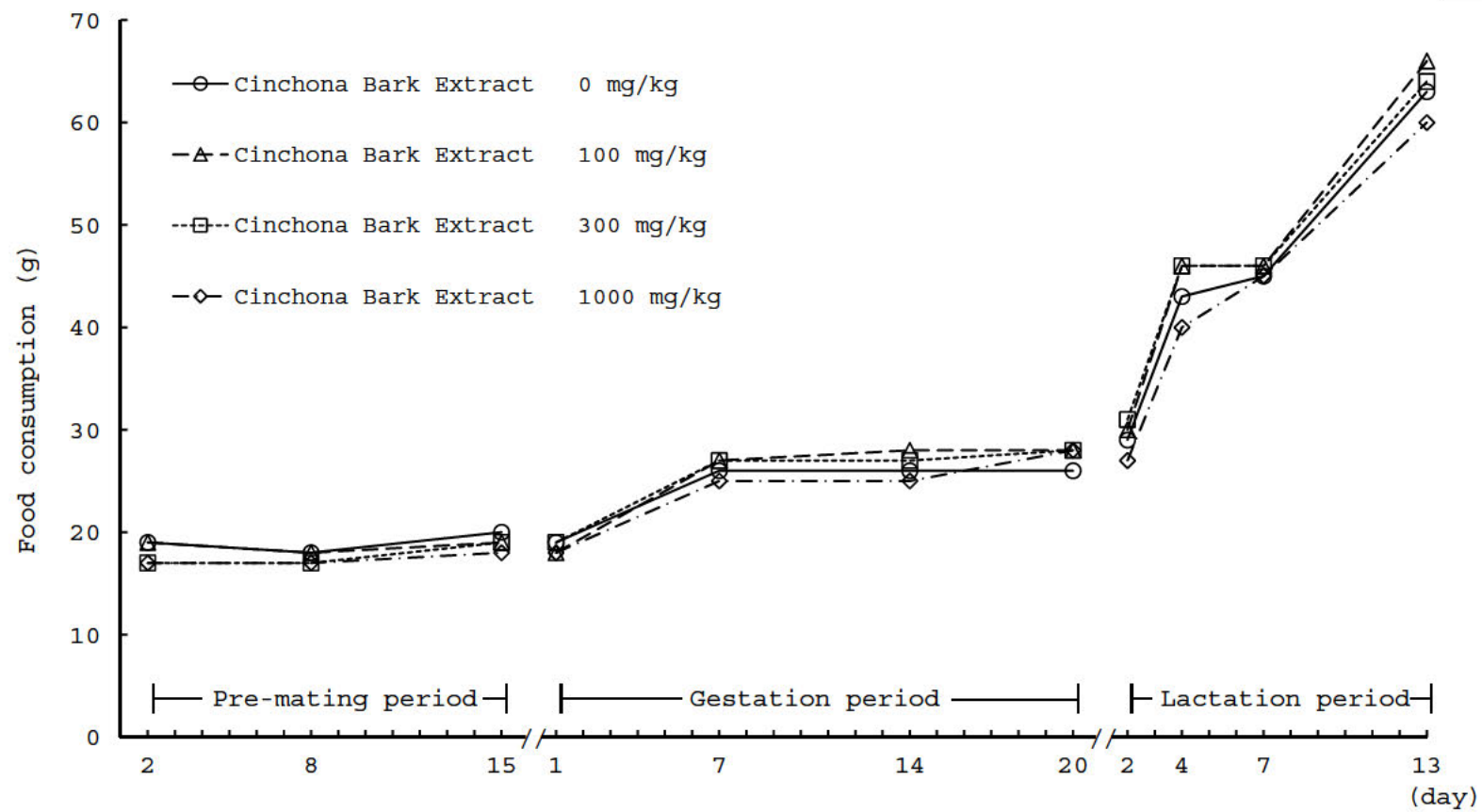


Fig.10 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Food consumption of female rats (Main group)

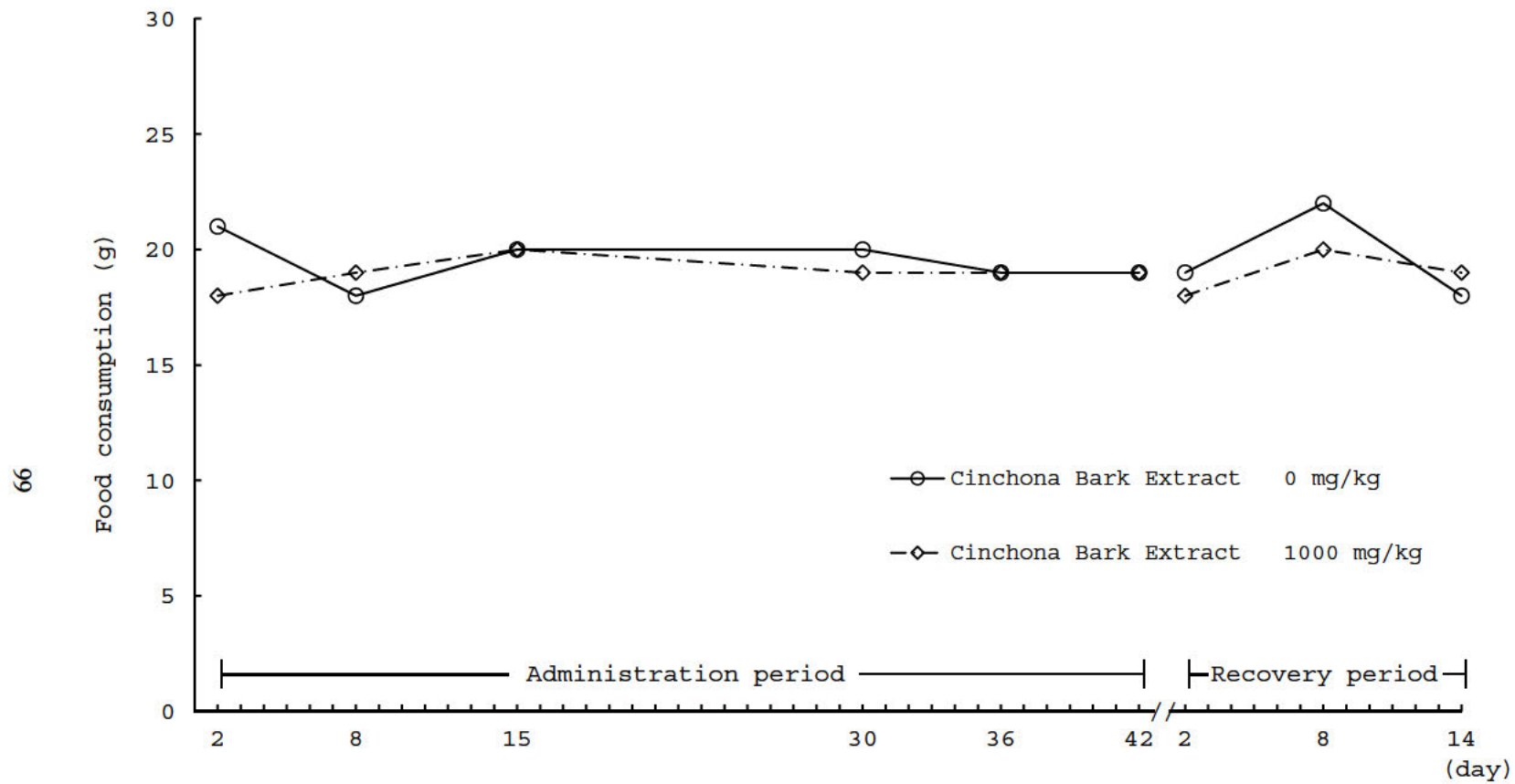


Fig.11 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Food consumption of female rats (Non-mating group)

Table 1-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Clinical signs

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : male

Species : Rat

		Species : Rat																												
		Sex : male																												
Test article Dose	Signs	/Day																												
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Cinchona Bark Extract 0 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 100 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 300 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 1000 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Clinical signs

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : male

Species : Rat

Test article		/Day															Species : Rat
Dose	Signs	30	31	32	33	34	35	36	37	38	39	40	41	42	43 a)		
Cinchona Bark Extract 0 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	7		
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Cinchona Bark Extract 100 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Cinchona Bark Extract 300 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Cinchona Bark Extract 1000 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	7		
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0		

a): Day of necropsy

Table 1-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

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
Cinchona Bark Extract 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
Cinchona Bark Extract 100 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
Cinchona Bark Extract 300 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
Cinchona Bark Extract 1000 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

Table 1-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Clinical signs

Period : F0 gestation Day 0-25

Sex : Female

Species : Rat

Sex : Female		Species : Rat																									
Test article		/Day																									
Dose	Signs	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Cinchona Bark Extract 0 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	0	0	0
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 100 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	0	0	0
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 300 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	0	0	0	0
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 1000 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	1	0	0	0
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Clinical signs

Period : F0 lactation Day 0-14

Sex : Female

Species : Rat

Test article		/Day														Species : Rat
Dose	Signs	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14 a)
Cinchona Bark Extract 0 mg/kg	Number of dams	5	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 100 mg/kg	Number of dams	7	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 300 mg/kg	Number of dams	10	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 1000 mg/kg	Number of dams	6	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a): Day of necropsy

Table 1-6		Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats																									Study No. : XXXXXXXXXX			
		Clinical signs																									Period : Administration Day 1-43 (non-mating group)			
		Sex : Female																									Species : Rat			
Test article		/Day																												
Dose	Signs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Cinchona Bark Extract 0 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	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract 1000 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	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 1-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Clinical signs

Period : Administration Day 1-43 (non-mating group)

Sex : Female

Species : Rat

Test article Dose	Signs	/Day													
		30	31	32	33	34	35	36	37	38	39	40	41	42	43 a)
Cinchona Bark Extract 0 mg/kg	Number of animals	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
Cinchona Bark Extract 1000 mg/kg	Number of animals	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

a): Day of necropsy

Table 1-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Male

Study No. : [REDACTED]

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	15 a)
Cinchona Bark Extract 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
Cinchona Bark Extract 1000 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 1-9

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Clinical signs

Period : Recovery Day 1-15 (non-mating group)

Sex : Female

Species : Rat

Test article Dose	Signs	/Day														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 a)
Cinchona Bark Extract 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
Cinchona Bark Extract 1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Home cage observation

Generation : F0 Sex : Male Week : 1 Period : F0 before mating

Study No. : [REDACTED]

Generation : F0		Sex : Male			Week : 1						Species : Rat	
		Posture NC			Convulsion NC							
Test article												
Dose		N	F	H	0	1	2	3				
Cinchona Bark Extract	n	12	0	0	12	0	0	0				
0 mg/kg												
Cinchona Bark Extract	n	12	0	0	12	0	0	0				
100 mg/kg												
Cinchona Bark Extract	n	12	0	0	12	0	0	0				
300 mg/kg												
Cinchona Bark Extract	n	12	0	0	12	0	0	0				
1000 mg/kg												
		Abnormal NC behavior										
Test article												
Dose		0	1	2	3							
Cinchona Bark Extract	n	12	0	0	0							
0 mg/kg												
Cinchona Bark Extract	n	12	0	0	0							
100 mg/kg												
Cinchona Bark Extract	n	12	0	0	0							
300 mg/kg												
Cinchona Bark Extract	n	12	0	0	0							
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Home cage observation

Generation : F0 Sex : Male Week : 2 Period : F0 before mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male			Week : 2						Species : Rat		
		Posture NC						Convulsion NC					
Test article													
Dose		N	F	H	0	1	2	3					
Cinchona Bark Extract	n	12	0	0	12	0	0	0					
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	12	0	0	0					
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	12	0	0	0					
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	12	0	0	0					
1000 mg/kg													
		Abnormal NC behavior											
Test article		0	1	2	3								
Dose													
Cinchona Bark Extract	n	12	0	0	0								
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	0								
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	0								
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	0								
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Male Week : 3 Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male	Week : 3	Convulsion NC					Species : Rat
		Posture NC							
Test article		N	F	H	0	1	2	3	
Dose									
Cinchona Bark Extract	n	12	0	0	12	0	0	0	
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	12	0	0	0	
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	12	0	0	0	
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	12	0	0	0	
1000 mg/kg									
Abnormal NC behavior									
Test article		0	1	2	3				
Dose									
Cinchona Bark Extract	n	12	0	0	0				
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0				
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0				
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0				
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Home cage observation

Generation : F0 Sex : Male Week : 4 Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male	Week : 4	Convulsion NC					Species : Rat
		Posture NC							
Test article		N	F	H	0	1	2	3	
Dose									
Cinchona Bark Extract	n	12	0	0	12	0	0	0	
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	12	0	0	0	
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	12	0	0	0	
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	12	0	0	0	
1000 mg/kg									
Abnormal NC behavior									
Test article		0	1	2	3				
Dose									
Cinchona Bark Extract	n	12	0	0	0				
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0				
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0				
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0				
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Male Week : 5 Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male	Week : 5	Convulsion NC					Species : Rat
		Posture NC							
Test article									
Dose		N	F	H	0	1	2	3	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
Abnormal NC behavior									
Test article									
Dose		0	1	2	3				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 1000 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 2-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Male Week : 6 Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male	Week : 6	Convulsion NC					Species : Rat
		Posture NC							
Test article									
Dose		N	F	H	0	1	2	3	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
Abnormal NC behavior									
Test article									
Dose		0	1	2	3				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 1000 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 2-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Female Week : 1 Period : F0 before mating

Study No. : [REDACTED]

Generation : F0		Sex : Female	Week : 1	Convulsion NC					Species : Rat
		Posture NC							
Test article		N	F	H	0	1	2	3	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
		Abnormal NC behavior							
Test article		0	1	2	3				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 1000 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 2-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Female Week : 2 Period : F0 before mating

Study No. : XXXXXXXXXX

Species : Rat

Test article	Dose	Posture NC			Convulsion NC			
		N	F	H	0	1	2	3
Cinchona Bark Extract	n	12	0	0	12	0	0	0
0 mg/kg								
Cinchona Bark Extract	n	12	0	0	12	0	0	0
100 mg/kg								
Cinchona Bark Extract	n	12	0	0	12	0	0	0
300 mg/kg								
Cinchona Bark Extract	n	12	0	0	12	0	0	0
1000 mg/kg								

Test article	n	Abnormal NC behavior			
		0	1	2	3
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0
Cinchona Bark Extract 1000 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 2-9

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Female Day : 1 Period : F0 gestation

Study No. : [REDACTED]

Species : Rat

Test article	Dose	Posture NC			Convulsion NC			
		N	F	H	0	1	2	3
Cinchona Bark Extract	n	12	0	0	12	0	0	0
0 mg/kg								
Cinchona Bark Extract	n	12	0	0	12	0	0	0
100 mg/kg								
Cinchona Bark Extract	n	12	0	0	12	0	0	0
300 mg/kg								
Cinchona Bark Extract	n	12	0	0	12	0	0	0
1000 mg/kg								

Test article	Dose	Abnormal NC behavior			
		0	1	2	3
Cinchona Bark Extract	n	12	0	0	0
0 mg/kg					
Cinchona Bark Extract	n	12	0	0	0
100 mg/kg					
Cinchona Bark Extract	n	12	0	0	0
300 mg/kg					
Cinchona Bark Extract	n	12	0	0	0
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Female Day : 7 Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 7		Convulsion NC				Species : Rat	
		Posture NC									
Test article											
Dose		N	F	H	0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0			
		Abnormal NC behavior									
Test article											
Dose		0	1	2	3						
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0						
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0						
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0						
Cinchona Bark Extract 1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Female Day : 14 Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female			Day : 14			Species : Rat			
		Posture NC			Convulsion NC						
Test article											
Dose		N	F	H	0	1	2	3			
Cinchona Bark Extract	n	12	0	0	12	0	0	0			
0 mg/kg											
Cinchona Bark Extract	n	12	0	0	12	0	0	0			
100 mg/kg											
Cinchona Bark Extract	n	12	0	0	12	0	0	0			
300 mg/kg											
Cinchona Bark Extract	n	12	0	0	12	0	0	0			
1000 mg/kg											
		Abnormal NC behavior									
Test article											
Dose		0	1	2	3						
Cinchona Bark Extract	n	12	0	0	0						
0 mg/kg											
Cinchona Bark Extract	n	12	0	0	0						
100 mg/kg											
Cinchona Bark Extract	n	12	0	0	0						
300 mg/kg											
Cinchona Bark Extract	n	12	0	0	0						
1000 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 2-12

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Home cage observation

Generation : F0 Sex : Female Day : 20 Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female	Day : 20	Convulsion NC					Species : Rat
		Posture NC							
Test article									
Dose		N	F	H	0	1	2	3	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
Abnormal NC behavior									
Test article									
Dose		0	1	2	3				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0				
Cinchona Bark Extract 1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Home cage observation Period : F0 lactation

Generation : F0 Sex : Female Day : 6

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 6		Convulsion NC				Species : Rat	
		Posture NC									
Test article											
Dose		N	F	H	0	1	2	3			
Cinchona Bark Extract	n	12	0	0	12	0	0	0			
0 mg/kg											
Cinchona Bark Extract	n	12	0	0	12	0	0	0			
100 mg/kg											
Cinchona Bark Extract	n	12	0	0	12	0	0	0			
300 mg/kg											
Cinchona Bark Extract	n	12	0	0	12	0	0	0			
1000 mg/kg											
Abnormal NC behavior											
Test article											
Dose		0	1	2	3						
Cinchona Bark Extract	n	12	0	0	0						
0 mg/kg											
Cinchona Bark Extract	n	12	0	0	0						
100 mg/kg											
Cinchona Bark Extract	n	12	0	0	0						
300 mg/kg											
Cinchona Bark Extract	n	12	0	0	0						
1000 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 2-14

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Home cage observation Period : F0 lactation

Generation : F0 Sex : Female Day : 13

Study No. : [REDACTED]

Generation : F0		Sex : Female			Day : 13							Species : Rat	
		Posture NC			Convulsion NC								
Test article													
Dose		N	F	H	0	1	2	3					
Cinchona Bark Extract	n	12	0	0	12	0	0	0					
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	12	0	0	0					
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	12	0	0	0					
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	12	0	0	0					
1000 mg/kg													
		Abnormal NC behavior											
Test article													
Dose		0	1	2	3								
Cinchona Bark Extract	n	12	0	0	0								
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	0								
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	0								
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	0								
1000 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 2-15

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Home cage observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female Week : 1

Species : Rat

		Posture NC				Convulsion NC				Species : Rat			
Test article													
Dose		N F H				0 1 2 3							
Cinchona Bark Extract	n	10	0	0		10	0	0	0				
0 mg/kg													
Cinchona Bark Extract	n	10	0	0		10	0	0	0				
1000 mg/kg													
		Abnormal NC behavior											
Test article													
Dose		0 1 2 3											
Cinchona Bark Extract	n	10	0	0		0							
0 mg/kg													
Cinchona Bark Extract	n	10	0	0		0							
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Species : Rat

		Posture NC			Convulsion NC						
Test article											
Dose		N	F	H	0	1	2	3			
Cinchona Bark Extract	n	10	0	0	10	0	0	0			
0 mg/kg											
Cinchona Bark Extract	n	10	0	0	10	0	0	0			
1000 mg/kg											
		Abnormal NC behavior									
Test article											
Dose		0	1	2	3						
Cinchona Bark Extract	n	10	0	0	0						
0 mg/kg											
Cinchona Bark Extract	n	10	0	0	0						
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female Week : 3

Species : Rat

		Posture NC				Convulsion NC							
Test article													
Dose		N F H				0 1 2 3							
Cinchona Bark Extract	n	10	0	0		10	0	0	0				
0 mg/kg													
Cinchona Bark Extract	n	10	0	0		10	0	0	0				
1000 mg/kg													
		Abnormal NC behavior											
Test article													
Dose		0 1 2 3											
Cinchona Bark Extract	n	10	0	0		0							
0 mg/kg													
Cinchona Bark Extract	n	10	0	0		0							
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female Week : 4

Species : Rat

		Posture NC				Convulsion NC			
Test article									
Dose		N	F	H		0	1	2	3
Cinchona Bark Extract	n	10	0	0		10	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	10	0	0		10	0	0	0
1000 mg/kg									
		Abnormal NC behavior							
Test article									
Dose		0	1	2	3				
Cinchona Bark Extract	n	10	0	0	0				
0 mg/kg									
Cinchona Bark Extract	n	10	0	0	0				
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Home cage observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female Week : 5

Species : Rat

		Posture NC				Convulsion NC			
Test article									
Dose		N	F	H		0	1	2	3
Cinchona Bark Extract	n	10	0	0		10	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	10	0	0		10	0	0	0
1000 mg/kg									
Abnormal NC behavior									
Test article									
Dose		0	1	2		3			
Cinchona Bark Extract	n	10	0	0		0			
0 mg/kg									
Cinchona Bark Extract	n	10	0	0		0			
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female Week : 6

Species : Rat

		Posture NC				Convulsion NC				Species : Rat			
Test article													
Dose		N F H				0 1 2 3							
Cinchona Bark Extract	n	10	0	0		10	0	0	0				
0 mg/kg													
Cinchona Bark Extract	n	10	0	0		10	0	0	0				
1000 mg/kg													
		Abnormal NC behavior											
Test article													
Dose		0 1 2 3											
Cinchona Bark Extract	n	10	0	0		0							
0 mg/kg													
Cinchona Bark Extract	n	10	0	0		0							
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Male Week : 1 Period : Recovery

Study No. : [REDACTED]

		Generation : F0		Sex : Male		Week : 1						Species : Rat			
		Posture NC				Convulsion NC									
Test article															
Dose															
Cinchona Bark Extract	n		N		F		H		0		1		2		3
0 mg/kg			5		0		0		5		0		0		0
Cinchona Bark Extract	n		5		0		0		5		0		0		0
1000 mg/kg															
		Abnormal NC behavior													
Test article															
Dose															
Cinchona Bark Extract	n		0		1		2		3						
0 mg/kg			5		0		0		0						
Cinchona Bark Extract	n		5		0		0		0						
1000 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 2-22

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Male Week : 2 Period : Recovery

Study No. : [REDACTED]

		Generation : F0		Sex : Male		Week : 2		Dose : 1000 mg/kg				Species : Rat					
		Posture NC				Convulsion NC											
Test article																	
Dose		N				F		H		0		1		2		3	
Cinchona Bark Extract		n	5	0	0	5	0	0	0	0	0	0	0	0	0	0	0
0 mg/kg																	
Cinchona Bark Extract		n	5	0	0	5	0	0	0	0	0	0	0	0	0	0	0
1000 mg/kg																	

Table 2-23

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Home cage observation Period : Recovery (non-mating group)

Study No. : XXXXXXXXXX

Home cage observation		Sex : Female Week : 1				Period : Recovery (non-mating group)				Species : Rat	
		Posture NC				Convulsion NC					
Test article											
Dose		N	F	H		0	1	2	3		
Cinchona Bark Extract 0 mg/kg	n	5	0	0		5	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	5	0	0		5	0	0	0		
		Abnormal NC behavior									
Test article											
Dose		0	1	2	3						
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0						
Cinchona Bark Extract 1000 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 2-24

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Home cage observation
 Generation : F0 Sex : Female Week : 2 Period : Recovery (non-mating group)

Study No. : [REDACTED]

		Generation : F0		Sex : Female		Week : 2		Cinchona Bark Extract (Non mating group)				Species : Rat	
		Posture NC				Convulsion NC							
Test article													
Dose													
Cinchona Bark Extract	n	5	0	0		5	0	0	0	0			
0 mg/kg													
Cinchona Bark Extract	n	5	0	0		5	0	0	0	0			
1000 mg/kg													

Table 2-25

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 before mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 1		Week : 2		Week : 3		Week : 4		Species : Rat	
		Ease of remov- NC al from cage						Fur condition NC					
Test article													
Dose		-1	0	1	2	3	0	1	2	3			
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	0			
0 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	0			
100 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	0			
300 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	0			
1000 mg/kg													
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC					
Test article		0	1	2	3	0	1	0	1				
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0				
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0				
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0				
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0				
1000 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													
Not calculated : NC													

Table 2-26

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 1						Species : Rat			
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC			
Test article													
Dose		0	1	2	3	0	1	2	3	0	1		
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Piloerection NC				Pupil size NC				Salivation NC					
Test article													
Dose		0	1	-1	0	1	2	0	1	2	3		
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
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													
Piloerection) 0: Absent, 1: Present													
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis													
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked													
Not calculated : NC													

Table 2-27

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Period : F0 before mating

Generation : F0 Sex : Male Week : 1

Study No. : [REDACTED]

Generation : F0		Sex : Male		Week : 1				Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	11	0	1	0
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
1000 mg/kg									
Reactivity to NC handling									
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract	n	0	12	0	0	0			
0 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
100 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
300 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
1000 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 2-28

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 before mating

Study No. : [REDACTED]

		Generation : F0		Sex : Male		Week : 2		Ease of remov- NC		Fur condition NC		Species : Rat	
								al from cage					
Test article	Dose												
		-1	0	1	2	3	0	1	2	3			
Cinchona Bark Extract	0 mg/kg	n	0	12	0	0	0	12	0	0	0		
Cinchona Bark Extract	100 mg/kg	n	0	12	0	0	0	12	0	0	0		
Cinchona Bark Extract	300 mg/kg	n	0	12	0	0	0	12	0	0	0		
Cinchona Bark Extract	1000 mg/kg	n	0	12	0	0	0	12	0	0	0		
Test article	Dose												
		0	1	2	3	0	1	0	1	0	1		
Cinchona Bark Extract	0 mg/kg	n	12	0	0	0	12	0	12	0			
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	12	0	12	0			
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	12	0	12	0			
Cinchona Bark Extract	1000 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: 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
Not calculated : NC

Table 2-29

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 2						Species : Rat	
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC	
Test article	Dose										
Cinchona Bark Extract	n	0	1	2	3	0	1	2	3	0	1
0 mg/kg		12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0
100 mg/kg											
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0
300 mg/kg											
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0
1000 mg/kg											
Piloerection NC				Pupil size NC				Salivation NC			
Test article	Dose										
Cinchona Bark Extract	n	0	1	-1	0	1	2	0	1	2	3
0 mg/kg		12	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract	n	12	0	0	12	0	0	12	0	0	0
100 mg/kg											
Cinchona Bark Extract	n	12	0	0	12	0	0	12	0	0	0
300 mg/kg											
Cinchona Bark Extract	n	12	0	0	12	0	0	12	0	0	0
1000 mg/kg											
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											
Piloerection) 0: Absent, 1: Present											
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis											
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked											
Not calculated : NC											

Table 2-30

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Generation : F0 Sex : Male Week : 2 Period : F0 before mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 2				Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
1000 mg/kg									
Reactivity to NC handling									
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract	n	0	12	0	0	0			
0 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
100 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
300 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
1000 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 2-31

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 mating
Generation : F0 Sex : Male Week : 3

Study No. : [REDACTED]

		Ease of removal- NC al from cage								Fur condition NC				Species : Rat	
Test article															
Dose		-1	0	1	2	3		0	1	2	3				
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0			
		Skin NC				Secretions- NC Eye, Nose				Exophthalmos NC					
Test article															
Dose		0	1	2	3	0	1	0		0	1				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0		12	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0		12	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0		12	0				
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	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: 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

Not calculated : NC

Table 2-32

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 3						Species : Rat			
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC			
Test article													
Dose		0	1	2	3	0	1	2	3	0	1		
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0		
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0		
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0		
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0		
1000 mg/kg													
Piloerection NC				Pupil size NC				Salivation NC					
Test article													
Dose		0	1	-1	0	1	2	0	1	2	3		
Cinchona Bark Extract	n	12	0	0	12	0	0	12	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	12	0	0	12	0	0	0		
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	12	0	0	12	0	0	0		
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	12	0	0	12	0	0	0		
1000 mg/kg													
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													
Piloerection) 0: Absent, 1: Present													
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis													
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked													
Not calculated : NC													

Table 2-33

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 3				Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
1000 mg/kg									
Reactivity to NC handling									
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract	n	0	12	0	0	0			
0 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
100 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
300 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
1000 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									

	In-the-hand observation	Sex : Male	Week : 4	Period : 10 mating	Species : Rat		
			Ease of removal from cage		Fur condition NC		
Test article							
Dose		-1	0	1	2	3	
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	0	12	0	0	0	
			Skin NC	Secretions- NC Eye, Nose	Exophthalmos NC		
Test article							
Dose		0	1	2	3	0	1
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	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: 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 Not calculated : NC							

Table 2-35

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation

Generation : F0	Sex : Male	Week : 4	Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 4						Species : Rat	
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC	
Test article											
Dose		0	1	2	3	0	1	2	3	0	1
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Piloerection NC				Pupil size NC				Salivation NC			
Test article		0	1	-1	0	1	2	0	1	2	3
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	12	0	0	0
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											
Piloerection) 0: Absent, 1: Present											
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis											
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked											
Not calculated : NC											

Table 2-36

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation

Generation : F0	Sex : Male	Week : 4	Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 4		Phase 1: Pre-mating		Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0
		Reactivity to NC handling							
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0			
Cinchona Bark Extract 1000 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 2-37

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 mating

Study No. : [REDACTED]

Generation : F0		Sex : Male		Week : 5				Species : Rat			
		Ease of remov- NC al from cage				Fur condition NC					
Test article											
Dose		-1	0	1	2	3	0	1	2	3	
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	0	
0 mg/kg											
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	0	
100 mg/kg											
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	0	
300 mg/kg											
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	0	
1000 mg/kg											
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC			
Test article		0	1	2	3	0	1	0	1		
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0		
0 mg/kg											
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0		
100 mg/kg											
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0		
300 mg/kg											
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0		
1000 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											
Not calculated : NC											

Table 2-38

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 5		Species : Rat						
		Palpebral NC closure				Mucosal NC membranes			Lacrimation NC			
Test article	Dose											
Cinchona Bark Extract	0 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract	1000 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Piloerection NC				Pupil size NC				Salivation NC				
Test article	Dose											
Cinchona Bark Extract	0 mg/kg	n	12	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract	100 mg/kg	n	12	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract	300 mg/kg	n	12	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract	1000 mg/kg	n	12	0	0	12	0	0	12	0	0	0
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												
Piloerection) 0: Absent, 1: Present												
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis												
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked												
Not calculated : NC												

Table 2-39

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 mating

Study No. : [REDACTED]

Generation : F0		Sex : Male		Week : 5				Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
1000 mg/kg									
Reactivity to NC handling									
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract	n	0	12	0	0	0			
0 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
100 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
300 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
1000 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 2-40

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 6				Fur condition NC				Species : Rat	
		Ease of remov- NC al from cage											
Test article													
Dose		-1	0	1	2	3		0	1	2	3		
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0	0		
100 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0	0		
300 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0	0		
1000 mg/kg													
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC					
Test article		0	1	2	3	0	1	0	1				
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0				
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0				
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0				
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	0	12	0	12	0				
1000 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													
Not calculated : NC													

Table 2-41

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 6		Species : Rat									
		Palpebral NC closure					Mucosal NC membranes					Lacrimation NC			
Test article															
Dose		0	1	2	3		0	1	2	3		0	1		
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	0	12	0	0	0	0	12	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	0	12	0	0	0	0	12	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	0	12	0	0	0	0	12	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	0	12	0	0	0	0	12	0	0	
Piloerection NC					Pupil size NC					Salivation NC					
Test article															
Dose		0	1		-1	0	1	2		0	1	2	3		
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0	12	0	0	0	0	
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															
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Not calculated : NC															

Table 2-42

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Generation : F0 Sex : Male Week : 6 Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 6				Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
1000 mg/kg									
Reactivity to NC handling									
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract	n	0	12	0	0	0			
0 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
100 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
300 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
1000 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 2-43

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 before mating
Generation : F0 Sex : Female Week : 1

Study No. : [REDACTED]

		Ease of remov- NC al from cage								Fur condition NC				Species : Rat
Test article														
Dose		-1	0	1	2	3	0	12	1	2	3	0		
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0		
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0		
		Skin NC				Secretions- NC Eye, Nose			Exophthalmos NC					
Test article														
Dose		0	1	2	3	0	1	0	0	1	0			
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	12	0	0			
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	12	0	0			
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	12	0	0			
Cinchona Bark Extract 1000 mg/kg	n	12	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: 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

Not calculated : NC

Table 2-44

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Generation : F0 Sex : Female Week : 1 Period : F0 before mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Week : 1						Species : Rat	
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC	
Test article											
Dose		0	1	2	3	0	1	2	3	0	1
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0	12	0
Piloerection NC				Pupil size NC				Salivation NC			
Test article											
Dose		0	1	-1	0	1	2	0	1	2	3
Cinchona Bark Extract 0 mg/kg	n	12	0		0	12	0	0	12	0	0
Cinchona Bark Extract 100 mg/kg	n	12	0		0	12	0	0	12	0	0
Cinchona Bark Extract 300 mg/kg	n	12	0		0	12	0	0	12	0	0
Cinchona Bark Extract 1000 mg/kg	n	12	0		0	12	0	0	12	0	0
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											
Piloerection) 0: Absent, 1: Present											
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis											
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked											
Not calculated : NC											

Table 2-45

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Generation : F0 Sex : Female Week : 1 Period : F0 before mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Week : 1		Cinchoa bark extract treatment		Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0
		Reactivity to NC handling							
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0			
Cinchona Bark Extract 1000 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 2-46

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 before mating

Study No. : XXXXXXXXXX

		Generation : F0	Sex : Female	Week : 2	Ease of removal from cage				Fur condition NC				Species : Rat
Test article	Dose				-1	0	1	2	3				
Cinchona Bark Extract	0 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0
Cinchona Bark Extract	100 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0
Cinchona Bark Extract	300 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0
Cinchona Bark Extract	1000 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC					
Test article	Dose				0	1	2	3			0	1	
Cinchona Bark Extract	0 mg/kg	n	12	0	0	0	0	12	0	12	0		
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	0	12	0	12	0		
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	0	12	0	12	0		
Cinchona Bark Extract	1000 mg/kg	n	12	0	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: 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													
Not calculated : NC													

Table 2-47

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation
Generation : F0 Sex : Female Week : 2 Period : F0 before mating

Study No. : [REDACTED]

Generation : F0		Sex : Female				Week : 2				Species : Rat					
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC					
Test article															
Dose		0	1	2	3	0	1	2	3	0	1				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	12	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	12	0				
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0	12	0				
				Piloerection NC				Pupil size NC				Salivation NC			
Test article															
Dose		0	1	-1	0	1	2	0	1	2	3				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	12	0	0	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	12	0	0	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	12	0	0	0				
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	12	0	0	0				
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															
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Not calculated : NC															

Table 2-48

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation
Generation : F0 Sex : Female Week : 2 Period : F0 before mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Week : 2				Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article	Dose								
		0	1	2	3	0	1	2	3
Cinchona Bark Extract	0 mg/kg	n	12	0	0	0	12	0	0
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	12	0	0
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	12	0	0
Cinchona Bark Extract	1000 mg/kg	n	12	0	0	0	12	0	0
		Reactivity to NC handling							
Test article	Dose								
		-1	0	1	2	3			
Cinchona Bark Extract	0 mg/kg	n	0	12	0	0	0		
Cinchona Bark Extract	100 mg/kg	n	0	12	0	0	0		
Cinchona Bark Extract	300 mg/kg	n	0	12	0	0	0		
Cinchona Bark Extract	1000 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 2-49

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 gestation
Generation : F0 Sex : Female Day : 1

Study No. : [REDACTED]

		Ease of removal NC al from cage								Fur condition NC				Species : Rat
Test article														
Dose		-1	0	1	2	3		0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	0	12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	0	12	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	0	12	0	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				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0		12		0			
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0		12		0			
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0		12		0			
Cinchona Bark Extract 1000 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: 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

Not calculated : NC

Table 2-50

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation
Generation : F0 Sex : Female Day : 1 Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female Day : 1					Species : Rat									
		Palpebral NC closure					Mucosal NC membranes					Lacrimation NC				
Test article	Dose															
Cinchona Bark Extract	0 mg/kg	n	0	1	2	3	0	0	1	2	3	0	0	1	0	
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	12	0	0	0	0	12	0			
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	12	0	0	0	0	12	0			
Cinchona Bark Extract	1000 mg/kg	n	12	0	0	0	12	0	0	0	0	12	0			
		Piloerection NC					Pupil size NC					Salivation NC				
Test article	Dose															
Cinchona Bark Extract	0 mg/kg	n	0	1	-1	0	1	2	0	0	1	2	3	0		
Cinchona Bark Extract	100 mg/kg	n	12	0	0	12	0	0	12	0	0	0	0			
Cinchona Bark Extract	300 mg/kg	n	12	0	0	12	0	0	12	0	0	0	0			
Cinchona Bark Extract	1000 mg/kg	n	12	0	0	12	0	0	12	0	0	0	0			
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																
Piloerection) 0: Absent, 1: Present																
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis																
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked																
Not calculated : NC																

Table 2-51

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation
Generation : F0 Sex : Female Day : 1 Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 1				Species : Rat	
		Abnormal NC respiration			Vocalization NC				
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
1000 mg/kg									
Reactivity to NC handling									
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract	n	0	12	0	0	0			
0 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
100 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
300 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
1000 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 2-52

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation
Generation : F0 Sex : Female Day : 7 Period : F0 gestation

Study No. : [REDACTED]

Generation : F0		Sex : Female		Day : 7		Ease of removal from cage		Fur condition NC		Species : Rat	
Test article	Dose	-1	0	1	2	3	0	1	2	3	0
Cinchona Bark Extract	0 mg/kg	n	0	12	0	0	0	12	0	0	0
Cinchona Bark Extract	100 mg/kg	n	0	12	0	0	0	12	0	0	0
Cinchona Bark Extract	300 mg/kg	n	0	12	0	0	0	12	0	0	0
Cinchona Bark Extract	1000 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		
Cinchona Bark Extract	0 mg/kg	n	12	0	0	0	12	0	12	0	
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	12	0	12	0	
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	12	0	12	0	
Cinchona Bark Extract	1000 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: 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											
Not calculated : NC											

Table 2-53

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 7		Species : Rat									
		Palpebral NC closure					Mucosal NC membranes					Lacrimation NC			
Test article															
Dose		0	1	2	3	0	1	2	3	0	1	0			
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	12	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	12	0				
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0	12	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				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	12	0	0	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	12	0	0	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	12	0	0	0				
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	12	0	0	0				
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															
Piloerection) 0: Absent, 1: Present															
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis															
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked															
Not calculated : NC															

Table 2-54

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

In-the-hand observation

Period : F0 gestation

Generation : F0

Sex : Female Day : 7

Species : Rat

		Abnormal NC respiration					Vocalization NC				
Test article		0	1	2	3		0	1	2	3	
Dose											
Cinchona Bark Extract	n	12	0	0	0		12	0	0	0	
0 mg/kg											
Cinchona Bark Extract	n	12	0	0	0		12	0	0	0	
100 mg/kg											
Cinchona Bark Extract	n	12	0	0	0		12	0	0	0	
300 mg/kg											
Cinchona Bark Extract	n	12	0	0	0		12	0	0	0	
1000 mg/kg											
		Reactivity to NC handling									
Test article		-1	0	1	2	3					
Dose											
Cinchona Bark Extract	n	0	12	0	0	0					
0 mg/kg											
Cinchona Bark Extract	n	0	12	0	0	0					
100 mg/kg											
Cinchona Bark Extract	n	0	12	0	0	0					
300 mg/kg											
Cinchona Bark Extract	n	0	12	0	0	0					
1000 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 2-55

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation
Generation : F0 Sex : Female Day : 14 Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 14		Ease of removal from cage		Fur condition NC		Species : Rat	
Test article	Dose	-1	0	1	2	3	0	1	2	3	0
Cinchona Bark Extract	0 mg/kg	n	0	12	0	0	0	12	0	0	0
Cinchona Bark Extract	100 mg/kg	n	0	12	0	0	0	12	0	0	0
Cinchona Bark Extract	300 mg/kg	n	0	12	0	0	0	12	0	0	0
Cinchona Bark Extract	1000 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		
Cinchona Bark Extract	0 mg/kg	n	12	0	0	0	12	0	12	0	
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	12	0	12	0	
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	12	0	12	0	
Cinchona Bark Extract	1000 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: 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											
Not calculated : NC											

Table 2-56

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation
Generation : F0 Sex : Female Day : 14 Period : F0 gestation

Study No. : XXXXXXXXXX

		Palpebral NC closure					Mucosal NC membranes					Lacrimation NC		
Test article														
Dose		0	1	2	3		0	1	2	3		0	1	
Cinchona Bark Extract	n	12	0	0	0	0	12	0	0	0	0	12	0	0
0 mg/kg														
Cinchona Bark Extract	n	12	0	0	0	0	12	0	0	0	0	12	0	0
100 mg/kg														
Cinchona Bark Extract	n	12	0	0	0	0	12	0	0	0	0	12	0	0
300 mg/kg														
Cinchona Bark Extract	n	12	0	0	0	0	12	0	0	0	0	12	0	0
1000 mg/kg														
		Piloerection NC			Pupil size NC				Salivation NC					
Test article														
Dose		0	1		-1	0	1	2	0	1	2	3		
Cinchona Bark Extract	n	12	0	0	0	12	0	0	12	0	0	0	0	0
0 mg/kg														
Cinchona Bark Extract	n	12	0	0	0	12	0	0	12	0	0	0	0	0
100 mg/kg														
Cinchona Bark Extract	n	12	0	0	0	12	0	0	12	0	0	0	0	0
300 mg/kg														
Cinchona Bark Extract	n	12	0	0	0	12	0	0	12	0	0	0	0	0
1000 mg/kg														

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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis

Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked

Not calculated : NC

Table 2-57

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation
Generation : F0 Sex : Female Day : 14 Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 14				Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
1000 mg/kg									
		Reactivity to NC handling							
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract	n	0	12	0	0	0			
0 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
100 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
300 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
1000 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 2-58

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Period : F0 gestation

Generation : F0 Sex : Female Day : 20

Species : Rat

Study No. : [REDACTED]

		Ease of removal from cage						Fur condition NC				
Test article												
Dose		-1	0	1	2	3		0	1	2	3	
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	0	12	0	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			
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	12	0			
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	12	0			
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	12	0			
Cinchona Bark Extract 1000 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: 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

Not calculated : NC

Table 2-59

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 20						Species : Rat			
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC			
Test article													
Dose		0	1	2	3	0	1	2	3	0	1		
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Piloerection NC				Pupil size NC				Salivation NC					
Test article													
Dose		0	1	-1	0	1	2	0	1	2	3		
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
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													
Piloerection) 0: Absent, 1: Present													
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis													
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked													
Not calculated : NC													

Table 2-60

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Generation : F0 Sex : Female Day : 20 Period : F0 gestation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 20				Species : Rat	
		Abnormal NC respiration				Vocalization NC			
Test article									
Dose		0	1	2	3	0	1	2	3
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
100 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
300 mg/kg									
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0
1000 mg/kg									
Reactivity to NC handling									
Test article									
Dose		-1	0	1	2	3			
Cinchona Bark Extract	n	0	12	0	0	0			
0 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
100 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
300 mg/kg									
Cinchona Bark Extract	n	0	12	0	0	0			
1000 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 2-61

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Period : F0 lactation

Generation : F0 Sex : Female Day : 6

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 6		Ease of remov- NC al from cage								Fur condition NC				Species : Rat			
Test article	Dose	-1				0				1				2				3			
Cinchona Bark Extract	0 mg/kg	n	0	12	0	0	0	0	0	12	0	0	0	0	0						
Cinchona Bark Extract	100 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0	0	0						
Cinchona Bark Extract	300 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0	0	0						
Cinchona Bark Extract	1000 mg/kg	n	0	12	0	0	0	0	12	0	0	0	0	0	0						
		Skin NC				Secretions- NC Eye, Nose				Exophthalmos NC											
Test article	Dose	0				1				2				3							
Cinchona Bark Extract	0 mg/kg	n	12	0	0	0	0	12	0	12	0	12	0	0	0						
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	0	12	0	12	0	12	0	0	0						
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	0	12	0	12	0	12	0	0	0						
Cinchona Bark Extract	1000 mg/kg	n	12	0	0	0	0	12	0	12	0	12	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																					
Not calculated : NC																					

Table 2-62

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 lactation

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 6		Species : Rat					
		Palpebral NC closure			Mucosal NC membranes			Lacrimation NC			
Test article	Dose	0	1	2	3	0	1	2	3	0	1
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0
0 mg/kg											
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0
100 mg/kg											
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0
300 mg/kg											
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	12	0
1000 mg/kg											
		Piloerection NC			Pupil size NC			Salivation NC			
Test article	Dose	0	1	-1	0	1	2	0	1	2	3
Cinchona Bark Extract	n	12	0		0	12	0	0	12	0	0
0 mg/kg											
Cinchona Bark Extract	n	12	0		0	12	0	0	12	0	0
100 mg/kg											
Cinchona Bark Extract	n	12	0		0	12	0	0	12	0	0
300 mg/kg											
Cinchona Bark Extract	n	12	0		0	12	0	0	12	0	0
1000 mg/kg											
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											
Piloerection) 0: Absent, 1: Present											
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis											
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked											
Not calculated : NC											

Table 2-63

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Period : F0 lactation

Generation : F0 Sex : Female Day : 6

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 6		Species : Rat				
		Abnormal NC respiration				Vocalization NC				
Test article										
Dose		0	1	2	3	0	1	2	3	
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	
0 mg/kg										
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	
100 mg/kg										
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	
300 mg/kg										
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0	
1000 mg/kg										
		Reactivity to NC handling								
Test article										
Dose		-1	0	1	2	3				
Cinchona Bark Extract	n	0	12	0	0	0				
0 mg/kg										
Cinchona Bark Extract	n	0	12	0	0	0				
100 mg/kg										
Cinchona Bark Extract	n	0	12	0	0	0				
300 mg/kg										
Cinchona Bark Extract	n	0	12	0	0	0				
1000 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 2-64

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Period : F0 lactation

Generation : F0 Sex : Female Day : 13

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female		Day : 13		Species : Rat					
		Ease of remov- NC al from cage						Fur condition NC			
Test article											
Dose		-1	0	1	2	3	0	1	2	3	0
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0	0	0
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0	0	0
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	0	12	0	0	0	12	0	0	0	0
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC			
Test article											
Dose		0	1	2	3	0	1	0	1	0	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	12	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	12	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	12	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	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: 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 Not calculated : NC											

Table 2-65

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : F0 lactation

Study No. : [REDACTED]

Generation : F0		Sex : Female		Day : 13		Piloerection NC		Pupil size NC		Salivation NC		Species : Rat	
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC			
Test article													
Dose		0	1	2	3	0	1	2	3	0	1		
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	0	0	12	0		
		Piloerection NC				Pupil size NC				Salivation NC			
Test article		0	1	-1	0	1	2	0	1	2	3		
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	12	0	0	0		
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													
Piloerection) 0: Absent, 1: Present													
Pupil size) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis													
Salivation) 0: None, 1: Slight, 2: Moderate, 3: Marked													
Not calculated : NC													

Table 2-66

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation

Period : F0 lactation

Generation : F0 Sex : Female Day : 13

Study No. : [REDACTED]

Generation : F0		Sex : Female		Day : 13							Species : Rat	
		Abnormal NC respiration					Vocalization NC					
Test article												
Dose		0	1	2	3	0	1	2	3			
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0			
0 mg/kg												
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0			
100 mg/kg												
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0			
300 mg/kg												
Cinchona Bark Extract	n	12	0	0	0	12	0	0	0			
1000 mg/kg												
		Reactivity to NC handling										
Test article												
Dose		-1	0	1	2	3						
Cinchona Bark Extract	n	0	12	0	0	0						
0 mg/kg												
Cinchona Bark Extract	n	0	12	0	0	0						
100 mg/kg												
Cinchona Bark Extract	n	0	12	0	0	0						
300 mg/kg												
Cinchona Bark Extract	n	0	12	0	0	0						
1000 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 2-67

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 1

Study No. : [REDACTED]

		Ease of removal- NC al from cage								Fur condition NC								Species : Rat
Test article																		
Dose		-1	0	1	2	3	0	10	1	2	3	0	10	1	2	3	0	
Cinchona Bark Extract	n	0	10	0	0	0	0	10	0	0	0	10	0	0	0	0	0	
0 mg/kg																		
Cinchona Bark Extract	n	0	10	0	0	0	0	10	0	0	0	10	0	0	0	0	0	
1000 mg/kg																		
		Skin NC								Secretions- NC Eye, Nose				Exophthalmos NC				
Test article																		
Dose		0	1	2	3	0	10	1	0	0	10	1	0	0	10	1	0	
Cinchona Bark Extract	n	10	0	0	0	0	10	0	0	10	0	0	10	0	0	0	0	
0 mg/kg																		
Cinchona Bark Extract	n	10	0	0	0	0	10	0	0	10	0	0	10	0	0	0	0	
1000 mg/kg																		
		Palpebral NC closure								Mucosal NC membranes				Lacrimation NC				
Test article																		
Dose		0	1	2	3	0	10	1	0	2	3	0	10	1	0	10	1	0
Cinchona Bark Extract	n	10	0	0	0	0	10	0	0	0	0	0	10	0	0	10	0	0
0 mg/kg																		
Cinchona Bark Extract	n	10	0	0	0	0	10	0	0	0	0	0	10	0	0	10	0	0
1000 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 2-68

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 1

Study No. : [REDACTED]

		Piloerection NC					Pupil size NC					Salivation NC				
Test article																
Dose		0	1		-1	0	1	2		0	1	2	3			
Cinchona Bark Extract	n	10	0		0	10	0	0		10	0	0	0			
0 mg/kg																
Cinchona Bark Extract	n	10	0		0	10	0	0		10	0	0	0			
1000 mg/kg																
		Abnormal NC respiration					Vocalization NC									
Test article																
Dose		0	1	2	3		0	1	2	3						
Cinchona Bark Extract	n	10	0	0	0		10	0	0	0						
0 mg/kg																
Cinchona Bark Extract	n	10	0	0	0		10	0	0	0						
1000 mg/kg																
		Reactivity to NC handling														
Test article																
Dose		-1	0	1	2	3										
Cinchona Bark Extract	n	0	10	0	0	0										
0 mg/kg																
Cinchona Bark Extract	n	0	10	0	0	0										
1000 mg/kg																

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)

Study No. : XXXXXXXXXX

		Generation : F0		Sex : Female		Week : 2		Fur condition Administration (non mating group)		Species : Rat		
		Ease of removal from cage NC						Fur condition NC				
Test article												
Dose												
Cinchona Bark Extract	n	-1	0	10	0	0	0	0	10	0	0	0
0 mg/kg												
Cinchona Bark Extract	n	0	10	0	0	0	0	10	0	0	0	
1000 mg/kg												
		Skin NC				Secretions- NC Eye, Nose		Exophthalmos NC				
Test article												
Dose												
Cinchona Bark Extract	n	0	1	2	3	0	0	1	0	0	1	0
0 mg/kg												
Cinchona Bark Extract	n	10	0	0	0	10	0	10	0			
1000 mg/kg												
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC		
Test article												
Dose												
Cinchona Bark Extract	n	0	1	2	3	0	1	2	3	0	1	0
0 mg/kg												
Cinchona Bark Extract	n	10	0	0	0	10	0	0	0	10	0	
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 2

Study No. : [REDACTED]

		Generation : F0		Sex : Female		Week : 2		Piloerection NC					Pupil size NC					Salivation NC					Species : Rat	
Test article																								
Dose																								
Cinchona Bark Extract	n	0	10	1	0	-1	0	0	10	1	0	2	0	0	10	1	0	2	0	3	0			
0 mg/kg																								
Cinchona Bark Extract	n	10	0	0	0	10	0	0	0	10	0	0	0	10	0	0	0	0	0					
1000 mg/kg																								
Abnormal NC respiration											Vocalization NC													
Test article																								
Dose																								
Cinchona Bark Extract	n	0	10	1	0	2	0	3	0	0	10	1	0	2	0	3	0							
0 mg/kg																								
Cinchona Bark Extract	n	10	0	0	0	0	10	0	0	0	10	0	0	0	0									
1000 mg/kg																								
Reactivity to NC handling																								
Test article																								
Dose																								
Cinchona Bark Extract	n	-1	0	10	1	0	2	0	3	0														
0 mg/kg																								
Cinchona Bark Extract	n	0	10	0	0	0	0																	
1000 mg/kg																								

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 3

Study No. : XXXXXXXXXX

		Generation : F0		Sex : Female		Week : 3		Cinchona Administration (non-mating group)								Species : Rat	
		Ease of removal- NC al from cage								Fur condition NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	-1	0	10	0	0	0	0	0	10	0	0	0	0			
0 mg/kg																	
Cinchona Bark Extract	n	0	10	0	0	0	0	10	0	0	0	0	0	0			
1000 mg/kg																	
		Skin NC				Secretions- NC Eye, Nose				Exophthalmos NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	0	1	2	3	0	0	10	1	0	0	1	0	0			
0 mg/kg																	
Cinchona Bark Extract	n	10	0	0	0	10	0	10	0	10	0	0	0	0			
1000 mg/kg																	
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	0	1	2	3	0	1	2	3	0	1	0	0	0			
0 mg/kg																	
Cinchona Bark Extract	n	10	0	0	0	10	0	0	0	10	0	0	0	0			
1000 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 2-72

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 3

Study No. : XXXXXXXXXX

		Generation : F0		Sex : Female		Week : 3		Cinchona Administration (non-mating group)										Species : Rat	
		Piloerection NC				Pupil size NC				Salivation NC									
Test article																			
Dose		0 1				-1 0 1 2				0 1 2 3									
Cinchona Bark Extract	n	10 0				0 10 0 0				10 0 0 0									
0 mg/kg																			
Cinchona Bark Extract	n	10 0				0 10 0 0				10 0 0 0									
1000 mg/kg																			
		Abnormal NC respiration								Vocalization NC									
Test article																			
Dose		0 1 2 3								0 1 2 3									
Cinchona Bark Extract	n	10 0 0 0								10 0 0 0									
0 mg/kg																			
Cinchona Bark Extract	n	10 0 0 0								10 0 0 0									
1000 mg/kg																			
		Reactivity to NC handling																	
Test article																			
Dose		-1 0 1 2 3																	
Cinchona Bark Extract	n	0 10 0 0 0																	
0 mg/kg																			
Cinchona Bark Extract	n	0 10 0 0 0																	
1000 mg/kg																			

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 4

Study No. : [REDACTED]

		Generation : F0		Sex : Female		Week : 4		Postnatal Administration (non mating group)				Species : Rat					
		Ease of removal- NC al from cage								Fur condition NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	-1	0	10	0	0	0	3	0	0	10	0	2	0	3	0	
0 mg/kg																	
Cinchona Bark Extract	n	0	10	0	0	0	0	0	10	0	0	0	0	0	0	0	
1000 mg/kg																	
		Skin NC				Secretions- NC Eye, Nose				Exophthalmos NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	0	1	2	3	0	0	0	10	1	0	0	1	0	0	0	
0 mg/kg																	
Cinchona Bark Extract	n	10	0	0	0	0	10	0	10	0	10	0	0	0	0	0	
1000 mg/kg																	
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	0	1	2	3	0	0	10	0	0	0	3	0	0	10	1	0
0 mg/kg																	
Cinchona Bark Extract	n	10	0	0	0	0	10	0	0	0	0	0	0	10	0	0	0
1000 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 2-74

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 4

Study No. : XXXXXXXXXX

		Generation : F0				Sex : Female				Week : 4				Species : Rat			
		Piloerection NC				Pupil size NC				Salivation NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	0	10	0	0	0	10	0	0	0	10	0	0	0	0		
0 mg/kg																	
Cinchona Bark Extract	n	10	0	0	0	10	0	0	0	10	0	0	0				
1000 mg/kg																	
		Abnormal NC respiration								Vocalization NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	0	10	0	0	0	0	0	0	10	0	0	0	0	0		
0 mg/kg																	
Cinchona Bark Extract	n	10	0	0	0	0	10	0	0	0	0	0					
1000 mg/kg																	
		Reactivity to NC handling															
Test article																	
Dose																	
Cinchona Bark Extract	n	-1	0	10	0	0	0	0	0								
0 mg/kg																	
Cinchona Bark Extract	n	0	10	0	0	0	0										
1000 mg/kg																	

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 5

Study No. : [REDACTED]

		Ease of removal- NC al from cage								Fur condition NC							
Test article																	
Dose																	
		-1	0	1	2	3	0	10	0	1	2	3	0	10	0	0	0
Cinchona Bark Extract	n																
0 mg/kg																	
Cinchona Bark Extract	n																
1000 mg/kg																	
		Skin NC					Secretions- NC Eye, Nose			Exophthalmos NC							
Test article																	
Dose		0	1	2	3	0	0	1	0	0	1	0					
Cinchona Bark Extract	n																
0 mg/kg																	
Cinchona Bark Extract	n																
1000 mg/kg																	
		Palpebral NC closure					Mucosal NC membranes					Lacrimation NC					
Test article																	
Dose		0	1	2	3	0	0	1	2	3	0	0	1	0			
Cinchona Bark Extract	n																
0 mg/kg																	
Cinchona Bark Extract	n																
1000 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 2-76

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 5

Study No. : [REDACTED]

		Piloerection NC					Pupil size NC					Salivation NC				
Test article																
Dose		0	1		-1	0	1	2		0	1	2	3			
Cinchona Bark Extract	n	10	0		0	10	0	0		10	0	0	0			
0 mg/kg																
Cinchona Bark Extract	n	10	0		0	10	0	0		10	0	0	0			
1000 mg/kg																
		Abnormal NC respiration					Vocalization NC									
Test article																
Dose		0	1	2	3		0	1	2	3						
Cinchona Bark Extract	n	10	0	0	0		10	0	0	0						
0 mg/kg																
Cinchona Bark Extract	n	10	0	0	0		10	0	0	0						
1000 mg/kg																
		Reactivity to NC handling														
Test article																
Dose		-1	0	1	2	3										
Cinchona Bark Extract	n	0	10	0	0	0										
0 mg/kg																
Cinchona Bark Extract	n	0	10	0	0	0										
1000 mg/kg																

Piloerection) 0: Absent, 1: Present
 Pupil size) -1: Miosis, 0: Normal, 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 6

Study No. : [REDACTED]

		Generation : F0		Sex : Female		Week : 6		Fur condition NC				Species : Rat					
		Ease of removal- NC al from cage															
Test article																	
Dose																	
Cinchona Bark Extract	n	-1	0	10	0	0	0	3	0	0	10	0	0	0			
0 mg/kg																	
Cinchona Bark Extract	n		0	10	0	0	0	0	0	10	0	0	0	0			
1000 mg/kg																	
		Skin NC				Secretions- NC Eye, Nose				Exophthalmos NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	0	1	2	3	0	0	10	1	0	0	10	1	0			
0 mg/kg																	
Cinchona Bark Extract	n		10	0	0	0	0	10	0	0	10	0	0	0			
1000 mg/kg																	
		Palpebral NC closure				Mucosal NC membranes				Lacrimation NC							
Test article																	
Dose																	
Cinchona Bark Extract	n	0	1	2	3	0	0	10	1	0	0	3	0	0	10	1	0
0 mg/kg																	
Cinchona Bark Extract	n		10	0	0	0	0	10	0	0	0	0	0	0	10	0	0
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 6

Study No. : [REDACTED]

		Generation : F0		Sex : Female		Week : 6		Cinchona Administration (non-mating group)										Species : Rat	
		Piloerection NC				Pupil size NC				Salivation NC									
Test article																			
Dose		0 1				-1 0 1 2				0 1 2 3									
Cinchona Bark Extract	n	10	0	0	0	10	0	0	0	10	0	0	0	0	0	0			
0 mg/kg																			
Cinchona Bark Extract	n	10	0	0	0	10	0	0	0	10	0	0	0	0	0	0			
1000 mg/kg																			
		Abnormal NC respiration								Vocalization NC									
Test article																			
Dose		0 1 2 3								0 1 2 3									
Cinchona Bark Extract	n	10	0	0	0	0	10	0	0	0	0	0	0	0	0	0			
0 mg/kg																			
Cinchona Bark Extract	n	10	0	0	0	0	10	0	0	0	0	0	0	0	0	0			
1000 mg/kg																			
		Reactivity to NC handling																	
Test article																			
Dose		-1 0 1 2 3																	
Cinchona Bark Extract	n	0	10	0	0	0	0	0	0										
0 mg/kg																			
Cinchona Bark Extract	n	0	10	0	0	0	0	0	0										
1000 mg/kg																			

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Recovery
Generation : F0 Sex : Male Week : 1

Study No. : [REDACTED]

		Ease of removal- NC al from cage					Fur condition NC					Species : Rat	
Test article													
Dose		-1	0	1	2	3	0	1	2	3			
Cinchona Bark Extract	n	0	5	0	0	0	5	0	0	0			
0 mg/kg													
Cinchona Bark Extract	n	0	5	0	0	0	5	0	0	0			
1000 mg/kg													
		Skin NC					Secretions- NC Eye, Nose			Exophthalmos NC			
Test article													
Dose		0	1	2	3		0	1		0	1		
Cinchona Bark Extract	n	5	0	0	0		5	0		5	0		
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0		5	0		5	0		
1000 mg/kg													
		Palpebral NC closure					Mucosal NC membranes					Lacrimation NC	
Test article													
Dose		0	1	2	3		0	1	2	3		0	1
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0		5	0
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0		5	0
1000 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Recovery

Study No. : XXXXXXXXXX

		Piloerection NC					Pupil size NC					Salivation NC				
Test article																
Dose		0	1		-1	0	1	2		0	1	2	3			
Cinchona Bark Extract	n	5	0		0	5	0	0		5	0	0	0			
0 mg/kg																
Cinchona Bark Extract	n	5	0		0	5	0	0		5	0	0	0			
1000 mg/kg																
		Abnormal NC respiration					Vocalization NC									
Test article																
Dose		0	1	2	3		0	1	2	3						
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0						
0 mg/kg																
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0						
1000 mg/kg																
		Reactivity to NC handling														
Test article																
Dose		-1	0	1	2	3										
Cinchona Bark Extract	n	0	5	0	0	0										
0 mg/kg																
Cinchona Bark Extract	n	0	5	0	0	0										
1000 mg/kg																

Piloerection) 0: Absent, 1: Present
Pupil size) -1: Miosis, 0: Normal, 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Recovery

Study No. : XXXXXXXXXX

		Generation : F0	Sex : Male	Week : 2					Period : Recovery					Species : Rat												
		Ease of removal from cage NC										Fur condition NC														
Test article	Dose	-1					0					1					2					3				
Cinchona Bark Extract	0 mg/kg	n	0	5	0	0	0	0	0	0	5	0	0	0	0	0	0									
Cinchona Bark Extract	1000 mg/kg	n	0	5	0	0	0	0	5	0	0	0	0	0	0	0	0									
		Skin NC					Secretions- NC Eye, Nose					Exophthalmos NC														
Test article	Dose	0					1					2					3									
Cinchona Bark Extract	0 mg/kg	n	5	0	0	0	0	5	0	0	5	0	0	5	0	0	0									
Cinchona Bark Extract	1000 mg/kg	n	5	0	0	0	5	0	5	0	5	0	0	0	0	0	0									
		Palpebral NC closure					Mucosal NC membranes					Lacrimation NC														
Test article	Dose	0					1					2					3									
Cinchona Bark Extract	0 mg/kg	n	5	0	0	0	5	0	0	0	0	0	0	0	5	0	0									
Cinchona Bark Extract	1000 mg/kg	n	5	0	0	0	5	0	0	0	0	0	0	5	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 2-82

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

In-the-hand observation	Period : Recovery

Study No. : [REDACTED]

Generation : F0		Sex : Male	Week : 2	Species : Rat									
		Piloerection NC				Pupil size NC				Salivation NC			
Test article													
Dose													
Cinchona Bark Extract	n	0	1	-1	0	1	2	0	0	1	2	3	
0 mg/kg		5	0	0	5	0	0	5	0	0	0	0	
Cinchona Bark Extract	n	5	0	0	5	0	0	5	0	0	0	0	
1000 mg/kg													
		Abnormal NC respiration				Vocalization NC							
Test article													
Dose													
Cinchona Bark Extract	n	0	1	2	3	0	1	2	3	0			
0 mg/kg		5	0	0	0	5	0	0	0	0			
Cinchona Bark Extract	n	5	0	0	0	5	0	0	0	0			
1000 mg/kg													
		Reactivity to NC handling											
Test article													
Dose													
Cinchona Bark Extract	n	-1	0	1	2	3	0						
0 mg/kg		0	5	0	0	0	0						
Cinchona Bark Extract	n	0	5	0	0	0	0						
1000 mg/kg													
Piloerection) 0: Absent, 1: Present													
Pupil size) -1: Miosis, 0: Normal, 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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Recovery (non-mating group)
Generation : F0 Sex : Female Week : 1

Study No. : [REDACTED]

		Generation : F0		Sex : Female		Week : 1		Fur condition recovery (non mating group)		Species : Rat								
		Ease of removal- NC al from cage						Fur condition NC										
Test article																		
Dose																		
Cinchona Bark Extract	n	-1	0	5	1	0	2	0	3	0	0	5	1	0	2	0	3	0
0 mg/kg																		
Cinchona Bark Extract	n		0	5	0	0	0	0	5	0	0	0	0	0	0	0	0	0
1000 mg/kg																		
		Skin NC						Secretions- NC Eye, Nose				Exophthalmos NC						
Test article																		
Dose																		
Cinchona Bark Extract	n	0	1	2	3	0	0	5	1	0	0	5	1	0				
0 mg/kg																		
Cinchona Bark Extract	n	5	0	0	0	5	0	5	0			5	0					
1000 mg/kg																		
		Palpebral NC closure						Mucosal NC membranes				Lacrimation NC						
Test article																		
Dose																		
Cinchona Bark Extract	n	0	1	2	3	0	0	5	1	2	3	0	0	5	1	0		
0 mg/kg																		
Cinchona Bark Extract	n	5	0	0	0	5	0	0	0	0	0	0	5	0				
1000 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 2-84

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Recovery (non-mating group)
Generation : F0 Sex : Female Week : 1

Study No. : [REDACTED]

		Piloerection NC					Pupil size NC					Salivation NC				
Test article																
Dose		0	1		-1	0	1	2		0	1	2	3			
Cinchona Bark Extract	n	5	0		0	5	0	0		5	0	0	0			
0 mg/kg																
Cinchona Bark Extract	n	5	0		0	5	0	0		5	0	0	0			
1000 mg/kg																
		Abnormal NC respiration					Vocalization NC									
Test article																
Dose		0	1	2	3		0	1	2	3						
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0						
0 mg/kg																
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0						
1000 mg/kg																
		Reactivity to NC handling														
Test article																
Dose		-1	0	1	2	3										
Cinchona Bark Extract	n	0	5	0	0	0										
0 mg/kg																
Cinchona Bark Extract	n	0	5	0	0	0										
1000 mg/kg																

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 2-85

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Recovery (non-mating group)
Generation : F0 Sex : Female Week : 2

Study No. : [REDACTED]

		Ease of removal- NC al from cage					Fur condition NC					Species : Rat	
Test article													
Dose		-1	0	1	2	3	0	1	2	3			
Cinchona Bark Extract	n	0	5	0	0	0	5	0	0	0			
0 mg/kg													
Cinchona Bark Extract	n	0	5	0	0	0	5	0	0	0			
1000 mg/kg													
		Skin NC					Secretions- NC Eye, Nose			Exophthalmos NC			
Test article													
Dose		0	1	2	3		0	1		0	1		
Cinchona Bark Extract	n	5	0	0	0		5	0		5	0		
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0		5	0		5	0		
1000 mg/kg													
		Palpebral NC closure					Mucosal NC membranes					Lacrimation NC	
Test article													
Dose		0	1	2	3		0	1	2	3		0	1
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0		5	0
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0		5	0
1000 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 2-86

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
In-the-hand observation Period : Recovery (non-mating group)
Generation : F0 Sex : Female Week : 2

Study No. : XXXXXXXXXX

		Piloerection NC					Pupil size NC					Salivation NC				
Test article																
Dose		0	1		-1	0	1	2		0	1	2	3			
Cinchona Bark Extract	n	5	0		0	5	0	0		5	0	0	0			
0 mg/kg																
Cinchona Bark Extract	n	5	0		0	5	0	0		5	0	0	0			
1000 mg/kg																
		Abnormal NC respiration					Vocalization NC									
Test article																
Dose		0	1	2	3		0	1	2	3						
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0						
0 mg/kg																
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0						
1000 mg/kg																
		Reactivity to NC handling														
Test article																
Dose		-1	0	1	2	3										
Cinchona Bark Extract	n	0	5	0	0	0										
0 mg/kg																
Cinchona Bark Extract	n	0	5	0	0	0										
1000 mg/kg																

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 2-87

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Female PVE before mating

Species : Rat

Study No. : XXXXXXXXXX

Generation 1: F0		Sex 1: Male					Sex 2: Female					Arousal NC					Convulsion NC					Species 1: Rat																	
Test article	Dose																																						
		-2					-1					0					1					2					3												
Cinchona Bark Extract	0 mg/kg	n	0	0	0	12	0	0	0	0	12	0	0	0	0	12	0	0	0	0	0	0																	
Cinchona Bark Extract	100 mg/kg	n	0	0	0	12	0	0	0	0	12	0	0	0	0	12	0	0	0	0	0	0																	
Cinchona Bark Extract	300 mg/kg	n	0	0	0	12	0	0	0	0	12	0	0	0	0	12	0	0	0	0	0	0																	
Cinchona Bark Extract	1000 mg/kg	n	0	0	0	12	0	0	0	0	12	0	0	0	0	12	0	0	0	0	0	0																	
Abnormal NC behavior												Stereotypy NC																											
Test article	Dose																																						
		0					1					2					3					0					1					2					3		
Cinchona Bark Extract	0 mg/kg	n	12	0	0	0	0	0	0	12	0	0	0	0	12	0	0	0	0	0	0	0																	
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	0	0	0	12	0	0	0	0	12	0	0	0	0	0	0	0																	
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	0	0	0	12	0	0	0	0	12	0	0	0	0	0	0	0																	
Cinchona Bark Extract	1000 mg/kg	n	12	0	0	0	0	0	0	12	0	0	0	0	12	0	0	0	0	0	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

Not calculated : NC

Table 2-88

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Male Week : 1 Period : F0 before mating

Study No. : XXXXXXXXXX

Cinchona bark extract		Gait NC					Posture NC		
Test article									
Dose		U	0	1	2	3	N	F	H
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	11	1	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
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 2-89

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Male Week : 1 Period : F0 before mating

Study No. : XXXXXXXXXX

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	3	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	5	0	
	S.D.	1	0	
		DT **		
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	3	0	
	S.D.	1	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	

Significantly different from Cinchona Bark Extract 0 mg/kg : ** P<0.01
DT : Dunnett test (two-side)

Table 2-90

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Male Week : 2 Period : F0 before mating

Study No. :

Generation : F0		Sex : Male		Week : 2		Species : Rat				
		Arousal NC				Convulsion NC				
Test article										
Dose		-2	-1	0	1	2	0	1	2	3
Cinchona Bark Extract 0 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 100 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 300 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	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 Not calculated : NC										

Table 2-91

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Male Week : 2 Period : F0 before mating

Study No. : XXXXXXXXXX

Cinchona bark extract		Gait NC					Posture NC		
Test article									
Dose		U	0	1	2	3	N	F	H
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	11	1	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	11	1	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	11	1	0	0	
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 2-92

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Male Week : 2 Period : F0 before mating

Study No. : [REDACTED]

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	3	0	
	S.D.	1	1	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	5	0	
	S.D.	2	0	
		DT *		
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	3	0	
	S.D.	2	1	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	5	0	
	S.D.	2	0	

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05

DT : Dunnett test (two-side)

Table 2-93

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Male Week : 3 Period : F0 mating

Study No. : XXXXXXXXXX

Generation : F0		Sex : Male		Week : 3						Species : Rat			
		Arousal NC						Convulsion NC					
Test article													
Dose		-2	-1	0	1	2		0	1	2	3		
Cinchona Bark Extract 0 mg/kg	n	0	0	12	0	0		12	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	0	0	12	0	0		12	0	0	0		
Cinchona Bark Extract 300 mg/kg	n	0	0	12	0	0		12	0	0	0		
Cinchona Bark Extract 1000 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				
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0				
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0				
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0				
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	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 Not calculated : NC													

Table 2-94

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Male Week : 3 Period : F0 mating

Study No. : [REDACTED]

Cinchona bark extract		Gait NC					Posture NC		
Test article									
Dose		U	0	1	2	3	N	F	H
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
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 2-95

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Male Week : 3 Period : F0 mating

Study No. : XXXXXXXXXX

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	3	0	
	S.D.	1	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-96

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation Period : F0 mating
Generation : F0 Sex : Male Week : 4

Study No. : XXXXXXXXXX

		Arousal NC						Convulsion NC						Species : Rat
Test article														
Dose		-2	-1	0	1	2		0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 1000 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			
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0			12	0	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
 Not calculated : NC

Table 2-97

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Male Week : 4 Period : F0 mating

Study No. : [REDACTED]

Generation : F0		Sex : Male		Week : 4				Posture NC				Species : Rat	
		Gait NC											
Test article													
Dose		U	0	1	2	3		N	F	H			
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
0 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
100 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
300 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
1000 mg/kg													
Grooming NC						Urination NC							
Test article													
Dose		0	1	2		0	1	2	3				
Cinchona Bark Extract	n	12	0	0		12	0	0	0				
0 mg/kg													
Cinchona Bark Extract	n	12	0	0		12	0	0	0				
100 mg/kg													
Cinchona Bark Extract	n	12	0	0		11	1	0	0				
300 mg/kg													
Cinchona Bark Extract	n	12	0	0		12	0	0	0				
1000 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 2-98

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Male Week : 4 Period : F0 mating

Study No. : [REDACTED]

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	1	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	3	0	
	S.D.	1	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-99

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Male Week : 5 Period : F0 mating

Study No. : [REDACTED]

		Arousal NC						Convulsion NC						Species : Rat
Test article														
Dose		-2	-1	0	1	2		0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	0	0	12	0	0	0	12	0	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	0	0	12	0	0	0	12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	0	0	12	0	0	0	12	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	0	0	12	0	0	0	12	0	0	0			
		Abnormal NC behavior						Stereotypy NC						
Test article														
Dose		0	1	2	3			0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	0	0	12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	0	0	12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	0	0	12	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	0	0	12	0	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
Not calculated : NC

Table 2-100

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Male Week : 5 Period : F0 mating

Study No. : [REDACTED]

Generation : F0		Sex : Male		Week : 5				Posture NC				Species : Rat	
		Gait NC											
Test article													
Dose		U	0	1	2	3		N	F	H			
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
0 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
100 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
300 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
1000 mg/kg													
Grooming NC						Urination NC							
Test article													
Dose		0	1	2		0	1	2	3				
Cinchona Bark Extract	n	12	0	0		12	0	0	0				
0 mg/kg													
Cinchona Bark Extract	n	12	0	0		11	1	0	0				
100 mg/kg													
Cinchona Bark Extract	n	12	0	0		9	3	0	0				
300 mg/kg													
Cinchona Bark Extract	n	12	0	0		12	0	0	0				
1000 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 2-101

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Male Week : 5 Period : F0 mating

Study No. : [REDACTED]

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	1	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-102

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation Period : F0 mating
Generation : F0 Sex : Male Week : 6

Study No. : [REDACTED]

		Arousal NC						Convulsion NC						Species : Rat
Test article														
Dose		-2	-1	0	1	2		0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 1000 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			
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0			12	0	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
Not calculated : NC

Table 2-103

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Male Week : 6 Period : F0 mating

Study No. : [REDACTED]

Generation : F0		Sex : Male		Week : 6				Posture NC				Species : Rat	
		Gait NC											
Test article													
Dose		U	0	1	2	3		N	F	H			
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
0 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
100 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
300 mg/kg													
Cinchona Bark Extract	n	0	12	0	0	0		12	0	0			
1000 mg/kg													
Grooming NC						Urination NC							
Test article													
Dose		0	1	2		0	1	2	3				
Cinchona Bark Extract	n	12	0	0		11	1	0	0				
0 mg/kg													
Cinchona Bark Extract	n	12	0	0		11	1	0	0				
100 mg/kg													
Cinchona Bark Extract	n	12	0	0		11	1	0	0				
300 mg/kg													
Cinchona Bark Extract	n	12	0	0		12	0	0	0				
1000 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 2-104

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Male Week : 6 Period : F0 mating

Study No. : [REDACTED]

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	3	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-105

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Period : F0 before mating

Generation : F0 Sex : Female Week : 1

Study No. : [REDACTED]

Generation : F0		Sex : Female		Week : 1		Species : Rat				
		Arousal NC				Convulsion NC				
Test article										
Dose		-2	-1	0	1	2	0	1	2	3
Cinchona Bark Extract 0 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 100 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 300 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	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 Not calculated : NC										

Table 2-106

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Female Week : 1 Period : F0 before mating

Study No. : [REDACTED]

		Gait NC					Posture NC		
Test article									
Dose		U	0	1	2	3	N	F	H
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
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 2-107

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Female Week : 1 Period : F0 before mating

Study No. : [REDACTED]

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	9	0	
	S.D.	2	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	8	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	8	0	
	S.D.	3	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-108

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

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		
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0		
100 mg/kg													
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0		
300 mg/kg													
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0		
1000 mg/kg													
		Abnormal NC behavior						Stereotypy NC					
Test article													
Dose		0	1	2	3			0	1	2	3		
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0		
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0		
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0		
1000 mg/kg													

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

Not calculated : NC

Table 2-109

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Female Week : 2 Period : F0 before mating

Study No. : [REDACTED]

		Gait NC					Posture NC		
Test article									
Dose		U	0	1	2	3	N	F	H
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 1000 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
Cinchona Bark Extract 0 mg/kg	n	12	0	0		12	0	0	0
Cinchona Bark Extract 100 mg/kg	n	12	0	0		12	0	0	0
Cinchona Bark Extract 300 mg/kg	n	12	0	0		12	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	12	0	0		12	0	0	0
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 2-110

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Female Week : 2 Period : F0 before mating

Study No. : [REDACTED]

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	8	0	
	S.D.	3	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	1	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-111

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Day : 1 Period : F0 gestation

Study No. : [REDACTED]

Generation : F0		Sex : Female		Day : 1		Arousal NC		Convulsion NC		Species : Rat	
Test article	Dose	-2	-1	0	1	2	0	1	2	3	
Cinchona Bark Extract	0 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract	100 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract	300 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract	1000 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		
Cinchona Bark Extract	0 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract	100 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract	300 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract	1000 mg/kg	n	12	0	0	0	12	0	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 Not calculated : NC											

Table 2-112

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Day : 1 Period : F0 gestation

Study No. : [REDACTED]

Cinchona bark extract		Gait NC					Posture NC		
Test article									
Dose		U	0	1	2	3	N	F	H
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
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 2-113

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Female Day : 1 Period : F0 gestation

Study No. : [REDACTED]

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	1	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-114

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Day : 7 Period : F0 gestation

Study No. : [REDACTED]

		Arousal NC						Convulsion NC						Species : Rat
Test article														
Dose		-2	-1	0	1	2		0	1	2	3			
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0			
0 mg/kg														
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0			
100 mg/kg														
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0			
300 mg/kg														
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0			
1000 mg/kg														
		Abnormal NC behavior						Stereotypy NC						
Test article														
Dose		0	1	2	3			0	1	2	3			
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0			
0 mg/kg														
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0			
100 mg/kg														
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0			
300 mg/kg														
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0			
1000 mg/kg														

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
Not calculated : NC

Table 2-115

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation
Generation : F0 Sex : Female Day : 7 Period : F0 gestation

Study No. : XXXXXXXXXX

Open field observation		Sex : Female		Day : 7		Period : P0 gestation		Species : Rat		
		Gait NC						Posture NC		
Test article										
Dose		U	0	1	2	3	N	F	H	
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0	
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0	
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0	
Cinchona Bark Extract 1000 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		
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0		
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0		
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 2-116

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Female Day : 7 Period : F0 gestation

Study No. : [REDACTED]

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	1	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	2	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-117

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Species : Rat

		Arousal NC						Convulsion NC					
Test article													
Dose		-2	-1	0	1	2		0	1	2	3		
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0		
100 mg/kg													
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0		
300 mg/kg													
Cinchona Bark Extract	n	0	0	12	0	0		12	0	0	0		
1000 mg/kg													
		Abnormal NC behavior						Stereotypy NC					
Test article													
Dose		0	1	2	3			0	1	2	3		
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0		
100 mg/kg													
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0		
300 mg/kg													
Cinchona Bark Extract	n	12	0	0	0			12	0	0	0		
1000 mg/kg													

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
 Not calculated : NC

Table 2-118

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Species : Rat

		Gait NC					Posture NC			
Test article		U	0	1	2	3	N	F	H	
Dose										
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	
0 mg/kg										
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	
100 mg/kg										
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	
300 mg/kg										
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	
1000 mg/kg										
		Grooming NC			Urination NC					
Test article		0	1	2	0	1	2	3		
Dose										
Cinchona Bark Extract	n	12	0	0	12	0	0	0		
0 mg/kg										
Cinchona Bark Extract	n	12	0	0	12	0	0	0		
100 mg/kg										
Cinchona Bark Extract	n	12	0	0	12	0	0	0		
300 mg/kg										
Cinchona Bark Extract	n	12	0	0	12	0	0	0		
1000 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 2-119

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Female Day : 14 Period : F0 gestation

Study No. : XXXXXXXXXX

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	5	0	
	S.D.	1	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	3	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-120

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation Period : F0 gestation
Generation : F0 Sex : Female Day : 20

Study No. : [REDACTED]

		Arousal NC						Convulsion NC						Species : Rat
Test article														
Dose		-2	-1	0	1	2		0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 1000 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			
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0			12	0	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
Not calculated : NC

Table 2-121

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

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										
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	
0 mg/kg										
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	
100 mg/kg										
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	
300 mg/kg										
Cinchona Bark Extract	n	0	12	0	0	0	12	0	0	
1000 mg/kg										
		Grooming NC			Urination NC					
Test article		0	1	2	0	1	2	3		
Dose										
Cinchona Bark Extract	n	12	0	0	12	0	0	0		
0 mg/kg										
Cinchona Bark Extract	n	12	0	0	12	0	0	0		
100 mg/kg										
Cinchona Bark Extract	n	12	0	0	12	0	0	0		
300 mg/kg										
Cinchona Bark Extract	n	12	0	0	12	0	0	0		
1000 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 2-122

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Day : 20 Period : F0 gestation

Study No. : XXXXXXXXXX

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	5	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	5	0	
	S.D.	2	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	3	0	
	S.D.	1	0	
		DT **		
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	4	0	
	S.D.	2	0	

Significantly different from Cinchona Bark Extract 0 mg/kg : ** P<0.01
DT : Dunnett test (two-side)

Table 2-123

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation Period : F0 lactation
Generation : F0 Sex : Female Day : 6

Study No. : [REDACTED]

		Arousal NC						Convulsion NC						Species : Rat
Test article														
Dose		-2	-1	0	1	2		0	1	2	3			
Cinchona Bark Extract 0 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	0	0	12	0	0		12	0	0	0			
Cinchona Bark Extract 1000 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			
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0			12	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0			12	0	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
Not calculated : NC

Table 2-124

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Female Day : 6 Period : F0 lactation

Study No. : [REDACTED]

Cinchona bark extract		Gait NC					Posture NC		
Test article									
Dose		U	0	1	2	3	N	F	H
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
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 2-125

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Day : 6 Period : F0 lactation

Study No. : XXXXXXXXXX

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	1	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	5	0	
	S.D.	2	0	
		DT *		
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	2	0	

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05

DT : Dunnett test (two-side)

Table 2-126

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Female Day : 13 Period : F0 lactation

Study No. : [REDACTED]

Generation : F0		Sex : Female		Day : 13		Species : Rat				
		Arousal NC				Convulsion NC				
Test article										
Dose		-2	-1	0	1	2	0	1	2	3
Cinchona Bark Extract 0 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 100 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 300 mg/kg	n	0	0	12	0	0	12	0	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	0	12	0	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 Not calculated : NC										

Table 2-127

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Open field observation

Generation : F0 Sex : Female Day : 13 Period : F0 lactation

Study No. : [REDACTED]

Cinchona bark extract		Gait NC					Posture NC		
Test article									
Dose		U	0	1	2	3	N	F	H
Cinchona Bark Extract 0 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 100 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 300 mg/kg	n	0	12	0	0	0	12	0	0
Cinchona Bark Extract 1000 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	
Cinchona Bark Extract 0 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	12	0	0	12	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	12	0	0	12	0	0	0	
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 2-128

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Female Day : 13 Period : F0 lactation

Study No. : [REDACTED]

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 100 mg/kg	n	12	12	
	Mean	7	0	
	S.D.	2	0	
Cinchona Bark Extract 300 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	12	12	
	Mean	6	0	
	S.D.	2	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-129

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Week : 1
Period : Administration (non-mating group)

Study No. : XXXXXXXXXX

		Arousal NC					Convulsion NC				
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
Cinchona Bark Extract 0 mg/kg	n	0	0	10	0	0	10	0	0	0	
Cinchona Bark Extract 1000 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		
Cinchona Bark Extract 0 mg/kg	n	10	0	0	0	10	0	0	0		
Cinchona Bark Extract 1000 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		
Cinchona Bark Extract 0 mg/kg	n	0	10	0	0	0	10	0	0		
Cinchona Bark Extract 1000 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 2-130

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Grooming NC				Urination NC				
Test article		0	1	2		0	1	2	3	
Dose										
Cinchona Bark Extract	n	10	0	0		10	0	0	0	
0 mg/kg										
Cinchona Bark Extract	n	10	0	0		10	0	0	0	
1000 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 2-131

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
Cinchona Bark Extract 0 mg/kg	n	10	10
	Mean	9	0
	S.D.	2	0
Cinchona Bark Extract 1000 mg/kg	n	10	10
	Mean	8	0
	S.D.	3	0

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-132

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Species : Rat

		Arousal NC						Convulsion NC					
Test article													
Dose		-2	-1	0	1	2		0	1	2	3		
Cinchona Bark Extract	n	0	0	10	0	0		10	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	0	0	10	0	0		10	0	0	0		
1000 mg/kg													
		Abnormal NC behavior						Stereotypy NC					
Test article													
Dose		0	1	2	3			0	1	2	3		
Cinchona Bark Extract	n	10	0	0	0			10	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	10	0	0	0			10	0	0	0		
1000 mg/kg													
		Gait NC						Posture NC					
Test article													
Dose		U	0	1	2	3		N	F	H			
Cinchona Bark Extract	n	0	10	0	0	0		10	0	0			
0 mg/kg													
Cinchona Bark Extract	n	0	10	0	0	0		10	0	0			
1000 mg/kg													

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 2-133

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Species : Rat

		Grooming NC				Urination NC			
Test article		0	1	2		0	1	2	3
Dose	n								
Cinchona Bark Extract 0 mg/kg	n	10	0	0		10	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	10	0	0		10	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 2-134

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
Cinchona Bark Extract 0 mg/kg	n	10	10
	Mean	8	0
	S.D.	2	0
Cinchona Bark Extract 1000 mg/kg	n	10	10
	Mean	8	0
	S.D.	2	0

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-135

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Week : 3 Period : Administration (non-mating group)

Study No. : XXXXXXXXXX

		Arousal NC								Convulsion NC								Species : Rat
Test article																		
Dose		-2	-1	0	1	2	3	4	5	0	1	2	3	4	5	6	7	
Cinchona Bark Extract	n	0	0	10	0	0	0	0	0	10	0	0	0	0	0	0	0	
0 mg/kg																		
Cinchona Bark Extract	n	0	0	10	0	0	0	0	0	10	0	0	0	0	0	0	0	
1000 mg/kg																		
		Abnormal NC behavior								Stereotypy NC								
Test article																		
Dose		0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7	
Cinchona Bark Extract	n	10	0	0	0	0	0	0	0	10	0	0	0	0	0	0	0	
0 mg/kg																		
Cinchona Bark Extract	n	10	0	0	0	0	0	0	0	10	0	0	0	0	0	0	0	
1000 mg/kg																		
		Gait NC								Posture NC								
Test article																		
Dose		U	0	1	2	3	4	5	6	N	F	H	0	1	2	3	4	
Cinchona Bark Extract	n	0	10	0	0	0	0	0	0	10	0	0	0	0	0	0	0	
0 mg/kg																		
Cinchona Bark Extract	n	0	10	0	0	0	0	0	0	10	0	0	0	0	0	0	0	
1000 mg/kg																		

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 2-136

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 3

Species : Rat

		Grooming NC				Urination NC			
Test article		0	1	2		0	1	2	3
Dose	n								
Cinchona Bark Extract 0 mg/kg	n	10	0	0		10	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	10	0	0		10	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 2-137

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 3

Species : Rat

		Rearing	Defecation count	
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	10	10	
	Mean	10	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	10	10	
	Mean	8	0	
	S.D.	3	0	

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-138

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Open field observation	Period : Administration (non-mating group)	
Generation : F0	Sex : Female	Week : 4

Study No. : XXXXXXXXXX

		Arousal NC					Convulsion NC				
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
Cinchona Bark Extract 0 mg/kg	n	0	0	10	0	0	10	0	0	0	
Cinchona Bark Extract 1000 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		
Cinchona Bark Extract 0 mg/kg	n	10	0	0	0	10	0	0	0		
Cinchona Bark Extract 1000 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		
Cinchona Bark Extract 0 mg/kg	n	0	10	0	0	0	10	0	0		
Cinchona Bark Extract 1000 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 2-139

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 4

Species : Rat

		Grooming NC				Urination NC			
Test article		0	1	2		0	1	2	3
Dose	n								
Cinchona Bark Extract 0 mg/kg	n	10	0	0		10	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	10	0	0		10	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 2-140

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 4

Species : Rat

		Rearing	Defecation count
Test article			
Dose			
Cinchona Bark Extract 0 mg/kg	n	10	10
	Mean	7	0
	S.D.	3	0
Cinchona Bark Extract 1000 mg/kg	n	10	10
	Mean	8	0
	S.D.	2	0

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-141

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Week : 5 Period : Administration (non-mating group)

Study No. : [REDACTED]

		Arousal NC								Convulsion NC								Species : Rat
Test article																		
Dose		-2	-1	0	1	2	0	0	0	0	1	2	3	0	0	0	0	
Cinchona Bark Extract	n	0	0	10	0	0	0	0	0	10	0	0	0	0	0	0	0	
0 mg/kg																		
Cinchona Bark Extract	n	0	0	10	0	0	0	0	0	10	0	0	0	0	0	0	0	
1000 mg/kg																		
		Abnormal NC behavior								Stereotypy NC								
Test article																		
Dose		0	1	2	3	0	0	0	0	0	1	2	3	0	0	0	0	
Cinchona Bark Extract	n	10	0	0	0	0	0	0	0	10	0	0	0	0	0	0	0	
0 mg/kg																		
Cinchona Bark Extract	n	10	0	0	0	0	0	0	0	10	0	0	0	0	0	0	0	
1000 mg/kg																		
		Gait NC								Posture NC								
Test article																		
Dose		U	0	1	2	3	0	0	0	N	F	H	0	0	0	0	0	
Cinchona Bark Extract	n	0	10	0	0	0	0	0	0	10	0	0	0	0	0	0	0	
0 mg/kg																		
Cinchona Bark Extract	n	0	10	0	0	0	0	0	0	10	0	0	0	0	0	0	0	
1000 mg/kg																		

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 2-142

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 5

Species : Rat

		Grooming NC				Urination NC			
Test article		0	1	2		0	1	2	3
Dose	n								
Cinchona Bark Extract 0 mg/kg	n	10	0	0		10	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	10	0	0		10	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 2-143

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 5

Species : Rat

		Rearing	Defecation count	
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	10	10	
	Mean	8	0	
	S.D.	1	0	
Cinchona Bark Extract 1000 mg/kg	n	10	10	
	Mean	7	0	
	S.D.	2	0	

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-144

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation Period : Administration (non-mating group)
Generation : F0 Sex : Female Week : 6

Study No. : XXXXXXXXXX

		Arousal NC					Convulsion NC					Species : Rat	
Test article													
Dose		-2	-1	0	1	2	0	1	2	3			
Cinchona Bark Extract	n	0	0	10	0	0	10	0	0	0			
0 mg/kg													
Cinchona Bark Extract	n	0	0	10	0	0	10	0	0	0			
1000 mg/kg													
		Abnormal NC behavior					Stereotypy NC						
Test article													
Dose		0	1	2	3		0	1	2	3			
Cinchona Bark Extract	n	10	0	0	0		10	0	0	0			
0 mg/kg													
Cinchona Bark Extract	n	10	0	0	0		10	0	0	0			
1000 mg/kg													
		Gait NC					Posture NC						
Test article													
Dose		U	0	1	2	3	N	F	H				
Cinchona Bark Extract	n	0	10	0	0	0	10	0	0				
0 mg/kg													
Cinchona Bark Extract	n	0	10	0	0	0	10	0	0				
1000 mg/kg													

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 2-145

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Species : Rat

		Grooming NC				Urination NC			
Test article		0	1	2		0	1	2	3
Dose	n								
Cinchona Bark Extract 0 mg/kg	n	10	0	0		10	0	0	0
Cinchona Bark Extract 1000 mg/kg	n	10	0	0		10	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 2-146

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Species : Rat

		Rearing	Defecation count	
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	10	10	
	Mean	8	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	10	10	
	Mean	9	0	
	S.D.	3	0	

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-147

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Open field observation Period : Recovery

Study No. : [REDACTED]

Generation : F0		Sex : Male		Week : 1		Species : Rat					
		Arousal NC				Convulsion NC					
Test article											
Dose											
Cinchona Bark Extract	n	-2	-1	0	1	2	0	1	2	3	0
0 mg/kg		0	0	5	0	0	5	0	0	0	0
Cinchona Bark Extract	n	0	0	5	0	0	5	0	0	0	0
1000 mg/kg											
		Abnormal NC behavior				Stereotypy NC					
Test article											
Dose											
Cinchona Bark Extract	n	0	1	2	3	0	1	2	3	0	0
0 mg/kg		5	0	0	0	5	0	0	0	0	0
Cinchona Bark Extract	n	5	0	0	0	5	0	0	0	0	0
1000 mg/kg											
		Gait NC				Posture NC					
Test article											
Dose											
Cinchona Bark Extract	n	U	0	1	2	3	N	F	H	0	0
0 mg/kg		0	5	0	0	0	5	0	0	0	0
Cinchona Bark Extract	n	0	5	0	0	0	5	0	0	0	0
1000 mg/kg											

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 2-148

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Recovery

Generation : F0

Sex : Male

Week : 1

Species : Rat

		Grooming NC				Urination NC			
Test article		0	1	2		0	1	2	3
Dose	n	5	0	0		5	0	0	0
Cinchona Bark Extract	n	5	0	0		5	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	5	0	0		5	0	0	0
1000 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 2-149

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Male Week : 1 Period : Recovery

Study No. : XXXXXXXXXX

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	5	5	
	Mean	2	0	
	S.D.	1	0	
Cinchona Bark Extract 1000 mg/kg	n	5	5	
	Mean	3	0	
	S.D.	2	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-150

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation Period : Recovery

Study No. : XXXXXXXXXX

		Open mouth observation		Sex : Male		Week : 2		Tended : Recovery		Species : Rat			
		Arousal NC						Convulsion NC					
Test article													
Dose													
Cinchona Bark Extract	n	-2	-1	0	1	2		0	1	2	3		
0 mg/kg		0	0	5	0	0		5	0	0	0		
Cinchona Bark Extract	n	0	0	5	0	0		5	0	0	0		
1000 mg/kg													
		Abnormal NC behavior						Stereotypy NC					
Test article													
Dose													
Cinchona Bark Extract	n	0	1	2	3		0	1	2	3			
0 mg/kg		5	0	0	0		5	0	0	0			
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0			
1000 mg/kg													
		Gait NC						Posture NC					
Test article													
Dose													
Cinchona Bark Extract	n	U	0	1	2	3		N	F	H			
0 mg/kg		0	5	0	0	0		5	0	0			
Cinchona Bark Extract	n	0	5	0	0	0		5	0	0			
1000 mg/kg													

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 2-151

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation Period : Recovery

Study No. : XXXXXXXXXX

		Generation : F0				Sex : Male		Week : 2		Period : Recovery				Species : Rat	
		Grooming NC				Urination NC									
Test article															
Dose		0		1		2		0		1		2		3	
Cinchona Bark Extract	n	5	0	0	4	1	0	0							
0 mg/kg															
Cinchona Bark Extract	n	5	0	0	4	1	0	0							
1000 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 2-152

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Male Week : 2 Period : Recovery

Study No. : XXXXXXXXXX

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	5	5	
	Mean	4	0	
	S.D.	1	0	
Cinchona Bark Extract 1000 mg/kg	n	5	5	
	Mean	6	0	
	S.D.	2	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-153

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Open field observation Period : Recovery (non-mating group)

Generation : F0 Sex : Female Week : 1

Study No. : XXXXXXXXXX

		Arousal NC					Convulsion NC				
Test article											
Dose		-2	-1	0	1	2	0	1	2	3	
Cinchona Bark Extract 0 mg/kg	n	0	0	5	0	0	5	0	0	0	
Cinchona Bark Extract 1000 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		
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	5	0	0	0		
Cinchona Bark Extract 1000 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		
Cinchona Bark Extract 0 mg/kg	n	0	5	0	0	0	5	0	0		
Cinchona Bark Extract 1000 mg/kg	n	0	5	0	0	0	5	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 2-154

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Recovery (non-mating group)

Generation : F0

Sex : Female

Week : 1

Species : Rat

		Grooming NC				Urination NC			
Test article		0	1	2		0	1	2	3
Dose	n								
Cinchona Bark Extract 0 mg/kg	n	5	0	0		5	0	0	0
Cinchona Bark Extract 1000 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 2-155

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Week : 1 Period : Recovery (non-mating group)

Study No. : XXXXXXXXXX

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	5	5	
	Mean	6	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	5	5	
	Mean	5	0	
	S.D.	0	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-156

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Week : 2 Period : Recovery (non-mating group)

Study No. : XXXXXXXXXX

		Arousal NC					Convulsion NC					Species : Rat	
Test article													
Dose		-2	-1	0	1	2	0	1	2	3			
Cinchona Bark Extract	n	0	0	5	0	0	5	0	0	0			
0 mg/kg													
Cinchona Bark Extract	n	0	0	5	0	0	5	0	0	0			
1000 mg/kg													
		Abnormal NC behavior					Stereotypy NC						
Test article													
Dose		0	1	2	3		0	1	2	3			
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0			
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0			
1000 mg/kg													
		Gait NC					Posture NC						
Test article													
Dose		U	0	1	2	3	N	F	H				
Cinchona Bark Extract	n	0	5	0	0	0	5	0	0				
0 mg/kg													
Cinchona Bark Extract	n	0	5	0	0	0	5	0	0				
1000 mg/kg													

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 2-157

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Recovery (non-mating group)

Generation : F0

Sex : Female

Week : 2

Species : Rat

		Grooming NC				Urination NC			
Test article		0	1	2		0	1	2	3
Dose	n								
Cinchona Bark Extract 0 mg/kg	n	5	0	0		5	0	0	0
Cinchona Bark Extract 1000 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 2-158

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Week : 2 Period : Recovery (non-mating group)

Study No. : XXXXXXXXXX

		Rearing	Defecation count	Species : Rat
Test article				
Dose				
Cinchona Bark Extract 0 mg/kg	n	5	5	
	Mean	6	0	
	S.D.	2	0	
Cinchona Bark Extract 1000 mg/kg	n	5	5	
	Mean	6	0	
	S.D.	1	0	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-159

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Manipulative test
Generation : F0

Sex : Male Week : 6

Period : F0 mating

Study No. : [REDACTED]

		Auditory response					Approach response					Touch response				
Test article																
Dose		-2	-1	0	1		-1	0	1			-1	0	1		
Cinchona Bark Extract	n	0	0	0	5	0	0	0	5	0		0	0	5	0	
0 mg/kg																
Cinchona Bark Extract	n	0	0	5	0		0	5	0			0	5	0		
100 mg/kg																
Cinchona Bark Extract	n	0	0	5	0		0	5	0			0	5	0		
300 mg/kg																
Cinchona Bark Extract	n	0	0	5	0		0	5	0			0	5	0		
1000 mg/kg																
		Tail pinch response					Pupillary reflex									
Test article																
Dose		-2	-1	0	1		P	F	L	R						
Cinchona Bark Extract	n	0	0	5	0		5	0	0	0						
0 mg/kg																
Cinchona Bark Extract	n	0	0	5	0		5	0	0	0						
100 mg/kg																
Cinchona Bark Extract	n	0	0	5	0		5	0	0	0						
300 mg/kg																
Cinchona Bark Extract	n	0	0	5	0		5	0	0	0						
1000 mg/kg																

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

Table 2-160

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Manipulative test
Generation : F0 Sex : Male Week : 6 Period : F0 mating

Study No. : [REDACTED]

Generation : F0		Sex : Male		Week : 6		Postnatal Week		Species : Rat	
Test article		Aerial right-ing reflex-total							
Dose		0 1 2 3 4 5 6							
Cinchona Bark Extract	n	5	0	0	0	0	0	0	0
0 mg/kg									
Cinchona Bark Extract	n	5	0	0	0	0	0	0	0
100 mg/kg									
Cinchona Bark Extract	n	5	0	0	0	0	0	0	0
300 mg/kg									
Cinchona Bark Extract	n	5	0	0	0	0	0	0	0
1000 mg/kg									
Aerial righting reflex-total) Total score of 3 times									
\									

Table 2-161

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Manipulative test Period : F0 lactation

Study No. : [REDACTED]

		Auditory response					Approach response					Touch response				
Test article	Dose	-2	-1	0	1		-1	0	1			-1	0	1		
Cinchona Bark Extract	0 mg/kg	n	0	0	5	0	0	0	5	0		0	0	5	0	
Cinchona Bark Extract	100 mg/kg	n	0	0	5	0	0	5	0			0	5	0		
Cinchona Bark Extract	300 mg/kg	n	0	0	5	0	0	5	0			0	5	0		
Cinchona Bark Extract	1000 mg/kg	n	0	0	5	0	0	5	0			0	5	0		
		Tail pinch response					Pupillary reflex									
Test article	Dose	-2	-1	0	1		P	F	L	R						
Cinchona Bark Extract	0 mg/kg	n	0	0	5	0	5	0	0	0						
Cinchona Bark Extract	100 mg/kg	n	0	0	5	0	5	0	0	0						
Cinchona Bark Extract	300 mg/kg	n	0	0	5	0	5	0	0	0						
Cinchona Bark Extract	1000 mg/kg	n	0	0	5	0	5	0	0	0						

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

Table 2-162

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Manipulative test
Generation : F0 Sex : Female Day : 13 Period : F0 lactation

Study No. : [REDACTED]

Generation : F0		Sex : Female		Day : 13		Postnatal day 13		Species : Rat	
Test article		Aerial right- ing reflex-total							
Dose		0	1	2	3	4	5	6	
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	5	0	0	0	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	5	0	0	0	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	5	0	0	0	0	0	0	
Aerial righting reflex-total) Total score of 3 times									

Table 2-163

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Manipulative test

Period : Administration (non-mating group)

Generation : F0

Sex : Female Week : 6

Species : Rat

		Auditory response					Approach response					Touch response				
Test article	Dose															
		-2	-1	0	1		-1	0	1		-1	0	1			
Cinchona Bark Extract	0 mg/kg	n	0	0	5	0	0	0	5	0	0	0	5	0		
Cinchona Bark Extract	1000 mg/kg	n	0	0	5	0	0	5	0	0	5	0				
		Tail pinch response					Pupillary reflex									
Test article	Dose	-2	-1	0	1		P	F	L	R						
Cinchona Bark Extract	0 mg/kg	n	0	0	5	0	5	0	0	0						
Cinchona Bark Extract	1000 mg/kg	n	0	0	5	0	5	0	0	0						
		Aerial right-ing reflex-total														
Test article	Dose	0	1	2	3		4	6								
Cinchona Bark Extract	0 mg/kg	n	5	0	0	0	0	0								
Cinchona Bark Extract	1000 mg/kg	n	5	0	0	0	0	0								

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

Aerial righting reflex-total) Total score of 3 times

Table 2-164

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Manipulative test Period : Recovery

Study No. : XXXXXXXXXX

		Generation : F0		Sex : Male		Week : 2		Cinchona Recovery				Species : Rat		
		Auditory response					Approach response					Touch response		
Test article														
Dose														
Cinchona Bark Extract	n	-2	-1	0	5	1	-1	0	5	1	-1	0	5	1
0 mg/kg		0	0	0	0	0	0	0	0	0	0	0	0	0
Cinchona Bark Extract	n	0	0	5	0		0	5	0		0	5	0	
1000 mg/kg														
		Tail pinch response					Pupillary reflex							
Test article														
Dose														
Cinchona Bark Extract	n	-2	-1	0	5	1	P	F	L	R				
0 mg/kg		0	0	0	0	0	5	0	0	0	0			
Cinchona Bark Extract	n	0	0	5	0		5	0	0	0				
1000 mg/kg														
		Aerial right-ing reflex-total												
Test article														
Dose														
Cinchona Bark Extract	n	0	1	2	3	4	5	6						
0 mg/kg		5	0	0	0	0	0	0	0	0				
Cinchona Bark Extract	n	5	0	0	0	0	0	0	0					
1000 mg/kg														

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

Aerial righting reflex-total) Total score of 3 times

Table 2-165

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Manipulative test Period : Recovery

Study No. : [REDACTED]

		Auditory response					Approach response					Touch response				
Test article																
Dose																
Cinchona Bark Extract	n	0	0	5	0		0	5	0		0	5	0			
0 mg/kg																
Cinchona Bark Extract	n	0	0	5	0		0	5	0		0	5	0			
1000 mg/kg																
		Tail pinch response					Pupillary reflex									
Test article																
Dose																
Cinchona Bark Extract	n	0	0	5	0		P	F	L	R						
0 mg/kg																
Cinchona Bark Extract	n	0	0	5	0		5	0	0	0						
1000 mg/kg																
		Aerial right-ing reflex-total														
Test article																
Dose																
Cinchona Bark Extract	n	5	0	0	0		0	0	0	0						
0 mg/kg																
Cinchona Bark Extract	n	5	0	0	0		0	0	0	0						
1000 mg/kg																

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

Aerial righting reflex-total) Total score of 3 times

Table 2-166

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Grip strength
Generation : F0 Sex : Male Week : 6 Period : F0 mating

Study No. : XXXXXXXXXX

		Grip strength		Species : Rat
		of fore limb	of hind limb	
		g	g	
Test article				
Dose				
Cinchona Bark Extract	n	5	5	
0 mg/kg	Mean	1516	710	
	S.D.	123	59	
Cinchona Bark Extract	n	5	5	
100 mg/kg	Mean	1528	671	
	S.D.	141	48	
Cinchona Bark Extract	n	5	5	
300 mg/kg	Mean	1578	758	
	S.D.	126	54	
Cinchona Bark Extract	n	5	5	
1000 mg/kg	Mean	1421	681	
	S.D.	43	56	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-167

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Grip strength
Generation : F0 Sex : Female Day : 13 Period : F0 lactation

Study No. : [REDACTED]

		Grip strength		Species : Rat
		of fore limb	of hind limb	
		g	g	
Test article				
Dose				
Cinchona Bark Extract	n	5	5	
0 mg/kg	Mean	1106	431	
	S.D.	88	59	
Cinchona Bark Extract	n	5	5	
100 mg/kg	Mean	1193	485	
	S.D.	69	100	
Cinchona Bark Extract	n	5	5	
300 mg/kg	Mean	1121	432	
	S.D.	40	55	
Cinchona Bark Extract	n	5	5	
1000 mg/kg	Mean	1106	450	
	S.D.	59	92	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 2-168

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in ratsStudy No. : XXXXXXXXXX

Grip strength

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Species : Rat

Test article Dose		Grip strength	
		of fore limb g	of hind limb g
Cinchona Bark Extract 0 mg/kg	n	5	5
	Mean	1125	616
	S.D.	115	92
Cinchona Bark Extract 1000 mg/kg	n	5	5
	Mean	1100	547
	S.D.	86	50

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-169

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Grip strength
Generation : F0 Sex : Male Week : 2 Period : Recovery

Study No. : XXXXXXXXXX

		Species : Rat	
Test article		Grip strength of fore limb	Grip strength of hind limb
Dose		g	g
Cinchona Bark Extract 0 mg/kg	n	5	5
	Mean	1650	662
	S.D.	193	135
Cinchona Bark Extract 1000 mg/kg	n	5	5
	Mean	1622	696
	S.D.	87	86

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-170

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Grip strength
Generation : F0 Sex : Female Week : 2 Period : Recovery (non-mating group)

Study No. : XXXXXXXXXX

		Species : Rat	
		Grip strength of fore limb g	Grip strength of hind limb g
Test article	Dose		
Cinchona Bark Extract 0 mg/kg	n	5	5
	Mean	1124	428
	S.D.	46	21
Cinchona Bark Extract 1000 mg/kg	n	5	5
	Mean	1188	472
	S.D.	49	62

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-171

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Motor activity
Generation : F0
Sex : Male
Week : 6
Period : F0 mating

Study No. : XXXXXXXXXX

		Species : Rat					
		0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'
		Total(0'-60')					
Test article		Count	Count	Count	Count	Count	Count
Dose							
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5
	Mean	310	249	133	31	38	10
	S.D.	99	140	163	37	38	14
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5
	Mean	335	169	98	92	110	72
	S.D.	54	136	110	146	145	134
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5
	Mean	350	165	165	50	29	62
	S.D.	51	96	119	50	63	65
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5
	Mean	313	235	171	117	117	151
	S.D.	117	99	76	107	96	181

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-172

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Motor activity
Generation : F0 Sex : Female Day : 13
Period : F0 lactation

Study No. : XXXXXXXXXX

		0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')	Species : Rat
Test article		Count	Count	Count	Count	Count	Count	Count	
Dose									
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	
	Mean	424	286	240	150	116	113	1328	
	S.D.	58	124	148	126	157	139	658	
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5	5	
	Mean	417	328	206	234	204	163	1552	
	S.D.	61	78	118	106	131	140	533	
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5	5	
	Mean	448	371	285	223	151	81	1558	
	S.D.	37	62	108	95	106	90	269	
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	
	Mean	388	239	142	114	91	32	1006	
	S.D.	36	123	147	109	90	40	302	

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-173

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Motor activity		Period : Administration (non-mating group)						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	
Dose								
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	
	Mean	425	320	190	102	130	46	1214
	S.D.	44	39	110	111	162	67	219
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	
	Mean	399	274	132	156	129	81	1172
	S.D.	29	89	80	130	104	130	332

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-174

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Motor activity
Generation : F0 Sex : Male Week : 2 Period : Recovery

Study No. : [REDACTED]

		Species : Rat					
		0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'
		Total(0'-60')					
Test article		Count	Count	Count	Count	Count	Count
Dose							
Cinchona Bark Extract	n	5	5	5	5	5	5
0 mg/kg	Mean	349	198	147	86	48	37
	S.D.	45	102	107	111	69	58
Cinchona Bark Extract	n	5	5	5	5	5	5
1000 mg/kg	Mean	367	227	121	84	39	73
	S.D.	42	74	93	72	71	61

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 2-175

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Motor activity
Generation : F0 Sex : Female Week : 2 Period : Recovery (non-mating group)

Study No. : XXXXXXXXXX

		Species : Rat						
		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								
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5
	Mean	360	285	106	99	70	122	1042
	S.D.	60	97	129	117	117	68	495
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5
	Mean	340	208	75	13	3	24	663
	S.D.	57	108	85	17	2	19	195
		A2 *						

A2 *

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05

A2 : Welch test (two-side)

Table 3-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Body weight

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Unit : g

Species : Rat

Test article		/Day							Body weight
Dose		1	8	15	22	29	36	42	gain
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12	12	12	12	12
	Mean	419	452	482	509	534	561	577	158
	S.D.	25	26	33	34	38	40	42	28
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12	12	12	12
	Mean	418	451	483	507	535	558	569	152
	S.D.	26	27	31	35	35	35	32	20
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12	12	12	12
	Mean	416	450	481	505	531	552	562	146
	S.D.	22	25	30	29	29	32	36	22
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12	12	12	12	12
	Mean	418	454	486	514	543	566	578	161
	S.D.	24	30	35	40	43	46	49	29

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 3-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight
Sex : Female
Period : F0 before mating Day 1-15

Study No. : [REDACTED]

Test article		/Day			Body weight	Unit : g	Species : Rat
Dose		1	8	15	gain		
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12		
	Mean	253	265	277	24		
	S.D.	16	18	23	14		
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12		
	Mean	254	266	280	27		
	S.D.	12	14	17	9		
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12		
	Mean	251	258	271	19		
	S.D.	14	18	25	15		
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12		
	Mean	251	260	270	19		
	S.D.	14	14	17	11		

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 3-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight
Sex : Female
Period : F0 gestation Day 0-25

Study No. : XXXXXXXXXX

		/Day				Unit : g	Species : Rat
Test article	Dose	0	7	14	20	Body weight gain	
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12	12	
	Mean	286	324	364	452	166	
	S.D.	22	19	17	25	17	
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12	
	Mean	286	332	374	462	176	
	S.D.	16	15	19	24	13	
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12	
	Mean	279	326	367	462	183	
	S.D.	23	26	30	32	16	
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12	12	
	Mean	278	321	365	458	180	
	S.D.	15	12	15	19	17	

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05

DT : Dunnett test (two-side)

Table 3-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight
Sex : Female
Period : F0 lactation Day 0-14

Study No. : [REDACTED]

		/Day				Unit : g	Species : Rat
Test article	Dose	0	4	7	13	Body weight gain	
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12	12	
	Mean	355	358	360	376	21	
	S.D.	21	21	23	21	14	
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12	
	Mean	362	368	369	380	18	
	S.D.	22	22	23	22	22	
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12	
	Mean	350	362	362	374	24	
	S.D.	38	32	27	25	23	
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12	12	
	Mean	362	363	368	376	14	
	S.D.	19	24	19	18	12	

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 3-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight
Sex : Female
Period : Administration (non-mating group)

Study No. : [REDACTED]

Test article		Unit : g							Species : Rat
Dose		/Day	1	8	15	22	29	36	42
Cinchona Bark Extract		n	10	10	10	10	10	10	10
0 mg/kg		Mean	252	262	274	286	297	303	311
		S.D.	14	15	17	24	27	25	25
Cinchona Bark Extract		n	10	10	10	10	10	10	10
1000 mg/kg		Mean	251	264	277	290	301	311	315
		S.D.	16	19	19	27	27	25	30

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 3-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight
Sex : Male
Period : Recovery Day 1-15

Study No. : XXXXXXXXXX

		/Day			Body weight gain	Unit : g	Species : Rat
Test article	Dose	1	8	14			
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5		
	Mean	570	588	599	29		
	S.D.	35	36	40	5		
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5		
	Mean	589	605	617	28		
	S.D.	36	42	38	6		

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 3-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Body weight

Period : Recovery Day 1-15 (non-mating group)

Unit : g

Species : Rat

Test article Dose		/Day			Body weight gain
		1	8	14	
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5
	Mean	311	321	319	8
	S.D.	25	23	26	8
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5
	Mean	311	318	323	12
	S.D.	33	36	30	5

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 4-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Food consumption Period : F0 before mating Day 1-15
Sex : Male

Study No. : [REDACTED]

		/Day			Total food consumption	Unit : g	Species : Rat
Test article	Dose	2	8	15			
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12		
	Mean	28	27	27	82		
	S.D.	3	2	3	7		
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12		
	Mean	28	28	28	83		
	S.D.	2	3	3	5		
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12		
	Mean	27	26	27	80		
	S.D.	2	2	3	6		
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12		
	Mean	25	26	28	79		
	S.D.	3	2	3	7		

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 4-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Food consumption Period : F0 mating Day 15-43
Sex : Male

Study No. : XXXXXXXXXX

		Unit : g			Species : Rat	
Test article		/Day				
Dose		30	36	42		
Cinchona Bark Extract 0 mg/kg	n	12	12	12		
	Mean	29	29	30		
	S.D.	3	3	3		
Cinchona Bark Extract 100 mg/kg	n	12	12	12		
	Mean	29	28	28		
	S.D.	2	2	4		
Cinchona Bark Extract 300 mg/kg	n	12	12	12		
	Mean	28	28	27		
	S.D.	2	2	3		
Cinchona Bark Extract 1000 mg/kg	n	12	12	12		
	Mean	28	28	28		
	S.D.	2	3	3		

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 4-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Food consumption Period : F0 before mating Day 1-15
Sex : Female

Study No. : [REDACTED]

		/Day			Total food consumption	Unit : g	Species : Rat
Test article	Dose	2	8	15			
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12		
	Mean	19	18	20	57		
	S.D.	2	3	3	6		
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12		
	Mean	19	18	19	56		
	S.D.	2	3	3	5		
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12		
	Mean	17	17	19	53		
	S.D.	3	4	4	8		
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12		
	Mean	17	17	18	52		
	S.D.	3	3	3	5		

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 4-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Food consumption
Sex : Female
Period : F0 gestation Day 0-25

Study No. : [REDACTED]

		/Day				Unit : g	Species : Rat
Test article	Dose	1	7	14	20	Total food consumption	
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12	12	
	Mean	19	26	26	26	97	
	S.D.	2	3	2	3	6	
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12	
	Mean	18	27	28	28	100	
	S.D.	3	2	2	2	7	
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12	
	Mean	19	27	27	28	100	
	S.D.	3	4	4	3	11	
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12	12	
	Mean	18	25	25	28	96	
	S.D.	2	2	4	2	7	

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 4-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Food consumption
Sex : Female
Period : F0 lactation Day 0-14

Study No. : [REDACTED]

		Unit : g				Species : Rat
Test article	/Day	Total food consumption				
Dose		2	4	7	13	
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12	12
	Mean	29	43	45	63	179
	S.D.	7	7	6	8	24
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12
	Mean	30	46	46	66	189
	S.D.	8	8	7	7	26
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12
	Mean	31	46	46	64	187
	S.D.	5	5	4	7	15
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12	12
	Mean	27	40	45	60	172
	S.D.	10	8	6	7	27

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 4-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Administration Day 1-15 (non-mating group)

Sex : Female

Unit : g

Species : Rat

Test article Dose		/Day			Total food consumption
		2	8	15	
Cinchona Bark Extract 0 mg/kg	n	10	10	10	10
	Mean	21	18	20	59
	S.D.	2	4	3	8
Cinchona Bark Extract 1000 mg/kg	n	10	10	10	10
	Mean	18	19	20	56
	S.D.	3	3	2	4

T2 **

Significantly different from Cinchona Bark Extract 0 mg/kg : ** P<0.01

T2 : Student t-test (two-side)

Table 4-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Administration Day 15-43 (non-mating group)

Sex : Female

Unit : g

Species : Rat

Test article		/Day		
Dose		30	36	42
Cinchona Bark Extract 0 mg/kg	n	10	10	10
	Mean	20	19	19
	S.D.	3	4	2
Cinchona Bark Extract 1000 mg/kg		10	10	10
	Mean	19	19	19
	S.D.	3	3	3

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 4-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Food consumption
Sex : Male

Study No. : XXXXXXXXXX

Period : Recovery Day 1-15

Unit : g

Species : Rat

Test article Dose		/Day			Total food consumption
		2	8	14	
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5
	Mean	29	29	28	86
	S.D.	3	3	3	7
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5
	Mean	31	30	29	91
	S.D.	2	3	3	7

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 4-9

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Recovery Day 1-15 (non-mating group)

Sex : Female

Unit : g

Species : Rat

Test article Dose		/Day			Total food consumption
		2	8	14	
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5
	Mean	19	22	18	60
	S.D.	5	2	3	9
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5
	Mean	18	20	19	57
	S.D.	2	3	2	2

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 5-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Urinalysis	Stage : Week 6 of administration
Sex : Male	

Study No. : XXXXXXXXXX

Sex : Male		Stage I: Week 0 or administration										Species : Rat	
		pH											
Test article													
Dose		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0			
Cinchona Bark Extract 0 mg/kg	n	0	0	0	0	0	1	1	3	0			
Cinchona Bark Extract 100 mg/kg	n	0	0	0	0	0	0	0	4	1			
Cinchona Bark Extract 300 mg/kg	n	0	0	0	0	0	0	0	5	0			
Cinchona Bark Extract 1000 mg/kg	n	0	0	0	0	0	0	0	5	0			
Protein						Ketones							
Test article													
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+		
Cinchona Bark Extract 0 mg/kg	n	2	3	0	0	0	1	4	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	2	3	0	0	0	3	2	0	0	0		
Cinchona Bark Extract 300 mg/kg	n	2	2	1	0	0	3	0	2	0	0		
Cinchona Bark Extract 1000 mg/kg	n	0	5	0	0	0	2	3	0	0	0		
Protein) -:Negative , +/-:15 , 1+:30 , 2+:100 , 3+:>=300 mg/dL													
Ketones) -:Negative , +/-:5 , 1+:15 , 2+:40 , 3+:80 mg/dL													

Table 5-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Urinalysis	Stage : Week 6 of administration
Sex : Male	

Study No. : XXXXXXXXXX

Sex : Male		Glucose								Occult Blood					Species : Rat	
Test article	Dose	-	1+	2+	3+	4+	-	+/-	1+	2+	3+	-	+/-	1+	2+	3+
Cinchona Bark Extract	0 mg/kg	n	5	0	0	0	0	2	3	0	0	0	2	3	0	0
Cinchona Bark Extract	100 mg/kg	n	5	0	0	0	0	3	2	0	0	0	3	2	0	0
Cinchona Bark Extract	300 mg/kg	n	5	0	0	0	0	3	2	0	0	0	3	2	0	0
Cinchona Bark Extract	1000 mg/kg	n	5	0	0	0	0	5	0	0	0	0	5	0	0	0
Bilirubin																
Test article	Dose	-	1+	2+	3+	+/-	1+	2+	3+	-	+/-	1+	2+	3+	-	+/-
Cinchona Bark Extract	0 mg/kg	n	5	0	0	0	5	0	0	0	5	0	0	0	0	0
Cinchona Bark Extract	100 mg/kg	n	5	0	0	0	5	0	0	0	5	0	0	0	0	0
Cinchona Bark Extract	300 mg/kg	n	5	0	0	0	5	0	0	0	5	0	0	0	0	0
Cinchona Bark Extract	1000 mg/kg	n	5	0	0	0	5	0	0	0	5	0	0	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

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Urinalysis	Stage : Week 6 of administration
Sex : Male	

Study No. : XXXXXXXXXX

Species : Rat

Sex : male		specific gravity						Species : Rat					
Test article													
Dose		<=1.005	1.010	1.015	1.020	1.025	>=1.030						
Cinchona Bark Extract 0 mg/kg	n	1	3	1	0	0	0						
Cinchona Bark Extract 100 mg/kg	n	3	2	0	0	0	0						
Cinchona Bark Extract 300 mg/kg	n	2	3	0	0	0	0						
Cinchona Bark Extract 1000 mg/kg	n	1	4	0	0	0	0						
Color													
Test article													
Dose		LY	Y	DY	BR	RE	RB	WH	BL	CL	OT		
Cinchona Bark Extract 0 mg/kg	n	0	5	0	0	0	0	0	0	0	0		
Cinchona Bark Extract 100 mg/kg	n	0	5	0	0	0	0	0	0	0	0		
Cinchona Bark Extract 300 mg/kg	n	0	5	0	0	0	0	0	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	0	5	0	0	0	0	0	0	0	0		
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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Female
Stage : Week 6 of administration (non-mating group)

Study No. : [REDACTED]

Sex : Female		pH										Species : Rat	
Test article													
Dose		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0			
Cinchona Bark Extract	n	0	0	0	0	1	1	1	1	1			
0 mg/kg													
Cinchona Bark Extract	n	0	0	0	0	1	1	0	3	0			
1000 mg/kg													
		Protein					Ketones						
Test article													
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+		
Cinchona Bark Extract	n	5	0	0	0	0	5	0	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0	0	5	0	0	0	0		
1000 mg/kg													
		Glucose					Occult Blood						
Test article													
Dose		-	1+	2+	3+	4+	-	+/-	1+	2+	3+		
Cinchona Bark Extract	n	5	0	0	0	0	5	0	0	0	0		
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0	0	5	0	0	0	0		
1000 mg/kg													
		Bilirubin					Urobilinogen						
Test article													
Dose		-	1+	2+	3+		+/-	1+	2+	3+			
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0			
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0		5	0	0	0			
1000 mg/kg													

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

Table 5-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Female
Stage : Week 6 of administration (non-mating group)

Study No. : XXXXXXXXXX

Species : Rat

Cinchona bark extract		specific gravity							Species : Bark		
Test article											
Dose		<=1.005	1.010	1.015	1.020	1.025	>=1.030				
Cinchona Bark Extract	n	2	2	1	0	0	0				
0 mg/kg											
Cinchona Bark Extract	n	1	3	0	1	0	0				
1000 mg/kg											
Color											
Test article		LY	Y	DY	BR	RE	RB	WH	BL	CL	OT
Dose											
Cinchona Bark Extract	n	0	5	0	0	0	0	0	0	0	0
0 mg/kg											
Cinchona Bark Extract	n	0	5	0	0	0	0	0	0	0	0
1000 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 5-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Urinalysis	Stage : Week 6 of administration
Sex : Male	

Study No. : [REDACTED]

Sex : Male		RBC								WBC								Species : Rat
Test article		-	+/-	1+	2+	3+				-	+/-	1+	2+	3+				
Dose																		
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	5	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	5	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	5	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	
Squamous epithelial cells									Small round epithelial cells									
Test article		-	+/-	1+	2+	3+				-	+/-	1+	2+	3+				
Dose																		
Cinchona Bark Extract 0 mg/kg	n	0	5	0	0	0	0	0	0	5	0	0	0	0	0	0	0	
Cinchona Bark Extract 100 mg/kg	n	0	5	0	0	0	0	0	0	5	0	0	0	0	0	0	0	
Cinchona Bark Extract 300 mg/kg	n	0	5	0	0	0	0	0	0	5	0	0	0	0	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	0	5	0	0	0	0	0	0	5	0	0	0	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 5-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Urinalysis	Stage : Week 6 of administration
Sex : Male	

Study No. : XXXXXXXXXX

Analysis		Stage : Week 0 of administration								Species : Rat				
Sex : Male		Cast					Crystal phosphate salts							
Test article														
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+			
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	0	5	0	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	5	0	0	0	0	5	0	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	5	0	0	0	0	5	0	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	5	0	0	0	0	5	0	0	0	0			
Crystal calcium oxalate														
Test article														
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+			
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	0	5	0	0	0	0			
Cinchona Bark Extract 100 mg/kg	n	5	0	0	0	0	5	0	0	0	0			
Cinchona Bark Extract 300 mg/kg	n	5	0	0	0	0	5	0	0	0	0			
Cinchona Bark Extract 1000 mg/kg	n	5	0	0	0	0	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 5-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Female
Stage : Week 6 of administration (non-mating group)

Study No. : [REDACTED]

		RBC						WBC					
Test article		-	+/-	1+	2+	3+		-	+/-	1+	2+	3+	
Dose													
Cinchona Bark Extract	n	5	0	0	0	0		5	0	0	0	0	
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0	0		5	0	0	0	0	
1000 mg/kg													
		Squamous epithelial cells						Small round epithelial cells					
Test article		-	+/-	1+	2+	3+		-	+/-	1+	2+	3+	
Dose													
Cinchona Bark Extract	n	0	5	0	0	0		5	0	0	0	0	
0 mg/kg													
Cinchona Bark Extract	n	0	5	0	0	0		5	0	0	0	0	
1000 mg/kg													
		Cast						Crystal phosphate salts					
Test article		-	+/-	1+	2+	3+		-	+/-	1+	2+	3+	
Dose													
Cinchona Bark Extract	n	5	0	0	0	0		4	1	0	0	0	
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0	0		5	0	0	0	0	
1000 mg/kg													
		Crystal calcium oxalate											
Test article		-	+/-	1+	2+	3+							
Dose													
Cinchona Bark Extract	n	5	0	0	0	0							
0 mg/kg													
Cinchona Bark Extract	n	5	0	0	0	0							
1000 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
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 5-9

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Male
Stage : Week 6 of administration

Study No. : [REDACTED]

Species : Rat

Test article Dose		Water consumption mL/24h	Urine volume mL/24h
Cinchona Bark Extract 0 mg/kg	n	5	5
	Mean	43	19.6
	S.D.	6	2.0
Cinchona Bark Extract 100 mg/kg	n	5	5
	Mean	40	17.7
	S.D.	5	4.9
Cinchona Bark Extract 300 mg/kg	n	5	5
	Mean	50	22.4
	S.D.	8	7.2
Cinchona Bark Extract 1000 mg/kg	n	5	5
	Mean	48	20.4
	S.D.	10	4.7

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 5-10

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 6 of administration (non-mating group)

Sex : Female

Species : Rat

Test article		Water	Urine
Dose		consumption	volume
		mL/24h	mL/24h
Cinchona Bark Extract 0 mg/kg	n	5	5
	Mean	38	10.3
	S.D.	8	3.1
Cinchona Bark Extract 1000 mg/kg	n	5	5
	Mean	39	11.4
	S.D.	3	4.1

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 5-11

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Urinalysis
Sex : Male

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		
Cinchona Bark Extract 0 mg/kg	n	0	0	0	0	0	0	1	4	0		
Cinchona Bark Extract 1000 mg/kg	n	0	0	0	0	0	0	2	3	0		
		Protein					Ketones					
Test article												
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+	
Cinchona Bark Extract 0 mg/kg	n	3	1	1	0	0	0	1	4	0	0	
Cinchona Bark Extract 1000 mg/kg	n	2	2	0	1	0	1	2	1	1	0	
		Glucose					Occult Blood					
Test article												
Dose		-	1+	2+	3+	4+	-	+/-	1+	2+	3+	
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	0	4	1	0	0	0	
Cinchona Bark Extract 1000 mg/kg	n	5	0	0	0	0	2	3	0	0	0	
		Bilirubin					Urobilinogen					
Test article												
Dose		-	1+	2+	3+		+/-	1+	2+	3+		
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	0	5	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	5	0	0	0	0	5	0	0	0		

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

Table 5-12

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Male

Study No. : XXXXXXXXXX

specific gravity

Species : Rat

Test article							
Dose		<=1.005	1.010	1.015	1.020	1.025	>=1.030
Cinchona Bark Extract	n	0	1	0	1	1	2
0 mg/kg							
Cinchona Bark Extract	n	0	0	3	2	0	0
1000 mg/kg							

Color

Test article											
Dose		LY	Y	DY	BR	RE	RB	WH	BL	CL	OT
Cinchona Bark Extract	n	0	5	0	0	0	0	0	0	0	0
0 mg/kg											
Cinchona Bark Extract	n	0	5	0	0	0	0	0	0	0	0
1000 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 5-13

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Female
Stage : Week 2 of recovery (non-mating group)

Study No. : XXXXXXXXXX

Sex : Female		pH										Species : Rat	
Test article													
Dose		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0			
Cinchona Bark Extract 0 mg/kg	n	0	0	0	0	0	0	1	4	0			
Cinchona Bark Extract 1000 mg/kg	n	0	0	1	0	2	1	0	1	0			
Test article		Protein					Ketones						
Dose		-	+/-	1+	2+	3+	-	+/-	1+	2+	3+		
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	0	5	0	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	5	0	0	0	0	5	0	0	0	0		
Test article		Glucose					Occult Blood						
Dose		-	1+	2+	3+	4+	-	+/-	1+	2+	3+		
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	0	5	0	0	0	0		
Cinchona Bark Extract 1000 mg/kg	n	5	0	0	0	0	5	0	0	0	0		
Test article		Bilirubin					Urobilinogen						
Dose		-	1+	2+	3+	+/-	1+	2+	3+				
Cinchona Bark Extract 0 mg/kg	n	5	0	0	0	5	0	0	0				
Cinchona Bark Extract 1000 mg/kg	n	5	0	0	0	5	0	0	0				
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													

Table 5-15

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Male
Stage : Week 2 of recovery

Study No. : XXXXXXXXXX

Sex : Male		RBC								WBC								Species : Rat	
Test article																			
Dose		-	+/-	1+	2+	3+				-	+/-	1+	2+	3+					
Cinchona Bark Extract	n	5	0	0	0	0	0	0	5	0	0	0	0	0	0	0			
0 mg/kg																			
Cinchona Bark Extract	n	5	0	0	0	0			5	0	0	0	0			0			
1000 mg/kg																			
Squamous epithelial cells									Small round epithelial cells										
Test article																			
Dose		-	+/-	1+	2+	3+				-	+/-	1+	2+	3+					
Cinchona Bark Extract	n	0	5	0	0	0	0	0	5	0	0	0	0	0	0	0			
0 mg/kg																			
Cinchona Bark Extract	n	0	5	0	0	0			5	0	0	0	0			0			
1000 mg/kg																			
Cast									Crystal phosphate salts										
Test article																			
Dose		-	+/-	1+	2+	3+				-	+/-	1+	2+	3+					
Cinchona Bark Extract	n	5	0	0	0	0	0	0	4	1	0	0	0	0	0	0			
0 mg/kg																			
Cinchona Bark Extract	n	5	0	0	0	0			4	1	0	0	0			0			
1000 mg/kg																			
Crystal calcium oxalate																			
Test article																			
Dose		-	+/-	1+	2+	3+													
Cinchona Bark Extract	n	5	0	0	0	0													
0 mg/kg																			
Cinchona Bark Extract	n	5	0	0	0	0													
1000 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																			
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 5-16

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Female
Stage : Week 2 of recovery (non-mating group)

Study No. : XXXXXXXXXX

Sex : Female		RBC								WBC					Species : Rat	
Test article		-	+/-	1+	2+	3+				-	+/-	1+	2+	3+		
Dose																
Cinchona Bark Extract	n	5	0	0	0	0	0	0	5	0	0	0	0	0	0	
0 mg/kg																
Cinchona Bark Extract	n	5	0	0	0	0	0	0	5	0	0	0	0	0	0	
1000 mg/kg																
Squamous epithelial cells								Small round epithelial cells								
Test article		-	+/-	1+	2+	3+				-	+/-	1+	2+	3+		
Dose																
Cinchona Bark Extract	n	0	5	0	0	0	0	0	5	0	0	0	0	0	0	
0 mg/kg																
Cinchona Bark Extract	n	0	5	0	0	0	0	0	5	0	0	0	0	0	0	
1000 mg/kg																
Cast								Crystal phosphate salts								
Test article		-	+/-	1+	2+	3+				-	+/-	1+	2+	3+		
Dose																
Cinchona Bark Extract	n	5	0	0	0	0	0	0	5	0	0	0	0	0	0	
0 mg/kg																
Cinchona Bark Extract	n	5	0	0	0	0	0	0	5	0	0	0	0	0	0	
1000 mg/kg																
Crystal calcium oxalate																
Test article		-	+/-	1+	2+	3+										
Dose																
Cinchona Bark Extract	n	5	0	0	0	0										
0 mg/kg																
Cinchona Bark Extract	n	5	0	0	0	0										
1000 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																
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 5-17

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Male
Stage : Week 2 of recovery

Study No. : XXXXXXXXXX

		W.C.	Uri.Vol.	Species : Rat
Test article		mL/24h	mL/24h	
Dose				
Cinchona Bark Extract 0 mg/kg	n	5	5	
	Mean	41	16.2	
	S.D.	5	3.1	
Cinchona Bark Extract 1000 mg/kg	n	5	5	
	Mean	48	20.7	
	S.D.	12	8.7	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 5-18

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Urinalysis
Sex : Female
Stage : Week 2 of recovery (non-mating group)

Study No. : XXXXXXXXXX

		W.C.	Uri.Vol.	Species : Rat
		mL/24h	mL/24h	
Test article				
Dose				
Cinchona Bark Extract	n	5	5	
0 mg/kg	Mean	43	12.5	
	S.D.	10	3.8	
Cinchona Bark Extract	n	5	5	
1000 mg/kg	Mean	47	10.3	
	S.D.	23	5.6	
Not significantly different from Cinchona Bark Extract 0 mg/kg				

Table 6-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Hematology
Sex : Male
Stage : End of administration

Study No. : XXXXXXXXXX

Sex : Male		Stage : End of administration								Species : Rat	
		RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC
Test article		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	837	15.1	45.1	54.0	18.1	33.5	13.3	217.2	99.9	68.1
	S.D.	30	0.3	0.8	2.2	0.8	0.3	0.8	11.2	11.8	5.9
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	847	15.3	45.4	53.6	18.0	33.6	12.8	182.7	108.1	81.1
	S.D.	27	0.5	1.5	2.0	0.7	0.5	0.8	49.3	11.0	21.6
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	809	15.0	44.8	55.4	18.5	33.5	12.7	199.1	99.9	74.3
	S.D.	42	0.8	2.2	0.7	0.1	0.4	0.7	29.3	8.8	12.0
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	830	15.3	45.7	55.1	18.5	33.5	12.7	220.5	97.7	72.5
	S.D.	18	0.2	1.2	2.2	0.6	0.3	0.6	35.0	11.5	18.1
		#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC				
Test article		10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL				
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5				
	Mean	52.0	12.6	1.1	0.1	1.7	0.5				
	S.D.	6.0	3.5	0.3	0.1	0.2	0.3				
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5				
	Mean	57.4	19.0	1.5	0.2	2.1	0.8				
	S.D.	13.4	7.2	0.5	0.1	1.0	0.5				
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5				
	Mean	58.6	12.5	1.0	0.2	1.6	0.5				
	S.D.	11.6	2.8	0.3	0.1	0.4	0.2				
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5				
	Mean	54.1	14.6	1.1	0.1	1.7	0.9				
	S.D.	10.8	6.5	0.5	0.0	0.7	0.7				

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 6-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Hematology
Sex : Female
Stage : End of lactation (F0 dams)

Study No. : XXXXXXXXXX

Sex : Female		Stage : End of lactation (p 0 dams)								Species : Rat	
		RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC
Test article		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	765	15.2	44.6	58.3	19.8	34.1	14.5	247.8	121.5	103.8
	S.D.	28	0.3	1.2	1.5	0.5	0.5	0.8	26.2	9.8	18.9
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	736	14.7	43.3	58.8	19.9	33.9	14.4	213.9	108.8	84.7
	S.D.	30	0.8	2.3	2.4	0.6	0.4	0.7	38.9	13.6	16.0
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	761	14.9	43.7	57.4	19.6	34.1	14.5	201.5	125.6	95.6
	S.D.	26	0.5	1.6	2.0	0.6	0.2	0.7	19.9	13.7	23.1
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	731	14.7	43.0	58.8	20.1	34.2	13.4	200.3	109.3	80.2
	S.D.	25	0.2	1.2	1.4	0.4	0.5	0.5	24.9 DT *	5.2	16.2
		#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC				
Test article		10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL				
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5				
	Mean	59.1	38.4	0.9	0.2	4.1	1.1				
	S.D.	12.4	11.1	0.3	0.0	1.3	0.6				
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5				
	Mean	41.7	38.2	0.7	0.1	2.7	1.3				
	S.D.	6.4	10.7	0.2	0.1	1.1	0.5				
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5				
	Mean	50.9	36.9	1.2	0.2	4.5	2.0				
	S.D.	15.3	6.9	1.0	0.1	1.3	0.8				
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5				
	Mean	41.6	34.0	0.5	0.1	2.7	1.2				
	S.D.	17.1	7.3	0.2	0.1	0.7	0.6				

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05

DT : Dunnett test (two-side)

Table 6-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Hematology
Stage : End of administration (non-mating group)
Sex : Female

Study No. : XXXXXXXXXX

Sex : Female		Stage : End of administration (Non mating group)							Species : Rat		
		RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC
Test article		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	784	14.9	43.1	55.0	19.0	34.6	11.9	174.1	99.7	62.3
	S.D.	9	0.2	0.9	1.0	0.4	0.5	0.2	28.0	15.4	12.4
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	775	14.7	43.2	55.7	18.9	34.0	11.7	160.3	98.0	49.9
	S.D.	30	0.4	1.5	0.6	0.2	0.2	0.5	39.3	14.6	13.2
A2 *											
		#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC				
Test article		10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL				
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5				
	Mean	49.4	10.0	1.1	0.1	1.4	0.4				
	S.D.	12.9	2.8	0.3	0.0	0.4	0.1				
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5				
	Mean	38.9	8.0	1.2	0.1	1.3	0.5				
	S.D.	9.8	3.8	0.4	0.1	0.6	0.4				

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05

A2 : Welch test (two-side)

Table 6-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Hematology
Stage : End of recovery
Sex : Male

Study No. : XXXXXXXXXX

Hematology		Stage : End of recovery							Species : Rat		
Sex : Male		RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC
Test article		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	896	15.7	46.1	51.5	17.5	33.9	13.0	152.7	109.0	85.7
	S.D.	57	0.6	2.1	1.4	0.9	1.0	0.1	19.3	16.3	16.9
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	858	15.0	44.5	51.8	17.5	33.9	13.0	187.6	109.6	79.9
	S.D.	21	0.4	1.4	1.8	0.7	0.4	0.8	51.6	5.8	6.3
		#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC				
Test article		10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL				
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5				
	Mean	64.7	16.3	1.5	0.2	2.1	0.9				
	S.D.	16.4	4.3	0.4	0.1	0.6	0.3				
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5				
	Mean	61.0	14.5	1.4	0.2	2.0	0.8				
	S.D.	4.4	3.4	0.5	0.1	0.6	0.5				

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 6-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Hematology
Sex : Female
Stage : End of recovery (non-mating group)

Study No. : XXXXXXXXXX

		Stage : End of recovery (non mating group)								Species : Rat	
Sex : Female		RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC
Test article		10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	751	14.3	41.0	54.7	19.1	34.9	11.7	131.5	110.3	51.7
	S.D.	51	0.6	2.5	1.3	0.7	0.9	0.3	34.1	22.8	9.5
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	758	14.4	41.6	54.9	18.9	34.5	11.8	157.1	101.9	65.4
	S.D.	16	0.4	1.4	0.9	0.3	0.7	0.5	12.8	5.6	29.0
		#LYMP	#NEUT	#EOS	#BASO	#MONO	#LUC				
Test article		10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL				
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5				
	Mean	40.3	8.9	0.8	0.1	1.1	0.5				
	S.D.	10.2	1.8	0.6	0.0	0.2	0.5				
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5				
	Mean	54.8	7.6	1.0	0.1	1.5	0.6				
	S.D.	26.4	3.1	0.2	0.1	0.7	0.2				

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 7-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Coagulation test Stage : End of administration
 Sex : Male

Study No. : XXXXXXXXXX

		PT	APTT	FIB	Species : Rat
Test article		s	s	mg/dL	
Dose					
Cinchona Bark Extract 0 mg/kg	n	5	5	5	
	Mean	12.5	17.1	333	
	S.D.	1.2	2.4	31	
Cinchona Bark Extract 100 mg/kg	n	5	5	5	
	Mean	13.6	17.2	305	
	S.D.	0.4	1.7	27	
Cinchona Bark Extract 300 mg/kg	n	5	5	5	
	Mean	13.7	17.2	315	
	S.D.	0.8	2.9	24	
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	
	Mean	14.0	17.9	329	
	S.D.	1.1	2.2	21	
Not significantly different from Cinchona Bark Extract 0 mg/kg					

Table 7-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Coagulation test Stage : End of lactation (F0 dams)
 Sex : Female

Study No. : XXXXXXXXXX

		PT	APTT	FIB	Species : Rat
Test article		s	s	mg/dL	
Dose					
Cinchona Bark Extract 0 mg/kg	n	5	5	5	
	Mean	12.4	15.2	353	
	S.D.	1.4	2.8	71	
Cinchona Bark Extract 100 mg/kg	n	5	5	5	
	Mean	12.2	14.4	447	
	S.D.	0.9	1.2	93	
Cinchona Bark Extract 300 mg/kg	n	5	5	5	
	Mean	12.2	14.3	416	
	S.D.	1.0	2.6	88	
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	
	Mean	13.0	15.5	344	
	S.D.	0.8	1.4	46	
Not significantly different from Cinchona Bark Extract 0 mg/kg					

Table 7-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Coagulation test
Sex : Female

Study No. : XXXXXXXXXX

Stage : End of administration (non-mating group)

Species : Rat

		PT	APTT	FIB
Test article		s	s	mg/dL
Dose				
Cinchona Bark Extract 0 mg/kg	n	5	5	5
	Mean	15.3	15.6	213
	S.D.	0.9	1.9	20
Cinchona Bark Extract 1000 mg/kg	n	5	5	5
	Mean	14.5	15.8	212
	S.D.	0.5	1.0	26

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 7-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Coagulation test
Sex : Male

Study No. : XXXXXXXXXX

Stage : End of recovery

Species : Rat

		PT	APTT	FIB
Test article		s	s	mg/dL
Dose				
Cinchona Bark Extract 0 mg/kg	n	5	5	5
	Mean	14.3	18.9	287
	S.D.	1.5	2.5	27
Cinchona Bark Extract 1000 mg/kg	n	5	5	5
	Mean	13.6	16.4	305
	S.D.	0.7	2.8	28

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 7-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Coagulation test Stage : End of recovery (non-mating group)
 Sex : Female

Study No. : XXXXXXXXXX

		PT	APTT	FIB
		s	s	mg/dL
Test article				
Dose				
Cinchona Bark Extract	n	5	5	5
0 mg/kg	Mean	12.8	13.1	206
	S.D.	0.3	1.3	12
Cinchona Bark Extract	n	5	5	5
1000 mg/kg	Mean	13.2	12.8	201
	S.D.	1.1	1.4	26

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 8-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Blood chemistry
Stage : End of administration
Sex : Male

Study No. : XXXXXXXXXX

Sex : Male		Stage : End of administration								Species : Rat	
		AST	ALT	ALP	γ-GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Test article		IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	64	32	367	0	30.2	68	43	107	0.1	143
	S.D.	7	2	92	0	14.1	17	12	19	0.0	7
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	68	35	393	0	14.3	56	54	95	0.1	149
	S.D.	6	4	91	0	4.4	13	28	13	0.0	12
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	67	37	416	0	20.4	61	42	96	0.1	154
	S.D.	9	4	110	0	16.2	6	14	5	0.0	12
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	64	37	370	0	17.5	55	51	95	0.1	141
	S.D.	8	6	46	0	11.6	3	15	3	0.0	12

		BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB
		mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
Test article										
Dose										
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	18	0.33	145	3.8	106	10.3	6.1	6.6	3.3
	S.D.	5	0.03	1	0.2	1	0.2	0.2	0.3	0.1
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	17	0.35	145	3.7	106	10.2	5.6	6.5	3.2
	S.D.	2	0.01	1	0.3	1	0.5	0.6	0.3	0.1
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	21	0.35	145	3.8	107	10.1	5.8	6.4	3.2
	S.D.	1	0.06	0	0.0	1	0.2	0.4	0.2	0.1
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	17	0.38	145	3.7	107	10.3	6.1	6.5	3.3
	S.D.	3	0.07	1	0.2	1	0.3	0.7	0.2	0.1

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 8-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Blood chemistry
Sex : Female
Stage : End of lactation (F0 dams)

Study No. : XXXXXXXXXX

Sex : Female		Stage : End circulation (P & S same)								Species : Rat	
		AST	ALT	ALP	γ-GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Test article		IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	97	64	338	1	24.0	101	109	193	0.1	139
	S.D.	19	19	116	0	13.2	15	57	21	0.0	22
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	104	59	255	1	20.3	89	93	176	0.0	126
	S.D.	31	12	40	0	4.8	15	90	42	0.0	10
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	90	56	280	1	32.0	102	100	195	0.0	128
	S.D.	17	10	84	0	13.5	23	50	34	0.0	16
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	109	72	340	1	38.0	87	117	184	0.1	128
	S.D.	29	16	53	0	27.1	15	44	29	0.0	9

		BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB
		mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
Test article										
Dose										
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	23	0.48	141	3.7	102	10.6	8.6	6.7	3.5
	S.D.	4	0.11	1	0.3	2	0.4	1.6	0.2	0.1
Cinchona Bark Extract 100 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	22	0.43	142	3.2	104	10.5	7.6	6.7	3.4
	S.D.	5	0.05	4	0.4	4	0.5	1.6	0.3	0.2
Cinchona Bark Extract 300 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	24	0.40	141	3.4	101	10.6	8.1	6.6	3.4
	S.D.	1	0.04	2	0.4	3	0.5	1.9	0.2	0.2
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	26	0.45	140	3.4	101	11.0	8.1	6.8	3.6
	S.D.	4	0.07	1	0.3	2	0.3	0.5	0.2	0.1

Not significantly different from Cinchona Bark Extract 0 mg/kg

Study No. : XXXXXXXXXX

Table 8-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Blood chemistry
Stage : End of administration (non-mating group)
Sex : Female

Species : Rat

		AST	ALT	ALP	γ-GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU
Test article		IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
Dose											
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	64	29	220	0	36.5	69	36	133	0.1	125
	S.D.	7	3	78	0	29.7	8	34	16	0.0	15
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	61	32	202	0	20.2	63	41	132	0.1	136
	S.D.	13	8	27	0	9.2	4	16	9	0.0	6

		BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB
Test article		mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
Dose										
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	17	0.35	143	3.5	106	10.0	4.5	6.5	3.5
	S.D.	1	0.03	1	0.3	2	0.3	0.5	0.3	0.3
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	19	0.40	142	3.5	107	10.1	4.4	6.9	3.8
	S.D.	4	0.09	2	0.1	2	0.2	0.5	0.1	0.1

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 8-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Blood chemistry
Sex : Male
Stage : End of recovery

Study No. : XXXXXXXXXX

		Species : Rat								
		AST	ALT	ALP	γ-GTP	T-BA	T-CHO	TG	PL	T-BIL
		IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL
Test article	Dose									
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	62	36	329	1	21.3	58	73	102	0.1
	S.D.	9	6	107	1	8.5	16	43	16	0.0
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	68	36	328	0	21.6	65	62	104	0.1
	S.D.	11	6	25	1	19.8	5	7	9	0.0
		BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB
		mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	21	0.40	144	3.8	106	10.2	5.5	6.5	3.3
	S.D.	5	0.06	1	0.2	1	0.3	0.6	0.2	0.1
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	17	0.37	144	3.9	106	10.2	5.5	6.5	3.2
	S.D.	2	0.03	2	0.1	1	0.4	0.1	0.2	0.1

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 8-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Blood chemistry
Sex : Female
Stage : End of recovery (non-mating group)

Study No. : XXXXXXXXXX

		Species : Rat								
		AST	ALT	ALP	γ-GTP	T-BA	T-CHO	TG	PL	T-BIL
		IU/L	IU/L	IU/L	IU/L	μmol/L	mg/dL	mg/dL	mg/dL	mg/dL
Test article	Dose									
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	78	31	190	1	21.6	62	31	131	0.1
	S.D.	26	9	76	0	14.0	15	16	29	0.0
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	63	33	141	1	29.9	75	62	158	0.1
	S.D.	28	16	45	1	17.0	7	38	13	0.1
		BUN	CRNN	Na	K	Cl	Ca	P	TP	ALB
		mg/dL	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	18	0.49	143	3.5	107	10.2	4.1	6.8	3.7
	S.D.	2	0.05	1	0.2	2	0.5	0.7	0.4	0.3
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5
	Mean	18	0.41	141	3.7	106	10.4	3.9	7.0	3.9
	S.D.	2	0.07	1	0.4	2	0.3	0.4	0.2	0.2

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05

T2 : Student t-test (two-side)

Table 9-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : End of administration

Species : Rat

		Body weight		Brain		Thyroid-RL		Thymus		Heart	
				AB	RE	AB	RE	AB	RE	AB	RE
Test article		g		g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g
Dose											
Cinchona Bark Extract 0 mg/kg	n	7	7	7	7	7	7	7	7	7	7
	Mean	557	2.22	0.40	24.2	4.4	391	70	1.59	0.29	
	S.D.	44	0.08	0.04	4.8	1.1	65	11	0.21	0.03	
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	548	2.19	0.40	22.8	4.1	357	65	1.50	0.27	
	S.D.	31	0.05	0.02	3.1	0.5	67	13	0.08	0.02	
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	544	2.22	0.41	24.8	4.6	368	67	1.55	0.29	
	S.D.	35	0.11	0.04	3.7	0.7	98	16	0.20	0.05	
Cinchona Bark Extract 1000 mg/kg	n	7	7	7	7	7	7	7	7	7	7
	Mean	549	2.23	0.41	22.2	4.1	341	62	1.57	0.29	
	S.D.	56	0.08	0.04	3.1	0.7	84	13	0.17	0.03	
		Liver		Spleen		Kidney-RL		Adrenal-RL		Testis-RL	
				AB	RE	AB	RE	AB	RE	AB	RE
Test article		g		g	g/100g	g	g/100g	mg	mg/100g	g	g/100g
Dose											
Cinchona Bark Extract 0 mg/kg	n	7	7	7	7	7	7	7	7	7	7
	Mean	14.67	2.63	0.76	0.14	3.55	0.64	67	12.2	3.55	0.64
	S.D.	1.44	0.14	0.14	0.02	0.22	0.04	8	2.1	0.26	0.06
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	14.65	2.67	0.80	0.14	3.58	0.66	64	11.7	3.36	0.62
	S.D.	1.42	0.17	0.10	0.01	0.28	0.04	8	1.5	0.25	0.06
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	14.10	2.59	0.84	0.15	3.71	0.68	75	13.9	3.46	0.64
	S.D.	1.28	0.13	0.18	0.03	0.24	0.06	11	2.0	0.30	0.07
Cinchona Bark Extract 1000 mg/kg	n	7	7	7	7	7	7	7	7	7	7
	Mean	14.37	2.61	0.75	0.14	3.66	0.67	66	12.1	3.51	0.64
	S.D.	1.78	0.09	0.11	0.02	0.37	0.04	11	2.4	0.40	0.06

AB : Absolute weight, RE : Relative weight by body weight
Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 9-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Organ weight

Stage : End of administration

Species : Rat

Sex : Male

		Epididymis-RL		Prostate		Seminal vesicle		LABC		Cowper's gland-RL	
Test article Dose		AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
		mg	mg/100g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
Cinchona Bark Extract 0 mg/kg	n	7	7	7	7	7	7	7	7	7	7
	Mean	1345	242	1.23	0.22	1.65	0.30	1.67	0.30	151.5	27.2
	S.D.	113	25	0.11	0.02	0.18	0.03	0.16	0.04	21.7	2.8
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	1341	246	1.36	0.25	1.83	0.33	1.65	0.30	144.2	26.5
	S.D.	85	19	0.24	0.05	0.26	0.04	0.18	0.04	17.1	4.0
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	1315	243	1.40	0.26	1.80	0.33	1.54	0.28	151.9	28.0
	S.D.	91	27	0.24	0.04	0.33	0.06	0.24	0.04	32.5	6.1
Cinchona Bark Extract 1000 mg/kg	n	7	7	7	7	7	7	7	7	7	7
	Mean	1314	241	1.56	0.29	1.95	0.36	1.80	0.33	155.4	28.7
	S.D.	138	34	DT *	DT **	0.36	0.09	0.16	0.04	37.5	8.3
Glans penis											
Test article Dose		AB	RE								
		mg	mg/100g								
Cinchona Bark Extract 0 mg/kg	n	7	7								
	Mean	144.8	26.1								
	S.D.	41.2	7.2								
Cinchona Bark Extract 100 mg/kg	n	12	12								
	Mean	142.0	26.2								
	S.D.	38.5	8.1								
Cinchona Bark Extract 300 mg/kg	n	12	12								
	Mean	135.5	24.9								
	S.D.	38.0	6.5								
Cinchona Bark Extract 1000 mg/kg	n	7	7								
	Mean	166.7	30.2								
	S.D.	47.1	7.7								

AB : Absolute weight, RE : Relative weight by body weight

LABC: Levator ani and bulbocavernosus muscle

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05, ** P<0.01

DT : Dunnett test (two-side)

Table 9-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Organ weight
Sex : Female

Stage : End of lactation (F0 dams)

Species : Rat

Test article Dose		Body weight g	Brain		Thyroid-RL		Thymus		Heart		
			AB	RE	AB	RE	AB	RE	AB	RE	
			g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g	
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12	12	12	12	12	12	
	Mean	344	2.03	0.59	17.4	5.1	256	74	1.14	0.33	
	S.D.	20	0.07	0.04	2.2	0.7	70	19	0.10	0.02	
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12	12	12	12	12	
	Mean	350	2.01	0.58	18.1	5.2	232	66	1.22	0.35	
	S.D.	23	0.09	0.04	4.1	1.4	48	12	0.24	0.05	
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12	12	12	12	12	
	Mean	349	2.03	0.59	19.0	5.4	258	73	1.20	0.34	
	S.D.	26	0.07	0.03	2.4	0.7	89	21	0.10	0.03	
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12	12	12	12	12	12	
	Mean	355	2.04	0.57	17.5	4.9	268	76	1.15	0.32	
	S.D.	14	0.09	0.03	2.7	0.7	76	22	0.12	0.03	
Test article Dose		Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
		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
Cinchona Bark Extract 0 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	11.67	3.40	0.62	0.18	2.32	0.67	77	22.5	92.4	26.9
	S.D.	0.72	0.18	0.08	0.02	0.15	0.04	11	3.4	8.3	2.6
Cinchona Bark Extract 100 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	12.20	3.49	0.57	0.16	2.36	0.68	77	22.2	97.2	27.8
	S.D.	0.84	0.22	0.09	0.03	0.14	0.04	7	3.4	13.6	3.6
Cinchona Bark Extract 300 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	12.28	3.53	0.57	0.16	2.40	0.69	74	21.2	92.2	26.5
	S.D.	1.00	0.23	0.07	0.02	0.14	0.05	8	2.5	14.5	3.7
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	12	12	12	12	12	12	12
	Mean	12.19	3.43	0.61	0.17	2.39	0.68	75	21.3	88.9	25.1
	S.D.	0.96	0.22	0.09	0.02	0.15	0.04	8	2.2	7.2	2.1

AB : Absolute weight, RE : Relative weight by body weight
Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 9-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight
Sex : Female

Stage : End of lactation (F0 dams)

Species : Rat

		Uterus	
Test article		AB	RE
Dose		mg	mg/100g
Cinchona Bark Extract 0 mg/kg	n	12	12
	Mean	517	151
	S.D.	55	20
Cinchona Bark Extract 100 mg/kg	n	12	12
	Mean	582	167
	S.D.	87	26
Cinchona Bark Extract 300 mg/kg	n	12	12
	Mean	571	164
	S.D.	62	18
Cinchona Bark Extract 1000 mg/kg	n	12	12
	Mean	526	148
	S.D.	74	22

AB : Absolute weight, RE : Relative weight by body weight
Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 9-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Organ weight
Sex : Female

Stage : End of administration (non-mating group)

Species : Rat

		Body weight		Brain		Thyroid-RL		Thymus		Heart	
Test article				AB	RE	AB	RE	AB	RE	AB	RE
Dose		g		g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	301	2.00	0.67	17.6	5.9	296	99	0.94	0.31	
	S.D.	28	0.04	0.06	1.3	0.6	46	16	0.11	0.02	
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	308	2.00	0.65	17.9	5.8	314	102	1.02	0.33	
	S.D.	23	0.09	0.06	2.0	0.7	47	12	0.04	0.03	
		Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
Test article				AB	RE	AB	RE	AB	RE	AB	RE
Dose		g		g	g/100g	g	g/100g	mg	mg/100g	mg	mg/100g
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	6.95	2.31	0.54	0.18	1.93	0.65	71	23.6	92.1	30.7
	S.D.	0.88	0.09	0.06	0.02	0.18	0.06	4	1.5	9.9	2.8
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	8.33	2.71	0.52	0.17	2.12	0.69	86	28.1	88.6	28.8
	S.D.	0.66	0.13	0.06	0.01	0.18	0.06	13	6.2	12.7	3.5
		T2 *	T2 **								
		Uterus									
Test article				AB	RE						
Dose				mg	mg/100g						
Cinchona Bark Extract 0 mg/kg	n	5	5								
	Mean	610	204								
	S.D.	117	40								
Cinchona Bark Extract 1000 mg/kg	n	5	5								
	Mean	570	184								
	S.D.	145	38								

AB : Absolute weight, RE : Relative weight by body weight

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05, ** P<0.01

T2 : Student t-test (two-side)

Table 9-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : End of recovery

Species : Rat

Sex : Male

		Body weight		Brain		Thyroid-RL		Thymus		Heart	
Test article				AB	RE	AB	RE	AB	RE	AB	RE
Dose		g		g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g
Cinchona Bark Extract	n	5		5	5	5	5	5	5	5	5
0 mg/kg	Mean	575		2.20	0.38	26.3	4.6	330	57	1.52	0.27
	S.D.	35		0.12	0.03	5.0	1.1	83	13	0.10	0.01
Cinchona Bark Extract	n	5		5	5	5	5	5	5	5	5
1000 mg/kg	Mean	592		2.20	0.37	22.2	3.8	303	51	1.60	0.27
	S.D.	39		0.10	0.02	1.5	0.4	61	9	0.14	0.01
		Liver		Spleen		Kidney-RL		Adrenal-RL		Testis-RL	
Test article		AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
Dose		g	g/100g	g	g/100g	g	g/100g	mg	mg/100g	g	g/100g
Cinchona Bark Extract	n	5		5	5	5	5	5	5	5	5
0 mg/kg	Mean	15.06		2.62	0.73	0.13	3.47	0.60	65	11.3	3.45
	S.D.	1.73		0.29	0.10	0.02	0.17	0.03	6	1.6	0.26
Cinchona Bark Extract	n	5		5	5	5	5	5	5	5	5
1000 mg/kg	Mean	15.81		2.66	0.87	0.15	3.75	0.63	60	10.2	3.53
	S.D.	2.32		0.23	0.11	0.02	0.44	0.05	11	2.1	0.26
		Epididymis-RL		Prostate		Seminal vesicle		LABC		Cowper's gland-RL	
Test article		AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
Dose		mg	mg/100g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
Cinchona Bark Extract	n	5		5	5	5	5	5	5	5	5
0 mg/kg	Mean	1352		236	1.26	0.22	1.67	0.29	1.54	126.3	22.1
	S.D.	46		9	0.28	0.06	0.29	0.06	0.22	14.8	3.5
Cinchona Bark Extract	n	5		5	5	5	5	5	5	5	5
1000 mg/kg	Mean	1391		236	1.44	0.25	1.87	0.32	1.71	139.1	23.7
	S.D.	142		32	0.14	0.04	0.23	0.04	0.17	20.0	4.8

AB : Absolute weight, RE : Relative weight by body weight

LABC: Levator ani and bulbocavernosus muscle

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 9-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight
Sex : Male

Stage : End of recovery

Species : Rat

		Glans penis	
Test article		AB	RE
Dose		mg	mg/100g
Cinchona Bark Extract	n	5	5
0 mg/kg	Mean	108.6	18.9
	S.D.	10.9	1.3
Cinchona Bark Extract	n	5	5
1000 mg/kg	Mean	107.9	18.3
	S.D.	5.5	1.3

AB : Absolute weight, RE : Relative weight by body weight

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 9-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Organ weight

Stage : End of recovery (non-mating group)

Species : Rat

Sex : Female

		Body weight		Brain		Thyroid-RL		Thymus		Heart	
Test article				AB	RE	AB	RE	AB	RE	AB	RE
Dose		g		g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	306	2.05	0.67	15.2	5.0	438	140	0.99	0.32	
	S.D.	24	0.05	0.04	1.7	0.7	464	142	0.11	0.03	
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	311	2.00	0.65	18.5	6.0	263	85	0.94	0.30	
	S.D.	33	0.05	0.08	1.2	0.5	49	17	0.05	0.03	
						T2 **	T2 *				
		Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
Test article		AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
Dose		g	g/100g	g	g/100g	g	g/100g	mg	mg/100g	mg	mg/100g
Cinchona Bark Extract 0 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	7.72	2.52	0.48	0.16	2.02	0.66	73	23.9	87.7	28.6
	S.D.	0.94	0.19	0.08	0.02	0.22	0.06	7	2.1	13.6	3.7
Cinchona Bark Extract 1000 mg/kg	n	5	5	5	5	5	5	5	5	5	5
	Mean	7.98	2.56	0.51	0.16	1.99	0.64	69	22.3	85.7	27.3
	S.D.	1.24	0.16	0.04	0.02	0.10	0.05	11	4.7	22.0	5.4
		Uterus									
Test article		AB	RE								
Dose		mg	mg/100g								
Cinchona Bark Extract 0 mg/kg	n	5	5								
	Mean	637	208								
	S.D.	114	32								
Cinchona Bark Extract 1000 mg/kg	n	5	5								
	Mean	557	182								
	S.D.	80	42								

AB : Absolute weight, RE : Relative weight by body weight

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05, ** P<0.01

T2 : Student t-test (two-side)

Table 10-1 Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Gross pathological findings (End of dosing)

Organs	Sex:	M	M	M	M
	Dose (mg/kg) :	0	100	300	1000
Findings	Number:	7	12	12	7
All tissues					
Not remarkable		7	12	12	7

M : Male

Table 10-2 Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Gross pathological findings (End of dosing)

Organs	Sex:	F	F
	Dose (mg/kg) :	0	1000
Findings	Number:	5	5
All tissues			
Not remarkable		5	5

F : Female

Table 10-3 Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Gross pathological findings (End of dosing,dams)

Organs	Sex:	F	F	F	F
	Dose (mg/kg) :	0	100	300	1000
Findings	Number:	12	12	12	12
Stomach					
Focus,dark red,glandular stomach		1	1	0	0

F : Female

Table 10-4 Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Gross pathological findings (End of recovery)

Organs	Sex:	M	M
	Dose (mg/kg) :	0	1000
Findings	Number:	5	5
All tissues			
Not remarkable		5	5

M : Male

Table 10-5 Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Gross pathological findings (End of recovery)

Organs	Sex:	F	F
Findings	Dose (mg/kg) : Number:	0 5	1000 5
Thymus			
Nodule		1	0

F : Female

Table 11-1 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of dosing)

Organs	Sex:	M	M	M	M
Findings	Dose (mg/kg) : Number:	0 7	100 12	300 12	1000 7
Adrenal					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Bone marrow, femur					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Bone, femur					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Brain (cerebrum, cerebellum, pons)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Coagulating gland					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Epididymis					
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, cecum					
Number examined		5	0	0	5
Not remarkable		5	0	0	4
Infiltrate, inflammatory cell, mucosa		0	0	0	1
minimal		0	0	0	1
Intestine, colon					
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, ileum					
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, rectum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5

M : Male

Table 11-2 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of dosing)

Organs	Sex:	M	M	M	M
	Dose (mg/kg) :	0	100	300	1000
Findings	Number:	7	12	12	7
Kidney					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Liver					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Lung (bronchus)					
Number examined		5	0	0	5
Not remarkable		4	0	0	5
Aggregation, alveolar macrophage		1	0	0	0
minimal		1	0	0	0
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
Medulla oblongata					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Muscle, quadriceps femoris					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Optic nerve					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pancreas					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Parathyroid					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Peyer's patch, ileal					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pituitary					
Number examined		5	0	0	5
Not remarkable		4	0	0	5
Cyst, pars distalis		1	0	0	0
minimal		1	0	0	0

M : Male

Table 11-3 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of dosing)

Organs	Sex:	M	M	M	M
	Dose (mg/kg) :	0	100	300	1000
Findings	Number:	7	12	12	7
Prostate					
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
Seminal vesicle					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Skin, inguinal					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spinal cord, thoracic					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spleen					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Stomach					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Testis					
Number examined		5	0	0	5
Not remarkable		5	0	0	4
Atrophy, tubule		0	0	0	1
minimal		0	0	0	1
Thymus					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Thyroid					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
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

M : Male

Table 11-4 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of dosing)

Organs	Sex:	F	F
Findings	Dose (mg/kg) : Number:	0 5	1000 5
Adrenal			
Number examined		5	5
Not remarkable		5	5
Bone marrow, femur			
Number examined		5	5
Not remarkable		5	5
Bone, femur			
Number examined		5	5
Not remarkable		5	5
Brain (cerebrum, cerebellum, pons)			
Number examined		5	5
Not remarkable		5	5
Eye			
Number examined		5	5
Not remarkable		4	5
Retinal fold		1	0
minimal		1	0
Heart			
Number examined		5	5
Not remarkable		5	5
Intestine, cecum			
Number examined		5	5
Not remarkable		5	5
Intestine, colon			
Number examined		5	5
Not remarkable		5	5
Intestine, duodenum			
Number examined		5	5
Not remarkable		5	5
Intestine, ileum			
Number examined		5	5
Not remarkable		5	5
Intestine, jejunum			
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		5	4
Calculus		0	1
mild		0	1

F : Female

Table 11-5 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of dosing)

Organs	Sex:	F	F
Findings	Dose (mg/kg) : Number:	0 5	1000 5
Liver			
Number examined		5	5
Not remarkable		5	5
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
Medulla oblongata			
Number examined		5	5
Not remarkable		5	5
Muscle, quadriceps femoris			
Number examined		5	5
Not remarkable		5	5
Optic nerve			
Number examined		5	5
Not remarkable		5	5
Ovary			
Number examined		5	5
Not remarkable		5	5
Pancreas			
Number examined		5	5
Not remarkable		5	5
Parathyroid			
Number examined		5	5
Not remarkable		5	5
Peyer's patch, ileal			
Number examined		5	5
Not remarkable		5	5
Pituitary			
Number examined		5	5
Not remarkable		5	5
Salivary gland, submandibular			
Number examined		5	5
Not remarkable		5	5

F : Female

Table 11-6 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of dosing)

Organs	Sex:	F	F
Findings	Dose (mg/kg) : Number:	0 5	1000 5
Sciatic nerve			
Number examined		5	5
Not remarkable		5	5
Skin, inguinal			
Number examined		5	5
Not remarkable		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		5	5
Thymus			
Number examined		5	5
Not remarkable		5	5
Thyroid			
Number examined		5	5
Not remarkable		5	5
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		5	5

F : Female

Table 11-7 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of dosing,dams)

Organs	Sex:	F	F	F	F
	Dose (mg/kg) :	0	100	300	1000
Findings	Number:	12	12	12	12
Adrenal					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Bone marrow, femur					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Bone, femur					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Brain (cerebrum, cerebellum, pons)					
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, cecum					
Number examined		5	0	0	5
Not remarkable		2	0	0	3
Infiltrate, inflammatory cell, mucosa		3	0	0	2
minimal		3	0	0	2
Intestine, colon					
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, ileum					
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, 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		5	0	0	5

F : Female

Table 11-8 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of dosing,dams)

Organs	Sex:	F	F	F	F
Findings	Dose (mg/kg) : Number:	0 12	100 12	300 12	1000 12
Lung (bronchus)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
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
Medulla oblongata					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Muscle,quadriceps femoris					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Optic nerve					
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	5
Not remarkable		5	0	0	5
Peyer's patch,ileal					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pituitary					
Number examined		5	0	0	5
Not remarkable		5	0	0	4
Cyst,pars distalis		0	0	0	1
minimal		0	0	0	1
Salivary gland,submandibular					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Sciatic nerve					
Number examined		5	0	0	5
Not remarkable		5	0	0	5

F : Female

Table 11-9 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of dosing,dams)

Organs	Sex:	F	F	F	F
Findings	Dose (mg/kg) : Number:	0 12	100 12	300 12	1000 12
Skin,inguinal					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spinal cord,thoracic					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spleen					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Stomach					
Number examined		5	0	0	5
Not remarkable		4	0	0	5
Edema,limiting ridge		1	0	0	0
minimal		1	0	0	0
Thymus					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Thyroid					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
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 11-10 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of recovery)

Organs	Sex:	M	M
Findings	Dose (mg/kg) : Number:	0 5	1000 5
Adrenal			
Number examined		5	5
Not remarkable		5	5
Bone marrow, femur			
Number examined		5	5
Not remarkable		5	5
Bone, femur			
Number examined		5	5
Not remarkable		5	5
Brain (cerebrum, cerebellum, pons)			
Number examined		5	5
Not remarkable		5	5
Coagulating gland			
Number examined		5	5
Not remarkable		5	5
Epididymis			
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, cecum			
Number examined		5	5
Not remarkable		5	4
Infiltrate, inflammatory cell, mucosa		0	1
minimal		0	1
Intestine, colon			
Number examined		5	5
Not remarkable		5	5
Intestine, duodenum			
Number examined		5	5
Not remarkable		5	5
Intestine, ileum			
Number examined		5	5
Not remarkable		5	5
Intestine, jejunum			
Number examined		5	5
Not remarkable		5	5
Intestine, rectum			
Number examined		5	5
Not remarkable		5	5

M : Male

Table 11-11 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of recovery)

Organs	Sex:	M	M
Findings	Dose (mg/kg) : Number:	0 5	1000 5
Kidney			
Number examined		5	5
Not remarkable		5	4
Dilatation,tubule		0	1
minimal		0	1
Liver			
Number examined		5	5
Not remarkable		5	5
Lung (bronchus)			
Number examined		5	5
Not remarkable		5	4
Granuloma		0	1
minimal		0	1
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
Medulla oblongata			
Number examined		5	5
Not remarkable		5	5
Muscle,quadriceps femoris			
Number examined		5	5
Not remarkable		5	5
Optic nerve			
Number examined		5	5
Not remarkable		5	5
Pancreas			
Number examined		5	5
Not remarkable		5	3
Fibrosis,islet		0	2
minimal		0	1
mild		0	1
Focus,basophilic,acinar cell		0	1
minimal		0	1
Parathyroid			
Number examined		5	5
Not remarkable		5	5
Peyer's patch,ileal			
Number examined		5	5
Not remarkable		5	5

M : Male

Table 11-12 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of recovery)

Organs	Sex:	M	M
	Dose (mg/kg) :	0	1000
Findings	Number:	5	5
Pituitary			
Number examined		5	5
Not remarkable		5	5
Prostate			
Number examined		5	5
Not remarkable		5	4
Cell infiltration, interstitial		0	1
minimal		0	1
Salivary gland, submandibular			
Number examined		5	5
Not remarkable		5	5
Sciatic nerve			
Number examined		5	5
Not remarkable		5	5
Seminal vesicle			
Number examined		5	5
Not remarkable		5	5
Skin, inguinal			
Number examined		5	5
Not remarkable		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		5	5
Testis			
Number examined		5	5
Not remarkable		5	5
Thymus			
Number examined		5	5
Not remarkable		5	5
Thyroid			
Number examined		5	5
Not remarkable		5	5
Trachea			
Number examined		5	5
Not remarkable		5	5
Urinary bladder			
Number examined		5	5
Not remarkable		5	5

M : Male

Table 11-13 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of recovery)

Organs	Sex:	F	F
Findings	Dose (mg/kg) : Number:	0 5	1000 5
Adrenal			
Number examined		5	5
Not remarkable		5	5
Bone marrow, femur			
Number examined		5	5
Not remarkable		5	5
Bone, femur			
Number examined		5	5
Not remarkable		5	5
Brain (cerebrum, cerebellum, pons)			
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, cecum			
Number examined		5	5
Not remarkable		4	3
Infiltrate, inflammatory cell, mucosa		1	2
minimal		1	2
Intestine, colon			
Number examined		5	5
Not remarkable		5	5
Intestine, duodenum			
Number examined		5	5
Not remarkable		5	5
Intestine, ileum			
Number examined		5	5
Not remarkable		5	5
Intestine, jejunum			
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		5	5
Liver			
Number examined		5	5
Not remarkable		5	5

F : Female

Table 11-14 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of recovery)

Organs	Sex:	F	F
Findings	Dose (mg/kg) : Number:	0 5	1000 5
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
Medulla oblongata			
Number examined		5	5
Not remarkable		5	5
Muscle, quadriceps femoris			
Number examined		5	5
Not remarkable		5	5
Optic nerve			
Number examined		5	5
Not remarkable		5	5
Ovary			
Number examined		5	5
Not remarkable		4	4
Cyst, luteal		1	0
minimal		1	0
Cyst, follicular		0	1
mild		0	1
Pancreas			
Number examined		5	5
Not remarkable		5	5
Parathyroid			
Number examined		5	5
Not remarkable		5	5
Peyer's patch, ileal			
Number examined		5	5
Not remarkable		5	5
Pituitary			
Number examined		5	5
Not remarkable		5	4
Aberrant craniopharyngeal tissue		0	1
present		0	1
Salivary gland, submandibular			
Number examined		5	5
Not remarkable		5	5

F : Female

Table 11-15 Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Histopathological findings (End of recovery)

Organs	Sex:	F	F
Findings	Dose (mg/kg) : Number:	0 5	1000 5
Sciatic nerve			
Number examined		5	5
Not remarkable		5	5
Skin, inguinal			
Number examined		5	5
Not remarkable		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		5	5
Thymus			
Number examined		5	5
Not remarkable		4	5
THYMOMA, MALIGNANT present		1 1	0 0
Thyroid			
Number examined		5	5
Not remarkable		5	4
Infiltrate, lymphocytic minimal		0 0	1 1
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	4
Hypertrophy, endometrial epithelial cell mild		0 0	1 1
Vagina			
Number examined		5	5
Not remarkable		5	4
Vacuolation, mucosa mild		0 0	1 1

F : Female

Table 12

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Estrus cycles
Generation : F0

Study No. : [REDACTED]

Species : Rat

		Generation : F ₁				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)				
Cinchona Bark Extract 0 mg/kg	n	12	12	12	8.3	
				(1)		
	Mean S.D.	4.2 0.4	3.5 0.7			
Cinchona Bark Extract 100 mg/kg	n	12	12	12	0.0	
				(0)		
	Mean S.D.	4.2 0.4	3.5 0.5			
Cinchona Bark Extract 300 mg/kg	n	12	12	12	0.0	
				(0)		
	Mean S.D.	4.2 0.4	3.5 0.5			
Cinchona Bark Extract 1000 mg/kg	n	12	12	12	0.0	
				(0)		
	Mean S.D.	4.2 0.3	3.7 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 Cinchona Bark Extract 0 mg/kg

Table 13-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No.: [REDACTED]

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)
Cinchona Bark Extract 0 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.7	100.0	100.0
	S.D.		1.1		
Cinchona Bark Extract 100 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.6	100.0	100.0
	S.D.		1.4		
Cinchona Bark Extract 300 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.0	100.0	100.0
	S.D.		1.0		
Cinchona Bark Extract 1000 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.3	100.0	100.0
	S.D.		1.3		

Not significantly different from Cinchona Bark Extract 0 mg/kg

a): (Number of copulated animals / Number of mated animals)x 100

b): (Number of males which impregnated females / Number of copulated males)x 100

Table 13-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No.: [REDACTED]

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)
Cinchona Bark Extract 0 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.7	100.0	100.0
	S.D.		1.1		
Cinchona Bark Extract 100 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.6	100.0	100.0
	S.D.		1.4		
Cinchona Bark Extract 300 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.0	100.0	100.0
	S.D.		1.0		
Cinchona Bark Extract 1000 mg/kg	n	12	12	(12/12)	(12/12)
	Mean		2.3	100.0	100.0
	S.D.		1.3		

Not significantly different from Cinchona Bark Extract 0 mg/kg

a): (Number of copulated animals / Number of mated animals)x 100

b): (Number of pregnant females / Number of copulated females)x 100

Table 14

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Delivery data

Generation : F0

Species : Rat

Test article Dose		Gestation period (day)	Gestation index (%) a)	Number of implan- tation	Delivery index (%) b)	Live birth index (%) c)	Number of offspring	Number of live newborns			Sex ratio (%) d)	Number of dead newborns
								M	F	Total		
Cinchona Bark Extract 0 mg/kg	n	12	12/12	12	12	12	12	12	12	12	93/179	12
	Mean	22.1	100.0	15.9	96.0	97.7	15.3	7.8	7.2	14.9	52.0	0.3
	S.D.	0.4		1.4	5.4	6.3	1.4	1.9	1.7	1.8		0.9
Cinchona Bark Extract 100 mg/kg	n	12	12/12	12	12	12	12	12	12	12	85/176	12
	Mean	22.3	100.0	16.1	92.0	99.4	14.8	7.1	7.6	14.7	48.3	0.1
	S.D.	0.4		1.7	6.6	2.0	1.4	1.8	2.2	1.5		0.3
Cinchona Bark Extract 300 mg/kg	n	12	12/12	12	12	12	12	12	12	12	101/192	12
	Mean	22.0	100.0	17.0	94.6	99.3	16.1	8.4	7.6	16.0	52.6	0.1
	S.D.	0.3		1.4	8.5	2.4	1.9	2.3	2.5	2.1		0.3
Cinchona Bark Extract 1000 mg/kg	n	12	12/12	12	12	12	12	12	12	12	97/184	12
	Mean	21.8	100.0	16.2	95.2	100.0	15.3	8.1	7.3	15.3	52.7	0.0
	S.D.	0.4		1.4	7.5	0.0	1.2	2.4	2.1	1.2		0.0

M : Male, F : Female

Not significantly different from Cinchona Bark Extract 0 mg/kg

a): (Number of females delivered live newborns / Number of pregnant females) x 100

b): (Number of delivered pups / Number of implantation) x 100

c): (Number of liveborns / Number of delivered pups) x 100

d): (Number of live males / Number of liveborns) x 100

Table 15

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
External examination of offspring
Generation : F0

Study No. : [REDACTED]

Days after birth : 0
Species : Rat

	Cinchona Bark Extract	Cinchona Bark Extract	Cinchona Bark Extract	Cinchona Bark Extract
Test article	0	100	300	1000
Dose	mg/kg	mg/kg	mg/kg	mg/kg
Dose unit	12	12	12	12
Number of dams	183	177	193	184
Number of offspring				
Number of dams with anomalous offspring (incidence %) a)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Number of offspring with any anomaly (incidence %) b)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Not significantly different from Cinchona Bark Extract 0 mg/kg
a): (Number of dams bearing pups with external anomalies / Number of dams) x 100
b): (Number of pups with external anomalies / Number of delivered pups) x 100

Table 16

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Anogenital of offspring
Generation : F0

Study No. : [REDACTED]

				Unit : mm	Species : Rat
Dose		Sex	/Days after birth		
				0	
Test article				AGD	Normalized a)
				AGD	AGD
Cinchona Bark Extract 0 mg/kg	Male	n	12	12	
		Mean	2.3	1.3	
		S.D.	0.1	0.1	
	Female	n	12	12	
		Mean	0.9	0.5	
		S.D.	0.1	0.0	
Cinchona Bark Extract 100 mg/kg	Male	n	12	12	
		Mean	2.5	1.3	
		S.D.	0.1	0.1	
	Female	n	12	12	
		Mean	0.8	0.5	
		S.D.	0.1	0.1	
Cinchona Bark Extract 300 mg/kg	Male	n	12	12	
		Mean	2.4	1.3	
		S.D.	0.1	0.1	
	Female	n	12	12	
		Mean	0.8	0.5	
		S.D.	0.1	0.1	
Cinchona Bark Extract 1000 mg/kg	Male	n	12	12	
		Mean	2.3	1.2	
		S.D.	0.2	0.1	
	Female	n	12	12	
		Mean	0.8	0.4	
		S.D.	0.1	0.0	

AGD : Anogenital Distance

Significantly different from Cinchona Bark Extract 0 mg/kg : * P<0.05

DT : Dunnett test (two-side)

a): AGD (mm) / Cube root of body weight (g)

Table 17

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Litter size and viability index of offspring
Generation : F0

Study No. : XXXXXXXXXX

Species : Rat

		/Days after birth					
Test article Dose		0	4	4	4	13	13
			Pre-culled	Viability index (%) a)	Culled		Viability index (%) b)
Cinchona Bark Extract 0 mg/kg	Total	179	176		96	96	
	n	12	12	12	12	12	12
	Mean			98.4			100.0
	S.D.			4.1			0.0
Cinchona Bark Extract 100 mg/kg	Total	176	174		96	96	
	n	12	12	12	12	12	12
	Mean			98.7			100.0
	S.D.			3.0			0.0
Cinchona Bark Extract 300 mg/kg	Total	192	187		96	96	
	n	12	12	12	12	12	12
	Mean			97.3			100.0
	S.D.			4.3			0.0
Cinchona Bark Extract 1000 mg/kg	Total	184	169		94	94	
	n	12	12	12	12	12	12
	Mean			91.7			100.0
	S.D.			17.2			0.0

Not significantly different from Cinchona Bark Extract 0 mg/kg

a): (Number of pups alive on day 4 after birth / Number of live born pups) × 100

b): (Number of pups alive on day 13 after birth / Number of pups after culling on day 4 after birth) × 100

Table 18

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Sex ratio
Generation : F0

Study No. : [REDACTED]

Species : Rat

Test article Dose	Number of dams	day 4 after birth		
		Number of males	Number of females	Sex ratio (%) a)
Cinchona Bark Extract 0 mg/kg	12	Total (%)	91	85 91/176 51.7
Cinchona Bark Extract 100 mg/kg	12	Total (%)	83	91 83/173 47.7
Cinchona Bark Extract 300 mg/kg	12	Total (%)	100	87 100/187 53.5
Cinchona Bark Extract 1000 mg/kg	12	Total (%)	88	81 88/169 52.1

Not significantly different from Cinchona Bark Extract 0 mg/kg
a): (Number of male pups alive on day 4 after birth / Number of pups alive on day 4 after birth) × 100

Table 19-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Body weight of offspring
Generation : F0

Unit : g

Species : Rat

Test article Dose	Generation : F0		/Days after birth					Unit : g	Species : Rat
			0	4/Pre-culled	4/Culled	7	13		
Cinchona Bark Extract 0 mg/kg	Male	n	12	12	12	12	12		
		Mean	6.5	10.4	10.8	17.7	34.0		
		S.D.	0.5	1.0	0.9	1.4	2.6		
	Female	n	12	12	12	12	12		
		Mean	6.3	9.9	10.1	16.7	32.4		
		S.D.	0.5	0.9	0.9	1.5	2.6		
Cinchona Bark Extract 100 mg/kg	Male	n	12	12	12	12	12		
		Mean	6.8	10.8	11.1	18.0	34.3		
		S.D.	0.4	0.9	1.0	2.5	3.0		
	Female	n	12	12	12	12	12		
		Mean	6.5	10.4	10.7	17.2	33.2		
		S.D.	0.5	1.1	1.0	1.5	2.8		
Cinchona Bark Extract 300 mg/kg	Male	n	12	12	12	12	12		
		Mean	6.6	10.1	10.6	17.1	32.9		
		S.D.	0.5	1.2	1.1	1.9	2.8		
	Female	n	12	12	12	12	12		
		Mean	6.3	9.6	9.8	15.9	30.9		
		S.D.	0.4	1.2	1.1	1.8	2.5		
Cinchona Bark Extract 1000 mg/kg	Male	n	12	12	12	12	12		
		Mean	6.4	9.9	10.2	16.6	32.0		
		S.D.	0.5	1.2	1.3	2.5	4.2		
	Female	n	12	12	12	12	12		
		Mean	6.1	9.6	9.8	16.1	31.5		
		S.D.	0.5	1.2	1.2	2.2	3.3		

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 19-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight gain of offspring
Generation : F0

Study No. : [REDACTED]

Base : Day 4 after birth

Unit : g

Species : Rat

Test article Dose			/Days after birth		
			/Before culling	/After culling	
			0-4	4-7	4-13
Cinchona Bark Extract 0 mg/kg	Male	n	12	12	12
		Mean	3.9	6.9	23.2
		S.D.	0.8	0.7	1.9
	Female	n	12	12	12
		Mean	3.7	6.6	22.4
		S.D.	0.7	0.7	1.9
Cinchona Bark Extract 100 mg/kg	Male	n	12	12	12
		Mean	4.0	6.9	23.2
		S.D.	0.8	1.7	2.1
	Female	n	12	12	12
		Mean	3.9	6.6	22.5
		S.D.	0.9	0.7	2.0
Cinchona Bark Extract 300 mg/kg	Male	n	12	12	12
		Mean	3.5	6.6	22.3
		S.D.	0.8	0.9	1.9
	Female	n	12	12	12
		Mean	3.3	6.0	21.1
		S.D.	0.9	0.8	1.7
Cinchona Bark Extract 1000 mg/kg	Male	n	12	12	12
		Mean	3.5	6.4	21.8
		S.D.	1.0	1.3	3.0
	Female	n	12	12	12
		Mean	3.5	6.3	21.7
		S.D.	0.8	1.0	2.2

Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 20	Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats Externally for gross abnormalities in dead pups				Study No. : XXXXXXXXXX
					Species : Rat
	Test article Dose	Cinchona Bark Extract 0 mg/kg	Cinchona Bark Extract 100 mg/kg	Cinchona Bark Extract 300 mg/kg	Cinchona Bark Extract 1000 mg/kg
Male					
Number of pups examined		0	0	1	3
Number of pups with abnormal findings		0	0	0	0
Female					
Number of pups examined		1	0	2	0
Number of pups with abnormal findings		0	0	0	0

Table 21

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Nipple retention of male pups
Generation : F0

Study No. : XXXXXXXXXX

Generation : F0				Unit : No.	Species : Rat
Test article	/Days after birth				
Dose	13				
Cinchona Bark Extract 0 mg/kg	Male	n	12		
		Mean	0.0		
		S.D.	0.0		
Cinchona Bark Extract 100 mg/kg	Male	n	12		
		Mean	0.0		
		S.D.	0.0		
Cinchona Bark Extract 300 mg/kg	Male	n	12		
		Mean	0.0		
		S.D.	0.0		
Cinchona Bark Extract 1000 mg/kg	Male	n	12		
		Mean	0.0		
		S.D.	0.0		
Not significantly different from Cinchona Bark Extract 0 mg/kg					

Table 22

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Gross pathological findings in pups on postnatal day 13

Study No. : [REDACTED]

	Test article Dose	Cinchona Bark Extract 0 mg/kg	Cinchona Bark Extract 100 mg/kg	Cinchona Bark Extract 300 mg/kg	Cinchona Bark Extract 1000 mg/kg	Species : Rat
Male						
Number of pups examined		48	50	48	44	
Number of pups with abnormal findings		0	0	0	0	
Female						
Number of pups examined		48	46	48	50	
Number of pups with abnormal findings		0	0	0	0	

Table 23-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : After culled (F1 males)

Sex : Male

Species : Rat

Test article Dose		Body weight g	Thyroid-RL	
			AB mg	RE mg/100g
Cinchona Bark Extract 0 mg/kg	n	12	12	12
	Mean	34.2	4.5	13.3
	S.D.	3.3	0.9	2.5
Cinchona Bark Extract 100 mg/kg	n	12	12	12
	Mean	34.7	4.4	12.6
	S.D.	3.4	1.1	3.2
Cinchona Bark Extract 300 mg/kg	n	12	12	12
	Mean	33.8	4.2	12.5
	S.D.	3.2	1.0	3.1
Cinchona Bark Extract 1000 mg/kg	n	12	12	12
	Mean	32.6	4.3	13.2
	S.D.	3.6	1.2	4.0

AB : Absolute weight, RE : Relative weight by body weight
Not significantly different from Cinchona Bark Extract 0 mg/kg

Table 23-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : After culled (F1 females)

Sex : Female

Species : Rat

Test article Dose		Body weight g	Thyroid-RL	
			AB mg	RE mg/100g
Cinchona Bark Extract 0 mg/kg	n	12	12	12
	Mean	33.4	4.4	13.3
	S.D.	2.9	0.8	3.2
Cinchona Bark Extract 100 mg/kg	n	12	12	12
	Mean	33.7	4.2	12.6
	S.D.	2.7	1.0	3.1
Cinchona Bark Extract 300 mg/kg	n	12	12	12
	Mean	32.1	4.4	13.8
	S.D.	2.6	1.0	3.2
Cinchona Bark Extract 1000 mg/kg	n	12	12	12
	Mean	32.2	4.3	13.5
	S.D.	2.9	1.1	4.0

AB : Absolute weight, RE : Relative weight by body weight

Not significantly different from Cinchona Bark Extract 0 mg/kg

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43
Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	/Day																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Clinical signs

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	/Day														a)
	30	31	32	33	34	35	36	37	38	39	40	41	42	43	
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

:- No abnormal findings

a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43
Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	/Day																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Clinical signs

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	/Day														a)
	30	31	32	33	34	35	36	37	38	39	40	41	42	43	
2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

:- No abnormal findings

a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43
Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	/Day																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
3001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Clinical signs

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	/Day														a)
	30	31	32	33	34	35	36	37	38	39	40	41	42	43	
3001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

:- No abnormal findings

a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Male

Period : F0 before mating Day 1-15, F0 mating Day 15-43
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	/Day																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
4001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Clinical signs

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	/Day														a)
	30	31	32	33	34	35	36	37	38	39	40	41	42	43	
4001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

:- No abnormal findings

a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : F0 before mating Day 1-15
Dose : Cinchona Bark Extract 0 mg/kg

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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : F0 before mating Day 1-15
Dose : Cinchona Bark Extract 100 mg/kg

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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : F0 before mating Day 1-15
Dose : Cinchona Bark Extract 300 mg/kg

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 1-12

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Clinical signs

Period : F0 before mating Day 1-15

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-13

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Clinical signs
Sex : Female

Period : F0 gestation Day 0-25
Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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	24	25
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : F0 gestation Day 0-25
Dose : Cinchona Bark Extract 100 mg/kg
Species : Rat

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	24	25
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : F0 gestation Day 0-25
Dose : Cinchona Bark Extract 300 mg/kg
Species : Rat

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	24	25
3101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : F0 gestation Day 0-25
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

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	24	25
4101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-17

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No.: [REDACTED]

Clinical signs
Sex : Female

Period : F0 lactation Day 0-14
Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	/Day														
Animal No.	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14 a)
1101		-	-	-	-	-	-	-	-	-	-	-	-	-	-
1102		-	-	-	-	-	-	-	-	-	-	-	-	-	-
1103		-	-	-	-	-	-	-	-	-	-	-	-	-	-
1104		-	-	-	-	-	-	-	-	-	-	-	-	-	-
1105	-			-	-	-	-	-	-	-	-	-	-	-	-
1106		-	-	-	-	-	-	-	-	-	-	-	-	-	-
1107	-		-	-	-	-	-	-	-	-	-	-	-	-	-
1108	-	-		-	-	-	-	-	-	-	-	-	-	-	-
1109		-	-	-	-	-	-	-	-	-	-	-	-	-	-
1110	-	-		-	-	-	-	-	-	-	-	-	-	-	-
1111		-	-	-	-	-	-	-	-	-	-	-	-	-	-
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

:- No abnormal findings

a): Day of necropsy

Appendix 1-18

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Clinical signs

Period : F0 lactation Day 0-14

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Dose : 10mg/kg														Species : Rat
	Dose : 10mg/kg														
Animal No.	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14 a)
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

:- No abnormal findings

a): Day of necropsy

Appendix 1-19

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No.: [REDACTED]

Clinical signs
Sex : Female

Period : F0 lactation Day 0-14
Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	/Day														
Animal No.	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14 a)
3101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

:- No abnormal findings

a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : F0 lactation Day 0-14
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	/Day														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14 a)
4101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : Administration Day 1-43 (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg
Species : Rat

Animal No.	/Day																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
5101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-22

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Clinical signs
Sex : Female

Period : Administration Day 1-43 (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	/Day														a)
	30	31	32	33	34	35	36	37	38	39	40	41	42	43	
5101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

:- No abnormal findings

a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : Administration Day 1-43 (non-mating group)
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	/Day																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
6101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : Administration Day 1-43 (non-mating group)
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	/Day														a)
	30	31	32	33	34	35	36	37	38	39	40	41	42	43	
6101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

-: No abnormal findings
a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Male

Period : Recovery Day 1-15
Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 a)
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Male

Period : Recovery Day 1-15
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 a)
4008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : Recovery Day 1-15 (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 a)
5106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
a): Day of necropsy

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Clinical signs
Sex : Female

Period : Recovery Day 1-15 (non-mating group)
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	/Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 a)
6106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
a): Day of necropsy

Appendix 2-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 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

Appendix 2-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 100 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

Appendix 2-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 300 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

Appendix 2-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 1000 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

Appendix 2-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 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

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 100 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

Appendix 2-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 300 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

Appendix 2-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 1000 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

Appendix 2-9

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : Cinchona Bark Extract 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 mating

Generation : F0

Sex : Male

Week : 3

Dose : Cinchona Bark Extract 100 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

Generation : F0

Sex : Male

Week : 3

Dose : Cinchona Bark Extract 300 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 mating

Generation : F0

Sex : Male

Week : 3

Dose : Cinchona Bark Extract 1000 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 : 4

Dose : Cinchona Bark Extract 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 mating

Generation : F0

Sex : Male

Week : 4

Dose : Cinchona Bark Extract 100 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

Generation : F0

Sex : Male

Week : 4

Dose : Cinchona Bark Extract 300 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 mating

Generation : F0

Sex : Male

Week : 4

Dose : Cinchona Bark Extract 1000 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

Appendix 2-17

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : Cinchona Bark Extract 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

Appendix 2-18

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : Cinchona Bark Extract 100 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

Generation : F0

Sex : Male

Week : 5

Dose : Cinchona Bark Extract 300 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 mating

Generation : F0

Sex : Male

Week : 5

Dose : Cinchona Bark Extract 1000 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

Appendix 2-21

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 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 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 100 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

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 300 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

Appendix 2-24

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 1000 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

Appendix 2-25

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 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 : Cinchona Bark Extract 100 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

Appendix 2-27

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 300 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 : 1

Dose : Cinchona Bark Extract 1000 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 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 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 : Cinchona Bark Extract 100 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

Appendix 2-31

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 300 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 : Cinchona Bark Extract 1000 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

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 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

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 100 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

Appendix 2-35

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 300 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 gestation

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 1000 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

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 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

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 100 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 gestation

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 300 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 gestation

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 1000 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

Generation : F0

Sex : Female

Day : 14

Dose : Cinchona Bark Extract 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

Generation : F0

Sex : Female

Day : 14

Dose : Cinchona Bark Extract 100 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 gestation

Generation : F0

Sex : Female

Day : 14

Dose : Cinchona Bark Extract 300 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 gestation

Generation : F0

Sex : Female

Day : 14

Dose : Cinchona Bark Extract 1000 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

Generation : F0

Sex : Female

Day : 20

Dose : Cinchona Bark Extract 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

Generation : F0

Sex : Female

Day : 20

Dose : Cinchona Bark Extract 100 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 gestation

Generation : F0

Sex : Female

Day : 20

Dose : Cinchona Bark Extract 300 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 gestation

Generation : F0

Sex : Female

Day : 20

Dose : Cinchona Bark Extract 1000 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 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 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

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 100 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 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 300 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 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 1000 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 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 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

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 100 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 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 300 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 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 1000 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

Appendix 2-57

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	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 : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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 : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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

Appendix 2-60

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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 (non-mating group)

Generation : F0

Sex : Female

Week : 3

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	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

Appendix 2-62

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 3

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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 (non-mating group)

Generation : F0

Sex : Female

Week : 4

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	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

Appendix 2-64

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 4

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Female Week : 5 Period : Administration (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg

	Posture	Convulsion	Abnormal behavior	Species : Rat
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 (non-mating group)

Generation : F0

Sex : Female

Week : 5

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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

Appendix 2-67

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Home cage observation
Generation : F0 Sex : Female Week : 6 Period : Administration (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg

Study No. : XXXXXXXXXX

	Posture	Convulsion	Abnormal behavior	Species : Rat
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 (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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

Appendix 2-69

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Recovery

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
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

Appendix 2-70

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Recovery

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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

Appendix 2-71

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Posture	Convulsion	Abnormal behavior
Animal No.			
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

Appendix 2-72

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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 (non-mating group)

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	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 (non-mating group)

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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

Appendix 2-75

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Recovery (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	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

Appendix 2-76

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Home cage observation

Period : Recovery (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	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							
	Generation : F0	Sex : Male	Week : 1	Period : F0 before mating	Dose : Cinchona Bark Extract 0 mg/kg	Species : Rat		
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Male	Week : 1	Period : F0 before mating	Dose : Cinchona Bark Extract 100 mg/kg	Species : Rat		
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Cinchona Bark Extract 300 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	2	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 before mating		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 1							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
4001	0	0	0	0	0	0	0		
4002	0	0	0	0	0	0	0		
4003	0	0	0	0	0	0	0		
4004	0	0	0	0	0	0	0		
4005	0	0	0	0	0	0	0		
4006	0	0	0	0	0	0	0		
4007	0	0	0	0	0	0	0		
4008	0	0	0	0	0	0	0		
4009	0	0	0	0	0	0	0		
4010	0	0	0	0	0	0	0		
4011	0	0	0	0	0	0	0		
4012	0	0	0	0	0	0	0		
n	12	12	12	12	12	12	12		

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
Animal No.							
4001	0	0	0	0	0		
4002	0	0	0	0	0		
4003	0	0	0	0	0		
4004	0	0	0	0	0		
4005	0	0	0	0	0		
4006	0	0	0	0	0		
4007	0	0	0	0	0		
4008	0	0	0	0	0		
4009	0	0	0	0	0		
4010	0	0	0	0	0		
4011	0	0	0	0	0		
4012	0	0	0	0	0		
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Male	Week : 2	Period : F0 before mating	Dose : Cinchona Bark Extract 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.	In-the-hand observation					
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Cinchona Bark Extract 100 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	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0	0	0	0	0
2004	0	0	0	0	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	0	0	0	0	0
2008	0	0	0	0	0	0	0	0	0	0	0	0
2009	0	0	0	0	0	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0	0	0	0	0	0
2011	0	0	0	0	0	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Cinchona Bark Extract 300 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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Male	Week : 2	Period : F0 before mating	Dose : Cinchona Bark Extract 1000 mg/kg	Species : Rat		
	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.	In-the-hand observation					
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Cinchona Bark Extract 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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 mating		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 3							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
2001	0	0	0	0	0	0	0		
2002	0	0	0	0	0	0	0		
2003	0	0	0	0	0	0	0		
2004	0	0	0	0	0	0	0		
2005	0	0	0	0	0	0	0		
2006	0	0	0	0	0	0	0		
2007	0	0	0	0	0	0	0		
2008	0	0	0	0	0	0	0		
2009	0	0	0	0	0	0	0		
2010	0	0	0	0	0	0	0		
2011	0	0	0	0	0	0	0		
2012	0	0	0	0	0	0	0		
n	12	12	12	12	12	12	12		

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
Animal No.					
2001	0	0	0	0	0
2002	0	0	0	0	0
2003	0	0	0	0	0
2004	0	0	0	0	0
2005	0	0	0	0	0
2006	0	0	0	0	0
2007	0	0	0	0	0
2008	0	0	0	0	0
2009	0	0	0	0	0
2010	0	0	0	0	0
2011	0	0	0	0	0
2012	0	0	0	0	0
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Cinchona Bark Extract 300 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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Cinchona Bark Extract 1000 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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Male	Week : 4	Period : F0 mating	Dose : Cinchona Bark Extract 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.	In-the-hand observation					
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 mating		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 4							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
2001	0	0	0	0	0	0	0	0	0
2002	0	0	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0	0	0
2004	0	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	0	0
2008	0	0	0	0	0	0	0	0	0
2009	0	0	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0	0	0
2011	0	0	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12	12

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
Animal No.							
2001	0	0	0	0	0		
2002	0	0	0	0	0		
2003	0	0	0	0	0		
2004	0	0	0	0	0		
2005	0	0	0	0	0		
2006	0	0	0	0	0		
2007	0	0	0	0	0		
2008	0	0	0	0	0		
2009	0	0	0	0	0		
2010	0	0	0	0	0		
2011	0	0	0	0	0		
2012	0	0	0	0	0		
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 mating		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 4							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
3001	0	0	0	0	0	0	0		
3002	0	0	0	0	0	0	0		
3003	0	0	0	0	0	0	0		
3004	0	0	0	0	0	0	0		
3005	0	0	0	0	0	0	0		
3006	0	0	0	0	0	0	0		
3007	0	0	0	0	0	0	0		
3008	0	0	0	0	0	0	0		
3009	0	0	0	0	0	0	0		
3010	0	0	0	0	0	0	0		
3011	0	0	0	0	0	0	0		
3012	0	0	0	0	0	0	0		
n	12	12	12	12	12	12	12		

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
Animal No.							
3001	0	0	0	0	0		
3002	0	0	0	0	0		
3003	0	0	0	0	0		
3004	0	0	0	0	0		
3005	0	0	0	0	0		
3006	0	0	0	0	0		
3007	0	0	0	0	0		
3008	0	0	0	0	0		
3009	0	0	0	0	0		
3010	0	0	0	0	0		
3011	0	0	0	0	0		
3012	0	0	0	0	0		
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 mating		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 4							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
4001	0	0	0	0	0	0	0		
4002	0	0	0	0	0	0	0		
4003	0	0	0	0	0	0	0		
4004	0	0	0	0	0	0	0		
4005	0	0	0	0	0	0	0		
4006	0	0	0	0	0	0	0		
4007	0	0	0	0	0	0	0		
4008	0	0	0	0	0	0	0		
4009	0	0	0	0	0	0	0		
4010	0	0	0	0	0	0	0		
4011	0	0	0	0	0	0	0		
4012	0	0	0	0	0	0	0		
n	12	12	12	12	12	12	12		

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
Animal No.					
4001	0	0	0	0	0
4002	0	0	0	0	0
4003	0	0	0	0	0
4004	0	0	0	0	0
4005	0	0	0	0	0
4006	0	0	0	0	0
4007	0	0	0	0	0
4008	0	0	0	0	0
4009	0	0	0	0	0
4010	0	0	0	0	0
4011	0	0	0	0	0
4012	0	0	0	0	0
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Cinchona Bark Extract 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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 mating			Species : Rat		
Generation : F0	Sex : Male	Week : 5	Dose : Cinchona Bark Extract 100 mg/kg	Secretions- Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation	
Ease of remov- al from cage	Fur condition	Skin							
Animal No.									
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	

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
Animal No.					
2001	0	0	0	0	0
2002	0	0	0	0	0
2003	0	0	0	0	0
2004	0	0	0	0	0
2005	0	0	0	0	0
2006	0	0	0	0	0
2007	0	0	0	0	0
2008	0	0	0	0	0
2009	0	0	0	0	0
2010	0	0	0	0	0
2011	0	0	0	0	0
2012	0	0	0	0	0
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Male	Week : 5	Period : F0 mating	Dose : Cinchona Bark Extract 300 mg/kg	Species : Rat		
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Cinchona Bark Extract 1000 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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-97

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

In-the-hand observation		Period : F0 mating		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 6							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
1001	0	0	0	0	0	0	0		
1002	0	0	0	0	0	0	0		
1003	0	0	0	0	0	0	0		
1004	0	0	0	0	0	0	0		
1005	0	0	0	0	0	0	0		
1006	0	0	0	0	0	0	0		
1007	0	0	0	0	0	0	0		
1008	0	0	0	0	0	0	0		
1009	0	0	0	0	0	0	0		
1010	0	0	0	0	0	0	0		
1011	0	0	0	0	0	0	0		
1012	0	0	0	0	0	0	0		
n	12	12	12	12	12	12	12		

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
Animal No.					
1001	0	0	0	0	0
1002	0	0	0	0	0
1003	0	0	0	0	0
1004	0	0	0	0	0
1005	0	0	0	0	0
1006	0	0	0	0	0
1007	0	0	0	0	0
1008	0	0	0	0	0
1009	0	0	0	0	0
1010	0	0	0	0	0
1011	0	0	0	0	0
1012	0	0	0	0	0
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Male	Week : 6	Period : F0 mating	Dose : Cinchona Bark Extract 100 mg/kg	Species : Rat		
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 mating		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 6							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
3001	0	0	0	0	0	0	0	0	0
3002	0	0	0	0	0	0	0	0	0
3003	0	0	0	0	0	0	0	0	0
3004	0	0	0	0	0	0	0	0	0
3005	0	0	0	0	0	0	0	0	0
3006	0	0	0	0	0	0	0	0	0
3007	0	0	0	0	0	0	0	0	0
3008	0	0	0	0	0	0	0	0	0
3009	0	0	0	0	0	0	0	0	0
3010	0	0	0	0	0	0	0	0	0
3011	0	0	0	0	0	0	0	0	0
3012	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12	12

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
Animal No.							
3001	0	0	0	0	0		
3002	0	0	0	0	0		
3003	0	0	0	0	0		
3004	0	0	0	0	0		
3005	0	0	0	0	0		
3006	0	0	0	0	0		
3007	0	0	0	0	0		
3008	0	0	0	0	0		
3009	0	0	0	0	0		
3010	0	0	0	0	0		
3011	0	0	0	0	0		
3012	0	0	0	0	0		
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 mating		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 6							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
4001	0	0	0	0	0	0	0	0	0
4002	0	0	0	0	0	0	0	0	0
4003	0	0	0	0	0	0	0	0	0
4004	0	0	0	0	0	0	0	0	0
4005	0	0	0	0	0	0	0	0	0
4006	0	0	0	0	0	0	0	0	0
4007	0	0	0	0	0	0	0	0	0
4008	0	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12	12

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
Animal No.							
4001	0	0	0	0	0		
4002	0	0	0	0	0		
4003	0	0	0	0	0		
4004	0	0	0	0	0		
4005	0	0	0	0	0		
4006	0	0	0	0	0		
4007	0	0	0	0	0		
4008	0	0	0	0	0		
4009	0	0	0	0	0		
4010	0	0	0	0	0		
4011	0	0	0	0	0		
4012	0	0	0	0	0		
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-101

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : Cinchona Bark Extract 0 mg/kg	Ease of removal from cage	Fur condition	Skin	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	0	0	0	0	0	0
1102	0	0	0	0	0	0	0	0	0	0	0	0
1103	0	0	0	0	0	0	0	0	0	0	0	0
1104	0	0	0	0	0	0	0	0	0	0	0	0
1105	0	0	0	0	0	0	0	0	0	0	0	0
1106	0	0	0	0	0	0	0	0	0	0	0	0
1107	0	0	0	0	0	0	0	0	0	0	0	0
1108	0	0	0	0	0	0	0	0	0	0	0	0
1109	0	0	0	0	0	0	0	0	0	0	0	0
1110	0	0	0	0	0	0	0	0	0	0	0	0
1111	0	0	0	0	0	0	0	0	0	0	0	0
1112	0	0	0	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-102

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Animal No.	Generation : F0	Sex : Female	Week : 1	Period : F0 before mating Dose : Cinchona Bark Extract 100 mg/kg					Species : Rat
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-103

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

In-the-hand observation		Period : F0 before mating		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Week : 1							
Ease of removal 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	0
3102	0	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0	0
3109	0	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0	0
n	12	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-104

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Animal No.	In-the-hand observation		Period : F0 before mating		Species : Rat			
	Generation : F0	Sex : Female	Week : 1	Dose : Cinchona Bark Extract 1000 mg/kg	Ease of removal from cage	Fur condition	Skin	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	0	0	0	0	0	0
4102	0	0	0	0	0	0	0	0	0	0	0	0
4103	0	0	0	0	0	0	0	0	0	0	0	0
4104	0	0	0	0	0	0	0	0	0	0	0	0
4105	0	0	0	0	0	0	0	0	0	0	0	0
4106	0	0	0	0	0	0	0	0	0	0	0	0
4107	0	0	0	0	0	0	0	0	0	0	0	0
4108	0	0	0	0	0	0	0	0	0	0	0	0
4109	0	0	0	0	0	0	0	0	0	0	0	0
4110	0	0	0	0	0	0	0	0	0	0	0	0
4111	0	0	0	0	0	0	0	0	0	0	0	0
4112	0	0	0	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-105

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

In-the-hand observation		Period : F0 before mating		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Week : 2							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
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

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
Animal No.					
1101	0	0	0	0	0
1102	0	0	0	0	0
1103	0	0	0	0	0
1104	0	0	0	0	0
1105	0	0	0	0	0
1106	0	0	0	0	0
1107	0	0	0	0	0
1108	0	0	0	0	0
1109	0	0	0	0	0
1110	0	0	0	0	0
1111	0	0	0	0	0
1112	0	0	0	0	0
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-106

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

In-the-hand observation		Period : F0 before mating		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Week : 2							
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	0
2102	0	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0	0
2104	0	0	0	0	0	0	0	0	0
2105	0	0	0	0	0	0	0	0	0
2106	0	0	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0	0	0
2108	0	0	0	0	0	0	0	0	0
2109	0	0	0	0	0	0	0	0	0
2110	0	0	0	0	0	0	0	0	0
2111	0	0	0	0	0	0	0	0	0
2112	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12	12

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
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
2105	0	0	0	0	0	0	0
2106	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0
2108	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	12	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-107

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

In-the-hand observation		Period : F0 before mating		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Week : 2							
Ease of removal 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
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

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
Animal No.					
3101	0	0	0	0	0
3102	0	0	0	0	0
3103	0	0	0	0	0
3104	0	0	0	0	0
3105	0	0	0	0	0
3106	0	0	0	0	0
3107	0	0	0	0	0
3108	0	0	0	0	0
3109	0	0	0	0	0
3110	0	0	0	0	0
3111	0	0	0	0	0
3112	0	0	0	0	0
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-108

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

In-the-hand observation		Period : F0 before mating		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Week : 2							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
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

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
Animal No.							
4101	0	0	0	0	0		
4102	0	0	0	0	0		
4103	0	0	0	0	0		
4104	0	0	0	0	0		
4105	0	0	0	0	0		
4106	0	0	0	0	0		
4107	0	0	0	0	0		
4108	0	0	0	0	0		
4109	0	0	0	0	0		
4110	0	0	0	0	0		
4111	0	0	0	0	0		
4112	0	0	0	0	0		
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Female	Day : 1	Period : F0 gestation	Dose : Cinchona Bark Extract 100 mg/kg	Species : Rat		
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Female	Day : 1	Period : F0 gestation	Dose : Cinchona Bark Extract 300 mg/kg	Species : Rat		
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Female	Day : 7	Period : F0 gestation	Dose : Cinchona Bark Extract 0 mg/kg	Species : Rat		
	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.	In-the-hand observation					
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Cinchona Bark Extract 100 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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Female	Day : 7	Period : F0 gestation	Dose : Cinchona Bark Extract 300 mg/kg	Species : Rat		
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Female	Day : 7	Period : F0 gestation	Dose : Cinchona Bark Extract 1000 mg/kg	Species : Rat		
	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.	In-the-hand observation					
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Female	Day : 14	Period : F0 gestation	Dose : Cinchona Bark Extract 100 mg/kg	Species : Rat		
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 14							
Ease of removal 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	0
3102	0	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0	0
3109	0	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12	12

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
Animal No.							
3101	0	0	0	0	0		
3102	0	0	0	0	0		
3103	0	0	0	0	0		
3104	0	0	0	0	0		
3105	0	0	0	0	0		
3106	0	0	0	0	0		
3107	0	0	0	0	0		
3108	0	0	0	0	0		
3109	0	0	0	0	0		
3110	0	0	0	0	0		
3111	0	0	0	0	0		
3112	0	0	0	0	0		
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Female	Day : 14	Period : F0 gestation	Dose : Cinchona Bark Extract 1000 mg/kg	Species : Rat		
	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.	In-the-hand observation					
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Female	Day : 20	Period : F0 gestation	Dose : Cinchona Bark Extract 100 mg/kg	Species : Rat		
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	Generation : F0	Sex : Female	Day : 20	Period : F0 gestation	Dose : Cinchona Bark Extract 300 mg/kg	Species : Rat		
	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.	In-the-hand observation					
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat	
	Generation : F0	Sex : Female	Day : 20					
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 6							
Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 6							
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	0
2102	0	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0	0
2104	0	0	0	0	0	0	0	0	0
2105	0	0	0	0	0	0	0	0	0
2106	-1	0	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0	0	0
2108	0	0	0	0	0	0	0	0	0
2109	0	0	0	0	0	0	0	0	0
2110	0	0	0	0	0	0	0	0	0
2111	0	0	0	0	0	0	0	0	0
2112	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12	12

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		
2105	0	0	0	0	0		
2106	0	0	0	0	0		
2107	0	0	0	0	0		
2108	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	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 6							
Ease of removal 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	0
3102	0	0	0	0	0	0	0	0	0
3103	0	0	0	0	0	0	0	0	0
3104	0	0	0	0	0	0	0	0	0
3105	0	0	0	0	0	0	0	0	0
3106	0	0	0	0	0	0	0	0	0
3107	0	0	0	0	0	0	0	0	0
3108	0	0	0	0	0	0	0	0	0
3109	0	0	0	0	0	0	0	0	0
3110	0	0	0	0	0	0	0	0	0
3111	0	0	0	0	0	0	0	0	0
3112	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12	12

Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling		
Animal No.							
3101	0	0	0	0	0		
3102	0	0	0	0	0		
3103	0	0	0	0	0		
3104	0	0	0	0	0		
3105	0	0	0	0	0		
3106	0	0	0	0	0		
3107	0	0	0	0	0		
3108	0	0	0	0	0		
3109	0	0	0	0	0		
3110	0	0	0	0	0		
3111	0	0	0	0	0		
3112	0	0	0	0	0		
n	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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							
	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 13							
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	0
2102	0	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0	0
2104	0	0	0	0	0	0	0	0	0
2105	0	0	0	0	0	0	0	0	0
2106	0	0	0	0	0	0	0	0	0
2107	0	0	0	0	0	0	0	0	0
2108	0	0	0	0	0	0	0	0	0
2109	0	0	0	0	0	0	0	0	0
2110	0	0	0	0	0	0	0	0	0
2111	0	0	0	0	0	0	0	0	0
2112	0	0	0	0	0	0	0	0	0
n	12	12	12	12	12	12	12	12	12

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		
2105	0	0	0	0	0		
2106	0	0	0	0	0		
2107	0	0	0	0	0		
2108	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	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-133

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

In-the-hand observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Appendix 2-135

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

In-the-hand observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 3

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 3

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 4

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 4

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 5

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 5

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 1							
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation		
Animal No.									
4008	0	0	0	0	0	0	0	0	0
4009	0	0	0	0	0	0	0	0	0
4010	0	0	0	0	0	0	0	0	0
4011	0	0	0	0	0	0	0	0	0
4012	0	0	0	0	0	0	0	0	0
n	5	5	5	5	5	5	5	5	5

	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling			
Animal No.									
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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 2						
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation	
Animal No.								
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

	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling	
Animal No.							
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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 : Recovery (non-mating group)			Species : Rat		
	Generation : F0	Sex : Female	Week : 1	Dose : Cinchona Bark Extract 0 mg/kg					
	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	

	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling
Animal No.						
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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 (non-mating group)

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 (non-mating group)		Species : Rat				
Generation : F0	Sex : Female	Week : 2	Dose : Cinchona Bark Extract 0 mg/kg					
Ease of removal from cage	Fur condition	Skin	Secretions-Eye, Nose	Exophthalmos	Palpebral closure	Mucosal membranes	Lacrimation	
Animal No.								
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

	Piloerection	Pupil size	Salivation	Abnormal respiration	Vocalization	Reactivity to handling	
Animal No.							
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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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 (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

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: 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

Piloerection) 0: Absent, 1: Present

Pupil size) -1: Miosis, 0: Normal, 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

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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	0
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	0
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: 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

Appendix 2-154

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	3	0
1002	4	0
1003	2	0
1004	6	0
1005	3	0
1006	3	0
1007	2	0
1008	3	0
1009	1	0
1010	2	1
1011	5	0
1012	1	0
n	12	12
Mean	3	0
S.D.	2	0

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
2001	0	0	0	0	0	N	0	0
2002	0	0	0	0	0	N	0	0
2003	0	0	0	0	0	N	0	0
2004	0	0	0	0	0	N	0	0
2005	0	0	0	0	0	N	0	0
2006	0	0	0	0	0	N	0	0
2007	0	0	0	0	0	N	0	0
2008	0	0	0	0	0	N	0	0
2009	0	0	0	0	0	N	0	0
2010	0	0	0	0	0	N	0	0
2011	0	0	0	0	0	N	0	0
2012	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: 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 : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	5	0
2002	5	0
2003	7	0
2004	6	0
2005	7	0
2006	4	0
2007	5	0
2008	6	0
2009	4	0
2010	4	0
2011	2	0
2012	4	0
n	12	12
Mean	5	0
S.D.	1	0

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
3001	0	0	0	0	0	N	0	0
3002	0	0	0	0	0	N	0	0
3003	0	0	0	0	0	N	0	0
3004	0	0	0	0	0	N	0	0
3005	0	0	0	0	0	N	0	0
3006	0	0	0	0	0	N	0	0
3007	0	0	0	0	0	N	0	0
3008	0	0	0	0	0	N	0	0
3009	0	0	0	0	0	N	0	0
3010	0	0	0	0	0	N	0	0
3011	0	0	0	0	0	N	0	1
3012	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: 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 : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	5	0
3002	3	0
3003	3	0
3004	4	0
3005	1	0
3006	4	0
3007	4	0
3008	3	0
3009	4	0
3010	5	0
3011	2	0
3012	3	0
n	12	12
Mean	3	0
S.D.	1	0

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
4001	0	0	0	0	0	N	0	0
4002	0	0	0	0	0	N	0	0
4003	0	0	0	0	0	N	0	0
4004	0	0	0	0	0	N	0	0
4005	0	0	0	0	0	N	0	0
4006	0	0	0	0	0	N	0	0
4007	0	0	0	0	0	N	0	0
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	0
4012	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: 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 : F0 before mating

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	7	0
4002	4	0
4003	3	0
4004	4	0
4005	6	0
4006	3	0
4007	3	0
4008	2	0
4009	6	0
4010	2	0
4011	5	0
4012	3	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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	0
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	0
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: 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 : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	2	0
1002	3	0
1003	4	0
1004	4	0
1005	6	0
1006	3	0
1007	3	0
1008	4	0
1009	1	0
1010	2	3
1011	4	0
1012	1	0
n	12	12
Mean	3	0
S.D.	1	1

Open field observation		Period : F0 before mating		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 2	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Arousal	Convulsion								
Animal No.									
2001	0	0	0	0	0	N	0	0	
2002	0	0	0	0	0	N	0	0	
2003	0	0	0	0	0	N	0	0	
2004	0	0	0	0	0	N	0	0	
2005	0	0	0	0	0	N	0	0	
2006	0	0	0	0	0	N	0	0	
2007	0	0	0	0	0	N	0	1	
2008	0	0	0	0	0	N	0	0	
2009	0	0	0	0	0	N	0	0	
2010	0	0	0	0	0	N	0	0	
2011	0	0	0	0	0	N	0	0	
2012	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: 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 : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	6	0
2002	6	0
2003	6	0
2004	3	0
2005	8	0
2006	4	0
2007	7	0
2008	5	0
2009	2	0
2010	5	0
2011	5	0
2012	4	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 before mating		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 2	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
3001	0	0	0	0	0	N	0	0
3002	0	0	0	0	0	N	0	0
3003	0	0	0	0	0	N	0	0
3004	0	0	0	0	0	N	0	0
3005	0	0	0	0	0	N	0	0
3006	0	0	0	0	0	N	0	0
3007	0	0	0	0	0	N	0	0
3008	0	0	0	0	0	N	0	1
3009	0	0	0	0	0	N	0	0
3010	0	0	0	0	0	N	0	0
3011	0	0	0	0	0	N	0	0
3012	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: 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 : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	6	0
3002	3	0
3003	2	0
3004	5	0
3005	6	0
3006	4	0
3007	2	0
3008	2	4
3009	3	0
3010	3	0
3011	2	0
3012	3	0
n	12	12
Mean	3	0
S.D.	2	1

Open field observation

Period : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
4001	0	0	0	0	0	N	0	0
4002	0	0	0	0	0	N	0	0
4003	0	0	0	0	0	N	0	0
4004	0	0	0	0	0	N	0	0
4005	0	0	0	0	0	N	0	0
4006	0	0	0	0	0	N	0	1
4007	0	0	0	0	0	N	0	0
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	0
4012	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: 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 : F0 before mating

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	6	0
4002	3	0
4003	5	0
4004	5	0
4005	8	0
4006	4	0
4007	3	0
4008	2	0
4009	3	0
4010	5	0
4011	7	0
4012	3	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 3	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Arousal	Convulsion								
Animal No.									
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	0	
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	0	
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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	4	0
1002	4	0
1003	4	0
1004	5	0
1005	3	0
1006	2	0
1007	2	0
1008	3	0
1009	2	0
1010	2	0
1011	3	0
1012	4	0
n	12	12
Mean	3	0
S.D.	1	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 3	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
2001	0	0	0	0	0	N	0	0
2002	0	0	0	0	0	N	0	0
2003	0	0	0	0	0	N	0	0
2004	0	0	0	0	0	N	0	0
2005	0	0	0	0	0	N	0	0
2006	0	0	0	0	0	N	0	0
2007	0	0	0	0	0	N	0	0
2008	0	0	0	0	0	N	0	0
2009	0	0	0	0	0	N	0	0
2010	0	0	0	0	0	N	0	0
2011	0	0	0	0	0	N	0	0
2012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	5	0
2002	4	0
2003	5	0
2004	3	0
2005	3	0
2006	3	0
2007	6	0
2008	3	0
2009	3	0
2010	7	0
2011	7	0
2012	4	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 3	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
3001	0	0	0	0	0	N	0	0
3002	0	0	0	0	0	N	0	0
3003	0	0	0	0	0	N	0	0
3004	0	0	0	0	0	N	0	0
3005	0	0	0	0	0	N	0	0
3006	0	0	0	0	0	N	0	0
3007	0	0	0	0	0	N	0	0
3008	0	0	0	0	0	N	0	0
3009	0	0	0	0	0	N	0	0
3010	0	0	0	0	0	N	0	0
3011	0	0	0	0	0	N	0	0
3012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	4	0
3002	5	0
3003	2	0
3004	5	0
3005	1	0
3006	4	0
3007	3	0
3008	2	0
3009	5	0
3010	6	0
3011	2	0
3012	3	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 3	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
4001	0	0	0	0	0	N	0	0
4002	0	0	0	0	0	N	0	0
4003	0	0	0	0	0	N	0	0
4004	0	0	0	0	0	N	0	0
4005	0	0	0	0	0	N	0	0
4006	0	0	0	0	0	N	0	0
4007	0	0	0	0	0	N	0	0
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	0
4012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 3

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	6	0
4002	4	0
4003	2	0
4004	4	0
4005	1	0
4006	3	0
4007	3	0
4008	0	0
4009	5	0
4010	7	0
4011	5	0
4012	2	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 4	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
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	0
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	0
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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 4

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	2	0
1002	5	0
1003	2	0
1004	3	0
1005	6	0
1006	4	0
1007	3	0
1008	3	0
1009	3	0
1010	5	0
1011	3	0
1012	3	0
n	12	12
Mean	4	0
S.D.	1	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 4	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Arousal	Convulsion								
Animal No.									
2001	0	0	0	0	0	N	0	0	
2002	0	0	0	0	0	N	0	0	
2003	0	0	0	0	0	N	0	0	
2004	0	0	0	0	0	N	0	0	
2005	0	0	0	0	0	N	0	0	
2006	0	0	0	0	0	N	0	0	
2007	0	0	0	0	0	N	0	0	
2008	0	0	0	0	0	N	0	0	
2009	0	0	0	0	0	N	0	0	
2010	0	0	0	0	0	N	0	0	
2011	0	0	0	0	0	N	0	0	
2012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 4

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	3	0
2002	3	0
2003	6	0
2004	4	0
2005	4	0
2006	4	0
2007	1	0
2008	6	0
2009	6	0
2010	2	0
2011	4	0
2012	4	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 4	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Arousal	Convulsion								
Animal No.									
3001	0	0	0	0	0	N	0	0	
3002	0	0	0	0	0	N	0	0	
3003	0	0	0	0	0	N	0	0	
3004	0	0	0	0	0	N	0	0	
3005	0	0	0	0	0	N	0	0	
3006	0	0	0	0	0	N	0	0	
3007	0	0	0	0	0	N	0	0	
3008	0	0	0	0	0	N	0	0	
3009	0	0	0	0	0	N	0	0	
3010	0	0	0	0	0	N	0	0	
3011	0	0	0	0	0	N	0	1	
3012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 4

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	5	0
3002	3	0
3003	2	0
3004	4	0
3005	2	0
3006	2	0
3007	3	0
3008	1	0
3009	4	0
3010	3	0
3011	4	0
3012	0	0
n	12	12
Mean	3	0
S.D.	1	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 4	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
4001	0	0	0	0	0	N	0	0
4002	0	0	0	0	0	N	0	0
4003	0	0	0	0	0	N	0	0
4004	0	0	0	0	0	N	0	0
4005	0	0	0	0	0	N	0	0
4006	0	0	0	0	0	N	0	0
4007	0	0	0	0	0	N	0	0
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	0
4012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 4

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	5	0
4002	2	0
4003	5	0
4004	3	0
4005	4	0
4006	3	0
4007	4	0
4008	3	0
4009	4	0
4010	7	0
4011	7	0
4012	3	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 5	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
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	0
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	0
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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	4	0
1002	5	0
1003	4	0
1004	7	0
1005	5	0
1006	6	0
1007	4	0
1008	3	0
1009	3	0
1010	5	0
1011	4	0
1012	0	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 5	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Arousal	Convulsion								
Animal No.									
2001	0	0	0	0	0	N	0	0	
2002	0	0	0	0	0	N	0	0	
2003	0	0	0	0	0	N	0	0	
2004	0	0	0	0	0	N	0	1	
2005	0	0	0	0	0	N	0	0	
2006	0	0	0	0	0	N	0	0	
2007	0	0	0	0	0	N	0	0	
2008	0	0	0	0	0	N	0	0	
2009	0	0	0	0	0	N	0	0	
2010	0	0	0	0	0	N	0	0	
2011	0	0	0	0	0	N	0	0	
2012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	4	0
2002	6	0
2003	5	0
2004	5	0
2005	6	0
2006	7	0
2007	3	0
2008	4	0
2009	4	0
2010	3	0
2011	3	0
2012	3	0
n	12	12
Mean	4	0
S.D.	1	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 5	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
3001	0	0	0	0	0	N	0	0
3002	0	0	0	0	0	N	0	0
3003	0	0	0	0	0	N	0	0
3004	0	0	0	0	0	N	0	1
3005	0	0	0	0	0	N	0	0
3006	0	0	0	0	0	N	0	0
3007	0	0	0	0	0	N	0	0
3008	0	0	0	0	0	N	0	1
3009	0	0	0	0	0	N	0	0
3010	0	0	0	0	0	N	0	0
3011	0	0	0	0	0	N	0	1
3012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	6	0
3002	4	0
3003	4	0
3004	5	0
3005	7	0
3006	5	0
3007	3	0
3008	2	0
3009	4	0
3010	1	0
3011	3	0
3012	0	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation

Period : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
4001	0	0	0	0	0	N	0	0
4002	0	0	0	0	0	N	0	0
4003	0	0	0	0	0	N	0	0
4004	0	0	0	0	0	N	0	0
4005	0	0	0	0	0	N	0	0
4006	0	0	0	0	0	N	0	0
4007	0	0	0	0	0	N	0	0
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	0
4012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 5

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	8	0
4002	1	0
4003	4	0
4004	5	0
4005	4	0
4006	2	0
4007	4	0
4008	1	0
4009	3	0
4010	3	0
4011	7	0
4012	2	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 6	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Arousal	Convulsion								
Animal No.									
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	0	
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	0	
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	1	
n	12	12	12	12	12	12	12	12	

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 : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1001	3	0
1002	5	0
1003	1	0
1004	6	0
1005	5	0
1006	1	0
1007	4	0
1008	5	0
1009	3	0
1010	5	0
1011	4	0
1012	1	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Male	Week : 6	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Arousal	Convulsion								
Animal No.									
2001	0	0	0	0	0	N	0	1	
2002	0	0	0	0	0	N	0	0	
2003	0	0	0	0	0	N	0	0	
2004	0	0	0	0	0	N	0	0	
2005	0	0	0	0	0	N	0	0	
2006	0	0	0	0	0	N	0	0	
2007	0	0	0	0	0	N	0	0	
2008	0	0	0	0	0	N	0	0	
2009	0	0	0	0	0	N	0	0	
2010	0	0	0	0	0	N	0	0	
2011	0	0	0	0	0	N	0	0	
2012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2001	5	0
2002	3	0
2003	4	0
2004	5	0
2005	8	0
2006	3	0
2007	3	0
2008	4	0
2009	3	0
2010	3	0
2011	3	0
2012	2	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 6	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
3001	0	0	0	0	0	N	0	0
3002	0	0	0	0	0	N	0	0
3003	0	0	0	0	0	N	0	0
3004	0	0	0	0	0	N	0	0
3005	0	0	0	0	0	N	0	0
3006	0	0	0	0	0	N	0	0
3007	0	0	0	0	0	N	0	0
3008	0	0	0	0	0	N	0	0
3009	0	0	0	0	0	N	0	0
3010	0	0	0	0	0	N	0	0
3011	0	0	0	0	0	N	0	0
3012	0	0	0	0	0	N	0	1
n	12	12	12	12	12	12	12	12

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 : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3001	9	0
3002	5	0
3003	3	0
3004	7	0
3005	4	0
3006	1	0
3007	1	0
3008	2	0
3009	5	0
3010	7	0
3011	4	0
3012	2	1
n	12	12
Mean	4	0
S.D.	3	0

Open field observation		Period : F0 mating		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat		
Generation : F0	Sex : Male	Week : 6	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
4001	0	0	0	0	0	N	0	0
4002	0	0	0	0	0	N	0	0
4003	0	0	0	0	0	N	0	0
4004	0	0	0	0	0	N	0	0
4005	0	0	0	0	0	N	0	0
4006	0	0	0	0	0	N	0	0
4007	0	0	0	0	0	N	0	0
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	0
4012	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: 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 : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4001	7	0
4002	1	0
4003	2	0
4004	5	0
4005	5	0
4006	6	0
4007	0	0
4008	3	0
4009	3	0
4010	5	0
4011	7	0
4012	1	0
n	12	12
Mean	4	0
S.D.	2	0

Animal No.	Open field observation							
	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: 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 : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	5	0
1102	8	0
1103	7	0
1104	7	0
1105	4	0
1106	7	0
1107	9	0
1108	8	0
1109	8	0
1110	7	0
1111	9	0
1112	9	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 before mating		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Week : 1	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Arousal	Convulsion								
Animal No.									
2101	0	0	0	0	0	N	0	0	
2102	0	0	0	0	0	N	0	0	
2103	0	0	0	0	0	N	0	0	
2104	0	0	0	0	0	N	0	0	
2105	0	0	0	0	0	N	0	0	
2106	0	0	0	0	0	N	0	0	
2107	0	0	0	0	0	N	0	0	
2108	0	0	0	0	0	N	0	0	
2109	0	0	0	0	0	N	0	0	
2110	0	0	0	0	0	N	0	0	
2111	0	0	0	0	0	N	0	0	
2112	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: 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

Appendix 2-204

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	10	0
2102	9	0
2103	12	0
2104	11	0
2105	9	0
2106	9	0
2107	7	0
2108	6	0
2109	9	0
2110	8	0
2111	6	0
2112	6	0
n	12	12
Mean	9	0
S.D.	2	0

Animal No.	Open field observation							
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
3101	0	0	0	0	0	N	0	0
3102	0	0	0	0	0	N	0	0
3103	0	0	0	0	0	N	0	0
3104	0	0	0	0	0	N	0	0
3105	0	0	0	0	0	N	0	0
3106	0	0	0	0	0	N	0	0
3107	0	0	0	0	0	N	0	0
3108	0	0	0	0	0	N	0	0
3109	0	0	0	0	0	N	0	0
3110	0	0	0	0	0	N	0	0
3111	0	0	0	0	0	N	0	0
3112	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: 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 : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	8	0
3102	11	0
3103	11	0
3104	8	0
3105	10	0
3106	6	0
3107	8	0
3108	7	0
3109	6	0
3110	9	0
3111	6	0
3112	4	0
n	12	12
Mean	8	0
S.D.	2	0

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

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: 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 : F0 before mating

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	13	0
4102	7	0
4103	3	0
4104	7	0
4105	7	0
4106	10	0
4107	10	0
4108	9	0
4109	8	0
4110	6	0
4111	12	0
4112	8	0
n	12	12
Mean	8	0
S.D.	3	0

Open field observation		Period : F0 before mating		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat		
Generation : F0	Sex : Female	Week : 2	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
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: 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

Appendix 2-210

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	8	0
1102	10	0
1103	9	0
1104	8	0
1105	4	0
1106	6	0
1107	7	0
1108	8	0
1109	7	0
1110	5	0
1111	8	0
1112	6	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
2101	0	0	0	0	0	N	0	0
2102	0	0	0	0	0	N	0	0
2103	0	0	0	0	0	N	0	0
2104	0	0	0	0	0	N	0	0
2105	0	0	0	0	0	N	0	0
2106	0	0	0	0	0	N	0	0
2107	0	0	0	0	0	N	0	0
2108	0	0	0	0	0	N	0	0
2109	0	0	0	0	0	N	0	0
2110	0	0	0	0	0	N	0	0
2111	0	0	0	0	0	N	0	0
2112	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: 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 : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	9	0
2102	7	0
2103	8	0
2104	14	0
2105	13	0
2106	6	0
2107	7	0
2108	9	0
2109	7	0
2110	7	0
2111	7	0
2112	4	0
n	12	12
Mean	8	0
S.D.	3	0

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
3101	0	0	0	0	0	N	0	0
3102	0	0	0	0	0	N	0	0
3103	0	0	0	0	0	N	0	0
3104	0	0	0	0	0	N	0	0
3105	0	0	0	0	0	N	0	0
3106	0	0	0	0	0	N	0	0
3107	0	0	0	0	0	N	0	0
3108	0	0	0	0	0	N	0	0
3109	0	0	0	0	0	N	0	0
3110	0	0	0	0	0	N	0	0
3111	0	0	0	0	0	N	0	0
3112	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: 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

Appendix 2-214

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	7	0
3102	8	0
3103	10	0
3104	8	0
3105	9	0
3106	6	0
3107	7	0
3108	7	0
3109	8	0
3110	6	0
3111	2	0
3112	4	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 before mating		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat		
Generation : F0	Sex : Female	Week : 2	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
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: 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 : F0 before mating

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	7	0
4102	6	0
4103	6	0
4104	6	0
4105	10	0
4106	7	0
4107	9	0
4108	7	0
4109	8	0
4110	5	0
4111	6	0
4112	6	0
n	12	12
Mean	7	0
S.D.	1	0

Open field observation		Period : F0 gestation		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat		
Generation : F0	Sex : Female	Day : 1						
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	12

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 : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	5	0
1102	8	0
1103	5	0
1104	10	0
1105	7	0
1106	7	0
1107	10	0
1108	6	0
1109	9	0
1110	3	0
1111	5	0
1112	9	0
n	12	12
Mean	7	0
S.D.	2	0

Animal No.	Open field observation			Period : F0 gestation			Species : Rat		
	Generation : F0	Sex : Female	Day : 1	Dose : Cinchona Bark Extract 100 mg/kg			Posture	Grooming	Urination
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait				
2101	0	0	0	0	0	N	0	0	
2102	0	0	0	0	0	N	0	0	
2103	0	0	0	0	0	N	0	0	
2104	0	0	0	0	0	N	0	0	
2105	0	0	0	0	0	N	0	0	
2106	0	0	0	0	0	N	0	0	
2107	0	0	0	0	0	N	0	0	
2108	0	0	0	0	0	N	0	0	
2109	0	0	0	0	0	N	0	0	
2110	0	0	0	0	0	N	0	0	
2111	0	0	0	0	0	N	0	0	
2112	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: 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

Appendix 2-220

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	11	0
2102	9	0
2103	7	0
2104	10	0
2105	8	0
2106	5	0
2107	5	0
2108	7	0
2109	6	0
2110	6	0
2111	5	0
2112	8	0
n	12	12
Mean	7	0
S.D.	2	0

Appendix 2-221

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
3101	0	0	0	0	0	N	0	0
3102	0	0	0	0	0	N	0	0
3103	0	0	0	0	0	N	0	0
3104	0	0	0	0	0	N	0	0
3105	0	0	0	0	0	N	0	0
3106	0	0	0	0	0	N	0	0
3107	0	0	0	0	0	N	0	0
3108	0	0	0	0	0	N	0	0
3109	0	0	0	0	0	N	0	0
3110	0	0	0	0	0	N	0	0
3111	0	0	0	0	0	N	0	0
3112	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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	7	0
3102	4	0
3103	6	0
3104	8	0
3105	5	0
3106	5	0
3107	8	0
3108	6	0
3109	8	0
3110	4	0
3111	3	0
3112	5	0
n	12	12
Mean	6	0
S.D.	2	0

Animal No.	Open field observation			Period : F0 gestation			Species : Rat		
	Generation : F0	Sex : Female	Day : 1	Dose : Cinchona Bark Extract 1000 mg/kg					
	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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	5	0
4102	5	0
4103	4	0
4104	7	0
4105	8	0
4106	7	0
4107	6	0
4108	5	0
4109	5	0
4110	5	0
4111	6	0
4112	4	0
n	12	12
Mean	6	0
S.D.	1	0

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	6	0
1102	7	0
1103	7	0
1104	9	0
1105	7	0
1106	6	0
1107	10	0
1108	6	0
1109	10	0
1110	2	0
1111	8	0
1112	8	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 gestation		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat		
Generation : F0	Sex : Female	Day : 7						
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	12

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 : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	8	0
2102	6	0
2103	5	0
2104	6	0
2105	9	0
2106	7	0
2107	6	0
2108	7	0
2109	5	0
2110	7	0
2111	7	0
2112	8	0
n	12	12
Mean	7	0
S.D.	1	0

Open field observation		Period : F0 gestation		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 7							
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination		
Animal No.									
3101	0	0	0	0	0	N	0	0	
3102	0	0	0	0	0	N	0	0	
3103	0	0	0	0	0	N	0	0	
3104	0	0	0	0	0	N	0	0	
3105	0	0	0	0	0	N	0	0	
3106	0	0	0	0	0	N	0	0	
3107	0	0	0	0	0	N	0	0	
3108	0	0	0	0	0	N	0	0	
3109	0	0	0	0	0	N	0	0	
3110	0	0	0	0	0	N	0	0	
3111	0	0	0	0	0	N	0	0	
3112	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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	8	0
3102	5	0
3103	7	0
3104	8	0
3105	4	0
3106	5	0
3107	5	0
3108	6	0
3109	9	0
3110	4	0
3111	4	0
3112	7	0
n	12	12
Mean	6	0
S.D.	2	0

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 7

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	5	0
4102	3	0
4103	4	0
4104	8	0
4105	8	0
4106	6	0
4107	4	0
4108	6	0
4109	6	0
4110	5	0
4111	7	0
4112	6	0
n	12	12
Mean	6	0
S.D.	2	0

Open field observation				Period : F0 gestation			Species : Rat	
Generation : F0	Sex : Female	Day : 14	Dose : Cinchona Bark Extract 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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 14

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	3	0
1102	5	0
1103	5	0
1104	8	0
1105	4	0
1106	6	0
1107	9	0
1108	9	0
1109	9	0
1110	5	0
1111	7	0
1112	7	0
n	12	12
Mean	6	0
S.D.	2	0

Animal No.	Open field observation		Period : F0 gestation					Species : Rat	
	Generation : F0	Sex : Female	Day : 14	Dose : Cinchona Bark Extract 100 mg/kg					
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
2101	0	0	0	0	0	N	0	0	
2102	0	0	0	0	0	N	0	0	
2103	0	0	0	0	0	N	0	0	
2104	0	0	0	0	0	N	0	0	
2105	0	0	0	0	0	N	0	0	
2106	0	0	0	0	0	N	0	0	
2107	0	0	0	0	0	N	0	0	
2108	0	0	0	0	0	N	0	0	
2109	0	0	0	0	0	N	0	0	
2110	0	0	0	0	0	N	0	0	
2111	0	0	0	0	0	N	0	0	
2112	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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 14

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	5	0
2102	10	0
2103	8	0
2104	9	0
2105	7	0
2106	5	0
2107	6	0
2108	6	0
2109	5	0
2110	7	0
2111	7	0
2112	7	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 gestation		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 14							
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination		
Animal No.									
3101	0	0	0	0	0	N	0	0	
3102	0	0	0	0	0	N	0	0	
3103	0	0	0	0	0	N	0	0	
3104	0	0	0	0	0	N	0	0	
3105	0	0	0	0	0	N	0	0	
3106	0	0	0	0	0	N	0	0	
3107	0	0	0	0	0	N	0	0	
3108	0	0	0	0	0	N	0	0	
3109	0	0	0	0	0	N	0	0	
3110	0	0	0	0	0	N	0	0	
3111	0	0	0	0	0	N	0	0	
3112	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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 14

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	3	0
3102	6	0
3103	7	0
3104	6	0
3105	3	0
3106	4	0
3107	6	0
3108	6	0
3109	5	0
3110	4	0
3111	5	0
3112	5	0
n	12	12
Mean	5	0
S.D.	1	0

	Open field observation		Period : F0 gestation				Species : Rat	
	Generation : F0	Sex : Female	Day : 14	Dose : Cinchona Bark Extract 1000 mg/kg				
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Animal No.								
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: 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

Appendix 2-240

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 14

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	6	0
4102	2	0
4103	4	0
4104	8	0
4105	12	0
4106	7	0
4107	9	0
4108	4	0
4109	4	0
4110	4	0
4111	7	0
4112	6	0
n	12	12
Mean	6	0
S.D.	3	0

Open field observation		Period : F0 gestation		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 20	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination	
Arousal	Convulsion								
Animal No.									
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: 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

Appendix 2-242

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	4	0
1102	7	0
1103	6	0
1104	8	0
1105	3	0
1106	7	0
1107	4	0
1108	6	0
1109	4	0
1110	4	0
1111	6	0
1112	5	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 gestation		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat		
Generation : F0	Sex : Female	Day : 20	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Arousal	Convulsion							
Animal No.								
2101	0	0	0	0	0	N	0	0
2102	0	0	0	0	0	N	0	0
2103	0	0	0	0	0	N	0	0
2104	0	0	0	0	0	N	0	0
2105	0	0	0	0	0	N	0	0
2106	0	0	0	0	0	N	0	0
2107	0	0	0	0	0	N	0	0
2108	0	0	0	0	0	N	0	0
2109	0	0	0	0	0	N	0	0
2110	0	0	0	0	0	N	0	0
2111	0	0	0	0	0	N	0	0
2112	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: 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

Appendix 2-244

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : F0 gestation

Generation : F0

Sex : Female

Day : 20

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	3	0
2102	6	0
2103	5	0
2104	8	0
2105	6	0
2106	5	0
2107	4	0
2108	7	0
2109	5	0
2110	4	0
2111	3	0
2112	5	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation		Period : F0 gestation		Dose : Cinchona Bark Extract 300 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 20							
Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination		
Animal No.									
3101	0	0	0	0	0	N	0	0	
3102	0	0	0	0	0	N	0	0	
3103	0	0	0	0	0	N	0	0	
3104	0	0	0	0	0	N	0	0	
3105	0	0	0	0	0	N	0	0	
3106	0	0	0	0	0	N	0	0	
3107	0	0	0	0	0	N	0	0	
3108	0	0	0	0	0	N	0	0	
3109	0	0	0	0	0	N	0	0	
3110	0	0	0	0	0	N	0	0	
3111	0	0	0	0	0	N	0	0	
3112	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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 20

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	4	0
3102	1	0
3103	7	0
3104	4	0
3105	2	0
3106	4	0
3107	3	0
3108	3	0
3109	2	0
3110	3	0
3111	3	0
3112	3	0
n	12	12
Mean	3	0
S.D.	1	0

Open field observation				Period : F0 gestation			Species : Rat	
Generation : F0	Sex : Female	Day : 20	Dose : Cinchona Bark Extract 1000 mg/kg					
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Animal No.								
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: 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 : F0 gestation

Generation : F0

Sex : Female

Day : 20

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	6	0
4102	4	0
4103	2	0
4104	3	0
4105	6	0
4106	5	0
4107	6	0
4108	3	0
4109	5	0
4110	1	0
4111	3	0
4112	5	0
n	12	12
Mean	4	0
S.D.	2	0

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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: 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 : F0 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	5	0
1102	5	0
1103	6	0
1104	7	0
1105	4	0
1106	6	0
1107	7	0
1108	7	0
1109	11	0
1110	6	0
1111	9	0
1112	8	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 lactation		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 6							
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: 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 : F0 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	4	0
2102	9	0
2103	7	0
2104	7	0
2105	6	0
2106	5	0
2107	5	0
2108	6	0
2109	5	0
2110	7	0
2111	7	0
2112	5	0
n	12	12
Mean	6	0
S.D.	1	0

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
3101	0	0	0	0	0	N	0	0
3102	0	0	0	0	0	N	0	0
3103	0	0	0	0	0	N	0	0
3104	0	0	0	0	0	N	0	0
3105	0	0	0	0	0	N	0	0
3106	0	0	0	0	0	N	0	0
3107	0	0	0	0	0	N	0	0
3108	0	0	0	0	0	N	0	0
3109	0	0	0	0	0	N	0	0
3110	0	0	0	0	0	N	0	0
3111	0	0	0	0	0	N	0	0
3112	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: 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 : F0 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	6	0
3102	4	0
3103	7	0
3104	5	0
3105	3	0
3106	4	0
3107	7	0
3108	5	0
3109	0	0
3110	4	0
3111	6	0
3112	7	0
n	12	12
Mean	5	0
S.D.	2	0

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

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: 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 : F0 lactation

Generation : F0

Sex : Female

Day : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	4	0
4102	4	0
4103	4	0
4104	8	0
4105	5	0
4106	3	0
4107	9	0
4108	5	0
4109	5	0
4110	9	0
4111	4	0
4112	7	0
n	12	12
Mean	6	0
S.D.	2	0

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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: 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 : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1101	6	0
1102	6	0
1103	9	0
1104	9	0
1105	8	0
1106	8	0
1107	7	0
1108	9	0
1109	8	0
1110	4	0
1111	7	0
1112	8	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation		Period : F0 lactation		Dose : Cinchona Bark Extract 100 mg/kg		Species : Rat			
Generation : F0	Sex : Female	Day : 13							
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: 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 : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
2101	5	0
2102	7	0
2103	9	0
2104	9	0
2105	9	0
2106	4	0
2107	7	0
2108	7	0
2109	4	0
2110	6	0
2111	6	0
2112	8	0
n	12	12
Mean	7	0
S.D.	2	0

Open field observation

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
3101	0	0	0	0	0	N	0	0
3102	0	0	0	0	0	N	0	0
3103	0	0	0	0	0	N	0	0
3104	0	0	0	0	0	N	0	0
3105	0	0	0	0	0	N	0	0
3106	0	0	0	0	0	N	0	0
3107	0	0	0	0	0	N	0	0
3108	0	0	0	0	0	N	0	0
3109	0	0	0	0	0	N	0	0
3110	0	0	0	0	0	N	0	0
3111	0	0	0	0	0	N	0	0
3112	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: 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 : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
3101	6	0
3102	9	0
3103	6	0
3104	9	0
3105	6	0
3106	6	0
3107	8	0
3108	5	0
3109	7	0
3110	2	0
3111	5	0
3112	6	0
n	12	12
Mean	6	0
S.D.	2	0

Open field observation				Period : F0 lactation			Species : Rat	
Generation : F0	Sex : Female	Day : 13	Dose : Cinchona Bark Extract 1000 mg/kg					
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Animal No.								
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: 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 : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4101	5	0
4102	5	0
4103	5	0
4104	9	0
4105	10	0
4106	6	0
4107	7	0
4108	7	0
4109	4	0
4110	5	0
4111	5	0
4112	5	0
n	12	12
Mean	6	0
S.D.	2	0

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Female Week : 1 Period : Administration (non-mating group)
 Dose : Cinchona Bark Extract 0 mg/kg

Animal No.	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 (non-mating group)

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	12	0
5102	5	0
5103	5	0
5104	9	0
5105	9	0
5106	9	0
5107	9	0
5108	8	0
5109	9	0
5110	10	0
n	10	10
Mean	9	0
S.D.	2	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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 (non-mating group)

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6101	6	0
6102	7	0
6103	8	0
6104	4	0
6105	8	0
6106	4	0
6107	7	0
6108	11	0
6109	7	0
6110	14	0
n	10	10
Mean	8	0
S.D.	3	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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

Appendix 2-270

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	7	0
5102	8	0
5103	8	0
5104	12	0
5105	11	0
5106	6	0
5107	9	0
5108	8	0
5109	7	0
5110	8	0
n	10	10
Mean	8	0
S.D.	2	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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 (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6101	11	0
6102	6	0
6103	9	0
6104	6	0
6105	11	0
6106	8	0
6107	10	0
6108	9	0
6109	5	0
6110	6	0
n	10	10
Mean	8	0
S.D.	2	0

Open field observation		Period : Administration (non-mating group)		Species : Rat				
Generation : F0		Sex : Female		Week : 3		Dose : Cinchona Bark Extract 0 mg/kg		
Animal No.	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

Appendix 2-274

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 3

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	9	0
5102	11	0
5103	8	0
5104	9	0
5105	14	0
5106	12	0
5107	7	0
5108	11	0
5109	10	0
5110	9	0
n	10	10
Mean	10	0
S.D.	2	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 3

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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 (non-mating group)

Generation : F0

Sex : Female

Week : 3

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6101	9	0
6102	5	0
6103	6	0
6104	4	0
6105	8	0
6106	6	0
6107	9	0
6108	11	0
6109	11	0
6110	11	0
n	10	10
Mean	8	0
S.D.	3	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 4

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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 (non-mating group)

Generation : F0

Sex : Female

Week : 4

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	6	0
5102	8	0
5103	9	0
5104	3	0
5105	4	0
5106	11	0
5107	8	0
5108	10	0
5109	9	0
5110	5	0
n	10	10
Mean	7	0
S.D.	3	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 4

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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 (non-mating group)

Generation : F0

Sex : Female

Week : 4

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6101	9	0
6102	7	0
6103	5	0
6104	8	0
6105	8	0
6106	6	0
6107	5	0
6108	11	0
6109	8	0
6110	10	0
n	10	10
Mean	8	0
S.D.	2	0

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Week : 5 Period : Administration (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg

	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Animal No.								
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 (non-mating group)

Generation : F0

Sex : Female

Week : 5

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	7	0
5102	7	0
5103	9	0
5104	8	0
5105	9	0
5106	9	0
5107	6	0
5108	6	0
5109	9	0
5110	6	0
n	10	10
Mean	8	0
S.D.	1	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 5

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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 (non-mating group)

Generation : F0

Sex : Female

Week : 5

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6101	6	0
6102	5	0
6103	8	0
6104	7	0
6105	12	0
6106	8	0
6107	3	0
6108	8	0
6109	9	0
6110	8	0
n	10	10
Mean	7	0
S.D.	2	0

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Open field observation
Generation : F0 Sex : Female Week : 6 Period : Administration (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg

	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Animal No.								
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 (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5101	5	0
5102	9	0
5103	11	0
5104	5	0
5105	8	0
5106	11	0
5107	8	0
5108	11	0
5109	8	0
5110	7	0
n	10	10
Mean	8	0
S.D.	2	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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 (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6101	9	0
6102	10	0
6103	10	0
6104	4	0
6105	12	0
6106	5	0
6107	10	0
6108	10	0
6109	11	0
6110	8	0
n	10	10
Mean	9	0
S.D.	3	0

Open field observation

Period : Recovery

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
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	5	5	5	5	5	5	5	5

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

Appendix 2-290

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Recovery

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1008	3	0
1009	3	0
1010	3	0
1011	1	0
1012	2	0
n	5	5
Mean	2	0
S.D.	1	0

Appendix 2-291

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Open field observation

Period : Recovery

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	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	0
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: 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 : Recovery

Generation : F0

Sex : Male

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4008	1	0
4009	3	0
4010	3	0
4011	5	0
4012	1	0
n	5	5
Mean	3	0
S.D.	2	0

Animal No.	Experimental anxiety testing results			Species : Rat				
	Open field observation		Week : 2	Period : Recovery		Posture	Grooming	Urination
	Generation : F0	Sex : Male		Dose : Cinchona Bark Extract 0 mg/kg				
	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait			
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	1
n	5	5	5	5	5	5	5	5

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

Appendix 2-294

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
1008	5	0
1009	5	0
1010	3	0
1011	4	0
1012	5	0
n	5	5
Mean	4	0
S.D.	1	0

Open field observation

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
4008	0	0	0	0	0	N	0	1
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	0
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: 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 : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
4008	4	0
4009	6	0
4010	7	0
4011	8	0
4012	3	0
n	5	5
Mean	6	0
S.D.	2	0

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Female Week : 1 Period : Administration (non-mating group)
 Dose : Cinchona Bark Extract 0 mg/kg

	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Animal No.								
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: 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

Appendix 2-298

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5106	7	0
5107	6	0
5108	7	0
5109	7	0
5110	3	0
n	5	5
Mean	6	0
S.D.	2	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Animal No.								
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: 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

Appendix 2-300

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 1

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6106	5	0
6107	5	0
6108	5	0
6109	5	0
6110	5	0
n	5	5
Mean	5	0
S.D.	0	0

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Open field observation
 Generation : F0 Sex : Female Week : 2 Period : Administration (non-mating group)
 Dose : Cinchona Bark Extract 0 mg/kg

	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Animal No.								
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: 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

Appendix 2-302

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
5106	8	0
5107	4	0
5108	9	0
5109	7	0
5110	4	0
n	5	5
Mean	6	0
S.D.	2	0

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Arousal	Convulsion	Abnormal behavior	Stereotypy	Gait	Posture	Grooming	Urination
Animal No.								
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: 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

Appendix 2-304

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Open field observation

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	Rearing	Defecation count
Animal No.		
6106	5	0
6107	7	0
6108	7	0
6109	6	0
6110	7	0
n	5	5
Mean	6	0
S.D.	1	0

Manipulative test

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
1008	0	0	0	0
1009	0	0	0	0
1010	0	0	0	0
1011	0	0	0	0
1012	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	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

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
2008	0	0	0	0
2009	0	0	0	0
2010	0	0	0	0
2011	0	0	0	0
2012	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
3008	0	0	0	0	P
3009	0	0	0	0	P
3010	0	0	0	0	P
3011	0	0	0	0	P
3012	0	0	0	0	P
n	5	5	5	5	5

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
3008	0	0	0	0
3009	0	0	0	0
3010	0	0	0	0
3011	0	0	0	0
3012	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
4008	0	0	0	0
4009	0	0	0	0
4010	0	0	0	0
4011	0	0	0	0
4012	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
1102	0	0	0	0	P
1105	0	0	0	0	P
1106	0	0	0	0	P
1109	0	0	0	0	P
1110	0	0	0	0	P
n	5	5	5	5	5

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
1102	0	0	0	0
1105	0	0	0	0
1106	0	0	0	0
1109	0	0	0	0
1110	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
2103	0	0	0	0	P
2105	0	0	0	0	P
2107	0	0	0	0	P
2109	0	0	0	0	P
2111	0	0	0	0	P
n	5	5	5	5	5

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
2103	0	0	0	0
2105	0	0	0	0
2107	0	0	0	0
2109	0	0	0	0
2111	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
3101	0	0	0	0	P
3102	0	0	0	0	P
3104	0	0	0	0	P
3106	0	0	0	0	P
3109	0	0	0	0	P
n	5	5	5	5	5

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
3101	0	0	0	0
3102	0	0	0	0
3104	0	0	0	0
3106	0	0	0	0
3109	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Auditory response	Approach response	Touch response	Tail pinch response	Pupillary reflex
4103	0	0	0	0	P
4105	0	0	0	0	P
4106	0	0	0	0	P
4108	0	0	0	0	P
4111	0	0	0	0	P
n	5	5	5	5	5

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
4103	0	0	0	0
4105	0	0	0	0
4106	0	0	0	0
4108	0	0	0	0
4111	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
5106	0	0	0	0
5107	0	0	0	0
5108	0	0	0	0
5109	0	0	0	0
5110	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
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	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
1008	0	0	0	0
1009	0	0	0	0
1010	0	0	0	0
1011	0	0	0	0
1012	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
4008	0	0	0	0
4009	0	0	0	0
4010	0	0	0	0
4011	0	0	0	0
4012	0	0	0	0
n	5	5	5	5
	0	0	0	0
	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : Recovery (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	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

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
5106	0	0	0	0
5107	0	0	0	0
5108	0	0	0	0
5109	0	0	0	0
5110	0	0	0	0
n	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Manipulative test

Period : Recovery (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	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

Animal No.	Aerial right-ing reflex-1	Aerial right-ing reflex-2	Aerial right-ing reflex-3	Aerial right-ing reflex-total
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	5	5	5	5
Mean	0	0	0	0
S.D.	0	0	0	0

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

Aerial righting reflex-1 to -3) 0: Normal, 1: Failure, 2:None

Aerial righting reflex-total) Total score of 3 times

Grip strength

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	Grip strength of fore limb-1	Grip strength of fore limb-2	Grip strength of fore limb-mean	Grip strength of hind limb-1	Grip strength of hind limb-2	Grip strength of hind limb-mean
Animal No.	g	g	g	g	g	g
1008	1492	1393	1443	679	775	727
1009	1400	1356	1378	666	637	652
1010	1612	1742	1677	701	690	696
1011	1493	1452	1473	688	657	673
1012	1514	1700	1607	837	768	803
n	5	5	5	5	5	5
Mean	1502	1529	1516	714	705	710
S.D.	76	180	123	70	63	59

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Grip strength of fore limb-1	Grip strength of fore limb-2	Grip strength of fore limb-mean	Grip strength of hind limb-1	Grip strength of hind limb-2	Grip strength of hind limb-mean
Animal No.	g	g	g	g	g	g
2008	1391	1480	1436	606	710	658
2009	1453	1361	1407	698	781	740
2010	1432	1495	1464	626	674	650
2011	1698	1806	1752	649	738	694
2012	1522	1635	1579	610	617	614
n	5	5	5	5	5	5
Mean	1499	1555	1528	638	704	671
S.D.	121	170	141	38	62	48

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
3008	1795	1808	1802	815	811	813
3009	1519	1500	1510	658	740	699
3010	1616	1453	1535	781	681	731
3011	1543	1505	1524	679	779	729
3012	1507	1529	1518	863	774	819
n	5	5	5	5	5	5
Mean	1596	1559	1578	759	757	758
S.D.	119	142	126	88	49	54

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : F0 mating

Generation : F0

Sex : Male

Week : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
4008	1460	1365	1413	621	604	613
4009	1512	1453	1483	639	724	682
4010	1374	1414	1394	663	688	676
4011	1496	1391	1444	729	806	768
4012	1356	1390	1373	682	654	668
n	5	5	5	5	5	5
Mean	1440	1403	1421	667	695	681
S.D.	71	33	43	42	76	56

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
1102	1191	1120	1156	426	400	413
1105	1016	1098	1057	372	319	346
1106	1009	1151	1080	508	468	488
1109	1042	970	1006	425	424	425
1110	1281	1177	1229	485	484	485
n	5	5	5	5	5	5
Mean	1108	1103	1106	443	419	431
S.D.	122	80	88	54	65	59

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
2103	1085	1140	1113	514	492	503
2105	1135	1167	1151	394	374	384
2107	1249	1166	1208	639	650	645
2109	1240	1351	1296	433	498	466
2111	1148	1243	1196	398	455	427
n	5	5	5	5	5	5
Mean	1171	1213	1193	476	494	485
S.D.	71	86	69	103	100	100

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
3101	1197	1119	1158	401	357	379
3102	1114	1127	1121	399	364	382
3104	1160	1116	1138	489	503	496
3106	1020	1088	1054	400	442	421
3109	1147	1122	1135	560	408	484
n	5	5	5	5	5	5
Mean	1128	1114	1121	450	415	432
S.D.	67	15	40	73	60	55

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : F0 lactation

Generation : F0

Sex : Female

Day : 13

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
4103	1231	1156	1194	554	459	507
4105	1047	1047	1047	304	434	369
4106	1140	1111	1126	607	560	584
4108	1080	1033	1057	399	371	385
4111	1146	1068	1107	323	483	403
n	5	5	5	5	5	5
Mean	1129	1083	1106	437	461	450
S.D.	71	50	59	137	69	92

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
5106	1297	1332	1315	728	774	751
5107	1002	1073	1038	485	616	551
5108	1115	1185	1150	599	547	573
5109	1049	1061	1055	488	579	534
5110	1129	1006	1068	756	583	670
n	5	5	5	5	5	5
Mean	1118	1131	1125	611	620	616
S.D.	112	130	115	128	90	92

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : Administration (non-mating group)

Generation : F0

Sex : Female

Week : 6

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
6106	1028	1068	1048	527	598	563
6107	1125	1101	1113	612	617	615
6108	1289	1173	1231	563	557	560
6109	1044	1171	1108	457	528	493
6110	1000	1003	1002	436	571	504
n	5	5	5	5	5	5
Mean	1097	1103	1100	519	574	547
S.D.	117	72	86	73	35	50

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
1008	1650	1416	1533	633	613	623
1009	1587	1485	1536	509	622	566
1010	1572	1403	1488	583	574	579
1011	1824	2062	1943	841	951	896
1012	1793	1711	1752	602	685	644
n	5	5	5	5	5	5
Mean	1685	1615	1650	634	689	662
S.D.	117	279	193	125	152	135

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : Recovery

Generation : F0

Sex : Male

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
4008	1759	1640	1700	571	586	579
4009	1594	1448	1521	741	701	721
4010	1772	1304	1538	717	675	696
4011	1675	1626	1651	871	761	816
4012	1690	1705	1698	667	670	669
n	5	5	5	5	5	5
Mean	1698	1545	1622	713	679	696
S.D.	72	165	87	110	63	86

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : Recovery (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
5106	997	1185	1091	424	425	425
5107	1159	1047	1103	438	483	461
5108	1207	1082	1145	355	479	417
5109	1185	1203	1194	338	473	406
5110	1019	1150	1085	373	492	433
n	5	5	5	5	5	5
Mean	1113	1133	1124	386	470	428
S.D.	98	67	46	44	26	21

Grip strength of fore/hind limb-mean) mean value of 2 times

Grip strength

Period : Recovery (non-mating group)

Generation : F0

Sex : Female

Week : 2

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Grip strength of fore limb-1 g	Grip strength of fore limb-2 g	Grip strength of fore limb-mean g	Grip strength of hind limb-1 g	Grip strength of hind limb-2 g	Grip strength of hind limb-mean g
6106	1187	1256	1222	546	472	509
6107	1138	1243	1191	471	420	446
6108	1257	1225	1241	400	482	441
6109	1195	1035	1115	435	375	405
6110	1066	1276	1171	541	580	561
n	5	5	5	5	5	5
Mean	1169	1207	1188	479	466	472
S.D.	71	98	49	64	77	62

Grip strength of fore/hind limb-mean) mean value of 2 times

Motor activity		Sex : Male		Week : 6		Period : F0 mating		Species : Rat	
Generation : F0		Dose : Cinchona Bark Extract 0 mg/kg		Dose : Cinchona Bark Extract 0 mg/kg		Dose : Cinchona Bark Extract 0 mg/kg		Dose : Cinchona Bark Extract 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	Count	Count
1008	323	438	418	97	12	34	1322		
1009	383	243	119	22	105	0	872		
1010	143	69	21	8	30	4	275		
1011	313	319	53	14	26	5	730		
1012	387	175	55	14	16	8	655		
n	5	5	5	5	5	5	5	5	5
Mean	310	249	133	31	38	10	771		
S.D.	99	140	163	37	38	14	379		

Motor activity		Sex : Male		Week : 6		Period : F0 mating		Species : Rat	
Generation : F0		Dose : Cinchona Bark Extract 100 mg/kg		Dose : Cinchona Bark Extract 100 mg/kg		Dose : Cinchona Bark Extract 100 mg/kg		Dose : Cinchona Bark Extract 100 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	Count	Count
2008	293	76	41	22	19	18	469		
2009	307	220	6	38	211	0	782		
2010	317	87	146	38	5	29	622		
2011	429	386	270	352	317	311	2065		
2012	330	75	28	9	0	3	445		
n	5	5	5	5	5	5	5	5	5
Mean	335	169	98	92	110	72	877		
S.D.	54	136	110	146	145	134	678		

Motor activity		Sex : Male		Week : 6		Period : F0 mating		Species : Rat	
Generation : F0		Dose : Cinchona Bark Extract 300 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	Count	Count
3008	284	199	187	132	141	164	1107		
3009	388	161	76	14	3	23	665		
3010	378	259	309	20	0	28	994		
3011	393	202	237	62	0	86	980		
3012	306	5	17	22	1	7	358		
n	5	5	5	5	5	5	5		
Mean	350	165	165	50	29	62	821		
S.D.	51	96	119	50	63	65	306		

Motor activity		Sex : Male		Week : 6		Period : F0 mating		Species : Rat	
Generation : F0		Dose : Cinchona Bark Extract 1000 mg/kg		Dose : Cinchona Bark Extract 1000 mg/kg		Dose : Cinchona Bark Extract 1000 mg/kg		Dose : Cinchona Bark Extract 1000 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	Count	Count
4008	343	293	173	199	212	307	1527		
4009	219	195	144	50	95	0	703		
4010	422	308	284	259	222	387	1882		
4011	163	78	74	6	50	37	408		
4012	417	300	178	70	8	26	999		
n	5	5	5	5	5	5	5		
Mean	313	235	171	117	117	151	1104		
S.D.	117	99	76	107	96	181	600		

Motor activity			Period : F0 lactation				
Generation : F0		Sex : Female	Day : 13	Dose : Cinchona Bark Extract 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
1102	348	208	257	215	151	160	1339
1105	394	153	26	12	7	6	598
1106	462	282	167	16	13	5	945
1109	419	307	369	223	32	59	1409
1110	498	480	379	282	376	335	2350
n	5	5	5	5	5	5	5
Mean	424	286	240	150	116	113	1328
S.D.	58	124	148	126	157	139	658

Appendix 2-338

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Motor activity		Period : F0 lactation		Species : Rat			
Generation : F0		Dose : Cinchona Bark Extract 100 mg/kg					
	0'-10'	Sex : Female 10'-20'	Day : 13 20'-30'	30'-40'	40'-50'	50'-60'	Total(0'-60')
Animal No.	Count	Count	Count	Count	Count	Count	Count
2103	417	350	334	240	321	222	1884
2105	444	420	207	251	290	238	1850
2107	393	224	70	349	146	9	1191
2109	498	371	312	272	262	324	2039
2111	333	274	106	60	2	22	797
n	5	5	5	5	5	5	5
Mean	417	328	206	234	204	163	1552
S.D.	61	78	118	106	131	140	533

Appendix 2-339

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Motor activity		Sex : Female		Day : 13		Period : F0 lactation		Species : Rat	
Generation : F0						Dose : Cinchona Bark Extract 300 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	Count	Count
3101	423	338	211	309	320	233			1834
3102	487	412	322	267	147	12			1647
3104	463	457	458	297	25	62			1762
3106	470	305	216	103	133	18			1245
3109	398	342	216	139	129	78			1302
n	5	5	5	5	5	5			5
Mean	448	371	285	223	151	81			1558
S.D.	37	62	108	95	106	90			269

Motor activity			Period : F0 lactation				
Generation : F0		Sex : Female	Day : 13	Dose : Cinchona Bark Extract 1000 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
4103	365	315	361	302	39	30	1412
4105	407	78	90	30	45	103	753
4106	442	376	216	62	137	11	1244
4108	352	148	4	106	226	7	843
4111	374	278	37	70	6	11	776
n	5	5	5	5	5	5	5
Mean	388	239	142	114	91	32	1006
S.D.	36	123	147	109	90	40	302

Appendix 2-341

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Motor activity		Period : Administration (non-mating group)		Species : Rat			
Generation : F0		Sex : Female		Week : 6		Dose : Cinchona Bark Extract 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
5106	446	327	221	153	31	10	1188
5107	393	326	281	74	4	0	1078
5108	489	319	8	269	326	42	1453
5109	419	369	175	0	287	162	1412
5110	379	259	266	13	4	16	937
n	5	5	5	5	5	5	5
Mean	425	320	190	102	130	46	1214
S.D.	44	39	110	111	162	67	219

Motor activity		Period : Administration (non-mating group)		Species : Rat			
Generation : F0		Sex : Female		Week : 6		Dose : Cinchona Bark Extract 1000 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
6106	388	261	187	277	115	47	1275
6107	397	152	22	279	153	4	1007
6108	371	374	193	183	80	39	1240
6109	392	237	70	6	10	6	721
6110	447	346	186	36	289	311	1615
n	5	5	5	5	5	5	5
Mean	399	274	132	156	129	81	1172
S.D.	29	89	80	130	104	130	332

Appendix 2-343

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Motor activity		Period : Recovery		Species : Rat			
Generation : F0		Sex : Male		Week : 2		Dose : Cinchona Bark Extract 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	397	90	40	10	3	2	542
1009	297	113	161	23	6	16	616
1010	317	204	33	9	31	18	612
1011	393	343	237	120	30	10	1133
1012	342	241	262	266	169	140	1420
n	5	5	5	5	5	5	5
Mean	349	198	147	86	48	37	865
S.D.	45	102	107	111	69	58	391

Motor activity		Sex : Male		Week : 2		Period : Recovery		Species : Rat	
Generation : F0		Dose : Cinchona Bark Extract 1000 mg/kg		Dose : Cinchona Bark Extract 1000 mg/kg		Dose : Cinchona Bark Extract 1000 mg/kg		Dose : Cinchona Bark Extract 1000 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	Count	Count
4008	305	351	259	130	2	62	1109		
4009	407	229	99	14	11	3	763		
4010	347	196	162	179	166	167	1217		
4011	403	204	26	15	8	90	746		
4012	372	155	57	82	9	45	720		
n	5	5	5	5	5	5	5		
Mean	367	227	121	84	39	73	911		
S.D.	42	74	93	72	71	61	234		

Appendix 2-345

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in ratsStudy No. : XXXXXXXXXX

Motor activity		Period : Recovery (non-mating group)		Species : Rat			
Generation : F0		Sex : Female		Week : 2		Dose : Cinchona Bark Extract 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
5106	422	311	30	50	13	118	944
5107	311	138	0	19	0	26	494
5108	380	397	67	64	8	176	1092
5109	405	328	324	306	275	197	1835
5110	284	251	111	56	52	93	847
n	5	5	5	5	5	5	5
Mean	360	285	106	99	70	122	1042
S.D.	60	97	129	117	117	68	495

Motor activity			Period : Recovery (non-mating group)				
Generation : F0	Sex : Female	Week : 2	Dose : Cinchona Bark Extract 1000 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	327	316	110	4	0	47	804
6107	339	198	11	0	6	39	593
6108	261	161	43	8	2	1	476
6109	421	57	3	8	5	20	514
6110	354	308	208	43	2	13	928
n	5	5	5	5	5	5	5
Mean	340	208	75	13	3	24	663
S.D.	57	108	85	17	2	19	195

Appendix 3-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day							Body weight gain
	1	8	15	22	29	36	42	
1001	435	466	495	532	553	581	597	162
1002	381	415	439	463	495	519	535	154
1003	451	485	526	555	593	619	642	191
1004	407	431	457	484	512	540	560	153
1005	402	427	453	487	514	542	560	158
1006	451	493	538	562	593	624	649	198
1007	391	431	462	480	505	527	545	154
1008	419	454	478	505	526	553	570	151
1009	402	452	482	514	540	568	576	174
1010	422	435	450	469	476	498	507	85
1011	455	491	528	546	573	605	608	153
1012	411	445	477	508	529	551	571	160
n	12	12	12	12	12	12	12	12
Mean	419	452	482	509	534	561	577	158
S.D.	25	26	33	34	38	40	42	28

Appendix 3-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Animal No.	/Day							Body weight gain
	1	8	15	22	29	36	42	
2001	389	412	432	450	476	491	498	109
2002	394	434	468	490	518	543	558	164
2003	456	493	537	566	592	614	597	141
2004	424	455	482	508	533	565	574	150
2005	413	441	469	488	513	533	547	134
2006	447	478	513	543	567	584	598	151
2007	379	405	436	459	493	517	536	157
2008	419	464	498	528	568	583	606	187
2009	390	437	471	497	524	551	568	178
2010	415	448	476	492	513	545	558	143
2011	439	463	497	517	553	577	589	150
2012	446	485	517	549	569	594	601	155
n	12	12	12	12	12	12	12	12
Mean	418	451	483	507	535	558	569	152
S.D.	26	27	31	35	35	35	32	20

Appendix 3-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Animal No.	/Day							Body weight gain
	1	8	15	22	29	36	42	
3001	402	441	463	486	510	537	549	147
3002	450	494	537	559	582	607	613	163
3003	407	425	455	479	509	531	539	132
3004	426	463	497	523	539	556	565	139
3005	437	481	522	540	571	596	611	174
3006	440	460	487	502	526	547	566	126
3007	422	449	481	507	536	561	590	168
3008	387	431	457	486	519	533	532	145
3009	385	419	450	483	518	546	553	168
3010	387	413	438	460	474	485	482	95
3011	431	471	503	530	556	577	583	152
3012	416	453	487	509	533	553	559	143
n	12	12	12	12	12	12	12	12
Mean	416	450	481	505	531	552	562	146
S.D.	22	25	30	29	29	32	36	22

Appendix 3-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 before mating Day 1-15, F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day							Body weight gain
	1	8	15	22	29	36	42	
4001	390	416	434	453	477	497	516	126
4002	413	452	489	518	544	564	580	167
4003	444	496	538	576	594	627	646	202
4004	416	448	486	518	544	574	595	179
4005	423	466	488	516	541	564	575	152
4006	438	473	515	548	588	599	624	186
4007	379	408	431	453	470	477	478	99
4008	403	437	469	496	529	559	568	165
4009	389	425	457	487	516	547	552	163
4010	446	490	530	559	600	615	629	183
4011	421	446	472	497	529	547	555	134
4012	453	491	522	551	587	617	623	170
n	12	12	12	12	12	12	12	12
Mean	418	454	486	514	543	566	578	161
S.D.	24	30	35	40	43	46	49	29

Appendix 3-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 before mating Day 1-15

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	15	
1101	242	258	269	27
1102	248	262	271	23
1103	237	252	270	33
1104	261	265	268	7
1105	261	290	319	58
1106	242	260	265	23
1107	253	260	259	6
1108	266	277	285	19
1109	235	231	249	14
1110	274	285	307	33
1111	281	290	310	29
1112	234	244	250	16
n	12	12	12	12
Mean	253	265	277	24
S.D.	16	18	23	14

Appendix 3-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 before mating Day 1-15

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	15	
2101	250	258	260	10
2102	236	254	262	26
2103	269	277	300	31
2104	257	268	281	24
2105	257	273	282	25
2106	249	260	279	30
2107	257	266	288	31
2108	247	265	280	33
2109	262	286	308	46
2110	243	254	262	19
2111	240	243	259	19
2112	279	292	303	24
n	12	12	12	12
Mean	254	266	280	27
S.D.	12	14	17	9

Appendix 3-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 before mating Day 1-15

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	15	
3101	241	252	264	23
3102	245	240	260	15
3103	261	275	292	31
3104	248	253	257	9
3105	264	256	281	17
3106	250	249	260	10
3107	244	260	275	31
3108	253	264	267	14
3109	257	250	259	2
3110	238	262	274	36
3111	284	300	332	48
3112	231	231	228	-3
n	12	12	12	12
Mean	251	258	271	19
S.D.	14	18	25	15

Appendix 3-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 before mating Day 1-15

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	15	
4101	249	254	257	8
4102	231	245	257	26
4103	232	248	251	19
4104	243	255	258	15
4105	244	253	266	22
4106	271	279	299	28
4107	254	259	278	24
4108	271	267	273	2
4109	250	269	274	24
4110	262	265	266	4
4111	240	240	258	18
4112	262	288	303	41
n	12	12	12	12
Mean	251	260	270	19
S.D.	14	14	17	11

Appendix 3-9

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 gestation Day 0-25

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Body weight gain
	0	7	14	20	
1101	276	327	364	435	159
1102	282	323	366	464	182
1103	276	322	367	459	183
1104	282	301	340	411	129
1105	319	344	385	493	174
1106	272	307	349	429	157
1107	274	318	355	434	160
1108	304	349	374	454	150
1109	255	302	351	447	192
1110	306	340	378	479	173
1111	323	352	396	486	163
1112	264	302	348	430	166
n	12	12	12	12	12
Mean	286	324	364	452	166
S.D.	22	19	17	25	17

Appendix 3-10

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 gestation Day 0-25

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Body weight gain
	0	7	14	20	
2101	279	328	374	454	175
2102	274	319	361	448	174
2103	302	344	387	473	171
2104	281	313	356	439	158
2105	289	336	385	489	200
2106	282	334	375	462	180
2107	285	339	376	462	177
2108	278	328	374	467	189
2109	314	359	404	507	193
2110	280	326	363	449	169
2111	261	306	334	417	156
2112	312	348	395	481	169
n	12	12	12	12	12
Mean	286	332	374	462	176
S.D.	16	15	19	24	13

Appendix 3-11

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 gestation Day 0-25

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Body weight gain
	0	7	14	20	
3101	274	312	338	429	155
3102	263	326	377	475	212
3103	304	340	387	491	187
3104	259	314	354	444	185
3105	298	354	395	489	191
3106	271	309	354	452	181
3107	275	326	369	462	187
3108	275	322	361	454	179
3109	265	310	352	435	170
3110	283	321	366	480	197
3111	335	389	436	525	190
3112	250	286	317	406	156
n	12	12	12	12	12
Mean	279	326	367	462	183
S.D.	23	26	30	32	16

Appendix 3-12

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 gestation Day 0-25

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Body weight gain
	0	7	14	20	
4101	274	316	351	452	178
4102	262	303	342	438	176
4103	262	314	364	453	191
4104	261	306	347	427	166
4105	274	308	354	430	156
4106	302	336	369	468	166
4107	283	324	365	453	170
4108	271	328	381	481	210
4109	290	330	379	461	171
4110	287	325	365	475	188
4111	264	323	379	477	213
4112	300	343	388	476	176
n	12	12	12	12	12
Mean	278	321	365	458	180
S.D.	15	12	15	19	17

Appendix 3-13

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 lactation Day 0-14

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Body weight gain
	0	4	7	13	
1101	348	339	328	352	4
1102	366	368	359	389	23
1103	386	397	388	407	21
1104	338	326	333	341	3
1105	365	362	360	377	12
1106	332	337	340	351	19
1107	342	346	366	372	30
1108	369	379	381	386	17
1109	346	341	336	368	22
1110	348	365	369	390	42
1111	392	383	399	406	14
1112	326	354	355	375	49
n	12	12	12	12	12
Mean	355	358	360	376	21
S.D.	21	21	23	21	14

Appendix 3-14

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 lactation Day 0-14

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Body weight gain
	0	4	7	13	
2101	376	377	386	406	30
2102	340	359	372	377	37
2103	376	362	333	340	-36
2104	314	353	360	365	51
2105	376	402	403	391	15
2106	385	393	394	410	25
2107	358	351	353	362	4
2108	351	348	346	365	14
2109	387	393	391	399	12
2110	371	350	349	372	1
2111	338	337	354	373	35
2112	377	393	389	404	27
n	12	12	12	12	12
Mean	362	368	369	380	18
S.D.	22	22	23	22	22

Appendix 3-15

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 lactation Day 0-14

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Body weight gain
	0	4	7	13	
3101	323	321	328	338	15
3102	359	364	357	365	6
3103	375	362	373	393	18
3104	353	352	351	364	11
3105	390	409	405	415	25
3106	308	342	338	356	48
3107	326	371	369	387	61
3108	370	352	366	389	19
3109	335	366	369	380	45
3110	335	351	337	360	25
3111	430	434	414	406	-24
3112	295	324	333	337	42
n	12	12	12	12	12
Mean	350	362	362	374	24
S.D.	38	32	27	25	23

Appendix 3-16

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : F0 lactation Day 0-14

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Body weight gain
	0	4	7	13	
4101	351	343	347	360	9
4102	328	330	346	341	13
4103	368	369	373	391	23
4104	354	340	343	358	4
4105	333	360	359	370	37
4106	370	395	390	387	17
4107	351	359	363	368	17
4108	372	375	384	385	13
4109	383	374	368	377	-6
4110	369	334	352	375	6
4111	371	407	404	404	33
4112	393	374	381	400	7
n	12	12	12	12	12
Mean	362	363	368	376	14
S.D.	19	24	19	18	12

Appendix 3-17

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight
Sex : Female
Period : Administration (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg

Study No. : [REDACTED]

Animal No.	/Day							Body weight gain
	1	8	15	22	29	36	42	
5101	259	261	262	279	290	292	298	39
5102	232	244	252	254	256	266	273	41
5103	245	264	280	292	294	313	323	78
5104	269	276	291	301	306	309	325	56
5105	265	285	306	324	336	347	349	84
5106	232	248	257	250	274	284	281	49
5107	253	249	266	272	282	284	296	43
5108	260	273	277	301	307	320	333	73
5109	266	274	284	314	342	333	334	68
5110	242	247	261	276	285	284	299	57
n	10	10	10	10	10	10	10	10
Mean	252	262	274	286	297	303	311	59
S.D.	14	15	17	24	27	25	25	16

Appendix 3-18

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : Administration (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day							Body weight gain
	1	8	15	22	29	36	42	
6101	236	244	256	258	270	282	274	38
6102	261	284	292	299	319	327	315	54
6103	240	262	272	287	291	312	320	80
6104	264	276	288	304	313	329	339	75
6105	270	292	301	327	335	338	345	75
6106	254	262	282	301	317	326	338	84
6107	254	260	280	297	299	303	315	61
6108	235	248	258	263	277	290	283	48
6109	226	235	246	244	257	266	269	43
6110	270	281	298	316	331	339	348	78
n	10	10	10	10	10	10	10	10
Mean	251	264	277	290	301	311	315	64
S.D.	16	19	19	27	27	25	30	17

Appendix 3-19

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : Recovery Day 1-15

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	14	
1008	581	594	606	25
1009	577	590	606	29
1010	512	530	535	23
1011	608	628	644	36
1012	574	596	605	31
n	5	5	5	5
Mean	570	588	599	29
S.D.	35	36	40	5

Appendix 3-20

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : Recovery Day 1-15

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	14	
4008	569	575	596	27
4009	560	571	584	24
4010	633	655	656	23
4011	560	576	588	28
4012	625	647	662	37
n	5	5	5	5
Mean	589	605	617	28
S.D.	36	42	38	6

Appendix 3-21

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : Recovery Day 1-15 (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	14	
5106	288	298	292	4
5107	300	309	306	6
5108	337	349	356	19
5109	338	342	337	-1
5110	292	305	305	13
n	5	5	5	5
Mean	311	321	319	8
S.D.	25	23	26	8

Appendix 3-22

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Body weight

Period : Recovery Day 1-15 (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Body weight gain
	1	8	14	
6106	339	349	347	8
6107	307	315	314	7
6108	291	289	306	15
6109	270	279	289	19
6110	348	360	361	13
n	5	5	5	5
Mean	311	318	323	12
S.D.	33	36	30	5

Appendix 4-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 before mating Day 1-15

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
1001	28	30	30	88
1002	26	27	25	78
1003	29	31	28	88
1004	24	25	25	74
1005	25	25	26	76
1006	36	27	35	98
1007	25	26	25	76
1008	28	28	24	80
1009	27	28	27	82
1010	31	24	24	79
1011	28	30	29	87
1012	26	24	24	74
n	12	12	12	12
Mean	28	27	27	82
S.D.	3	2	3	7

Appendix 4-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 before mating Day 1-15

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
2001	27	24	23	74
2002	26	25	28	79
2003	28	31	32	91
2004	29	27	25	81
2005	26	27	27	80
2006	29	27	27	83
2007	25	25	25	75
2008	29	33	29	91
2009	27	28	29	84
2010	29	28	26	83
2011	28	28	31	87
2012	30	28	28	86
n	12	12	12	12
Mean	28	28	28	83
S.D.	2	3	3	5

Appendix 4-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 before mating Day 1-15

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
3001	28	25	22	75
3002	25	29	29	83
3003	25	23	26	74
3004	27	25	25	77
3005	32	28	29	89
3006	27	25	33	85
3007	24	24	27	75
3008	27	27	27	81
3009	25	25	24	74
3010	24	24	26	74
3011	29	29	29	87
3012	29	30	26	85
n	12	12	12	12
Mean	27	26	27	80
S.D.	2	2	3	6

Appendix 4-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 before mating Day 1-15

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
4001	20	24	25	69
4002	28	31	30	89
4003	29	28	31	88
4004	23	25	27	75
4005	26	26	26	78
4006	27	28	31	86
4007	24	27	22	73
4008	24	24	27	75
4009	23	25	26	74
4010	30	29	30	89
4011	23	24	26	73
4012	27	26	30	83
n	12	12	12	12
Mean	25	26	28	79
S.D.	3	2	3	7

Appendix 4-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		
	30	36	42
1001	30	27	32
1002	27	27	26
1003	34	31	31
1004	30	30	30
1005	31	31	30
1006	33	37	34
1007	25	26	28
1008	31	29	28
1009	27	28	28
1010	25	27	27
1011	32	33	33
1012	26	27	27
n	12	12	12
Mean	29	29	30
S.D.	3	3	3

Appendix 4-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		
	30	36	42
2001	26	25	23
2002	28	26	25
2003	29	29	26
2004	30	30	26
2005	28	26	26
2006	29	29	28
2007	26	29	26
2008	32	27	33
2009	32	29	33
2010	30	29	30
2011	29	31	34
2012	33	30	27
n	12	12	12
Mean	29	28	28
S.D.	2	2	4

Appendix 4-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		
	30	36	42
3001	27	29	26
3002	29	28	29
3003	26	25	26
3004	28	26	29
3005	29	28	26
3006	27	29	30
3007	33	29	31
3008	30	29	26
3009	26	29	24
3010	25	26	22
3011	30	29	25
3012	25	30	26
n	12	12	12
Mean	28	28	27
S.D.	2	2	3

Appendix 4-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 mating Day 15-43

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		
	30	36	42
4001	28	25	25
4002	28	32	32
4003	32	30	32
4004	30	29	31
4005	27	26	25
4006	29	24	30
4007	24	24	23
4008	28	31	26
4009	27	27	24
4010	28	31	31
4011	28	27	26
4012	31	33	30
n	12	12	12
Mean	28	28	28
S.D.	2	3	3

Appendix 4-9

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 before mating Day 1-15

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
1101	20	16	19	55
1102	19	19	19	57
1103	19	17	20	56
1104	16	16	17	49
1105	21	20	22	63
1106	21	20	18	59
1107	14	20	17	51
1108	17	22	19	58
1109	19	11	20	50
1110	22	16	20	58
1111	21	21	27	69
1112	19	17	17	53
n	12	12	12	12
Mean	19	18	20	57
S.D.	2	3	3	6

Appendix 4-10

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 before mating Day 1-15

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
2101	21	18	15	54
2102	18	18	17	53
2103	21	17	21	59
2104	16	17	20	53
2105	18	19	19	56
2106	20	17	21	58
2107	19	12	22	53
2108	19	19	21	59
2109	22	22	23	67
2110	18	18	15	51
2111	20	14	19	53
2112	21	22	18	61
n	12	12	12	12
Mean	19	18	19	56
S.D.	2	3	3	5

Appendix 4-11

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 before mating Day 1-15

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
3101	20	21	23	64
3102	18	12	18	48
3103	16	18	21	55
3104	13	19	18	50
3105	20	11	22	53
3106	18	15	17	50
3107	20	18	20	58
3108	12	20	16	48
3109	17	12	17	46
3110	16	18	18	52
3111	20	22	29	71
3112	14	15	11	40
n	12	12	12	12
Mean	17	17	19	53
S.D.	3	4	4	8

Appendix 4-12

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 before mating Day 1-15

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
4101	17	17	13	47
4102	16	18	19	53
4103	17	19	15	51
4104	15	20	17	52
4105	20	15	19	54
4106	22	16	21	59
4107	17	17	21	55
4108	11	17	15	43
4109	19	20	17	56
4110	19	17	14	50
4111	17	11	18	46
4112	14	22	22	58
n	12	12	12	12
Mean	17	17	18	52
S.D.	3	3	3	5

Appendix 4-13

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Food consumption
Sex : Female
Period : F0 gestation Day 0-25
Dose : Cinchona Bark Extract 0 mg/kg

Study No. : [REDACTED]

Unit : g Species : Rat

Animal No.	/Day				Total food consumption
	1	7	14	20	
1101	16	28	22	21	87
1102	17	31	27	24	99
1103	19	25	28	28	100
1104	16	20	26	23	85
1105	17	23	24	28	92
1106	19	24	29	26	98
1107	19	25	26	27	97
1108	22	28	26	26	102
1109	22	30	26	30	108
1110	19	25	27	27	98
1111	21	24	27	28	100
1112	19	23	25	29	96
n	12	12	12	12	12
Mean	19	26	26	26	97
S.D.	2	3	2	3	6

Appendix 4-14

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 gestation Day 0-25

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Total food consumption
	1	7	14	20	
2101	20	28	31	31	110
2102	20	28	27	28	103
2103	15	30	26	26	97
2104	11	23	26	24	84
2105	22	27	29	29	107
2106	16	25	26	29	96
2107	20	28	30	29	107
2108	19	28	28	28	103
2109	17	30	29	29	105
2110	20	26	25	23	94
2111	21	24	23	27	95
2112	18	24	30	29	101
n	12	12	12	12	12
Mean	18	27	28	28	100
S.D.	3	2	2	2	7

Appendix 4-15

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 gestation Day 0-25

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Total food consumption
	1	7	14	20	
3101	20	29	20	25	94
3102	17	33	32	30	112
3103	19	23	29	31	102
3104	23	29	30	30	112
3105	21	26	26	30	103
3106	19	24	26	27	96
3107	20	27	27	28	102
3108	20	25	26	26	97
3109	16	25	25	24	90
3110	13	24	25	27	89
3111	22	34	33	33	122
3112	17	24	21	21	83
n	12	12	12	12	12
Mean	19	27	27	28	100
S.D.	3	4	4	3	11

Appendix 4-16

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 gestation Day 0-25

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Total food consumption
	1	7	14	20	
4101	14	24	20	26	84
4102	15	26	21	29	91
4103	19	25	28	29	101
4104	18	25	25	28	96
4105	20	22	24	26	92
4106	18	25	21	29	93
4107	19	27	25	27	98
4108	20	26	29	29	104
4109	20	22	30	27	99
4110	17	25	21	24	87
4111	22	26	30	31	109
4112	16	26	29	28	99
n	12	12	12	12	12
Mean	18	25	25	28	96
S.D.	2	2	4	2	7

Appendix 4-17

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 lactation Day 0-14

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Total food consumption
	2	4	7	13	
1101	27	38	34	55	154
1102	23	40	42	60	165
1103	32	47	45	77	201
1104	18	34	43	48	143
1105	24	35	38	55	152
1106	32	49	46	61	188
1107	25	42	52	65	184
1108	40	49	49	64	202
1109	21	34	41	65	161
1110	35	50	51	75	211
1111	31	52	57	66	206
1112	35	45	45	60	185
n	12	12	12	12	12
Mean	29	43	45	63	179
S.D.	7	7	6	8	24

Appendix 4-18

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 lactation Day 0-14

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Total food consumption
	2	4	7	13	
2101	41	46	50	75	212
2102	30	50	51	66	197
2103	27	36	36	61	160
2104	45	59	55	74	233
2105	39	52	49	70	210
2106	32	54	44	70	200
2107	24	47	52	73	196
2108	20	36	36	54	146
2109	31	42	46	68	187
2110	18	35	38	55	146
2111	24	49	52	66	191
2112	32	45	43	65	185
n	12	12	12	12	12
Mean	30	46	46	66	189
S.D.	8	8	7	7	26

Appendix 4-19

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 lactation Day 0-14

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Total food consumption
	2	4	7	13	
3101	23	51	47	66	187
3102	35	49	45	59	188
3103	32	47	45	66	190
3104	32	40	52	69	193
3105	38	51	46	71	206
3106	35	49	43	66	193
3107	36	46	46	63	191
3108	28	35	46	67	176
3109	33	51	55	73	212
3110	30	41	41	57	169
3111	22	46	44	47	159
3112	33	49	44	59	185
n	12	12	12	12	12
Mean	31	46	46	64	187
S.D.	5	5	4	7	15

Appendix 4-20

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : F0 lactation Day 0-14

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day				Total food consumption
	2	4	7	13	
4101	29	45	38	65	177
4102	30	44	49	49	172
4103	33	47	49	73	202
4104	19	35	42	62	158
4105	31	40	44	60	175
4106	41	48	48	57	194
4107	32	47	54	65	198
4108	27	39	40	59	165
4109	24	34	38	57	153
4110	11	25	44	57	137
4111	43	47	54	70	214
4112	9	28	35	51	123
n	12	12	12	12	12
Mean	27	40	45	60	172
S.D.	10	8	6	7	27

Appendix 4-21

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Administration Day 1-15 (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
5101	19	17	16	52
5102	18	18	20	56
5103	21	21	23	65
5104	22	17	21	60
5105	23	24	26	73
5106	19	19	19	57
5107	18	10	17	45
5108	22	21	14	57
5109	25	21	20	66
5110	22	13	20	55
n	10	10	10	10
Mean	21	18	20	59
S.D.	2	4	3	8

Appendix 4-22

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Administration Day 1-15 (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	15	
6101	14	20	19	53
6102	15	23	21	59
6103	18	21	20	59
6104	18	18	21	57
6105	20	21	17	58
6106	21	18	22	61
6107	18	15	18	51
6108	14	19	18	51
6109	18	16	20	54
6110	20	15	20	55
n	10	10	10	10
Mean	18	19	20	56
S.D.	3	3	2	4

Appendix 4-23

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Administration Day 15-43 (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		
	30	36	42
5101	20	17	17
5102	14	19	17
5103	21	25	22
5104	19	15	19
5105	22	25	23
5106	24	21	17
5107	17	14	18
5108	20	18	22
5109	24	18	18
5110	19	14	20
n	10	10	10
Mean	20	19	19
S.D.	3	4	2

Appendix 4-24

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Administration Day 15-43 (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day		
	30	36	42
6101	14	21	15
6102	15	26	18
6103	18	19	21
6104	19	18	18
6105	22	16	21
6106	24	19	24
6107	20	13	19
6108	16	22	14
6109	20	18	18
6110	22	20	22
n	10	10	10
Mean	19	19	19
S.D.	3	3	3

Appendix 4-25

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Recovery Day 1-15

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	14	
1008	27	30	28	85
1009	28	25	28	81
1010	27	29	24	80
1011	34	32	32	98
1012	28	28	29	85
n	5	5	5	5
Mean	29	29	28	86
S.D.	3	3	3	7

Appendix 4-26

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Recovery Day 1-15

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	14	
4008	33	30	31	94
4009	29	27	28	84
4010	33	32	29	94
4011	29	28	25	82
4012	33	33	33	99
n	5	5	5	5
Mean	31	30	29	91
S.D.	2	3	3	7

Appendix 4-27

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Recovery Day 1-15 (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	14	
5106	24	26	21	71
5107	14	21	13	48
5108	22	23	20	65
5109	21	20	19	60
5110	14	22	19	55
n	5	5	5	5
Mean	19	22	18	60
S.D.	5	2	3	9

Appendix 4-28

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Food consumption

Period : Recovery Day 1-15 (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Animal No.	/Day			Total food consumption
	2	8	14	
6106	17	22	18	57
6107	17	19	17	53
6108	21	16	22	59
6109	18	19	20	57
6110	18	23	17	58
n	5	5	5	5
Mean	18	20	19	57
S.D.	2	3	2	2

Appendix 5-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
Animal No.									
1008	8.5	-	-	-	-	-	+/-	1.010	Y
1009	7.5	+/-	+/-	-	+/-	-	+/-	1.010	Y
1010	8.5	+/-	+/-	-	-	-	+/-	1.010	Y
1011	8.0	-	+/-	-	+/-	-	+/-	<=1.005	Y
1012	8.5	+/-	+/-	-	+/-	-	+/-	1.015	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Animal No.	Urinalysis								
	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
2008	>=9.0	-	+/-	-	-	-	+/-	<=1.005	Y
2009	8.5	-	-	-	-	-	+/-	<=1.005	Y
2010	8.5	+/-	+/-	-	+/-	-	+/-	1.010	Y
2011	8.5	+/-	-	-	+/-	-	+/-	<=1.005	Y
2012	8.5	+/-	-	-	-	-	+/-	1.010	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Appendix 5-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No.: [REDACTED]

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
Animal No.									
3008	8.5	+/-	-	-	+/-	-	+/-	<=1.005	Y
3009	8.5	-	-	-	-	-	+/-	1.010	Y
3010	8.5	1+	1+	-	-	-	+/-	<=1.005	Y
3011	8.5	-	1+	-	-	-	+/-	1.010	Y
3012	8.5	+/-	-	-	+/-	-	+/-	1.010	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Appendix 5-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
Animal No.									
4008	8.5	+/-	-	-	-	-	+/-	1.010	Y
4009	8.5	+/-	-	-	-	-	+/-	1.010	Y
4010	8.5	+/-	+/-	-	-	-	+/-	<=1.005	Y
4011	8.5	+/-	+/-	-	-	-	+/-	1.010	Y
4012	8.5	+/-	+/-	-	-	-	+/-	1.010	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Animal No.	Urinalysis								
	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
5106	7.0	-	-	-	-	-	+/-	1.015	Y
5107	>=9.0	-	-	-	-	-	+/-	<=1.005	Y
5108	8.5	-	-	-	-	-	+/-	<=1.005	Y
5109	7.5	-	-	-	-	-	+/-	1.010	Y
5110	8.0	-	-	-	-	-	+/-	1.010	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Urinalysis

Stage : Week 6 of administration (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
Animal No.									
6106	8.5	-	-	-	-	-	+/-	1.010	Y
6107	7.5	-	-	-	-	-	+/-	1.020	Y
6108	8.5	-	-	-	-	-	+/-	1.010	Y
6109	8.5	-	-	-	-	-	+/-	1.010	Y
6110	7.0	-	-	-	-	-	+/-	<=1.005	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Appendix 5-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : Cinchona Bark Extract 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

Animal No.	RBC	WBC	Squamous epithelial cells	Small round epithelial cells	Cast	Crystal phosphate salts	Crystal calcium oxalate
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

Animal No.	RBC	WBC	Squamous epithelial cells	Small round epithelial cells	Cast	Crystal phosphate salts	Crystal calcium oxalate
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

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 6 of administration (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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

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

Appendix 5-13

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h
1008	39	20.3
1009	45	16.1
1010	37	19.8
1011	51	20.8
1012	45	21.2
n	5	5
Mean	43	19.6
S.D.	6	2.0

Appendix 5-14

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h
2008	37	10.4
2009	45	23.8
2010	35	17.1
2011	45	20.0
2012	38	17.4
n	5	5
Mean	40	17.7
S.D.	5	4.9

Appendix 5-15

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h
3008	60	30.9
3009	55	29.2
3010	41	14.6
3011	46	19.2
3012	46	18.2
n	5	5
Mean	50	22.4
S.D.	8	7.2

Appendix 5-16

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 6 of administration

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h
4008	58	24.2
4009	34	20.2
4010	44	22.1
4011	47	12.5
4012	57	23.2
n	5	5
Mean	48	20.4
S.D.	10	4.7

Urinalysis

Stage : Week 6 of administration (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h
5106	30	8.4
5107	33	9.5
5108	49	13.0
5109	35	6.7
5110	41	13.9
n	5	5
Mean	38	10.3
S.D.	8	3.1

Appendix 5-18

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 6 of administration (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h
6106	36	16.9
6107	36	7.6
6108	41	13.4
6109	39	7.0
6110	43	12.1
n	5	5
Mean	39	11.4
S.D.	3	4.1

Urinalysis

Stage : Week 2 of recovery

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
Animal No.									
1008	8.5	1+	1+	-	-	-	+/-	>=1.030	Y
1009	8.0	-	1+	-	+/-	-	+/-	>=1.030	Y
1010	8.5	+/-	1+	-	-	-	+/-	1.020	Y
1011	8.5	-	+/-	-	-	-	+/-	1.010	Y
1012	8.5	-	1+	-	-	-	+/-	1.025	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Urinalysis

Stage : Week 2 of recovery

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
Animal No.									
4008	8.0	-	+/-	-	-	-	+/-	1.015	Y
4009	8.5	+/-	-	-	+/-	-	+/-	1.015	Y
4010	8.5	-	1+	-	+/-	-	+/-	1.020	Y
4011	8.5	2+	2+	-	-	-	+/-	1.020	Y
4012	8.0	+/-	+/-	-	+/-	-	+/-	1.015	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Urinalysis

Stage : Week 2 of recovery (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
Animal No.									
5106	8.5	-	-	-	-	-	+/-	1.020	Y
5107	8.5	-	-	-	-	-	+/-	1.010	Y
5108	8.0	-	-	-	-	-	+/-	1.010	Y
5109	8.5	-	-	-	-	-	+/-	>=1.030	Y
5110	8.5	-	-	-	-	-	+/-	1.010	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Urinalysis

Stage : Week 2 of recovery (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	pH	Protein	Ketones	Glucose	Occult Blood	Bilirubin	Urobilinogen	specific gravity	Color
Animal No.									
6106	7.5	-	-	-	-	-	+/-	1.015	Y
6107	6.0	-	-	-	-	-	+/-	1.015	Y
6108	8.5	-	-	-	-	-	+/-	1.020	Y
6109	7.0	-	-	-	-	-	+/-	1.010	Y
6110	7.0	-	-	-	-	-	+/-	1.020	Y
n	5	5	5	5	5	5	5	5	5

Color LY: Light Yellow Y: Yellow DY: Dark Yellow BR: Brown RE: Red RB: Reddish brown WH: White BL: Blue CL: Colorless OT: Other

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

Urinalysis

Stage : Week 2 of recovery

Sex : Male

Dose : Cinchona Bark Extract 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

Stage : Week 2 of recovery

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

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

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 (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 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

Appendix 5-27

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 2 of recovery

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h
1008	46	17.8
1009	42	17.8
1010	35	10.7
1011	36	16.9
1012	46	18.0
n	5	5
Mean	41	16.2
S.D.	5	3.1

Appendix 5-28

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 2 of recovery

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h
4008	68	34.2
4009	48	21.9
4010	43	16.5
4011	38	10.5
4012	44	20.5
n	5	5
Mean	48	20.7
S.D.	12	8.7

Appendix 5-29

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Urinalysis

Stage : Week 2 of recovery (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Water consumption mL/24h	Urine volume mL/24h
5106	33	15.7
5107	33	7.1
5108	53	9.9
5109	54	14.7
5110	44	15.0
n	5	5
Mean	43	12.5
S.D.	10	3.8

Animal No.	Water consumption mL/24h	Urine volume mL/24h
6106	21	6.6
6107	38	5.6
6108	83	19.6
6109	47	9.3
6110	44	10.6
n	5	5
Mean	47	10.3
S.D.	23	5.6

Hematology
Sex : Male

Stage : End of administration

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
1001	866	14.9	44.7	51.6	17.2	33.4	14.3	227.4	100.7	71.2	57.9
1002	823	15.1	45.5	55.3	18.3	33.2	13.1	218.5	110.4	66.5	53.9
1003	791	15.2	44.9	56.8	19.2	33.9	12.5	216.2	79.8	58.5	42.6
1004	851	15.6	46.3	54.4	18.4	33.8	12.7	198.9	103.3	73.3	55.5
1005	852	14.8	44.2	51.9	17.4	33.4	14.0	224.8	105.3	71.2	50.2
n	5	5	5	5	5	5	5	5	5	5	5
Mean	837	15.1	45.1	54.0	18.1	33.5	13.3	217.2	99.9	68.1	52.0
S.D.	30	0.3	0.8	2.2	0.8	0.3	0.8	11.2	11.8	5.9	6.0

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
1001	9.4	1.2	0.1	1.9	0.6
1002	9.2	0.7	0.1	1.6	0.9
1003	12.5	1.4	0.1	1.7	0.2
1004	14.2	1.0	0.2	2.0	0.4
1005	17.6	1.3	0.2	1.4	0.6
n	5	5	5	5	5
Mean	12.6	1.1	0.1	1.7	0.5
S.D.	3.5	0.3	0.1	0.2	0.3

Hematology
Sex : Male

Stage : End of administration

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
2001	830	15.9	47.2	56.8	19.2	33.8	13.0	135.9	105.4	58.8	45.4
2002	859	15.3	44.6	51.9	17.8	34.2	11.8	140.0	117.0	113.2	76.0
2003	864	15.1	44.7	51.8	17.5	33.7	12.2	167.6	115.7	85.5	63.2
2004	809	14.6	43.7	54.0	18.0	33.3	13.6	236.0	112.0	84.3	59.0
2005	874	15.4	46.9	53.6	17.6	32.8	13.6	234.1	90.2	63.5	43.6
n	5	5	5	5	5	5	5	5	5	5	5
Mean	847	15.3	45.4	53.6	18.0	33.6	12.8	182.7	108.1	81.1	57.4
S.D.	27	0.5	1.5	2.0	0.7	0.5	0.8	49.3	11.0	21.6	13.4

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
2001	10.9	0.9	0.1	1.2	0.3
2002	30.5	1.9	0.4	3.2	1.1
2003	16.6	1.2	0.2	2.8	1.5
2004	20.0	2.2	0.2	2.2	0.5
2005	17.2	1.4	0.1	0.9	0.4
n	5	5	5	5	5
Mean	19.0	1.5	0.2	2.1	0.8
S.D.	7.2	0.5	0.1	1.0	0.5

Hematology

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
3001	825	15.3	45.8	55.5	18.6	33.5	12.5	188.9	99.2	57.6	44.6
3002	845	15.6	45.9	54.3	18.5	34.1	11.8	181.1	95.3	81.8	65.9
3003	767	14.2	42.9	56.0	18.6	33.2	13.7	199.5	88.1	77.2	57.1
3004	761	14.1	42.0	55.3	18.6	33.6	12.6	249.1	108.4	67.3	51.5
3005	848	15.6	47.3	55.8	18.4	33.0	13.1	176.8	108.6	87.7	74.0
n	5	5	5	5	5	5	5	5	5	5	5
Mean	809	15.0	44.8	55.4	18.5	33.5	12.7	199.1	99.9	74.3	58.6
S.D.	42	0.8	2.2	0.7	0.1	0.4	0.7	29.3	8.8	12.0	11.6

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
3001	10.2	0.5	0.1	1.4	0.8
3002	11.9	1.2	0.3	2.0	0.6
3003	17.2	1.4	0.1	1.1	0.3
3004	12.5	0.9	0.1	1.9	0.4
3005	10.7	0.9	0.2	1.5	0.6
n	5	5	5	5	5
Mean	12.5	1.0	0.2	1.6	0.5
S.D.	2.8	0.3	0.1	0.4	0.2

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
4001	835	15.6	47.1	56.5	18.7	33.2	13.4	278.7	98.7	77.0	52.8
4002	823	15.5	46.4	56.4	18.8	33.3	11.9	221.2	99.4	99.4	70.8
4003	829	15.2	45.4	54.7	18.3	33.4	12.2	206.4	107.7	70.8	54.8
4004	807	15.3	45.4	56.3	19.0	33.7	13.0	210.3	104.6	65.5	51.6
4005	856	15.0	44.0	51.4	17.5	34.0	12.9	185.8	78.3	49.7	40.7
n	5	5	5	5	5	5	5	5	5	5	5
Mean	830	15.3	45.7	55.1	18.5	33.5	12.7	220.5	97.7	72.5	54.1
S.D.	18	0.2	1.2	2.2	0.6	0.3	0.6	35.0	11.5	18.1	10.8

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
4001	20.0	1.6	0.1	1.9	0.5
4002	22.5	1.2	0.1	2.8	2.1
4003	12.9	1.4	0.1	1.2	0.4
4004	11.0	0.5	0.2	1.2	1.0
4005	6.7	0.6	0.1	1.2	0.5
n	5	5	5	5	5
Mean	14.6	1.1	0.1	1.7	0.9
S.D.	6.5	0.5	0.0	0.7	0.7

Hematology

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
1102	772	15.1	45.3	58.6	19.6	33.5	15.4	261.4	123.0	98.3	59.2
1105	774	15.4	45.9	59.3	19.9	33.6	15.2	232.3	135.7	117.3	54.8
1106	732	14.7	42.7	58.4	20.1	34.4	13.4	226.7	119.7	99.2	55.3
1109	804	15.3	44.9	55.8	19.1	34.2	14.3	287.7	108.2	77.7	46.7
1110	744	15.3	44.2	59.4	20.5	34.6	14.2	231.1	120.9	126.4	79.7
n	5	5	5	5	5	5	5	5	5	5	5
Mean	765	15.2	44.6	58.3	19.8	34.1	14.5	247.8	121.5	103.8	59.1
S.D.	28	0.3	1.2	1.5	0.5	0.5	0.8	26.2	9.8	18.9	12.4

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
1102	33.1	1.3	0.2	3.6	1.0
1105	56.4	1.1	0.1	4.5	0.5
1106	38.2	0.8	0.2	3.8	0.9
1109	26.6	0.5	0.2	2.6	1.1
1110	37.8	0.6	0.2	6.1	2.1
n	5	5	5	5	5
Mean	38.4	0.9	0.2	4.1	1.1
S.D.	11.1	0.3	0.0	1.3	0.6

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
2103	739	14.6	42.7	57.7	19.8	34.3	13.6	204.9	115.8	87.3	43.0
2105	731	15.3	45.5	62.2	20.9	33.6	14.4	198.1	88.8	94.9	45.4
2107	761	15.4	45.5	59.9	20.2	33.8	15.3	164.2	100.4	71.2	43.1
2109	762	14.6	42.5	55.8	19.2	34.3	14.9	266.7	119.2	104.3	46.4
2111	689	13.5	40.2	58.3	19.6	33.6	13.7	235.8	119.6	66.0	30.6
n	5	5	5	5	5	5	5	5	5	5	5
Mean	736	14.7	43.3	58.8	19.9	33.9	14.4	213.9	108.8	84.7	41.7
S.D.	30	0.8	2.3	2.4	0.6	0.4	0.7	38.9	13.6	16.0	6.4

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
2103	40.6	1.0	0.0	2.1	0.6
2105	43.7	0.4	0.2	3.9	1.3
2107	23.5	0.6	0.2	2.5	1.3
2109	51.2	0.7	0.1	3.8	2.0
2111	31.9	0.6	0.1	1.4	1.4
n	5	5	5	5	5
Mean	38.2	0.7	0.1	2.7	1.3
S.D.	10.7	0.2	0.1	1.1	0.5

Hematology
Sex : Female

Stage : End of lactation (F0 dams)

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
3101	788	15.2	44.6	56.6	19.3	34.1	13.8	206.5	114.1	87.8	50.4
3102	746	14.3	41.7	55.9	19.2	34.3	15.5	201.0	119.2	73.3	35.5
3104	790	15.0	44.4	56.2	19.0	33.8	14.6	213.6	114.0	122.2	65.8
3106	748	15.4	45.4	60.7	20.6	34.0	14.9	218.5	137.7	118.2	66.9
3109	735	14.5	42.3	57.6	19.7	34.2	13.8	167.9	142.8	76.5	36.1
n	5	5	5	5	5	5	5	5	5	5	5
Mean	761	14.9	43.7	57.4	19.6	34.1	14.5	201.5	125.6	95.6	50.9
S.D.	26	0.5	1.6	2.0	0.6	0.2	0.7	19.9	13.7	23.1	15.3

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
3101	33.1	0.4	0.2	2.8	1.0
3102	30.1	0.8	0.1	5.2	1.6
3104	47.6	1.1	0.3	5.2	2.2
3106	39.4	2.8	0.2	5.8	3.1
3109	34.3	0.7	0.1	3.3	2.0
n	5	5	5	5	5
Mean	36.9	1.2	0.2	4.5	2.0
S.D.	6.9	1.0	0.1	1.3	0.8

Hematology

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
4103	731	14.8	42.7	58.4	20.2	34.6	12.8	202.0	104.0	58.1	28.7
4105	696	14.3	41.1	59.1	20.6	34.8	14.1	242.5	111.8	83.8	42.4
4106	765	14.9	43.8	57.2	19.5	34.0	13.1	182.3	111.1	101.8	68.6
4108	739	14.7	43.1	58.3	19.9	34.2	13.6	192.0	115.7	72.5	25.3
4111	725	14.8	44.2	61.0	20.4	33.4	13.2	182.7	103.7	85.0	43.2
n	5	5	5	5	5	5	5	5	5	5	5
Mean	731	14.7	43.0	58.8	20.1	34.2	13.4	200.3	109.3	80.2	41.6
S.D.	25	0.2	1.2	1.4	0.4	0.5	0.5	24.9	5.2	16.2	17.1

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
4103	25.8	0.4	0.0	2.2	1.0
4105	38.6	0.2	0.0	1.8	0.7
4106	27.1	0.4	0.2	3.5	2.0
4108	42.7	0.8	0.1	2.8	0.7
4111	36.0	0.7	0.1	3.4	1.6
n	5	5	5	5	5
Mean	34.0	0.5	0.1	2.7	1.2
S.D.	7.3	0.2	0.1	0.7	0.6

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Hematology
 Sex : Female
 Stage : End of administration (non-mating group)
 Dose : Cinchona Bark Extract 0 mg/kg

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
5101	771	15.0	42.8	55.6	19.5	35.1	12.1	198.0	92.0	72.7	59.3
5102	783	14.6	42.1	53.7	18.6	34.6	11.6	155.9	91.5	55.4	46.5
5103	794	15.0	44.5	56.0	19.0	33.8	11.9	164.7	92.1	69.7	58.9
5104	790	14.8	42.7	54.1	18.8	34.7	12.1	208.5	96.0	43.7	28.2
5105	784	15.1	43.6	55.7	19.3	34.6	11.9	143.2	127.1	70.2	54.0
n	5	5	5	5	5	5	5	5	5	5	5
Mean	784	14.9	43.1	55.0	19.0	34.6	11.9	174.1	99.7	62.3	49.4
S.D.	9	0.2	0.9	1.0	0.4	0.5	0.2	28.0	15.4	12.4	12.9

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
5101	10.1	1.7	0.1	1.1	0.3
5102	6.5	1.1	0.1	0.9	0.3
5103	7.8	1.0	0.1	1.4	0.5
5104	12.8	0.8	0.0	1.5	0.3
5105	12.6	1.1	0.1	1.9	0.6
n	5	5	5	5	5
Mean	10.0	1.1	0.1	1.4	0.4
S.D.	2.8	0.3	0.0	0.4	0.1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Hematology
Sex : Female
Stage : End of administration (non-mating group)
Dose : Cinchona Bark Extract 1000 mg/kg

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
6101	751	14.2	41.7	55.5	18.9	34.0	11.4	125.4	81.8	63.1	50.8
6102	800	15.2	44.9	56.1	19.0	33.9	11.4	133.0	87.7	52.7	43.8
6103	801	14.9	44.0	55.0	18.7	33.9	11.6	139.5	116.2	60.4	41.3
6104	735	14.2	41.6	56.5	19.3	34.2	12.5	188.2	94.6	31.5	25.5
6105	790	14.8	43.8	55.5	18.7	33.8	11.5	215.2	109.7	42.0	33.0
n	5	5	5	5	5	5	5	5	5	5	5
Mean	775	14.7	43.2	55.7	18.9	34.0	11.7	160.3	98.0	49.9	38.9
S.D.	30	0.4	1.5	0.6	0.2	0.2	0.5	39.3	14.6	13.2	9.8

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
6101	9.5	1.5	0.0	0.9	0.4
6102	6.0	1.0	0.1	1.4	0.4
6103	13.9	1.8	0.1	2.2	1.1
6104	4.2	0.8	0.0	0.8	0.2
6105	6.6	1.1	0.1	1.1	0.2
n	5	5	5	5	5
Mean	8.0	1.2	0.1	1.3	0.5
S.D.	3.8	0.4	0.1	0.6	0.4

Hematology
Sex : Male

Stage : End of recovery

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
1008	927	16.1	47.8	51.5	17.3	33.6	12.9	179.9	111.4	85.1	62.9
1009	973	16.3	48.9	50.2	16.8	33.4	13.1	145.7	127.5	88.8	70.0
1010	869	15.2	45.3	52.2	17.4	33.4	12.9	140.4	82.5	65.5	51.1
1011	891	15.0	44.6	50.0	16.8	33.6	12.9	132.8	112.4	111.4	89.8
1012	822	15.7	43.9	53.4	19.1	35.7	13.1	164.8	111.3	77.5	49.6
n	5	5	5	5	5	5	5	5	5	5	5
Mean	896	15.7	46.1	51.5	17.5	33.9	13.0	152.7	109.0	85.7	64.7
S.D.	57	0.6	2.1	1.4	0.9	1.0	0.1	19.3	16.3	16.9	16.4

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
1008	18.1	1.3	0.2	2.0	0.7
1009	14.1	1.3	0.1	2.1	1.3
1010	10.8	1.2	0.1	1.4	1.0
1011	16.2	2.0	0.3	2.2	0.8
1012	22.2	1.8	0.2	3.0	0.7
n	5	5	5	5	5
Mean	16.3	1.5	0.2	2.1	0.9
S.D.	4.3	0.4	0.1	0.6	0.3

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
4008	828	15.4	44.9	54.2	18.6	34.3	12.8	194.0	115.6	74.7	59.2
4009	868	14.8	43.5	50.1	17.1	34.1	13.5	159.3	103.6	82.9	62.7
4010	866	14.7	43.4	50.1	16.9	33.8	11.9	137.5	113.6	74.9	59.6
4011	846	14.8	43.7	51.6	17.5	33.9	14.1	272.2	103.1	89.5	67.5
4012	882	15.5	46.8	53.0	17.6	33.2	12.9	175.0	112.0	77.3	55.9
n	5	5	5	5	5	5	5	5	5	5	5
Mean	858	15.0	44.5	51.8	17.5	33.9	13.0	187.6	109.6	79.9	61.0
S.D.	21	0.4	1.4	1.8	0.7	0.4	0.8	51.6	5.8	6.3	4.4

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
4008	10.1	1.3	0.2	2.6	1.4
4009	16.6	1.1	0.1	2.0	0.5
4010	12.1	1.5	0.1	1.2	0.3
4011	18.5	1.0	0.2	1.7	0.5
4012	15.3	2.2	0.2	2.4	1.4
n	5	5	5	5	5
Mean	14.5	1.4	0.2	2.0	0.8
S.D.	3.4	0.5	0.1	0.6	0.5

Hematology

Stage : End of recovery (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
5106	669	13.6	37.4	55.8	20.3	36.4	12.1	109.3	82.3	38.8	28.5
5107	805	15.0	43.1	53.5	18.7	34.9	11.5	86.8	134.5	65.1	55.8
5108	752	14.3	41.5	55.1	19.0	34.5	11.7	167.9	90.2	51.3	39.7
5109	752	13.9	39.8	53.0	18.5	34.9	11.7	160.1	125.6	54.4	42.6
5110	775	14.7	43.3	55.9	19.0	34.0	11.3	133.6	118.7	48.8	34.8
n	5	5	5	5	5	5	5	5	5	5	5
Mean	751	14.3	41.0	54.7	19.1	34.9	11.7	131.5	110.3	51.7	40.3
S.D.	51	0.6	2.5	1.3	0.7	0.9	0.3	34.1	22.8	9.5	10.2

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
5106	8.9	0.4	0.1	0.8	0.2
5107	5.9	0.6	0.1	1.4	1.4
5108	9.9	0.3	0.0	1.1	0.3
5109	9.6	0.7	0.1	1.1	0.4
5110	10.4	1.9	0.1	1.2	0.4
n	5	5	5	5	5
Mean	8.9	0.8	0.1	1.1	0.5
S.D.	1.8	0.6	0.0	0.2	0.5

Hematology

Stage : End of recovery (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	#RETIC	PLT	WBC	#LYMP
Animal No.	10 ⁴ /μL	g/dL	%	fL	pg	g/dL	%	10 ⁹ /L	10 ⁴ /μL	10 ² /μL	10 ² /μL
6106	775	14.8	43.8	56.5	19.1	33.7	11.4	142.2	107.7	116.2	100.8
6107	738	13.7	40.1	54.4	18.6	34.2	11.4	150.8	105.8	48.7	42.0
6108	749	14.5	40.9	54.6	19.4	35.5	11.7	161.8	93.5	62.8	52.8
6109	754	14.2	41.1	54.6	18.8	34.5	12.7	176.1	102.8	50.9	36.7
6110	775	14.6	42.0	54.2	18.8	34.7	12.0	154.4	99.6	48.6	41.5
n	5	5	5	5	5	5	5	5	5	5	5
Mean	758	14.4	41.6	54.9	18.9	34.5	11.8	157.1	101.9	65.4	54.8
S.D.	16	0.4	1.4	0.9	0.3	0.7	0.5	12.8	5.6	29.0	26.4

	#NEUT	#EOS	#BASO	#MONO	#LUC
Animal No.	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL	10 ² /μL
6106	11.7	1.0	0.2	1.7	0.8
6107	4.6	0.8	0.0	0.9	0.4
6108	7.1	0.7	0.1	1.4	0.7
6109	9.6	1.3	0.0	2.5	0.8
6110	4.9	1.1	0.1	0.8	0.3
n	5	5	5	5	5
Mean	7.6	1.0	0.1	1.5	0.6
S.D.	3.1	0.2	0.1	0.7	0.2

Appendix 7-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Coagulation test

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
1001	12.2	14.3	306
1002	13.0	18.6	308
1003	10.6	17.6	374
1004	13.8	19.9	356
1005	13.0	15.0	320
n	5	5	5
Mean	12.5	17.1	333
S.D.	1.2	2.4	31

Appendix 7-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Coagulation test

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
2001	14.1	19.9	272
2002	13.7	17.5	341
2003	13.6	15.8	315
2004	13.4	15.8	287
2005	13.1	17.1	308
n	5	5	5
Mean	13.6	17.2	305
S.D.	0.4	1.7	27

Coagulation test

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
3001	13.5	19.4	285
3002	13.7	20.3	312
3003	14.3	14.6	345
3004	12.6	13.7	332
3005	14.6	18.0	302
n	5	5	5
Mean	13.7	17.2	315
S.D.	0.8	2.9	24

	PT	APTT	FIB
Animal No.	s	s	mg/dL
4001	13.7	19.2	328
4002	13.3	20.6	298
4003	14.6	17.6	324
4004	12.8	14.8	343
4005	15.7	17.3	354
n	5	5	5
Mean	14.0	17.9	329
S.D.	1.1	2.2	21

Appendix 7-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Coagulation test

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
1102	12.1	15.1	463
1105	14.1	18.8	339
1106	10.4	11.0	269
1109	12.1	14.7	365
1110	13.4	16.4	330
n	5	5	5
Mean	12.4	15.2	353
S.D.	1.4	2.8	71

Appendix 7-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Coagulation test

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
2103	12.3	14.6	321
2105	13.3	16.1	443
2107	11.2	13.6	399
2109	11.5	14.6	539
2111	12.8	13.0	534
n	5	5	5
Mean	12.2	14.4	447
S.D.	0.9	1.2	93

	PT	APTT	FIB
Animal No.	s	s	mg/dL
3101	13.0	14.7	516
3102	11.0	13.1	306
3104	13.5	18.7	488
3106	11.8	12.1	358
3109	11.6	12.9	412
n	5	5	5
Mean	12.2	14.3	416
S.D.	1.0	2.6	88

Appendix 7-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Coagulation test

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
4103	11.8	14.7	398
4105	12.6	15.7	304
4106	13.2	14.5	315
4108	13.8	17.9	390
4111	13.4	14.7	312
n	5	5	5
Mean	13.0	15.5	344
S.D.	0.8	1.4	46

Appendix 7-9

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Coagulation test

Stage : End of administration (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
5101	13.9	16.0	210
5102	16.3	15.9	201
5103	15.5	12.8	189
5104	15.4	18.1	238
5105	15.2	15.4	227
n	5	5	5
Mean	15.3	15.6	213
S.D.	0.9	1.9	20

Appendix 7-10

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Coagulation test

Stage : End of administration (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
6101	14.1	15.1	190
6102	14.0	15.5	220
6103	15.0	15.1	228
6104	14.9	16.0	180
6105	14.5	17.4	241
n	5	5	5
Mean	14.5	15.8	212
S.D.	0.5	1.0	26

Appendix 7-11

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Coagulation test

Stage : End of recovery

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
1008	16.4	22.0	302
1009	14.5	20.8	310
1010	12.2	16.1	254
1011	14.5	18.2	262
1012	13.9	17.3	306
n	5	5	5
Mean	14.3	18.9	287
S.D.	1.5	2.5	27

	PT	APTT	FIB
Animal No.	s	s	mg/dL
4008	14.0	20.7	281
4009	13.4	15.9	269
4010	12.6	13.9	323
4011	13.9	17.5	329
4012	14.3	14.2	323
n	5	5	5
Mean	13.6	16.4	305
S.D.	0.7	2.8	28

	PT	APTT	FIB
Animal No.	s	s	mg/dL
5106	12.9	14.4	214
5107	12.9	13.4	205
5108	12.2	14.3	208
5109	12.8	11.7	217
5110	13.1	11.9	186
n	5	5	5
Mean	12.8	13.1	206
S.D.	0.3	1.3	12

Appendix 7-14

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Coagulation test
Sex : Female

Stage : End of recovery (non-mating group)
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	PT	APTT	FIB
Animal No.	s	s	mg/dL
6106	12.5	11.9	214
6107	11.7	10.8	237
6108	14.1	14.3	180
6109	13.7	13.7	174
6110	14.2	13.5	200
n	5	5	5
Mean	13.2	12.8	201
S.D.	1.1	1.4	26

Blood chemistry

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
1001	63	30	245	0	42.5	92	31	134	0.1	132	27
1002	61	30	359	0	13.0	62	53	102	0.1	151	14
1003	66	32	321	0	44.4	62	58	101	0.1	144	16
1004	75	33	435	0	32.5	77	42	114	0.1	145	16
1005	55	35	477	0	18.5	48	32	83	0.1	143	17
n	5	5	5	5	5	5	5	5	5	5	5
Mean	64	32	367	0	30.2	68	43	107	0.1	143	18
S.D.	7	2	92	0	14.1	17	12	19	0.0	7	5

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
1001	0.36	145	4.0	107	10.6	5.8	7.1	3.4
1002	0.30	144	4.0	106	10.2	6.1	6.4	3.4
1003	0.35	146	3.9	107	10.3	6.0	6.4	3.3
1004	0.33	146	3.5	107	10.1	6.3	6.6	3.2
1005	0.29	145	3.7	105	10.4	6.2	6.5	3.3
n	5	5	5	5	5	5	5	5
Mean	0.33	145	3.8	106	10.3	6.1	6.6	3.3
S.D.	0.03	1	0.2	1	0.2	0.2	0.3	0.1

Blood chemistry

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
2001	75	32	357	1	15.0	47	29	84	0.1	160	16
2002	72	42	542	0	17.0	44	46	84	0.1	151	20
2003	64	33	296	0	6.8	68	57	102	0.1	161	17
2004	60	32	375	0	14.5	72	101	114	0.1	143	16
2005	68	36	395	0	18.1	51	37	90	0.1	132	16
n	5	5	5	5	5	5	5	5	5	5	5
Mean	68	35	393	0	14.3	56	54	95	0.1	149	17
S.D.	6	4	91	0	4.4	13	28	13	0.0	12	2

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
2001	0.34	145	3.8	106	9.4	5.1	6.1	3.1
2002	0.35	144	3.7	105	10.3	6.5	6.4	3.2
2003	0.34	145	3.8	108	10.2	5.1	6.6	3.2
2004	0.35	144	3.8	106	10.7	5.9	6.6	3.2
2005	0.37	145	3.2	105	10.3	5.5	6.9	3.4
n	5	5	5	5	5	5	5	5
Mean	0.35	145	3.7	106	10.2	5.6	6.5	3.2
S.D.	0.01	1	0.3	1	0.5	0.6	0.3	0.1

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
3001	76	42	293	0	45.6	54	33	94	0.1	144	19
3002	75	41	343	0	13.2	62	40	91	0.1	139	22
3003	66	34	561	0	27.4	64	25	94	0.1	155	20
3004	66	36	493	0	10.2	68	48	105	0.1	170	22
3005	54	32	390	0	5.8	56	62	95	0.1	160	20
n	5	5	5	5	5	5	5	5	5	5	5
Mean	67	37	416	0	20.4	61	42	96	0.1	154	21
S.D.	9	4	110	0	16.2	6	14	5	0.0	12	1

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
3001	0.29	145	3.8	108	9.9	5.6	6.5	3.3
3002	0.39	145	3.8	106	10.1	5.6	6.7	3.2
3003	0.32	145	3.8	106	9.8	5.6	6.3	3.2
3004	0.34	144	3.9	107	10.3	5.7	6.2	3.0
3005	0.43	145	3.8	106	10.3	6.5	6.5	3.1
n	5	5	5	5	5	5	5	5
Mean	0.35	145	3.8	107	10.1	5.8	6.4	3.2
S.D.	0.06	0	0.0	1	0.2	0.4	0.2	0.1

Blood chemistry

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
4001	67	39	414	0	21.1	57	29	93	0.1	127	16
4002	66	38	341	0	8.4	59	51	97	0.1	142	16
4003	53	29	347	0	4.0	54	62	91	0.1	133	13
4004	74	44	424	0	33.5	55	45	99	0.1	157	21
4005	62	33	323	0	20.4	52	67	94	0.1	147	18
n	5	5	5	5	5	5	5	5	5	5	5
Mean	64	37	370	0	17.5	55	51	95	0.1	141	17
S.D.	8	6	46	0	11.6	3	15	3	0.0	12	3

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
4001	0.33	146	3.6	107	9.9	5.5	6.6	3.3
4002	0.35	145	3.6	107	10.5	5.6	6.5	3.2
4003	0.31	145	3.5	106	10.3	5.9	6.1	3.2
4004	0.47	144	3.7	107	10.4	6.4	6.7	3.5
4005	0.45	144	3.9	106	10.6	7.3	6.4	3.2
n	5	5	5	5	5	5	5	5
Mean	0.38	145	3.7	107	10.3	6.1	6.5	3.3
S.D.	0.07	1	0.2	1	0.3	0.7	0.2	0.1

Blood chemistry

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
1102	115	75	279	1	19.3	122	48	216	0.1	131	23
1105	69	35	243	1	28.3	95	112	172	0.1	132	23
1106	86	80	532	1	44.2	96	58	176	0.1	110	25
1109	107	55	282	1	9.1	83	180	184	0.0	159	17
1110	107	74	353	1	19.2	110	147	215	0.1	163	27
n	5	5	5	5	5	5	5	5	5	5	5
Mean	97	64	338	1	24.0	101	109	193	0.1	139	23
S.D.	19	19	116	0	13.2	15	57	21	0.0	22	4

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
1102	0.53	141	3.4	100	11.2	8.9	7.0	3.5
1105	0.55	141	3.9	103	10.5	9.5	6.6	3.4
1106	0.38	143	3.3	104	10.6	8.8	6.6	3.4
1109	0.35	141	3.8	104	10.1	5.9	6.6	3.7
1110	0.58	140	3.9	101	10.5	10.0	6.5	3.5
n	5	5	5	5	5	5	5	5
Mean	0.48	141	3.7	102	10.6	8.6	6.7	3.5
S.D.	0.11	1	0.3	2	0.4	1.6	0.2	0.1

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
2103	86	45	220	1	23.4	96	54	179	0.0	116	17
2105	91	72	235	0	24.1	92	73	180	0.1	124	29
2107	73	47	319	1	23.8	79	32	147	0.0	119	22
2109	121	66	269	1	14.3	108	251	241	0.0	130	24
2111	151	67	230	1	16.0	68	55	132	0.0	142	18
n	5	5	5	5	5	5	5	5	5	5	5
Mean	104	59	255	1	20.3	89	93	176	0.0	126	22
S.D.	31	12	40	0	4.8	15	90	42	0.0	10	5

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
2103	0.42	144	2.6	105	10.3	7.0	6.8	3.4
2105	0.50	138	3.3	100	10.4	8.2	6.8	3.5
2107	0.37	145	3.2	107	10.3	6.9	6.4	3.3
2109	0.41	138	3.6	101	11.3	10.1	7.1	3.6
2111	0.45	145	3.3	109	10.1	5.8	6.3	3.2
n	5	5	5	5	5	5	5	5
Mean	0.43	142	3.2	104	10.5	7.6	6.7	3.4
S.D.	0.05	4	0.4	4	0.5	1.6	0.3	0.2

Blood chemistry

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
3101	116	69	253	1	46.4	120	53	218	0.1	111	25
3102	87	52	324	1	43.1	80	94	159	0.0	129	22
3104	95	62	364	1	19.7	96	161	207	0.0	152	24
3106	78	42	147	1	34.3	132	140	231	0.0	118	26
3109	72	57	312	1	16.6	83	51	160	0.0	129	24
n	5	5	5	5	5	5	5	5	5	5	5
Mean	90	56	280	1	32.0	102	100	195	0.0	128	24
S.D.	17	10	84	0	13.5	23	50	34	0.0	16	1

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
3101	0.40	138	4.0	98	11.3	11.0	6.6	3.2
3102	0.46	142	3.1	102	10.8	7.9	6.6	3.5
3104	0.35	141	3.5	99	10.7	8.4	7.0	3.6
3106	0.37	142	3.0	105	10.3	6.2	6.6	3.5
3109	0.40	141	3.3	103	10.0	6.8	6.3	3.2
n	5	5	5	5	5	5	5	5
Mean	0.40	141	3.4	101	10.6	8.1	6.6	3.4
S.D.	0.04	2	0.4	3	0.5	1.9	0.2	0.2

Blood chemistry

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
4103	88	63	322	1	49.7	88	87	199	0.0	131	28
4105	108	78	295	1	15.2	96	108	187	0.1	124	30
4106	75	55	340	1	23.1	61	139	136	0.1	132	19
4108	148	97	314	1	80.3	101	181	212	0.1	114	26
4111	127	68	430	1	21.9	88	69	185	0.1	138	28
n	5	5	5	5	5	5	5	5	5	5	5
Mean	109	72	340	1	38.0	87	117	184	0.1	128	26
S.D.	29	16	53	0	27.1	15	44	29	0.0	9	4

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
4103	0.38	141	3.5	103	11.2	8.8	7.0	3.7
4105	0.56	139	3.8	102	11.0	7.7	6.8	3.6
4106	0.45	140	3.4	99	10.7	7.5	6.5	3.6
4108	0.43	139	3.1	100	10.9	8.2	6.6	3.5
4111	0.44	142	3.2	102	11.4	8.1	7.0	3.7
n	5	5	5	5	5	5	5	5
Mean	0.45	140	3.4	101	11.0	8.1	6.8	3.6
S.D.	0.07	1	0.3	2	0.3	0.5	0.2	0.1

Blood chemistry

Stage : End of administration (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
5101	74	31	192	1	88.0	70	18	135	0.1	114	19
5102	65	28	178	0	15.4	66	23	124	0.1	119	17
5103	65	25	320	0	34.1	57	19	111	0.1	119	18
5104	54	26	129	0	27.0	78	23	142	0.1	151	16
5105	60	33	280	0	18.2	74	97	152	0.1	122	16
n	5	5	5	5	5	5	5	5	5	5	5
Mean	64	29	220	0	36.5	69	36	133	0.1	125	17
S.D.	7	3	78	0	29.7	8	34	16	0.0	15	1

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
5101	0.36	143	3.0	104	9.7	4.9	6.4	3.6
5102	0.36	143	3.8	106	9.8	4.8	6.0	3.1
5103	0.38	143	3.8	108	10.1	4.7	6.5	3.6
5104	0.32	144	3.6	108	10.3	3.8	6.7	3.7
5105	0.32	144	3.3	106	10.3	4.3	6.9	3.7
n	5	5	5	5	5	5	5	5
Mean	0.35	143	3.5	106	10.0	4.5	6.5	3.5
S.D.	0.03	1	0.3	2	0.3	0.5	0.3	0.3

Blood chemistry

Stage : End of administration (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
6101	81	42	189	0	25.4	63	31	128	0.1	133	21
6102	48	28	205	0	16.2	62	35	131	0.1	138	17
6103	49	25	180	0	29.3	64	47	136	0.1	135	15
6104	61	38	247	0	24.0	67	66	144	0.1	129	18
6105	65	26	188	0	6.1	57	24	120	0.1	144	24
n	5	5	5	5	5	5	5	5	5	5	5
Mean	61	32	202	0	20.2	63	41	132	0.1	136	19
S.D.	13	8	27	0	9.2	4	16	9	0.0	6	4

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
6101	0.48	140	3.5	104	9.9	4.8	6.9	3.8
6102	0.40	142	3.3	107	10.3	4.8	6.7	3.7
6103	0.28	143	3.5	108	10.3	4.4	6.9	3.9
6104	0.36	144	3.5	108	10.3	4.2	7.0	4.0
6105	0.50	143	3.5	108	9.9	3.6	6.9	3.7
n	5	5	5	5	5	5	5	5
Mean	0.40	142	3.5	107	10.1	4.4	6.9	3.8
S.D.	0.09	2	0.1	2	0.2	0.5	0.1	0.1

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
1008	51	32	266	1	9.5	44	145	99	0.1	137	15
1009	73	46	515	0	32.9	55	34	94	0.1	151	27
1010	54	32	271	1	24.0	57	57	102	0.1	138	25
1011	63	36	323	1	21.6	49	52	86	0.1	178	20
1012	67	32	270	0	18.6	86	76	129	0.1	142	19
n	5	5	5	5	5	5	5	5	5	5	5
Mean	62	36	329	1	21.3	58	73	102	0.1	149	21
S.D.	9	6	107	1	8.5	16	43	16	0.0	17	5

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
1008	0.37	145	3.6	105	10.2	4.7	6.7	3.4
1009	0.43	143	4.1	107	9.9	5.6	6.4	3.3
1010	0.49	144	3.9	106	10.2	5.4	6.6	3.3
1011	0.35	144	3.8	107	9.9	5.3	6.3	3.2
1012	0.35	145	3.5	105	10.6	6.4	6.3	3.2
n	5	5	5	5	5	5	5	5
Mean	0.40	144	3.8	106	10.2	5.5	6.5	3.3
S.D.	0.06	1	0.2	1	0.3	0.6	0.2	0.1

Blood chemistry

Stage : End of recovery

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
4008	54	29	316	0	9.1	67	65	107	0.1	178	16
4009	76	42	290	0	55.1	66	65	112	0.1	130	16
4010	63	34	346	1	23.9	62	60	99	0.1	149	20
4011	63	33	346	1	7.7	72	70	111	0.1	176	16
4012	82	44	343	0	12.0	59	52	90	0.1	169	18
n	5	5	5	5	5	5	5	5	5	5	5
Mean	68	36	328	0	21.6	65	62	104	0.1	160	17
S.D.	11	6	25	1	19.8	5	7	9	0.0	21	2

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
4008	0.36	143	3.9	104	10.0	5.5	6.8	3.3
4009	0.36	145	3.8	106	10.6	5.5	6.5	3.1
4010	0.37	146	3.9	107	10.4	5.3	6.6	3.3
4011	0.35	142	4.1	106	9.6	5.5	6.4	3.2
4012	0.43	146	3.7	107	10.3	5.5	6.4	3.1
n	5	5	5	5	5	5	5	5
Mean	0.37	144	3.9	106	10.2	5.5	6.5	3.2
S.D.	0.03	2	0.1	1	0.4	0.1	0.2	0.1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
 with the reproduction/ developmental toxicity screening test in rats
 Blood chemistry
 Sex : Female
 Stage : End of recovery (non-mating group)
 Dose : Cinchona Bark Extract 0 mg/kg

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
5106	73	29	318	1	6.7	39	6	86	0.1	165	18
5107	62	26	161	1	25.7	65	32	129	0.2	125	21
5108	64	23	157	1	14.6	63	26	134	0.1	153	16
5109	125	45	121	0	43.5	61	41	140	0.1	129	18
5110	67	30	191	1	17.3	81	48	165	0.1	124	15
n	5	5	5	5	5	5	5	5	5	5	5
Mean	78	31	190	1	21.6	62	31	131	0.1	139	18
S.D.	26	9	76	0	14.0	15	16	29	0.0	19	2

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
5106	0.49	143	3.4	107	9.5	3.9	6.2	3.3
5107	0.55	143	3.5	106	10.4	4.9	6.8	4.0
5108	0.51	141	3.9	108	9.8	3.8	6.6	3.6
5109	0.42	142	3.4	105	10.6	4.7	7.2	3.9
5110	0.50	144	3.5	109	10.5	3.1	7.0	3.9
n	5	5	5	5	5	5	5	5
Mean	0.49	143	3.5	107	10.2	4.1	6.8	3.7
S.D.	0.05	1	0.2	2	0.5	0.7	0.4	0.3

Blood chemistry

Stage : End of recovery (non-mating group)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

	AST	ALT	ALP	γ -GTP	T-BA	T-CHO	TG	PL	T-BIL	GLU	BUN
Animal No.	IU/L	IU/L	IU/L	IU/L	μ mol/L	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL
6106	47	31	110	1	41.6	73	90	156	0.1	172	17
6107	55	25	189	1	13.0	77	37	152	0.1	118	21
6108	52	21	181	1	21.9	66	34	142	0.2	153	16
6109	113	60	142	0	53.6	86	34	174	0.2	143	19
6110	50	27	84	0	19.2	75	116	168	0.1	130	19
n	5	5	5	5	5	5	5	5	5	5	5
Mean	63	33	141	1	29.9	75	62	158	0.1	143	18
S.D.	28	16	45	1	17.0	7	38	13	0.1	21	2

	CRNN	Na	K	Cl	Ca	P	TP	ALB
Animal No.	mg/dL	mmol/L	mmol/L	mmol/L	mg/dL	mg/dL	g/dL	g/dL
6106	0.37	140	3.4	104	10.5	4.4	7.2	3.9
6107	0.47	139	4.3	107	10.4	3.9	7.1	3.8
6108	0.33	141	3.7	107	10.0	3.4	6.7	3.8
6109	0.38	142	3.3	106	10.3	3.7	7.0	4.2
6110	0.49	142	3.6	108	10.7	4.3	7.2	4.0
n	5	5	5	5	5	5	5	5
Mean	0.41	141	3.7	106	10.4	3.9	7.0	3.9
S.D.	0.07	1	0.4	2	0.3	0.4	0.2	0.2

Organ weight

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g
1001	564	2.15	0.38	22.2	3.9	387	69	1.53	0.27
1002	516	2.28	0.44	22.2	4.3	350	68	1.43	0.28
1003	611	2.24	0.37	18.7	3.1	329	54	1.57	0.26
1004	528	2.22	0.42	21.7	4.1	464	88	1.53	0.29
1005	537	2.30	0.43	31.0	5.8	362	67	1.71	0.32
1006	623	2.08	0.33	22.4	3.6	498	80	1.99	0.32
1007	521	2.27	0.44	31.0	6.0	348	67	1.36	0.26
n	7	7	7	7	7	7	7	7	7
Mean	557	2.22	0.40	24.2	4.4	391	70	1.59	0.29
S.D.	44	0.08	0.04	4.8	1.1	65	11	0.21	0.03

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Testis-RL	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB g	RE g/100g
1001	15.72	2.79	0.63	0.11	3.64	0.65	58	10.3	3.95	0.70
1002	13.01	2.52	0.59	0.11	3.40	0.66	81	15.7	3.72	0.72
1003	15.56	2.55	0.81	0.13	3.46	0.57	63	10.3	3.67	0.60
1004	14.23	2.70	0.73	0.14	3.29	0.62	66	12.5	3.17	0.60
1005	15.11	2.81	0.85	0.16	3.68	0.69	73	13.6	3.37	0.63
1006	16.45	2.64	0.99	0.16	3.94	0.63	62	10.0	3.42	0.55
1007	12.62	2.42	0.75	0.14	3.43	0.66	68	13.1	3.55	0.68
n	7	7	7	7	7	7	7	7	7	7
Mean	14.67	2.63	0.76	0.14	3.55	0.64	67	12.2	3.55	0.64
S.D.	1.44	0.14	0.14	0.02	0.22	0.04	8	2.1	0.26	0.06

Animal No.	Epididymis-RL		Prostate		Seminal vesicle		LABC		Cowper's gland-RL	
	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	1469	260	1.25	0.22	1.43	0.25	1.51	0.27	125.4	22.2
1002	1472	285	1.22	0.24	1.70	0.33	1.76	0.34	139.2	27.0
1003	1450	237	1.42	0.23	2.01	0.33	1.94	0.32	176.8	28.9
1004	1274	241	1.11	0.21	1.69	0.32	1.55	0.29	144.1	27.3
1005	1272	237	1.31	0.24	1.55	0.29	1.74	0.32	165.3	30.8
1006	1272	204	1.20	0.19	1.63	0.26	1.49	0.24	178.2	28.6
1007	1208	232	1.12	0.21	1.56	0.30	1.69	0.32	131.8	25.3
n	7	7	7	7	7	7	7	7	7	7
Mean	1345	242	1.23	0.22	1.65	0.30	1.67	0.30	151.5	27.2
S.D.	113	25	0.11	0.02	0.18	0.03	0.16	0.04	21.7	2.8

AB : Absolute weight, RE : Relative weight by body weight

LABC: Levator ani and bulbocavernosus muscle

Appendix 9-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Glans penis

Animal No.	AB mg	RE mg/100g
1001	104.0	18.4
1002	133.0	25.8
1003	212.4	34.8
1004	183.6	34.8
1005	102.9	19.2
1006	123.5	19.8
1007	154.4	29.6
n	7	7
Mean	144.8	26.1
S.D.	41.2	7.2

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Thyroid-RL		Thymus		Heart	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g
2001	481	2.14	0.44	16.1	3.3	366	76	1.50	0.31
2002	537	2.20	0.41	26.2	4.9	270	50	1.41	0.26
2003	583	2.27	0.39	27.5	4.7	379	65	1.51	0.26
2004	556	2.12	0.38	20.2	3.6	412	74	1.39	0.25
2005	525	2.22	0.42	22.2	4.2	354	67	1.42	0.27
2006	569	2.12	0.37	23.6	4.1	263	46	1.56	0.27
2007	518	2.23	0.43	24.0	4.6	468	90	1.53	0.30
2008	576	2.21	0.38	22.2	3.9	429	74	1.59	0.28
2009	544	2.16	0.40	20.9	3.8	369	68	1.62	0.30
2010	534	2.23	0.42	23.1	4.3	323	60	1.41	0.26
2011	564	2.25	0.40	21.5	3.8	262	46	1.55	0.27
2012	583	2.16	0.37	25.8	4.4	394	68	1.52	0.26
n	12	12	12	12	12	12	12	12	12
Mean	548	2.19	0.40	22.8	4.1	357	65	1.50	0.27
S.D.	31	0.05	0.02	3.1	0.5	67	13	0.08	0.02

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Testis-RL	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB g	RE g/100g
2001	11.22	2.33	0.67	0.14	2.95	0.61	56	11.6	2.90	0.60
2002	14.83	2.76	0.79	0.15	3.28	0.61	65	12.1	3.23	0.60
2003	16.01	2.75	0.89	0.15	3.45	0.59	53	9.1	3.20	0.55
2004	14.38	2.59	0.80	0.14	3.60	0.65	50	9.0	3.44	0.62
2005	13.71	2.61	0.77	0.15	3.65	0.70	65	12.4	3.74	0.71
2006	14.81	2.60	0.92	0.16	3.63	0.64	65	11.4	3.58	0.63
2007	13.65	2.64	0.71	0.14	3.40	0.66	68	13.1	3.62	0.70
2008	16.64	2.89	0.66	0.11	3.86	0.67	72	12.5	3.38	0.59
2009	15.58	2.86	0.89	0.16	3.89	0.72	69	12.7	3.50	0.64
2010	15.25	2.86	0.71	0.13	3.67	0.69	73	13.7	3.46	0.65
2011	14.05	2.49	0.78	0.14	3.72	0.66	62	11.0	3.05	0.54
2012	15.72	2.70	0.95	0.16	3.90	0.67	72	12.3	3.23	0.55
n	12	12	12	12	12	12	12	12	12	12
Mean	14.65	2.67	0.80	0.14	3.58	0.66	64	11.7	3.36	0.62
S.D.	1.42	0.17	0.10	0.01	0.28	0.04	8	1.5	0.25	0.06

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

	Epididymis-RL		Prostate		Seminal vesicle		LABC		Cowper's gland-RL	
Animal No.	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	1242	258	1.34	0.28	1.66	0.35	1.63	0.34	149.4	31.1
2002	1254	234	1.15	0.21	1.44	0.27	1.67	0.31	135.0	25.1
2003	1283	220	1.13	0.19	1.80	0.31	1.71	0.29	147.5	25.3
2004	1288	232	1.06	0.19	1.94	0.35	1.89	0.34	140.3	25.2
2005	1253	239	1.49	0.28	1.37	0.26	1.67	0.32	139.8	26.6
2006	1469	258	1.74	0.31	1.96	0.34	1.47	0.26	149.4	26.3
2007	1456	281	1.39	0.27	1.95	0.38	1.98	0.38	185.4	35.8
2008	1311	228	1.08	0.19	1.72	0.30	1.52	0.26	114.9	19.9
2009	1468	270	1.21	0.22	1.93	0.35	1.66	0.31	129.6	23.8
2010	1352	253	1.51	0.28	1.84	0.34	1.28	0.24	140.4	26.3
2011	1377	244	1.48	0.26	1.94	0.34	1.66	0.29	159.6	28.3
2012	1338	230	1.77	0.30	2.37	0.41	1.69	0.29	139.4	23.9
n	12	12	12	12	12	12	12	12	12	12
Mean	1341	246	1.36	0.25	1.83	0.33	1.65	0.30	144.2	26.5
S.D.	85	19	0.24	0.05	0.26	0.04	0.18	0.04	17.1	4.0

Glans penis

Animal No.	AB mg	RE mg/100g
2001	181.7	37.8
2002	95.0	17.7
2003	94.5	16.2
2004	160.4	28.8
2005	133.1	25.4
2006	118.1	20.8
2007	211.1	40.8
2008	105.0	18.2
2009	138.0	25.4
2010	184.9	34.6
2011	115.9	20.5
2012	166.7	28.6
n	12	12
Mean	142.0	26.2
S.D.	38.5	8.1

AB : Absolute weight, RE : Relative weight by body weight

LABC: Levator ani and bulbocavernosus muscle

Organ weight

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB	RE	AB	RE	AB	RE	AB	RE
		g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g
3001	528	2.10	0.40	27.0	5.1	432	82	1.47	0.28
3002	592	2.25	0.38	19.1	3.2	272	46	1.49	0.25
3003	521	2.32	0.45	23.6	4.5	346	66	1.52	0.29
3004	550	2.11	0.38	23.4	4.3	378	69	1.67	0.30
3005	591	2.08	0.35	24.1	4.1	569	96	1.38	0.23
3006	548	2.14	0.39	29.3	5.3	328	60	1.51	0.28
3007	569	2.41	0.42	24.3	4.3	464	82	1.62	0.28
3008	523	2.29	0.44	23.4	4.5	314	60	1.35	0.26
3009	530	2.14	0.40	19.0	3.6	464	88	1.41	0.27
3010	465	2.25	0.48	24.3	5.2	216	46	1.81	0.39
3011	566	2.33	0.41	30.6	5.4	319	56	2.01	0.36
3012	542	2.17	0.40	29.5	5.4	311	57	1.40	0.26
n	12	12	12	12	12	12	12	12	12
Mean	544	2.22	0.41	24.8	4.6	368	67	1.55	0.29
S.D.	35	0.11	0.04	3.7	0.7	98	16	0.20	0.05

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Testis-RL	
	AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g	g	g/100g
3001	12.81	2.43	0.75	0.14	3.66	0.69	62	11.7	3.75	0.71
3002	14.54	2.46	0.77	0.13	3.45	0.58	63	10.6	3.97	0.67
3003	13.76	2.64	0.86	0.17	3.54	0.68	67	12.9	3.56	0.68
3004	14.97	2.72	0.83	0.15	3.85	0.70	84	15.3	3.30	0.60
3005	16.40	2.77	0.73	0.12	3.79	0.64	87	14.7	3.10	0.52
3006	14.50	2.65	0.83	0.15	3.75	0.68	70	12.8	3.22	0.59
3007	14.13	2.48	1.37	0.24	4.13	0.73	90	15.8	3.52	0.62
3008	13.48	2.58	0.96	0.18	3.20	0.61	71	13.6	3.38	0.65
3009	14.65	2.76	0.74	0.14	3.74	0.71	85	16.0	2.99	0.56
3010	11.44	2.46	0.66	0.14	3.77	0.81	70	15.1	3.44	0.74
3011	15.21	2.69	0.84	0.15	3.97	0.70	64	11.3	3.41	0.60
3012	13.25	2.44	0.77	0.14	3.61	0.67	89	16.4	3.92	0.72
n	12	12	12	12	12	12	12	12	12	12
Mean	14.10	2.59	0.84	0.15	3.71	0.68	75	13.9	3.46	0.64
S.D.	1.28	0.13	0.18	0.03	0.24	0.06	11	2.0	0.30	0.07

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

	Epididymis-RL		Prostate		Seminal vesicle		LABC		Cowper's gland-RL	
Animal No.	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	1338	253	1.06	0.20	1.75	0.33	1.08	0.20	119.3	22.6
3002	1266	214	1.73	0.29	1.55	0.26	1.80	0.30	112.4	19.0
3003	1474	283	1.56	0.30	1.33	0.26	1.83	0.35	177.9	34.1
3004	1316	239	1.40	0.25	1.84	0.33	1.67	0.30	208.1	37.8
3005	1271	215	1.34	0.23	1.45	0.25	1.27	0.21	164.2	27.8
3006	1198	219	1.36	0.25	1.87	0.34	1.55	0.28	161.0	29.4
3007	1394	245	1.41	0.25	2.23	0.39	1.89	0.33	192.5	33.8
3008	1313	251	1.83	0.35	2.39	0.46	1.47	0.28	155.1	29.7
3009	1167	220	1.26	0.24	1.79	0.34	1.48	0.28	101.6	19.2
3010	1354	291	1.26	0.27	1.66	0.36	1.34	0.29	151.2	32.5
3011	1258	222	1.59	0.28	2.19	0.39	1.66	0.29	154.8	27.3
3012	1434	265	1.02	0.19	1.56	0.29	1.42	0.26	125.1	23.1
n	12	12	12	12	12	12	12	12	12	12
Mean	1315	243	1.40	0.26	1.80	0.33	1.54	0.28	151.9	28.0
S.D.	91	27	0.24	0.04	0.33	0.06	0.24	0.04	32.5	6.1

Glans penis

Animal No.	AB mg	RE mg/100g
3001	101.5	19.2
3002	172.9	29.2
3003	143.5	27.5
3004	123.3	22.4
3005	109.1	18.5
3006	134.3	24.5
3007	210.1	36.9
3008	93.7	17.9
3009	170.8	32.2
3010	123.4	26.5
3011	162.7	28.7
3012	81.0	14.9
n	12	12
Mean	135.5	24.9
S.D.	38.0	6.5

AB : Absolute weight, RE : Relative weight by body weight

LABC: Levator ani and bulbocavernosus muscle

Organ weight

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g
4001	496	2.30	0.46	25.2	5.1	307	62	1.48	0.30
4002	553	2.16	0.39	23.1	4.2	467	84	1.80	0.33
4003	623	2.28	0.37	26.4	4.2	368	59	1.62	0.26
4004	563	2.17	0.39	17.4	3.1	402	71	1.56	0.28
4005	552	2.29	0.41	20.6	3.7	240	43	1.38	0.25
4006	596	2.32	0.39	20.0	3.4	364	61	1.77	0.30
4007	460	2.11	0.46	22.7	4.9	240	52	1.41	0.31
n	7	7	7	7	7	7	7	7	7
Mean	549	2.23	0.41	22.2	4.1	341	62	1.57	0.29
S.D.	56	0.08	0.04	3.1	0.7	84	13	0.17	0.03

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Testis-RL	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB g	RE g/100g
4001	12.91	2.60	0.69	0.14	3.44	0.69	53	10.7	3.48	0.70
4002	14.78	2.67	0.93	0.17	4.11	0.74	75	13.6	3.46	0.63
4003	16.87	2.71	0.76	0.12	3.92	0.63	77	12.4	4.15	0.67
4004	14.01	2.49	0.77	0.14	3.54	0.63	63	11.2	3.04	0.54
4005	14.71	2.66	0.71	0.13	3.71	0.67	53	9.6	3.86	0.70
4006	15.80	2.65	0.79	0.13	3.92	0.66	62	10.4	3.53	0.59
4007	11.50	2.50	0.57	0.12	3.00	0.65	76	16.5	3.06	0.67
n	7	7	7	7	7	7	7	7	7	7
Mean	14.37	2.61	0.75	0.14	3.66	0.67	66	12.1	3.51	0.64
S.D.	1.78	0.09	0.11	0.02	0.37	0.04	11	2.4	0.40	0.06

Animal No.	Epididymis-RL		Prostate		Seminal vesicle		LABC		Cowper's gland-RL	
	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	1452	293	1.50	0.30	2.16	0.44	1.89	0.38	173.6	35.0
4002	1352	244	1.77	0.32	2.49	0.45	1.98	0.36	220.2	39.8
4003	1477	237	1.64	0.26	1.79	0.29	1.98	0.32	152.4	24.5
4004	1107	197	1.55	0.28	1.39	0.25	1.62	0.29	115.1	20.4
4005	1382	250	1.34	0.24	1.71	0.31	1.60	0.29	112.2	20.3
4006	1202	202	1.59	0.27	1.99	0.33	1.81	0.30	142.7	23.9
4007	1226	267	1.52	0.33	2.14	0.47	1.73	0.38	171.4	37.3
n	7	7	7	7	7	7	7	7	7	7
Mean	1314	241	1.56	0.29	1.95	0.36	1.80	0.33	155.4	28.7
S.D.	138	34	0.13	0.03	0.36	0.09	0.16	0.04	37.5	8.3

AB : Absolute weight, RE : Relative weight by body weight

LABC: Levator ani and bulbocavernosus muscle

Appendix 9-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : End of administration

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Glans penis

Animal No.	AB	RE
	mg	mg/100g
4001	182.1	36.7
4002	96.1	17.4
4003	202.3	32.5
4004	181.7	32.3
4005	218.7	39.6
4006	179.9	30.2
4007	105.8	23.0
n	7	7
Mean	166.7	30.2
S.D.	47.1	7.7

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Body weight		Brain		Thyroid-RL		Thymus		Heart	
	g		AB	RE	AB	RE	AB	RE	AB	RE
			g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g
1101	323		1.95	0.60	15.7	4.9	272	84	1.03	0.32
1102	349		2.06	0.59	19.4	5.6	205	59	1.13	0.32
1103	377		1.93	0.51	20.8	5.5	249	66	1.28	0.34
1104	324		2.06	0.64	16.7	5.2	208	64	1.08	0.33
1105	335		2.08	0.62	16.3	4.9	212	63	1.05	0.31
1106	326		2.01	0.62	17.3	5.3	221	68	1.20	0.37
1107	339		2.04	0.60	15.6	4.6	326	96	1.04	0.31
1108	366		1.95	0.53	16.2	4.4	407	111	1.33	0.36
1109	323		1.99	0.62	21.2	6.6	232	72	1.11	0.34
1110	348		2.11	0.61	19.0	5.5	149	43	1.13	0.32
1111	379		2.14	0.56	15.0	4.0	261	69	1.24	0.33
1112	343		2.00	0.58	15.3	4.5	335	98	1.08	0.31
n	12		12	12	12	12	12	12	12	12
Mean	344		2.03	0.59	17.4	5.1	256	74	1.14	0.33
S.D.	20		0.07	0.04	2.2	0.7	70	19	0.10	0.02

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
	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
1101	10.94	3.39	0.56	0.17	2.22	0.69	62	19.2	89.7	27.8
1102	12.20	3.50	0.64	0.18	2.18	0.62	75	21.5	98.4	28.2
1103	13.11	3.48	0.69	0.18	2.42	0.64	79	21.0	96.7	25.6
1104	11.77	3.63	0.58	0.18	2.28	0.70	88	27.2	76.8	23.7
1105	10.95	3.27	0.56	0.17	2.47	0.74	69	20.6	96.2	28.7
1106	11.19	3.43	0.67	0.21	2.12	0.65	80	24.5	89.2	27.4
1107	11.31	3.34	0.57	0.17	2.10	0.62	95	28.0	97.0	28.6
1108	11.14	3.04	0.63	0.17	2.47	0.67	82	22.4	103.1	28.2
1109	11.46	3.55	0.50	0.15	2.25	0.70	78	24.1	97.7	30.2
1110	12.67	3.64	0.56	0.16	2.43	0.70	89	25.6	99.5	28.6
1111	12.19	3.22	0.74	0.20	2.54	0.67	70	18.5	82.1	21.7
1112	11.15	3.25	0.73	0.21	2.33	0.68	59	17.2	81.8	23.8
n	12	12	12	12	12	12	12	12	12	12
Mean	11.67	3.40	0.62	0.18	2.32	0.67	77	22.5	92.4	26.9
S.D.	0.72	0.18	0.08	0.02	0.15	0.04	11	3.4	8.3	2.6

AB : Absolute weight, RE : Relative weight by body weight

Appendix 9-10

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Uterus		
Animal No.	AB mg	RE mg/100g
1101	555	172
1102	502	144
1103	458	121
1104	482	149
1105	421	126
1106	593	182
1107	590	174
1108	561	153
1109	547	169
1110	460	132
1111	520	137
1112	512	149
n	12	12
Mean	517	151
S.D.	55	20

AB : Absolute weight, RE : Relative weight by body weight

Organ weight
Sex : Female

Stage : End of lactation (F0 dams)

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB	RE	AB	RE	AB	RE	AB	RE
		g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g
2101	381	1.92	0.50	14.6	3.8	320	84	1.92	0.50
2102	337	2.04	0.61	19.3	5.7	160	47	1.18	0.35
2103	312	1.88	0.60	20.1	6.4	199	64	1.06	0.34
2104	338	1.98	0.59	19.1	5.7	202	60	1.21	0.36
2105	373	2.08	0.56	20.9	5.6	295	79	1.38	0.37
2106	379	2.05	0.54	12.5	3.3	211	56	1.15	0.30
2107	334	2.04	0.61	26.4	7.9	233	70	1.18	0.35
2108	340	1.88	0.55	17.2	5.1	300	88	1.08	0.32
2109	371	2.04	0.55	12.6	3.4	212	57	1.16	0.31
2110	334	2.01	0.60	22.0	6.6	225	67	1.08	0.32
2111	335	2.04	0.61	17.3	5.2	206	61	1.09	0.33
2112	366	2.18	0.60	15.3	4.2	220	60	1.19	0.33
n	12	12	12	12	12	12	12	12	12
Mean	350	2.01	0.58	18.1	5.2	232	66	1.22	0.35
S.D.	23	0.09	0.04	4.1	1.4	48	12	0.24	0.05

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
	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
2101	13.80	3.62	0.68	0.18	2.63	0.69	75	19.7	108.9	28.6
2102	12.49	3.71	0.56	0.17	2.29	0.68	76	22.6	83.1	24.7
2103	11.00	3.53	0.55	0.18	2.18	0.70	97	31.1	73.1	23.4
2104	13.36	3.95	0.72	0.21	2.51	0.74	76	22.5	119.4	35.3
2105	11.92	3.20	0.54	0.14	2.24	0.60	74	19.8	95.8	25.7
2106	13.04	3.44	0.54	0.14	2.38	0.63	70	18.5	112.2	29.6
2107	12.09	3.62	0.49	0.15	2.30	0.69	86	25.7	108.7	32.5
2108	11.87	3.49	0.53	0.16	2.43	0.71	72	21.2	103.1	30.3
2109	11.88	3.20	0.40	0.11	2.36	0.64	76	20.5	89.8	24.2
2110	11.92	3.57	0.59	0.18	2.22	0.66	75	22.5	85.3	25.5
2111	11.15	3.33	0.57	0.17	2.23	0.67	72	21.5	90.8	27.1
2112	11.93	3.26	0.67	0.18	2.54	0.69	74	20.2	95.8	26.2
n	12	12	12	12	12	12	12	12	12	12
Mean	12.20	3.49	0.57	0.16	2.36	0.68	77	22.2	97.2	27.8
S.D.	0.84	0.22	0.09	0.03	0.14	0.04	7	3.4	13.6	3.6

AB : Absolute weight, RE : Relative weight by body weight

Appendix 9-12

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Uterus		
Animal No.	AB mg	RE mg/100g
2101	722	190
2102	484	144
2103	635	204
2104	633	187
2105	570	153
2106	570	150
2107	693	207
2108	571	168
2109	491	132
2110	456	137
2111	501	150
2112	652	178
n	12	12
Mean	582	167
S.D.	87	26

AB : Absolute weight, RE : Relative weight by body weight

Organ weight
Sex : Female

Stage : End of lactation (F0 dams)

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB	RE	AB	RE	AB	RE	AB	RE
		g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g
3101	320	1.96	0.61	21.6	6.8	191	60	1.18	0.37
3102	345	2.11	0.61	17.0	4.9	174	50	1.24	0.36
3103	373	2.11	0.57	17.7	4.7	266	71	1.39	0.37
3104	330	2.03	0.62	21.1	6.4	224	68	1.13	0.34
3105	382	2.01	0.53	21.5	5.6	357	93	1.29	0.34
3106	323	1.98	0.61	18.1	5.6	256	79	1.19	0.37
3107	361	2.10	0.58	22.8	6.3	252	70	1.13	0.31
3108	353	2.07	0.59	19.7	5.6	367	104	1.30	0.37
3109	346	1.99	0.58	16.0	4.6	233	67	1.05	0.30
3110	339	2.08	0.61	17.3	5.1	121	36	1.14	0.34
3111	396	2.04	0.52	19.2	4.8	439	111	1.21	0.31
3112	315	1.90	0.60	15.4	4.9	220	70	1.09	0.35
n	12	12	12	12	12	12	12	12	12
Mean	349	2.03	0.59	19.0	5.4	258	73	1.20	0.34
S.D.	26	0.07	0.03	2.4	0.7	89	21	0.10	0.03

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
	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
3101	11.27	3.52	0.56	0.18	2.44	0.76	75	23.4	87.2	27.3
3102	12.65	3.67	0.55	0.16	2.11	0.61	67	19.4	91.7	26.6
3103	13.44	3.60	0.62	0.17	2.62	0.70	88	23.6	121.7	32.6
3104	12.99	3.94	0.54	0.16	2.27	0.69	74	22.4	111.0	33.6
3105	13.73	3.59	0.69	0.18	2.42	0.63	69	18.1	99.9	26.2
3106	12.41	3.84	0.60	0.19	2.50	0.77	83	25.7	85.6	26.5
3107	11.97	3.32	0.58	0.16	2.39	0.66	80	22.2	75.2	20.8
3108	11.65	3.30	0.58	0.16	2.59	0.73	75	21.2	83.8	23.7
3109	10.85	3.14	0.46	0.13	2.34	0.68	79	22.8	77.4	22.4
3110	12.10	3.57	0.55	0.16	2.42	0.71	68	20.1	91.8	27.1
3111	13.41	3.39	0.65	0.16	2.43	0.61	72	18.2	104.1	26.3
3112	10.84	3.44	0.46	0.15	2.23	0.71	56	17.8	76.7	24.3
n	12	12	12	12	12	12	12	12	12	12
Mean	12.28	3.53	0.57	0.16	2.40	0.69	74	21.2	92.2	26.5
S.D.	1.00	0.23	0.07	0.02	0.14	0.05	8	2.5	14.5	3.7

AB : Absolute weight, RE : Relative weight by body weight

Appendix 9-14

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in ratsStudy No. : XXXXXXXXXX

Organ weight

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Uterus		
Animal No.	AB mg	RE mg/100g
3101	489	153
3102	627	182
3103	612	164
3104	559	169
3105	492	129
3106	523	162
3107	681	189
3108	627	178
3109	566	164
3110	613	181
3111	558	141
3112	499	158
n	12	12
Mean	571	164
S.D.	62	18

AB : Absolute weight, RE : Relative weight by body weight

Organ weight
Sex : Female

Stage : End of lactation (F0 dams)

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g
4101	333	2.02	0.61	15.2	4.6	324	97	1.09	0.33
4102	331	2.00	0.60	18.0	5.4	179	54	1.18	0.36
4103	358	1.95	0.54	20.5	5.7	121	34	1.21	0.34
4104	347	1.96	0.56	17.0	4.9	218	63	1.00	0.29
4105	350	1.93	0.55	18.0	5.1	316	90	1.10	0.31
4106	380	2.07	0.54	14.1	3.7	272	72	1.26	0.33
4107	354	2.15	0.61	15.1	4.3	355	100	1.05	0.30
4108	363	2.04	0.56	18.4	5.1	232	64	1.12	0.31
4109	359	2.02	0.56	18.9	5.3	281	78	1.05	0.29
4110	349	1.99	0.57	16.2	4.6	400	115	1.06	0.30
4111	372	2.12	0.57	23.5	6.3	252	68	1.40	0.38
4112	362	2.24	0.62	14.5	4.0	265	73	1.26	0.35
n	12	12	12	12	12	12	12	12	12
Mean	355	2.04	0.57	17.5	4.9	268	76	1.15	0.32
S.D.	14	0.09	0.03	2.7	0.7	76	22	0.12	0.03

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
	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	11.50	3.45	0.65	0.20	2.54	0.76	63	18.9	77.1	23.2
4102	11.76	3.55	0.48	0.15	2.24	0.68	78	23.6	97.0	29.3
4103	13.42	3.75	0.55	0.15	2.35	0.66	82	22.9	91.7	25.6
4104	10.88	3.14	0.51	0.15	2.27	0.65	78	22.5	90.9	26.2
4105	12.23	3.49	0.61	0.17	2.19	0.63	81	23.1	76.0	21.7
4106	13.39	3.52	0.79	0.21	2.69	0.71	89	23.4	97.1	25.6
4107	13.03	3.68	0.54	0.15	2.51	0.71	59	16.7	86.6	24.5
4108	11.99	3.30	0.54	0.15	2.35	0.65	72	19.8	82.3	22.7
4109	12.47	3.47	0.66	0.18	2.30	0.64	75	20.9	87.7	24.4
4110	11.23	3.22	0.74	0.21	2.33	0.67	80	22.9	95.7	27.4
4111	13.41	3.60	0.63	0.17	2.40	0.65	77	20.7	92.1	24.8
4112	10.95	3.02	0.62	0.17	2.54	0.70	71	19.6	92.4	25.5
n	12	12	12	12	12	12	12	12	12	12
Mean	12.19	3.43	0.61	0.17	2.39	0.68	75	21.3	88.9	25.1
S.D.	0.96	0.22	0.09	0.02	0.15	0.04	8	2.2	7.2	2.1

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of lactation (F0 dams)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Uterus		
Animal No.	AB mg	RE mg/100g
4101	459	138
4102	545	165
4103	530	148
4104	647	186
4105	559	160
4106	606	159
4107	543	153
4108	426	117
4109	377	105
4110	551	158
4111	518	139
4112	548	151
n	12	12
Mean	526	148
S.D.	74	22

AB : Absolute weight, RE : Relative weight by body weight

Organ weight
Sex : FemaleStage : End of administration (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g
5101	287	1.99	0.69	15.4	5.4	292	102	0.84	0.29
5102	263	1.95	0.74	17.7	6.7	289	110	0.83	0.32
5103	305	2.03	0.67	18.4	6.0	355	116	0.93	0.30
5104	310	2.05	0.66	18.8	6.1	229	74	0.98	0.32
5105	338	1.96	0.58	17.6	5.2	317	94	1.10	0.33
n	5	5	5	5	5	5	5	5	5
Mean	301	2.00	0.67	17.6	5.9	296	99	0.94	0.31
S.D.	28	0.04	0.06	1.3	0.6	46	16	0.11	0.02

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
	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	6.62	2.31	0.54	0.19	2.04	0.71	74	25.8	89.4	31.1
5102	5.87	2.23	0.55	0.21	1.82	0.69	64	24.3	90.0	34.2
5103	6.85	2.25	0.51	0.17	1.74	0.57	71	23.3	83.9	27.5
5104	7.11	2.29	0.47	0.15	1.88	0.61	72	23.2	87.9	28.4
5105	8.29	2.45	0.63	0.19	2.19	0.65	73	21.6	109.4	32.4
n	5	5	5	5	5	5	5	5	5	5
Mean	6.95	2.31	0.54	0.18	1.93	0.65	71	23.6	92.1	30.7
S.D.	0.88	0.09	0.06	0.02	0.18	0.06	4	1.5	9.9	2.8

Animal No.	Uterus	
	AB mg	RE mg/100g
5101	720	251
5102	470	179
5103	616	202
5104	728	235
5105	516	153
n	5	5
Mean	610	204
S.D.	117	40

AB : Absolute weight, RE : Relative weight by body weight

Organ weight
Sex : FemaleStage : End of administration (non-mating group)
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g
6101	271	2.05	0.76	18.2	6.7	244	90	1.00	0.37
6102	309	2.05	0.66	15.0	4.9	367	119	1.06	0.34
6103	305	1.85	0.61	17.5	5.7	330	108	1.01	0.33
6104	326	2.06	0.63	18.2	5.6	296	91	0.96	0.29
6105	329	2.01	0.61	20.5	6.2	335	102	1.05	0.32
n	5	5	5	5	5	5	5	5	5
Mean	308	2.00	0.65	17.9	5.8	314	102	1.02	0.33
S.D.	23	0.09	0.06	2.0	0.7	47	12	0.04	0.03

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
	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	7.31	2.70	0.44	0.16	1.93	0.71	102	37.6	71.6	26.4
6102	9.04	2.93	0.51	0.17	2.11	0.68	82	26.5	90.0	29.1
6103	8.13	2.67	0.52	0.17	2.30	0.75	87	28.5	104.0	34.1
6104	8.54	2.62	0.55	0.17	2.31	0.71	90	27.6	81.1	24.9
6105	8.63	2.62	0.60	0.18	1.97	0.60	67	20.4	96.3	29.3
n	5	5	5	5	5	5	5	5	5	5
Mean	8.33	2.71	0.52	0.17	2.12	0.69	86	28.1	88.6	28.8
S.D.	0.66	0.13	0.06	0.01	0.18	0.06	13	6.2	12.7	3.5

Animal No.	Uterus	
	AB mg	RE mg/100g
6101	423	156
6102	436	141
6103	622	204
6104	773	237
6105	596	181
n	5	5
Mean	570	184
S.D.	145	38

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Thyroid-RL		Thymus		Heart	
	g	AB	RE	AB	RE	AB	RE	AB	RE
		g	g/100g	mg	mg/100g	mg	mg/100g	g	g/100g
1008	585	2.09	0.36	30.5	5.2	305	52	1.62	0.28
1009	579	2.23	0.39	20.6	3.6	222	38	1.48	0.26
1010	518	2.24	0.43	32.5	6.3	306	59	1.41	0.27
1011	614	2.36	0.38	23.9	3.9	442	72	1.63	0.27
1012	580	2.06	0.36	24.0	4.1	373	64	1.45	0.25
n	5	5	5	5	5	5	5	5	5
Mean	575	2.20	0.38	26.3	4.6	330	57	1.52	0.27
S.D.	35	0.12	0.03	5.0	1.1	83	13	0.10	0.01

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Testis-RL	
	AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g	g	g/100g
1008	17.67	3.02	0.61	0.10	3.63	0.62	64	10.9	3.07	0.52
1009	13.65	2.36	0.71	0.12	3.58	0.62	71	12.3	3.54	0.61
1010	14.51	2.80	0.65	0.13	3.21	0.62	70	13.5	3.53	0.68
1011	15.88	2.59	0.85	0.14	3.38	0.55	57	9.3	3.76	0.61
1012	13.59	2.34	0.82	0.14	3.56	0.61	61	10.5	3.33	0.57
n	5	5	5	5	5	5	5	5	5	5
Mean	15.06	2.62	0.73	0.13	3.47	0.60	65	11.3	3.45	0.60
S.D.	1.73	0.29	0.10	0.02	0.17	0.03	6	1.6	0.26	0.06

Animal No.	Epididymis-RL		Prostate		Seminal vesicle		LABC		Cowper's gland-RL	
	AB	RE	AB	RE	AB	RE	AB	RE	AB	RE
	mg	mg/100g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
1008	1379	236	1.44	0.25	1.88	0.32	1.60	0.27	140.4	24.0
1009	1343	232	1.07	0.18	1.84	0.32	1.75	0.30	129.7	22.4
1010	1277	247	1.32	0.25	1.60	0.31	1.61	0.31	139.0	26.8
1011	1368	223	0.88	0.14	1.18	0.19	1.16	0.19	116.5	19.0
1012	1392	240	1.57	0.27	1.83	0.32	1.56	0.27	106.1	18.3
n	5	5	5	5	5	5	5	5	5	5
Mean	1352	236	1.26	0.22	1.67	0.29	1.54	0.27	126.3	22.1
S.D.	46	9	0.28	0.06	0.29	0.06	0.22	0.05	14.8	3.5

AB : Absolute weight, RE : Relative weight by body weight

LABC: Levator ani and bulbocavernosus muscle

Appendix 9-20

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : End of recovery

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Glans penis

Animal No.	AB mg	RE mg/100g
1008	100.1	17.1
1009	109.6	18.9
1010	100.4	19.4
1011	126.7	20.6
1012	106.3	18.3
n	5	5
Mean	108.6	18.9
S.D.	10.9	1.3

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : End of recovery

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Body weight	Brain		Thyroid-RL		Thymus		Heart	
	g	AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g
4008	564	2.14	0.38	24.3	4.3	338	60	1.53	0.27
4009	559	2.23	0.40	22.3	4.0	220	39	1.49	0.27
4010	633	2.34	0.37	21.2	3.3	381	60	1.71	0.27
4011	568	2.09	0.37	20.5	3.6	287	51	1.48	0.26
4012	635	2.19	0.34	22.9	3.6	288	45	1.79	0.28
n	5	5	5	5	5	5	5	5	5
Mean	592	2.20	0.37	22.2	3.8	303	51	1.60	0.27
S.D.	39	0.10	0.02	1.5	0.4	61	9	0.14	0.01

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Testis-RL	
	AB g	RE g/100g	AB g	RE g/100g	AB g	RE g/100g	AB mg	RE mg/100g	AB g	RE g/100g
4008	14.18	2.51	0.69	0.12	3.42	0.61	55	9.8	3.83	0.68
4009	13.79	2.47	0.87	0.16	3.54	0.63	50	8.9	3.52	0.63
4010	19.21	3.03	0.84	0.13	3.68	0.58	62	9.8	3.62	0.57
4011	14.66	2.58	0.98	0.17	3.58	0.63	79	13.9	3.12	0.55
4012	17.19	2.71	0.95	0.15	4.51	0.71	56	8.8	3.54	0.56
n	5	5	5	5	5	5	5	5	5	5
Mean	15.81	2.66	0.87	0.15	3.75	0.63	60	10.2	3.53	0.60
S.D.	2.32	0.23	0.11	0.02	0.44	0.05	11	2.1	0.26	0.06

Animal No.	Epididymis-RL		Prostate		Seminal vesicle		LABC		Cowper's gland-RL	
	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	1607	285	1.47	0.26	1.68	0.30	1.63	0.29	147.1	26.1
4009	1289	231	1.56	0.28	1.72	0.31	1.53	0.27	150.2	26.9
4010	1249	197	1.34	0.21	1.73	0.27	1.80	0.28	116.7	18.4
4011	1368	241	1.59	0.28	2.22	0.39	1.64	0.29	162.0	28.5
4012	1440	227	1.26	0.20	1.99	0.31	1.97	0.31	119.4	18.8
n	5	5	5	5	5	5	5	5	5	5
Mean	1391	236	1.44	0.25	1.87	0.32	1.71	0.29	139.1	23.7
S.D.	142	32	0.14	0.04	0.23	0.04	0.17	0.01	20.0	4.8

AB : Absolute weight, RE : Relative weight by body weight

LABC: Levator ani and bulbocavernosus muscle

Appendix 9-22

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Organ weight

Stage : End of recovery

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Glans penis

Animal No.	AB mg	RE mg/100g
4008	115.7	20.5
4009	102.2	18.3
4010	109.9	17.4
4011	103.3	18.2
4012	108.5	17.1
n	5	5
Mean	107.9	18.3
S.D.	5.5	1.3

AB : Absolute weight, RE : Relative weight by body weight

Organ weight
Sex : FemaleStage : End of recovery (non-mating group)
Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g
5106	286	2.04	0.71	12.9	4.5	148	52	1.07	0.37
5107	291	2.03	0.70	15.4	5.3	295	101	0.90	0.31
5108	340	2.10	0.62	14.9	4.4	214	63	1.03	0.30
5109	323	2.09	0.65	15.1	4.7	1262	391	1.10	0.34
5110	291	1.99	0.68	17.6	6.0	271	93	0.84	0.29
n	5	5	5	5	5	5	5	5	5
Mean	306	2.05	0.67	15.2	5.0	438	140	0.99	0.32
S.D.	24	0.05	0.04	1.7	0.7	464	142	0.11	0.03

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
	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	7.62	2.66	0.43	0.15	2.06	0.72	79	27.6	95.6	33.4
5107	6.36	2.19	0.38	0.13	1.64	0.56	67	23.0	81.5	28.0
5108	8.70	2.56	0.57	0.17	2.18	0.64	79	23.2	105.8	31.1
5109	8.50	2.63	0.50	0.15	2.17	0.67	76	23.5	85.5	26.5
5110	7.41	2.55	0.52	0.18	2.06	0.71	65	22.3	70.3	24.2
n	5	5	5	5	5	5	5	5	5	5
Mean	7.72	2.52	0.48	0.16	2.02	0.66	73	23.9	87.7	28.6
S.D.	0.94	0.19	0.08	0.02	0.22	0.06	7	2.1	13.6	3.7

Animal No.	Uterus	
	AB mg	RE mg/100g
5106	665	233
5107	509	175
5108	807	237
5109	560	173
5110	646	222
n	5	5
Mean	637	208
S.D.	114	32

AB : Absolute weight, RE : Relative weight by body weight

Organ weight
Sex : FemaleStage : End of recovery (non-mating group)
Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Body weight g	Brain		Thyroid-RL		Thymus		Heart	
		AB g	RE g/100g	AB mg	RE mg/100g	AB mg	RE mg/100g	AB g	RE g/100g
6106	341	2.00	0.59	20.5	6.0	280	82	1.01	0.30
6107	302	2.03	0.67	17.9	5.9	331	110	0.88	0.29
6108	285	2.05	0.72	17.3	6.1	197	69	0.94	0.33
6109	276	1.98	0.72	18.3	6.6	263	95	0.91	0.33
6110	351	1.93	0.55	18.4	5.2	245	70	0.96	0.27
n	5	5	5	5	5	5	5	5	5
Mean	311	2.00	0.65	18.5	6.0	263	85	0.94	0.30
S.D.	33	0.05	0.08	1.2	0.5	49	17	0.05	0.03

Animal No.	Liver		Spleen		Kidney-RL		Adrenal-RL		Ovary-RL	
	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	9.26	2.72	0.50	0.15	2.09	0.61	62	18.2	106.3	31.2
6107	7.70	2.55	0.54	0.18	1.83	0.61	75	24.8	102.8	34.0
6108	6.57	2.31	0.44	0.15	1.98	0.69	54	18.9	69.0	24.2
6109	7.10	2.57	0.50	0.18	1.96	0.71	81	29.3	56.2	20.4
6110	9.29	2.65	0.55	0.16	2.07	0.59	71	20.2	94.4	26.9
n	5	5	5	5	5	5	5	5	5	5
Mean	7.98	2.56	0.51	0.16	1.99	0.64	69	22.3	85.7	27.3
S.D.	1.24	0.16	0.04	0.02	0.10	0.05	11	4.7	22.0	5.4

Animal No.	Uterus	
	AB mg	RE mg/100g
6106	490	144
6107	515	171
6108	690	242
6109	571	207
6110	521	148
n	5	5
Mean	557	182
S.D.	80	42

AB : Absolute weight, RE : Relative weight by body weight

Appendix 10-1(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1001 Male 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-2(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1002 Male 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Lung(bronchus) Aggregation,alveolar macrophage: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Parathyroid, Pancreas
Pituitary, Prostate, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Seminal vesicle
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 10-3(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1003 Male 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-4(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1004 Male 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Pituitary Cyst,pars distalis: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-5(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1005 Male 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-6(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1006 Male 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-7(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1007 Male 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-8(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2001 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-9(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2002 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-10(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2003 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-11(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2004 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-12(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2005 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-13(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2006 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-14(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2007 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-15(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2008 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-16(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2009 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-17(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2010 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-18(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2011 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-19(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2012 Male 100 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-20(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3001 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-21(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3002 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-22(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3003 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-23(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3004 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-24(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3005 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-25(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3006 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-26(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3007 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-27(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3008 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-28(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3009 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-29(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3010 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-30(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3011 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-31(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3012 Male 300 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-32(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4001 Male 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-33(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4002 Male 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine, cecum Infiltrate, inflammatory cell, mucosa: minimal

Following tissues : Not remarkable

Adrenal, Bone, femur, Bone marrow, femur, Brain(cerebrum, cerebellum, pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine, duodenum, Intestine, jejunum
Intestine, ileum, Intestine, colon, Intestine, rectum, Kidney
Lymph node, mesenteric, Lymph node, submandibular, Liver, Lung(bronchus)
Mammary gland, inguinal, Medulla oblongata, Muscle, quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch, ileal
Salivary gland, submandibular, Skin, inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord, thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-34(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4003 Male 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-35(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4004 Male 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Testis Atrophy,tubule: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 10-36(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4005 Male 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-37(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4006 Male 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-38(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4007 Male 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-39(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1008 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-40(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1009 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-41(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1010 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-42(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1011 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-43(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1012 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-44(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4008 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine, cecum Infiltrate, inflammatory cell, mucosa: minimal

Following tissues : Not remarkable

Adrenal, Bone, femur, Bone marrow, femur, Brain(cerebrum, cerebellum, pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine, duodenum, Intestine, jejunum
Intestine, ileum, Intestine, colon, Intestine, rectum, Kidney
Lymph node, mesenteric, Lymph node, submandibular, Liver, Lung(bronchus)
Mammary gland, inguinal, Medulla oblongata, Muscle, quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch, ileal
Salivary gland, submandibular, Skin, inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord, thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-45(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4009 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Prostate, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-46(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4010 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Pancreas Fibrosis, islet: mild
Focus, basophilic, acinar cell: minimal

Following tissues : Not remarkable

Adrenal, Bone, femur, Bone marrow, femur, Brain(cerebrum, cerebellum, pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine, duodenum, Intestine, jejunum
Intestine, ileum, Intestine, cecum, Intestine, colon, Intestine, rectum, Kidney
Lymph node, mesenteric, Lymph node, submandibular, Liver, Lung(bronchus)
Mammary gland, inguinal, Medulla oblongata, Muscle, quadriceps femoris
Optic nerve, Parathyroid, Pituitary, Prostate, Peyer's patch, ileal
Salivary gland, submandibular, Skin, inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord, thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-47(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4011 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Prostate Cell infiltration,interstitium: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Mammary gland,inguinal, Medulla oblongata, Muscle,quadriceps femoris
Optic nerve, Parathyroid, Pancreas, Pituitary, Peyer's patch,ileal
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen, Stomach
Seminal vesicle, Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 10-48(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4012 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Dilatation,tubule: minimal, unilateral

Lung(bronchus) Granuloma: minimal

Pancreas Fibrosis,islet: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons))
Coagulating gland, Epididymis, Eye, Heart, Intestine,duodenum, Intestine,jejunum
Intestine,ileum, Intestine,cecum, Intestine,colon, Intestine,rectum
Lymph node,mesenteric, Lymph node,submandibular, Liver, Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Parathyroid
Pituitary, Prostate, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Seminal vesicle
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 10-49(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1101 Female 0 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-50(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1102 Female 0 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine,cecum Infiltrate,inflammatory cell,mucosa: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,colon
Intestine,rectum, Kidney, Lymph node,mesenteric, Lymph node,submandibular, Liver
Lung(bronchus), Mammary gland,inguinal, Medulla oblongata
Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid, Pancreas, Pituitary
Peyer's patch,ileal, Salivary gland,submandibular, Skin,inguinal, Sciatic nerve
Spleen, Stomach, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder
Uterus, Vagina

Appendix 10-51(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1103 Female 0 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-52(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1104 Female 0 mg/kg Day 54 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-53(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1105 Female 0 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine,cecum Infiltrate,inflammatory cell,mucosa: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,colon
Intestine,rectum, Kidney, Lymph node,mesenteric, Lymph node,submandibular, Liver
Lung(bronchus), Mammary gland,inguinal, Medulla oblongata
Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid, Pancreas, Pituitary
Peyer's patch,ileal, Salivary gland,submandibular, Skin,inguinal, Sciatic nerve
Spleen, Stomach, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder
Uterus, Vagina

Appendix 10-54(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1106 Female 0 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Stomach Edema,limiting ridge: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-55(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1107 Female 0 mg/kg Day 54 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-56(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1108 Female 0 mg/kg Day 55 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-57(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1109 Female 0 mg/kg Day 51 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine,cecum Infiltrate,inflammatory cell,mucosa: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,colon
Intestine,rectum, Kidney, Lymph node,mesenteric, Lymph node,submandibular, Liver
Lung(bronchus), Mammary gland,inguinal, Medulla oblongata
Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid, Pancreas, Pituitary
Peyer's patch,ileal, Salivary gland,submandibular, Skin,inguinal, Sciatic nerve
Spleen, Stomach, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder
Uterus, Vagina

Appendix 10-58(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1110 Female 0 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-59(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1111 Female 0 mg/kg Day 55 End of administration,Dams

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present
5x2mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-60(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 1112 Female 0 mg/kg Day 55 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-61(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2101 Female 100 mg/kg Day 56 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-62(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2102 Female 100 mg/kg Day 55 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-63(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2103 Female 100 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-64(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2104 Female 100 mg/kg Day 54 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-65(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2105 Female 100 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-66(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2106 Female 100 mg/kg Day 54 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-67(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2107 Female 100 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-68(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2108 Female 100 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-69(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2109 Female 100 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-70(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2110 Female 100 mg/kg Day 54 End of administration,Dams

Gross pathology:

Stomach Focus,dark red,glandular stomach: 1 present
5x1mm

Other tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-71(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2111 Female 100 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-72(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 2112 Female 100 mg/kg Day 55 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-73(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3101 Female 300 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-74(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3102 Female 300 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-75(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3103 Female 300 mg/kg Day 54 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-76(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3104 Female 300 mg/kg Day 51 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-77(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3105 Female 300 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-78(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3106 Female 300 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-79(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3107 Female 300 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-80(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3108 Female 300 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-81(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3109 Female 300 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-82(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3110 Female 300 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-83(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3111 Female 300 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-84(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 3112 Female 300 mg/kg Day 55 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-85(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4101 Female 1000 mg/kg Day 54 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-86(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4102 Female 1000 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-87(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4103 Female 1000 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-88(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4104 Female 1000 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-89(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4105 Female 1000 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine,cecum Infiltrate,inflammatory cell,mucosa: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,colon
Intestine,rectum, Kidney, Lymph node,mesenteric, Lymph node,submandibular, Liver
Lung(bronchus), Mammary gland,inguinal, Medulla oblongata
Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid, Pancreas, Pituitary
Peyer's patch,ileal, Salivary gland,submandibular, Skin,inguinal, Sciatic nerve
Spleen, Stomach, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder
Uterus, Vagina

Appendix 10-90(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4106 Female 1000 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-91(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4107 Female 1000 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-92(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4108 Female 1000 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-93(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4109 Female 1000 mg/kg Day 54 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-94(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4110 Female 1000 mg/kg Day 54 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-95(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4111 Female 1000 mg/kg Day 52 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine,cecum Infiltrate,inflammatory cell,mucosa: minimal

Pituitary Cyst,pars distalis: minimal

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,colon
Intestine,rectum, Kidney, Lymph node,mesenteric, Lymph node,submandibular, Liver
Lung(bronchus), Mammary gland,inguinal, Medulla oblongata
Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid, Pancreas
Peyer's patch,ileal, Salivary gland,submandibular, Skin,inguinal, Sciatic nerve
Spleen, Stomach, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder
Uterus, Vagina

Appendix 10-96(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 4112 Female 1000 mg/kg Day 53 End of administration,Dams

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 10-97(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5101 Female 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone, femur, Bone marrow, femur, Brain(cerebrum, cerebellum, pons)), Eye
Heart, Intestine, duodenum, Intestine, jejunum, Intestine, ileum, Intestine, cecum
Intestine, colon, Intestine, rectum, Kidney, Lymph node, mesenteric
Lymph node, submandibular, Liver, Lung(bronchus), Mammary gland, inguinal
Medulla oblongata, Muscle, quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch, ileal, Salivary gland, submandibular
Skin, inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord, thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-98(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5102 Female 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-99(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5103 Female 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-100(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5104 Female 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Eye Retinal fold: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-101(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5105 Female 0 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-102(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6101 Female 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-103 (1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6102 Female 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Kidney Calculus: mild, unilateral

Following tissues : Not remarkable

Adrenal, Bone, femur, Bone marrow, femur, Brain (cerebrum, cerebellum, pons), Eye
Heart, Intestine, duodenum, Intestine, jejunum, Intestine, ileum, Intestine, cecum
Intestine, colon, Intestine, rectum, Lymph node, mesenteric
Lymph node, submandibular, Liver, Lung (bronchus), Mammary gland, inguinal
Medulla oblongata, Muscle, quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch, ileal, Salivary gland, submandibular
Skin, inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord, thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-104(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6103 Female 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-105(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6104 Female 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-106(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6105 Female 1000 mg/kg Day 43 End of dosing period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-107(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5106 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-108(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5107 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-109(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5108 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine, cecum Infiltrate, inflammatory cell, mucosa: minimal

Following tissues : Not remarkable

Adrenal, Bone, femur, Bone marrow, femur, Brain(cerebrum, cerebellum, pons), Eye
Heart, Intestine, duodenum, Intestine, jejunum, Intestine, ileum, Intestine, colon
Intestine, rectum, Kidney, Lymph node, mesenteric, Lymph node, submandibular, Liver
Lung(bronchus), Mammary gland, inguinal, Medulla oblongata
Muscle, quadriceps femoris, Optic nerve, Ovary, Parathyroid, Pancreas, Pituitary
Peyer's patch, ileal, Salivary gland, submandibular, Skin, inguinal, Sciatic nerve
Spleen, Stomach, Spinal cord, thoracic, Thymus, Trachea, Thyroid, Urinary bladder
Uterus, Vagina

Appendix 10-110(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5109 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

Thymus Nodule: 1 present
25x13x8mm

Other tissues Not remarkable

Histopathology:

Thymus THYMOMA,MALIGNANT: 1 present

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-111(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 5110 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Ovary Cyst,luteal: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Parathyroid, Pancreas
Pituitary, Peyer's patch,ileal, Salivary gland,submandibular, Skin,inguinal
Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 10-112(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6106 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-113 (1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6107 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine, cecum Infiltrate, inflammatory cell, mucosa: minimal

Following tissues : Not remarkable

Adrenal, Bone, femur, Bone marrow, femur, Brain (cerebrum, cerebellum, pons), Eye
Heart, Intestine, duodenum, Intestine, jejunum, Intestine, ileum, Intestine, colon
Intestine, rectum, Kidney, Lymph node, mesenteric, Lymph node, submandibular, Liver
Lung (bronchus), Mammary gland, inguinal, Medulla oblongata
Muscle, quadriceps femoris, Optic nerve, Ovary, Parathyroid, Pancreas, Pituitary
Peyer's patch, ileal, Salivary gland, submandibular, Skin, inguinal, Sciatic nerve
Spleen, Stomach, Spinal cord, thoracic, Thymus, Trachea, Thyroid, Urinary bladder
Uterus, Vagina

Appendix 10-114(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6108 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 10-115(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6109 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Intestine, cecum Infiltrate, inflammatory cell, mucosa: minimal

Ovary Cyst, follicular: mild, bilateral

Pituitary Aberrant craniopharyngeal tissue

Uterus Hypertrophy, endometrial epithelial cell: mild

Vagina Vacuolation, mucosa: mild

Following tissues : Not remarkable

Adrenal, Bone, femur, Bone marrow, femur, Brain(cerebrum, cerebellum, pons)), Eye
Heart, Intestine, duodenum, Intestine, jejunum, Intestine, ileum, Intestine, colon
Intestine, rectum, Kidney, Lymph node, mesenteric, Lymph node, submandibular, Liver
Lung (bronchus), Mammary gland, inguinal, Medulla oblongata
Muscle, quadriceps femoris, Optic nerve, Parathyroid, Pancreas
Peyer's patch, ileal, Salivary gland, submandibular, Skin, inguinal, Sciatic nerve
Spleen, Stomach, Spinal cord, thoracic, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 10-116(1/1) Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats

Individual gross and histopathological findings

Animal No. 6110 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Thyroid Infiltrate,lymphocytic: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone,femur, Bone marrow,femur, Brain(cerebrum,cerebellum,pons)), Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum, Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Mammary gland,inguinal
Medulla oblongata, Muscle,quadriceps femoris, Optic nerve, Ovary, Parathyroid
Pancreas, Pituitary, Peyer's patch,ileal, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Stomach, Spinal cord,thoracic, Thymus
Trachea, Urinary bladder, Uterus, Vagina

Appendix 11-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Estrus cycles and copulation

Generation : F0

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

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	M	D	P	E	M	D	P	E	M
1102	E	M	D	P	E	M	D	P	E	M	D	P	E	M
1103	E	M	D	P	E	M	D	P	E	M	D	P	E	M
1104	D	P	E	M	D	P	E	M	D	P	E	M	D	P
1105	E	M	D	P	E	M	D	D	D	D	D	D	D	D
1106	E	M	D	P	E	M	D	P	E	M	D	P	E	M
1107	P	E	M	D	P	E	M	D	P	E	M	D	P	E
1108	P	E	M	D	P	E	M	D	D	P	E	M	D	P
1109	M	D	P	E	M	D	P	E	M	D	P	E	M	D
1110	M	D	P	E	M	D	P	E	M	D	D	P	E	M
1111	M	D	P	E	M	D	D	P	E	M	D	D	P	E
1112	M	D	P	E	M	D	D	P	E	M	D	D	P	E

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus, - : Smear was not sampled or missing value

Appendix 11-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Estrus cycles and copulation
Generation : F0

Study No. : [REDACTED]

Animal No.	/Before mating (day)	Dose : Cinchona Bark Extract 0 mg/kg			Species : Rat		
		Length of estrous cycle (days)			Mean	Number of estrus	Animal with abnormal estrous cycle
1101	D	4	4	4	4.0	4	-
1102	D	4	4	4	4.0	4	-
1103	D	4	4	4	4.0	4	-
1104	E	4	4	4	4.0	4	-
1105	D	4			4.0	2	+
1106	D	4	4	4	4.0	4	-
1107	M	4	4	4	4.0	4	-
1108	E	4	5	4	4.3	4	-
1109	P	4	4		4.0	3	-
1110	D	4	5		4.5	3	-
1111	M	5	5		5.0	3	-
1112	M	5	5		5.0	3	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus, - : Smear was not sampled or missing value

+ : 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	M	D	D	P	E	M	D	D	P	E	M	D	D	P
2102	D	P	E	M	D	P	E	M	D	P	E	M	D	P
2103	M	D	P	E	M	D	P	E	M	D	P	E	M	D
2104	P	E	M	D	P	E	M	D	D	P	E	M	D	D
2105	E	M	D	P	E	M	D	P	E	M	D	P	E	M
2106	D	P	E	M	D	D	P	E	M	D	D	P	E	M
2107	M	D	P	E	M	D	P	E	M	D	P	E	M	D
2108	E	M	D	P	E	M	D	P	E	M	D	P	E	M
2109	E	M	D	P	E	M	D	P	E	M	D	P	E	M
2110	D	P	E	M	D	P	E	M	D	P	E	M	D	P
2111	M	D	P	E	M	D	P	E	M	D	P	E	M	D
2112	D	P	E	M	D	P	E	M	D	P	E	M	D	P

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus, - : Smear was not sampled or missing value

Generation : F0		Dose : Onchocerca Bark Extract 100 mg/kg				Species : Rat	
Animal No.	/Before mating (day)	Length of estrous cycle			Mean	Number of estrus	Animal with abnormal estrous cycle
		(days)					
2101	E	5	5		5.0	3	-
2102	E	4	4	4	4.0	4	-
2103	P	4	4		4.0	3	-
2104	P	4	5		4.5	3	-
2105	D	4	4	4	4.0	4	-
2106	D	5	5		5.0	3	-
2107	P	4	4		4.0	3	-
2108	D	4	4	4	4.0	4	-
2109	D	4	4	4	4.0	4	-
2110	E	4	4	4	4.0	4	-
2111	P	4	4		4.0	3	-
2112	E	4	4	4	4.0	4	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus, - : Smear was not sampled or missing value

+ : 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	M	D	D	P	E	M	D	P	E	M	D	P	E	M
3102	M	D	P	E	M	D	P	E	M	D	P	E	M	D
3103	P	E	M	D	P	E	M	D	P	E	M	D	P	E
3104	P	E	M	D	P	E	M	D	D	P	E	M	D	P
3105	D	P	E	M	D	D	P	E	M	D	D	P	E	M
3106	M	D	P	E	M	D	P	E	M	D	P	E	M	D
3107	E	M	D	P	E	M	D	P	E	M	D	P	E	M
3108	P	E	M	D	P	E	M	D	P	E	M	D	D	P
3109	M	D	P	E	M	D	P	E	M	D	P	E	M	D
3110	E	M	D	P	E	M	D	P	E	M	D	P	E	M
3111	P	E	M	D	D	P	E	M	D	D	P	E	M	D
3112	D	P	E	M	D	P	E	M	D	P	E	M	D	P

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus, - : Smear was not sampled or missing value

		Before mating (day)			Length of estrous cycle			Mean	Number of estrus	Animal with abnormal estrous cycle
Animal No.		15	(days)							
3101	D		4	4				4.0	3	-
3102	P		4	4				4.0	3	-
3103	M		4	4	4			4.0	4	-
3104	E		4	5	4			4.3	4	-
3105	D		5	5				5.0	3	-
3106	P		4	4				4.0	3	-
3107	D		4	4	4			4.0	4	-
3108	E		4	4	5			4.3	4	-
3109	P		4	4				4.0	3	-
3110	D		4	4	4			4.0	4	-
3111	D		5	5				5.0	3	-
3112	E		4	4	4			4.0	4	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus, - : Smear was not sampled or missing value

+ : 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	D	P	E	M	D	P	E	M	D	P	E	M	D	P
4102	E	M	D	P	E	M	D	P	E	M	D	P	E	M
4103	E	M	D	P	E	M	D	D	P	E	M	D	D	P
4104	P	E	M	D	P	E	M	D	P	E	M	D	P	E
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	E	M	D	P	E	M	D	P	E	M	D	P	E	M
4108	D	P	E	M	D	P	E	M	D	P	E	M	D	P
4109	E	M	D	P	E	M	D	P	E	M	D	D	P	E
4110	D	P	E	M	D	P	E	M	D	P	E	M	D	P
4111	M	D	P	E	M	D	P	E	M	D	P	E	M	D
4112	P	E	M	D	D	P	E	M	D	D	P	E	M	D

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus, - : Smear was not sampled or missing value

Generation : F0		Dose : Onchocerca Bark Extract 1000 mg/kg				Species : Rat	
Animal No.	/Before mating (day)	Length of estrous cycle			Mean	Number of estrus	Animal with abnormal estrous cycle
		(days)					
4101	E	4	4	4	4.0	4	-
4102	D	4	4	4	4.0	4	-
4103	E	4	5	5	4.7	4	-
4104	M	4	4	4	4.0	4	-
4105	P	4	4		4.0	3	-
4106	P	4	4		4.0	3	-
4107	D	4	4	4	4.0	4	-
4108	E	4	4	4	4.0	4	-
4109	M	4	4	5	4.3	4	-
4110	E	4	4	4	4.0	4	-
4111	P	4	4		4.0	3	-
4112	D	5	5		5.0	3	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus, - : Smear was not sampled or missing value

+ : Animal with abnormal estrous cycle, - : Animal with normal and regular cycle

Appendix 12-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Reproductive performance

Generation : F0

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving	1st mating		
		Paired animal	Copulation a)	Fertility b)
1001	2	1101	+	+
1002	2	1102	+	+
1003	2	1103	+	+
1004	4	1104	+	+
1005	2	1105	+	+
1006	2	1106	+	+
1007	3	1107	+	+
1008	4	1108	+	+
1009	1	1109	+	+
1010	2	1110	+	+
1011	4	1111	+	+
1012	4	1112	+	+
n	12		12	12
Mean	2.7			
S.D.	1.1			
No. of positives			12	12
%			100.0 c)	100.0 d)

a) + : Copulation, - : Not copulation

b) + : Pregnancy, - : Non-pregnancy

c) : (Number of copulated animals / Number of mated animals) x 100

d) : (Number of males which impregnated females / Number of copulated males) x 100

Animal No.	Elapsed day of conceiving	1st mating		
		Paired animal	Copulation a)	Fertility b)
2001	5	2101	+	+
2002	4	2102	+	+
2003	1	2103	+	+
2004	2	2104	+	+
2005	2	2105	+	+
2006	3	2106	+	+
2007	1	2107	+	+
2008	2	2108	+	+
2009	2	2109	+	+
2010	4	2110	+	+
2011	1	2111	+	+
2012	4	2112	+	+
n	12		12	12
Mean	2.6			
S.D.	1.4			
No. of positives			12	12
%			100.0 c)	100.0 d)

a) + : Copulation, - : Not copulation

b) + : Pregnancy, - : Non-pregnancy

c) : (Number of copulated animals / Number of mated animals) x 100

d) : (Number of males which impregnated females / Number of copulated males) x 100

Appendix 12-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Reproductive performance

Generation : F0

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving	1st mating		
		Paired animal	Copulation a)	Fertility b)
3001	2	3101	+	+
3002	1	3102	+	+
3003	3	3103	+	+
3004	1	3104	+	+
3005	2	3105	+	+
3006	1	3106	+	+
3007	2	3107	+	+
3008	3	3108	+	+
3009	1	3109	+	+
3010	2	3110	+	+
3011	2	3111	+	+
3012	4	3112	+	+
n	12		12	12
Mean	2.0			
S.D.	1.0			
No. of positives			12	12
%			100.0 c)	100.0 d)

a) + : Copulation, - : Not copulation

b) + : Pregnancy, - : Non-pregnancy

c) : (Number of copulated animals / Number of mated animals) x 100

d) : (Number of males which impregnated females / Number of copulated males) x 100

Generation : F0		Sex : Male		Dose : Cinchona Bark Extract 1000 mg/kg		Species : Rat
Animal No.	Elapsed day of conceiving	1st mating				
		Paired animal	Copulation a)	Fertility b)		
4001	4	4101	+	+		
4002	2	4102	+	+		
4003	1	4103	+	+		
4004	3	4104	+	+		
4005	1	4105	+	+		
4006	1	4106	+	+		
4007	2	4107	+	+		
4008	1	4108	+	+		
4009	4	4109	+	+		
4010	4	4110	+	+		
4011	1	4111	+	+		
4012	3	4112	+	+		
n	12		12	12		
Mean	2.3					
S.D.	1.3					
No. of positives			12	12		
%			100.0 c)	100.0 d)		

a) + : Copulation, - : Not copulation

b) + : Pregnancy, - : Non-pregnancy

c) : (Number of copulated animals / Number of mated animals) x 100

d) : (Number of males which impregnated females / Number of copulated males) x 100

Appendix 12-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Reproductive performance

Study No. : XXXXXXXXXX

Generation : F0		Sex : Female	Dose : Cinchona Bark Extract 0 mg/kg			Species : Rat
Animal No.	Elapsed day of conceiving	1st mating				
		Paired animal	Copulation a)	Fertility b)		
1101	2	1001	+	+		
1102	2	1002	+	+		
1103	2	1003	+	+		
1104	4	1004	+	+		
1105	2	1005	+	+		
1106	2	1006	+	+		
1107	3	1007	+	+		
1108	4	1008	+	+		
1109	1	1009	+	+		
1110	2	1010	+	+		
1111	4	1011	+	+		
1112	4	1012	+	+		
n	12		12	12		
Mean	2.7					
S.D.	1.1					
No. of positives			12	12		
%			100.0 c)	100.0 d)		

a) + : Copulation, - : Not copulation

b) + : Pregnancy, - : Non-pregnancy

c) : (Number of copulated animals / Number of mated animals) x 100

d) : (Number of pregnant females / Number of copulated females) x 100

Animal No.	Elapsed day of conceiving	1st mating		
		Paired animal	Copulation a)	Fertility b)
2101	5	2001	+	+
2102	4	2002	+	+
2103	1	2003	+	+
2104	2	2004	+	+
2105	2	2005	+	+
2106	3	2006	+	+
2107	1	2007	+	+
2108	2	2008	+	+
2109	2	2009	+	+
2110	4	2010	+	+
2111	1	2011	+	+
2112	4	2012	+	+
n	12		12	12
Mean	2.6			
S.D.	1.4			
No. of positives			12	12
%			100.0 c)	100.0 d)

a) + : Copulation, - : Not copulation

b) + : Pregnancy, - : Non-pregnancy

c) : (Number of copulated animals / Number of mated animals) x 100

d) : (Number of pregnant females / Number of copulated females) x 100

Appendix 12-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

Reproductive performance

Generation : F0

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Elapsed day of conceiving	1st mating		
		Paired animal	Copulation a)	Fertility b)
3101	2	3001	+	+
3102	1	3002	+	+
3103	3	3003	+	+
3104	1	3004	+	+
3105	2	3005	+	+
3106	1	3006	+	+
3107	2	3007	+	+
3108	3	3008	+	+
3109	1	3009	+	+
3110	2	3010	+	+
3111	2	3011	+	+
3112	4	3012	+	+
n	12		12	12
Mean	2.0			
S.D.	1.0			
No. of positives			12	12
%			100.0 c)	100.0 d)

a) + : Copulation, - : Not copulation

b) + : Pregnancy, - : Non-pregnancy

c) : (Number of copulated animals / Number of mated animals) x 100

d) : (Number of pregnant females / Number of copulated females) x 100

Animal No.	Elapsed day of conceiving	1st mating		
		Paired animal	Copulation a)	Fertility b)
4101	4	4001	+	+
4102	2	4002	+	+
4103	1	4003	+	+
4104	3	4004	+	+
4105	1	4005	+	+
4106	1	4006	+	+
4107	2	4007	+	+
4108	1	4008	+	+
4109	4	4009	+	+
4110	4	4010	+	+
4111	1	4011	+	+
4112	3	4012	+	+
n	12		12	12
Mean	2.3			
S.D.	1.3			
No. of positives			12	12
%			100.0 c)	100.0 d)

a) + : Copulation, - : Not copulation

b) + : Pregnancy, - : Non-pregnancy

c) : (Number of copulated animals / Number of mated animals) x 100

d) : (Number of pregnant females / Number of copulated females) x 100

Delivery data

Generation : F0

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Dam No.	Gestation period (day)	Number of implan- tation	Delivery index (%) a)	Live birth index (%) b)	Number of offspring	Number of live newborns			Number of dead newborns			
						M	F	Total	M	F	U	Total
1101	22.5	17(13/4)	88.2	100.0	15	7	8	15	0	0	0	0
1102	22.5	15(12/3)	100.0	93.3	15	6	8	14	0	1	0	1
1103	22.5	16(8/8)	87.5	100.0	14	6	8	14	0	0	0	0
1104	21.5	13(5/8)	100.0	100.0	13	5	8	13	0	0	0	0
1105	22.5	18(7/11)	100.0	100.0	18	10	8	18	0	0	0	0
1106	21.5	16(6/10)	100.0	100.0	16	11	5	16	0	0	0	0
1107	22.5	14(6/8)	100.0	78.6	14	7	4	11	1	2	0	3
1108	22	17(8/9)	88.2	100.0	15	10	5	15	0	0	0	0
1109	21.5	16(8/8)	93.8	100.0	15	7	8	15	0	0	0	0
1110	22	17(8/9)	100.0	100.0	17	8	9	17	0	0	0	0
1111	22.5	16(7/9)	100.0	100.0	16	7	9	16	0	0	0	0
1112	22	16(10/6)	93.8	100.0	15	9	6	15	0	0	0	0
n	12	12	12	12	12	12	12	12	12	12	12	12
Mean	22.1	15.9	96.0	97.7	15.3	7.8	7.2	14.9	0.1	0.3	0.0	0.3
S.D.	0.4	1.4	5.4	6.3	1.4	1.9	1.7	1.8	0.3	0.6	0.0	0.9

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

a): (Number of delivered pups / Number of implantation) x 100

b): (Number of liveborns / Number of delivered pups) x 100

Delivery data

Generation : F0

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Dam No.	Gestation period (day)	Number of implan- tation	Delivery index (%) a)	Live birth index (%) b)	Number of offspring	Number of live newborns			Number of dead newborns			
						M	F	Total	M	F	U	Total
2101	22.5	13(6/7)	100.0	100.0	13	6	7	13	0	0	0	0
2102	22	16(11/5)	81.3	100.0	13	7	6	13	0	0	0	0
2103	22	17(10/7)	94.1	100.0	16	8	8	16	0	0	0	0
2104	23	18(7/11)	88.9	100.0	16	8	8	16	0	0	0	0
2105	22	18(10/8)	88.9	100.0	16	7	9	16	0	0	0	0
2106	22.5	16(10/6)	93.8	100.0	15	7	8	15	0	0	0	0
2107	22.5	14(6/8)	100.0	92.9	14	11	2	13	1	0	0	1
2108	22.5	18(10/8)	94.4	100.0	17	6	11	17	0	0	0	0
2109	22	17(7/10)	94.1	100.0	16	9	7	16	0	0	0	0
2110	21.5	14(9/5)	100.0	100.0	14	6	8	14	0	0	0	0
2111	22.5	16(10/6)	87.5	100.0	14	4	10	14	0	0	0	0
2112	22	16(11/5)	81.3	100.0	13	6	7	13	0	0	0	0
n	12	12	12	12	12	12	12	12	12	12	12	12
Mean	22.3	16.1	92.0	99.4	14.8	7.1	7.6	14.7	0.1	0.0	0.0	0.1
S.D.	0.4	1.7	6.6	2.0	1.4	1.8	2.2	1.5	0.3	0.0	0.0	0.3

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

a): (Number of delivered pups / Number of implantation) x 100

b): (Number of liveborns / Number of delivered pups) x 100

Delivery data

Generation : F0

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Dam No.	Gestation period (day)	Number of implan- tation	Delivery index (%) a)	Live birth index (%) b)	Number of offspring	Number of live newborns			Number of dead newborns			
						M	F	Total	M	F	U	Total
3101	22	17(8/9)	100.0	100.0	17	10	7	17	0	0	0	0
3102	22	16(6/10)	100.0	100.0	16	6	10	16	0	0	0	0
3103	22.5	20(11/9)	95.0	100.0	19	7	12	19	0	0	0	0
3104	21.5	17(5/12)	100.0	100.0	17	6	11	17	0	0	0	0
3105	22	16(9/7)	93.8	100.0	15	11	4	15	0	0	0	0
3106	22	19(7/12)	94.7	100.0	18	13	5	18	0	0	0	0
3107	22	16(8/8)	100.0	100.0	16	8	8	16	0	0	0	0
3108	21.5	17(9/8)	88.2	100.0	15	7	8	15	0	0	0	0
3109	22	15(8/7)	93.3	100.0	14	8	6	14	0	0	0	0
3110	22	18(13/5)	100.0	100.0	18	11	7	18	0	0	0	0
3111	22.5	17(10/7)	70.6	91.7	12	6	5	11	0	1	0	1
3112	22	16(6/10)	100.0	100.0	16	8	8	16	0	0	0	0
n	12	12	12	12	12	12	12	12	12	12	12	12
Mean	22.0	17.0	94.6	99.3	16.1	8.4	7.6	16.0	0.0	0.1	0.0	0.1
S.D.	0.3	1.4	8.5	2.4	1.9	2.3	2.5	2.1	0.0	0.3	0.0	0.3

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

a): (Number of delivered pups / Number of implantation) x 100

b): (Number of liveborns / Number of delivered pups) x 100

Delivery data

Generation : F0

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Dam No.	Gestation period (day)	Number of implan- tation	Delivery index (%) a)	Live birth index (%) b)	Number of offspring	Number of live newborns			Number of dead newborns			
						M	F	Total	M	F	U	Total
4101	21.5	18(10/8)	94.4	100.0	17	8	9	17	0	0	0	0
4102	21.5	16(9/7)	100.0	100.0	16	6	10	16	0	0	0	0
4103	22	18(8/10)	77.8	100.0	14	7	7	14	0	0	0	0
4104	21.5	14(7/7)	92.9	100.0	13	8	5	13	0	0	0	0
4105	22.5	14(4/10)	100.0	100.0	14	3	11	14	0	0	0	0
4106	22	16(11/5)	100.0	100.0	16	9	7	16	0	0	0	0
4107	22.5	16(8/8)	93.8	100.0	15	9	6	15	0	0	0	0
4108	22	16(13/3)	100.0	100.0	16	11	5	16	0	0	0	0
4109	21.5	16(6/10)	100.0	100.0	16	8	8	16	0	0	0	0
4110	21.5	17(8/9)	100.0	100.0	17	12	5	17	0	0	0	0
4111	22	15(7/8)	100.0	100.0	15	10	5	15	0	0	0	0
4112	21.5	18(9/9)	83.3	100.0	15	6	9	15	0	0	0	0
n	12	12	12	12	12	12	12	12	12	12	12	12
Mean	21.8	16.2	95.2	100.0	15.3	8.1	7.3	15.3	0.0	0.0	0.0	0.0
S.D.	0.4	1.4	7.5	0.0	1.2	2.4	2.1	1.2	0.0	0.0	0.0	0.0

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

a): (Number of delivered pups / Number of implantation) x 100

b): (Number of liveborns / Number of delivered pups) x 100

Appendix 14-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

External examination of offspring

Unit : Number of anomalous offspring (incidence %)

Days after birth : 0

Generation : F0

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Dam No.	Number of offspring examined	/Findings
1101	15	No anomaly
1102	15	No anomaly
1103	14	No anomaly
1104	13	No anomaly
1105	18	No anomaly
1106	16	No anomaly
1107	14	No anomaly
1108	15	No anomaly
1109	15	No anomaly
1110	17	No anomaly
1111	16	No anomaly
1112	15	No anomaly
Total	183	
n	12	
Mean		
S.D.		

Mean : Average of incidence (%) : (Number of pups with external anomalies / Number of delivered pups) x 100

"No anomaly" was calculated as "0"

Appendix 14-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

External examination of offspring

Unit : Number of anomalous offspring (incidence %)

Days after birth : 0

Generation : F0

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Dam No.	Number of offspring examined	/Findings
2101	13	No anomaly
2102	13	No anomaly
2103	16	No anomaly
2104	16	No anomaly
2105	16	No anomaly
2106	15	No anomaly
2107	14	No anomaly
2108	17	No anomaly
2109	16	No anomaly
2110	14	No anomaly
2111	14	No anomaly
2112	13	No anomaly
Total	177	
n	12	
Mean		
S.D.		

Mean : Average of incidence (%) : (Number of pups with external anomalies / Number of delivered pups) x 100

"No anomaly" was calculated as "0"

Appendix 14-3

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

External examination of offspring

Unit : Number of anomalous offspring (incidence %)

Days after birth : 0

Generation : F0

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Dam No.	Number of offspring examined	/Findings
3101	17	No anomaly
3102	16	No anomaly
3103	19	No anomaly
3104	17	No anomaly
3105	15	No anomaly
3106	18	No anomaly
3107	16	No anomaly
3108	15	No anomaly
3109	14	No anomaly
3110	18	No anomaly
3111	12	No anomaly
3112	16	No anomaly
Total	193	
n	12	
Mean		
S.D.		

Mean : Average of incidence (%) : (Number of pups with external anomalies / Number of delivered pups) x 100

"No anomaly" was calculated as "0"

Appendix 14-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : XXXXXXXXXX

External examination of offspring

Unit : Number of anomalous offspring (incidence %)

Days after birth : 0

Generation : F0

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Dam No.	Number of offspring examined	/Findings
4101	17	No anomaly
4102	16	No anomaly
4103	14	No anomaly
4104	13	No anomaly
4105	14	No anomaly
4106	16	No anomaly
4107	15	No anomaly
4108	16	No anomaly
4109	16	No anomaly
4110	17	No anomaly
4111	15	No anomaly
4112	15	No anomaly
Total	184	
n	12	
Mean		
S.D.		

Mean : Average of incidence (%) : (Number of pups with external anomalies / Number of delivered pups) x 100

"No anomaly" was calculated as "0"

Dam No.	Sex	n	Normalized a)	
			AGD	AGD
1101	Male	7	2.3	1.2
	Female	8	0.9	0.5
1102	Male	6	2.5	1.3
	Female	8	1.0	0.5
1103	Male	6	2.3	1.2
	Female	8	0.9	0.5
1104	Male	5	2.3	1.3
	Female	8	0.8	0.4
1105	Male	10	2.3	1.3
	Female	8	0.9	0.5
1106	Male	11	2.3	1.3
	Female	5	0.8	0.5
1107	Male	7	2.3	1.2
	Female	4	0.8	0.4
1108	Male	10	2.4	1.3
	Female	5	0.9	0.5
1109	Male	7	2.2	1.2
	Female	8	0.9	0.5
1110	Male	8	2.2	1.2
	Female	9	0.7	0.4
1111	Male	7	2.4	1.2
	Female	9	0.9	0.5
1112	Male	9	2.4	1.3
	Female	6	0.9	0.5
n	Male	93		
	Female	86		
Mean	Male		2.3	1.3
	Female		0.9	0.5
S.D.	Male		0.1	0.1
	Female		0.1	0.0

AGD : Anogenital Distance

a): AGD (mm) / Cube root of body weight (g)

Anogenital of offspring

Generation : F0

Dose : Cinchona Bark Extract 100 mg/kg

Unit : mm

Species : Rat

Sex		/Days after birth		0	
Dam No.		n	AGD	Normalized a)	
				AGD	
2101	Male	6	2.3	1.2	
	Female	7	1.0	0.5	
2102	Male	7	2.4	1.3	
	Female	6	0.9	0.5	
2103	Male	8	2.4	1.3	
	Female	8	0.7	0.4	
2104	Male	8	2.6	1.4	
	Female	8	0.9	0.5	
2105	Male	7	2.5	1.3	
	Female	9	0.8	0.5	
2106	Male	7	2.6	1.4	
	Female	8	0.9	0.5	
2107	Male	11	2.5	1.3	
	Female	2	1.0	0.5	
2108	Male	6	2.3	1.2	
	Female	11	0.7	0.4	
2109	Male	9	2.4	1.3	
	Female	7	0.7	0.3	
2110	Male	6	2.6	1.4	
	Female	8	0.7	0.4	
2111	Male	4	2.6	1.4	
	Female	10	0.8	0.4	
2112	Male	6	2.4	1.3	
	Female	7	0.9	0.5	
n	Male	85			
	Female	91			
Mean	Male		2.5	1.3	
	Female		0.8	0.5	
S.D.	Male		0.1	0.1	
	Female		0.1	0.1	

AGD : Anogenital Distance

a): AGD (mm) / Cube root of body weight (g)

Anogenital of offspring

Generation : F0

Dose : Cinchona Bark Extract 300 mg/kg

Unit : mm

Species : Rat

Dam No.	Sex	n	Normalized a)	
			AGD	AGD
3101	Male	10	2.3	1.2
	Female	7	0.7	0.4
3102	Male	6	2.3	1.2
	Female	10	0.7	0.4
3103	Male	7	2.5	1.3
	Female	12	0.8	0.4
3104	Male	6	2.3	1.3
	Female	11	1.1	0.6
3105	Male	11	2.2	1.1
	Female	4	0.8	0.4
3106	Male	13	2.3	1.3
	Female	5	0.7	0.4
3107	Male	8	2.4	1.3
	Female	8	0.8	0.4
3108	Male	7	2.3	1.2
	Female	8	0.9	0.5
3109	Male	8	2.2	1.2
	Female	6	0.9	0.5
3110	Male	11	2.6	1.4
	Female	7	0.7	0.4
3111	Male	6	2.6	1.3
	Female	5	1.0	0.5
3112	Male	8	2.3	1.3
	Female	8	0.9	0.5
n	Male	101		
	Female	91		
Mean	Male		2.4	1.3
	Female		0.8	0.5
S.D.	Male		0.1	0.1
	Female		0.1	0.1

AGD : Anogenital Distance

a): AGD (mm) / Cube root of body weight (g)

Anogenital of offspring

Generation : F0

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : mm

Species : Rat

Dam No.	Sex	n	Normalized a)	
			AGD	AGD
4101	Male	8	2.4	1.3
	Female	9	0.8	0.4
4102	Male	6	2.4	1.3
	Female	10	0.9	0.5
4103	Male	7	2.4	1.3
	Female	7	0.7	0.4
4104	Male	8	2.2	1.2
	Female	5	0.9	0.5
4105	Male	3	1.8	0.9
	Female	11	0.7	0.4
4106	Male	9	2.3	1.2
	Female	7	0.7	0.4
4107	Male	9	2.3	1.2
	Female	6	0.9	0.5
4108	Male	11	2.2	1.2
	Female	5	0.8	0.4
4109	Male	8	2.3	1.3
	Female	8	0.8	0.4
4110	Male	12	2.3	1.3
	Female	5	0.8	0.4
4111	Male	10	2.2	1.2
	Female	5	0.8	0.4
4112	Male	6	2.5	1.4
	Female	9	0.8	0.4
n	Male	97		
	Female	87		
Mean	Male		2.3	1.2
	Female		0.8	0.4
S.D.	Male		0.2	0.1
	Female		0.1	0.0

AGD : Anogenital Distance

a): AGD (mm) / Cube root of body weight (g)

		/Days after birth					
		0	4	4	4	13	13
		Male/Female	Pre-culled Male/Female	Viability index (%) a)	Culled Male/Female	Male/Female	Viability index (%) b)
Dam No.	Sex						
1101	Total	15 (7/8)	15 (7/8)	100.0	8 (4/4)	8 (4/4)	100.0
1102	Total	14 (6/8)	14 (6/8)	100.0	8 (4/4)	8 (4/4)	100.0
1103	Total	14 (6/8)	14 (6/8)	100.0	8 (4/4)	8 (4/4)	100.0
1104	Total	13 (5/8)	13 (5/8)	100.0	8 (4/4)	8 (4/4)	100.0
1105	Total	18 (10/8)	18 (10/8)	100.0	8 (4/4)	8 (4/4)	100.0
1106	Total	16 (11/5)	16 (11/5)	100.0	8 (4/4)	8 (4/4)	100.0
1107	Total	11 (7/4)	11 (7/4)	100.0	8 (4/4)	8 (4/4)	100.0
1108	Total	15 (10/5)	15 (10/5)	100.0	8 (4/4)	8 (4/4)	100.0
1109	Total	15 (7/8)	15 (7/8)	100.0	8 (4/4)	8 (4/4)	100.0
1110	Total	17 (8/9)	16 (8/8)	94.1	8 (4/4)	8 (4/4)	100.0
1111	Total	16 (7/9)	16 (7/9)	100.0	8 (4/4)	8 (4/4)	100.0
1112	Total	15 (9/6)	13 (7/6)	86.7	8 (4/4)	8 (4/4)	100.0
Total		179	176		96	96	
Male/Female		93/86	91/85		48/48	48/48	
n		12	12	12	12	12	12
Mean				98.4			100.0
S.D.				4.1			0.0

a): (Number of pups alive on day 4 after birth / Number of live born pups) × 100

b): (Number of pups alive on day 13 after birth / Number of pups after culling on day 4 after birth) × 100

		/Days after birth					
		0	4	4	4	13	13
		Male/Female	Pre-culled Male/Female	Viability index (%) a)	Culled Male/Female	Male/Female	Viability index (%) b)
Dam No.	Sex						
2101	Total	13 (6/7)	12 (5/7)	92.3	8 (4/4)	8 (4/4)	100.0
2102	Total	13 (7/6)	13 (7/6)	100.0	8 (4/4)	8 (4/4)	100.0
2103	Total	16 (8/8)	16 (8/8)	100.0	8 (4/4)	8 (4/4)	100.0
2104	Total	16 (8/8)	16 (8/8)	100.0	8 (4/4)	8 (4/4)	100.0
2105	Total	16 (7/9)	16 (7/9)	100.0	8 (4/4)	8 (4/4)	100.0
2106	Total	15 (7/8)	15 (7/8)	100.0	8 (4/4)	8 (4/4)	100.0
2107	Total	13 (11/2)	13 (11/2)	100.0	8 (6/2)	8 (6/2)	100.0
2108	Total	17 (6/11)	17 (6/11)	100.0	8 (4/4)	8 (4/4)	100.0
2109	Total	16 (9/7)	16 (9/7)	100.0	8 (4/4)	8 (4/4)	100.0
2110	Total	14 (6/8)	14 (6/8)	100.0	8 (4/4)	8 (4/4)	100.0
2111	Total	14 (4/10)	14 (4/10)	100.0	8 (4/4)	8 (4/4)	100.0
2112	Total	13 (6/7)	12 (5/7)	92.3	8 (4/4)	8 (4/4)	100.0
Total		176	174		96	96	
Male/Female		85/91	83/91		50/46	50/46	
n		12	12	12	12	12	12
Mean				98.7			100.0
S.D.				3.0			0.0

a): (Number of pups alive on day 4 after birth / Number of live born pups) × 100

b): (Number of pups alive on day 13 after birth / Number of pups after culling on day 4 after birth) × 100

		/Days after birth					
		0	4	4	4	13	13
		Male/Female	Pre-culled Male/Female	Viability index (%) a	Culled Male/Female	Male/Female	Viability index (%) b
Dam No.	Sex						
3101	Total	17 (10/7)	17 (10/7)	100.0	8 (4/4)	8 (4/4)	100.0
3102	Total	16 (6/10)	15 (6/9)	93.8	8 (4/4)	8 (4/4)	100.0
3103	Total	19 (7/12)	18 (7/11)	94.7	8 (4/4)	8 (4/4)	100.0
3104	Total	17 (6/11)	15 (5/10)	88.2	8 (4/4)	8 (4/4)	100.0
3105	Total	15 (11/4)	15 (11/4)	100.0	8 (4/4)	8 (4/4)	100.0
3106	Total	18 (13/5)	18 (13/5)	100.0	8 (4/4)	8 (4/4)	100.0
3107	Total	16 (8/8)	16 (8/8)	100.0	8 (4/4)	8 (4/4)	100.0
3108	Total	15 (7/8)	15 (7/8)	100.0	8 (4/4)	8 (4/4)	100.0
3109	Total	14 (8/6)	14 (8/6)	100.0	8 (4/4)	8 (4/4)	100.0
3110	Total	18 (11/7)	18 (11/7)	100.0	8 (4/4)	8 (4/4)	100.0
3111	Total	11 (6/5)	10 (6/4)	90.9	8 (4/4)	8 (4/4)	100.0
3112	Total	16 (8/8)	16 (8/8)	100.0	8 (4/4)	8 (4/4)	100.0
Total		192	187		96	96	
Male/Female		101/91	100/87		48/48	48/48	
n		12	12	12	12	12	12
Mean				97.3			100.0
S.D.				4.3			0.0

a): (Number of pups alive on day 4 after birth / Number of live born pups) × 100

b): (Number of pups alive on day 13 after birth / Number of pups after culling on day 4 after birth) × 100

		/Days after birth					
		0	4	4	4	13	13
			Pre-culled	Viability	Culled		Viability
Dam No.	Sex	Male/Female	Male/Female	index (%) a	Male/Female	Male/Female	index (%) b
4101	Total	17	17	100.0	8	8	100.0
		(8/9)	(8/9)		(4/4)	(4/4)	
4102	Total	16	16	100.0	8	8	100.0
		(6/10)	(6/10)		(4/4)	(4/4)	
4103	Total	14	14	100.0	8	8	100.0
		(7/7)	(7/7)		(4/4)	(4/4)	
4104	Total	13	12	92.3	8	8	100.0
		(8/5)	(7/5)		(4/4)	(4/4)	
4105	Total	14	13	92.9	8	8	100.0
		(3/11)	(2/11)		(2/6)	(2/6)	
4106	Total	16	16	100.0	8	8	100.0
		(9/7)	(9/7)		(4/4)	(4/4)	
4107	Total	15	14	93.3	8	8	100.0
		(9/6)	(9/5)		(4/4)	(4/4)	
4108	Total	16	16	100.0	8	8	100.0
		(11/5)	(11/5)		(4/4)	(4/4)	
4109	Total	16	16	100.0	8	8	100.0
		(8/8)	(8/8)		(4/4)	(4/4)	
4110	Total	17	14	82.4	8	8	100.0
		(12/5)	(9/5)		(4/4)	(4/4)	
4111	Total	15	15	100.0	8	8	100.0
		(10/5)	(10/5)		(4/4)	(4/4)	
4112	Total	15	6	40.0	6	6	100.0
		(6/9)	(2/4)		(2/4)	(2/4)	
Total		184	169		94	94	
Male/Female		97/87	88/81		44/50	44/50	
n		12	12	12	12	12	12
Mean				91.7			100.0
S.D.				17.2			0.0

a): (Number of pups alive on day 4 after birth / Number of live born pups) × 100

b): (Number of pups alive on day 13 after birth / Number of pups after culling on day 4 after birth) × 100

Generation : F0		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat
Dam No.	day 4 after birth			
	Number of males	Number of females	Sex ratio (%) a)	
1101	7	8		
1102	6	8		
1103	6	8		
1104	5	8		
1105	10	8		
1106	11	5		
1107	7	4		
1108	10	5		
1109	7	8		
1110	8	8		
1111	7	9		
1112	7	6		
n	12	12		
Total	91	85	91/176	
(%)			51.7	

a): (Number of male pups alive on day 4 after birth / Number of pups alive on day 4 after birth) x 100

Sex ratio

Generation : F0

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Dam No.	day 4 after birth		
	Number of males	Number of females	Sex ratio (%) a)
2101	5	7	
2102	7	6	
2103	8	8	
2104	8	8	
2105	7	9	
2106	7	8	
2107	11	2	
2108	6	11	
2109	9	7	
2110	6	8	
2111	4	10	
2112	5	7	
n	12	12	
Total	83	91	83/174
(%)			47.7

a): (Number of male pups alive on day 4 after birth / Number of pups alive on day 4 after birth) x 100

Sex ratio

Generation : F0

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Dam No.	day 4 after birth		
	Number of males	Number of females	Sex ratio (%) a)
3101	10	7	
3102	6	9	
3103	7	11	
3104	5	10	
3105	11	4	
3106	13	5	
3107	8	8	
3108	7	8	
3109	8	6	
3110	11	7	
3111	6	4	
3112	8	8	
n	12	12	
Mean	100	87	100/187
S.D.			53.5

a): (Number of male pups alive on day 4 after birth / Number of pups alive on day 4 after birth) x 100

Sex ratio

Generation : F0

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Dam No.	day 4 after birth		
	Number of males	Number of females	Sex ratio (%) a)
4101	8	9	
4102	6	10	
4103	7	7	
4104	7	5	
4015	2	11	
4106	9	7	
4107	9	5	
4108	11	5	
4109	8	8	
4110	9	5	
4111	10	5	
4112	2	4	
n	12	12	
Mean	88	81	88/169
S.D.			52.1

a): (Number of male pups alive on day 4 after birth / Number of pups alive on day 4 after birth) x 100

Body weight of offspring

Generation : F0

Dose : Cinchona Bark Extract 0 mg/kg

Unit : g

Species : Rat

Dam No.	Sex	0 /Days after birth		4/Pre-culled		4/Culled		7		13	
		n	B.W.	n	B.W.	n	B.W.	n	B.W.	n	B.W.
1101	Male	7	6.9	7	10.4	4	10.5	4	18.0	4	34.1
	Female	8	6.7	8	10.4	4	10.6	4	18.3	4	33.8
1102	Male	6	6.9	6	10.5	4	11.0	4	17.8	4	33.0
	Female	8	7.0	8	10.4	4	10.6	4	17.4	4	31.7
1103	Male	6	6.9	6	11.7	4	12.2	4	19.0	4	36.2
	Female	8	6.5	8	10.9	4	11.2	4	18.4	4	35.9
1104	Male	5	5.9	5	8.9	4	9.6	4	15.8	4	30.5
	Female	8	5.9	8	9.0	4	9.1	4	15.1	4	29.3
1105	Male	10	6.7	10	9.1	4	9.9	4	16.9	4	31.5
	Female	8	6.1	8	8.1	4	8.7	4	15.0	4	29.3
1106	Male	11	5.8	11	9.4	4	9.5	4	16.2	4	32.7
	Female	5	5.5	5	8.7	4	8.8	4	15.3	4	30.4
1107	Male	7	6.8	7	11.9	4	11.9	4	18.8	4	35.2
	Female	4	6.6	4	11.2	4	11.2	4	18.2	4	34.2
1108	Male	10	6.0	10	10.1	4	10.9	4	18.5	4	35.1
	Female	5	5.8	5	10.3	4	10.6	4	17.1	4	33.3
1109	Male	7	6.2	7	10.0	4	10.1	4	15.7	4	31.1
	Female	8	6.0	8	9.6	4	9.5	4	14.8	4	29.3
1110	Male	8	6.8	8	11.3	4	11.8	4	19.2	4	38.1
	Female	9	6.4	8	10.5	4	10.4	4	17.1	4	34.1
1111	Male	7	7.1	7	11.2	4	11.6	4	19.5	4	38.3
	Female	9	6.8	9	10.3	4	10.7	4	18.2	4	36.7
1112	Male	9	5.8	7	10.2	4	10.4	4	16.6	4	32.1
	Female	6	6.0	6	9.8	4	9.6	4	15.3	4	31.1
n	Male	93		91		48		48		48	
	Female	86		85		48		48		48	
Mean	Male		6.5		10.4		10.8		17.7		34.0
	Female		6.3		9.9		10.1		16.7		32.4
S.D.	Male		0.5		1.0		0.9		1.4		2.6
	Female		0.5		0.9		0.9		1.5		2.6

Body weight of offspring

Generation : F0

Dose : Cinchona Bark Extract 100 mg/kg

Unit : g

Species : Rat

Dam No.	Sex	0 /Days after birth		4/Pre-culled		4/Culled		7		13	
		n	B.W.	n	B.W.	n	B.W.	n	B.W.	n	B.W.
2101	Male	6	7.0	5	11.9	4	12.1	4	23.9	4	36.3
	Female	7	7.0	7	11.9	4	12.3	4	19.0	4	36.8
2102	Male	7	6.6	7	11.4	4	11.7	4	18.4	4	36.8
	Female	6	6.4	6	11.4	4	11.4	4	17.8	4	34.5
2103	Male	8	6.6	8	10.9	4	11.5	4	18.4	4	35.1
	Female	8	6.2	8	10.4	4	10.6	4	17.7	4	33.5
2104	Male	8	7.2	8	11.2	4	11.2	4	17.7	4	34.7
	Female	8	6.6	8	10.4	4	10.7	4	16.8	4	33.5
2105	Male	7	6.8	7	11.5	4	12.1	4	19.6	4	37.5
	Female	9	6.2	9	10.8	4	11.1	4	18.6	4	36.1
2106	Male	7	6.7	7	10.2	4	10.2	4	15.3	4	32.8
	Female	8	6.4	8	9.9	4	10.3	4	16.0	4	31.1
2107	Male	11	7.8	11	11.6	6	11.7	6	19.3	6	37.3
	Female	2	7.6	2	11.3	2	11.3	2	18.7	2	34.8
2108	Male	6	7.1	6	9.6	4	9.9	4	15.8	4	28.6
	Female	11	6.4	11	8.4	4	9.1	4	14.7	4	27.0
2109	Male	9	6.7	9	11.3	4	12.1	4	19.2	4	36.8
	Female	7	6.4	7	11.2	4	11.2	4	18.1	4	35.6
2110	Male	6	6.1	6	8.6	4	8.8	4	14.2	4	29.3
	Female	8	5.8	8	8.6	4	8.8	4	14.7	4	29.9
2111	Male	4	6.9	4	10.8	4	10.8	4	17.6	4	33.3
	Female	10	6.5	10	10.3	4	10.5	4	16.8	4	31.8
2112	Male	6	6.4	5	10.9	4	11.0	4	16.9	4	32.9
	Female	7	6.1	7	10.3	4	10.5	4	17.6	4	33.6
n	Male	85		83		50		50		50	
	Female	91		91		46		46		46	
Mean	Male		6.8		10.8		11.1		18.0		34.3
	Female		6.5		10.4		10.7		17.2		33.2
S.D.	Male		0.4		0.9		1.0		2.5		3.0
	Female		0.5		1.1		1.0		1.5		2.8

Body weight of offspring

Generation : F0

Dose : Cinchona Bark Extract 300 mg/kg

Unit : g

Species : Rat

Dam No.	Sex	0 /Days after birth		4/Pre-culled		4/Culled		7		13	
		n	B.W.	n	B.W.	n	B.W.	n	B.W.	n	B.W.
3101	Male	10	6.8	10	9.9	4	10.7	4	17.7	4	34.6
	Female	7	6.3	7	9.5	4	10.0	4	15.6	4	31.4
3102	Male	6	6.7	6	10.5	4	11.4	4	18.6	4	34.5
	Female	10	6.3	9	10.3	4	10.6	4	17.4	4	32.2
3103	Male	7	7.2	7	9.6	4	10.0	4	15.3	4	28.3
	Female	12	6.6	11	8.8	4	9.5	4	14.9	4	27.5
3104	Male	6	6.1	5	9.1	4	9.8	4	16.7	4	30.4
	Female	11	5.7	10	8.5	4	9.3	4	15.4	4	31.1
3105	Male	11	6.8	11	11.4	4	11.5	4	18.0	4	36.8
	Female	4	6.3	4	10.8	4	10.8	4	16.7	4	34.6
3106	Male	13	6.1	13	9.4	4	9.8	4	15.1	4	30.6
	Female	5	6.1	5	8.7	4	8.6	4	13.4	4	27.2
3107	Male	8	6.5	8	9.9	4	10.3	4	15.7	4	32.9
	Female	8	6.0	8	9.0	4	10.0	4	15.0	4	31.7
3108	Male	7	6.3	7	9.1	4	8.9	4	14.8	4	30.1
	Female	8	6.0	8	8.8	4	8.7	4	14.8	4	29.6
3109	Male	8	6.8	8	10.6	4	11.2	4	19.2	4	35.3
	Female	6	6.4	6	9.8	4	9.8	4	16.7	4	31.4
3110	Male	11	6.2	11	8.9	4	10.3	4	16.9	4	32.2
	Female	7	6.3	7	9.0	4	9.0	4	14.5	4	28.2
3111	Male	6	7.9	6	13.1	4	13.1	4	21.1	4	37.0
	Female	5	7.4	4	12.6	4	12.6	4	20.4	4	35.2
3112	Male	8	6.3	8	9.8	4	10.4	4	16.6	4	32.0
	Female	8	6.1	8	9.3	4	9.2	4	15.7	4	30.7
n	Male	101		100		48		48		48	
	Female	91		87		48		48		48	
Mean	Male		6.6		10.1		10.6		17.1		32.9
	Female		6.3		9.6		9.8		15.9		30.9
S.D.	Male		0.5		1.2		1.1		1.9		2.8
	Female		0.4		1.2		1.1		1.8		2.5

Body weight of offspring

Generation : F0

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : g

Species : Rat

Dam No.	Sex	0 /Days after birth		4/Pre-culled		4/Culled		7		13	
		n	B.W.	n	B.W.	n	B.W.	n	B.W.	n	B.W.
4101	Male	8	5.9	8	8.6	4	9.2	4	15.2	4	31.2
	Female	9	5.6	9	8.4	4	8.6	4	13.9	4	29.4
4102	Male	6	6.5	6	9.5	4	9.9	4	16.9	4	33.0
	Female	10	6.4	10	9.8	4	9.9	4	16.4	4	32.0
4103	Male	7	6.6	7	11.2	4	11.4	4	18.8	4	35.9
	Female	7	6.3	7	11.3	4	11.5	4	19.0	4	35.9
4104	Male	8	5.9	7	10.3	4	10.2	4	16.8	4	32.8
	Female	5	5.7	5	9.3	4	9.4	4	15.5	4	30.8
4105	Male	3	6.8	2	10.4	2	10.4	2	15.7	2	29.7
	Female	11	6.5	11	10.2	6	10.4	6	16.7	6	31.1
4106	Male	9	6.3	9	10.8	4	11.2	4	17.8	4	32.5
	Female	7	6.1	7	9.9	4	10.7	4	17.4	4	32.6
4107	Male	9	7.2	9	11.3	4	11.9	4	20.2	4	38.0
	Female	6	6.8	5	11.2	4	11.2	4	19.4	4	37.3
4108	Male	11	6.4	11	10.0	4	10.4	4	16.7	4	32.6
	Female	5	6.2	5	9.5	4	9.9	4	15.8	4	30.6
4109	Male	8	5.6	8	9.0	4	9.0	4	15.6	4	29.6
	Female	8	5.2	8	8.0	4	8.3	4	14.7	4	29.3
4110	Male	12	6.0	9	9.1	4	9.8	4	16.3	4	30.4
	Female	5	5.6	5	8.8	4	9.0	4	15.2	4	28.9
4111	Male	10	7.0	10	11.1	4	11.8	4	18.8	4	36.6
	Female	5	6.6	5	10.6	4	10.8	4	17.4	4	34.5
4112	Male	6	6.1	2	7.3	2	7.3	2	10.3	2	21.9
	Female	9	5.8	4	7.6	4	7.6	4	11.5	4	25.1
n	Male	97		88		44		44		44	
	Female	87		81		50		50		50	
Mean	Male		6.4		9.9		10.2		16.6		32.0
	Female		6.1		9.6		9.8		16.1		31.5
S.D.	Male		0.5		1.2		1.3		2.5		4.2
	Female		0.5		1.2		1.2		2.2		3.3

Appendix 18-5

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats

Study No. : [REDACTED]

Body weight gain of offspring

Generation : F0

Dose : Cinchona Bark Extract 0 mg/kg

Base : Day 4 after birth

Unit : g

Species : Rat

Dam No.	Sex	/Days after birth /Before culling		/After culling			
		n	0-4	n	4-7	n	4-13
1101	Male	7	3.5	4	7.5	4	23.6
	Female	8	3.7	4	7.7	4	23.3
1102	Male	6	3.6	4	6.8	4	22.0
	Female	8	3.4	4	6.8	4	21.1
1103	Male	6	4.8	4	6.9	4	24.0
	Female	8	4.4	4	7.2	4	24.7
1104	Male	5	3.0	4	6.2	4	20.9
	Female	8	3.1	4	6.0	4	20.2
1105	Male	10	2.4	4	7.0	4	21.6
	Female	8	2.0	4	6.4	4	20.6
1106	Male	11	3.6	4	6.7	4	23.2
	Female	5	3.2	4	6.5	4	21.6
1107	Male	7	5.1	4	6.9	4	23.3
	Female	4	4.6	4	7.1	4	23.0
1108	Male	10	4.1	4	7.7	4	24.2
	Female	5	4.5	4	6.5	4	22.7
1109	Male	7	3.8	4	5.6	4	21.0
	Female	8	3.6	4	5.3	4	19.8
1110	Male	8	4.5	4	7.4	4	26.4
	Female	8	4.1	4	6.7	4	23.7
1111	Male	7	4.1	4	8.0	4	26.8
	Female	9	3.5	4	7.5	4	26.0
1112	Male	7	4.4	4	6.2	4	21.7
	Female	6	3.8	4	5.7	4	21.5
n	Male	91		48		48	
	Female	85		48		48	
Mean	Male		3.9		6.9		23.2
	Female		3.7		6.6		22.4
S.D.	Male		0.8		0.7		1.9
	Female		0.7		0.7		1.9

Appendix 18-6

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight gain of offspring

Study No. : [REDACTED]

Base : Day 4 after birth

Unit : g

Species : Rat

		/Days after birth		Dose : Cinchona Bark Extract 100 mg/kg			
		/Before culling		/After culling			
Dam No.	Sex	n	0-4	n	4-7	n	4-13
2101	Male	5	4.9	4	11.8	4	24.2
	Female	7	4.9	4	6.7	4	24.5
2102	Male	7	4.8	4	6.8	4	25.2
	Female	6	5.0	4	6.4	4	23.1
2103	Male	8	4.3	4	7.0	4	23.6
	Female	8	4.2	4	7.1	4	22.9
2104	Male	8	4.0	4	6.5	4	23.6
	Female	8	3.8	4	6.1	4	22.9
2105	Male	7	4.7	4	7.6	4	25.4
	Female	9	4.6	4	7.5	4	25.0
2106	Male	7	3.5	4	5.0	4	22.6
	Female	8	3.5	4	5.7	4	20.8
2107	Male	11	3.8	6	7.6	6	25.6
	Female	2	3.7	2	7.4	2	23.5
2108	Male	6	2.5	4	5.9	4	18.7
	Female	11	2.0	4	5.6	4	17.9
2109	Male	9	4.6	4	7.0	4	24.7
	Female	7	4.8	4	6.9	4	24.4
2110	Male	6	2.5	4	5.4	4	20.5
	Female	8	2.8	4	5.9	4	21.0
2111	Male	4	3.9	4	6.8	4	22.5
	Female	10	3.8	4	6.3	4	21.3
2112	Male	5	4.5	4	5.9	4	21.9
	Female	7	4.2	4	7.1	4	23.1
n	Male	83		50		50	
	Female	91		46		46	
Mean	Male		4.0		6.9		23.2
	Female		3.9		6.6		22.5
S.D.	Male		0.8		1.7		2.1
	Female		0.9		0.7		2.0

Appendix 18-7

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight gain of offspring

Study No. : [REDACTED]

Base : Day 4 after birth

Unit : g

Species : Rat

		/Days after birth		Dose : Cinchona Bark Extract 300 mg/kg			
		/Before culling		/After culling			
Dam No.	Sex	n	0-4	n	4-7	n	4-13
3101	Male	10	3.1	4	7.0	4	23.9
	Female	7	3.2	4	5.7	4	21.4
3102	Male	6	3.8	4	7.3	4	23.2
	Female	9	4.0	4	6.8	4	21.6
3103	Male	7	2.4	4	5.3	4	18.3
	Female	11	2.2	4	5.4	4	18.0
3104	Male	5	3.0	4	6.9	4	20.6
	Female	10	2.8	4	6.1	4	21.8
3105	Male	11	4.6	4	6.6	4	25.3
	Female	4	4.5	4	5.9	4	23.8
3106	Male	13	3.3	4	5.4	4	20.9
	Female	5	2.6	4	4.8	4	18.6
3107	Male	8	3.4	4	5.4	4	22.6
	Female	8	3.0	4	5.1	4	21.7
3108	Male	7	2.8	4	5.9	4	21.2
	Female	8	2.8	4	6.1	4	20.9
3109	Male	8	3.8	4	8.0	4	24.1
	Female	6	3.4	4	6.9	4	21.6
3110	Male	11	2.7	4	6.7	4	21.9
	Female	7	2.7	4	5.5	4	19.2
3111	Male	6	5.2	4	8.0	4	23.9
	Female	4	5.2	4	7.7	4	22.6
3112	Male	8	3.5	4	6.2	4	21.6
	Female	8	3.2	4	6.5	4	21.5
n	Male	100		48		48	
	Female	87		48		48	
Mean	Male		3.5		6.6		22.3
	Female		3.3		6.0		21.1
S.D.	Male		0.8		0.9		1.9
	Female		0.9		0.8		1.7

Appendix 18-8

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Body weight gain of offspring

Study No. : XXXXXXXXXX

		Generation : F0				Dose : Cinchona Bark Extract 1000 mg/kg		Base : Day 4 after birth		Unit : g		Species : Rat	
		/Days after birth											
		/Before culling				/After culling							
Dam No.	Sex	n	0-4	n	4-7	n	4-13						
4101	Male	8	2.7	4	6.0	4	22.1						
	Female	9	2.8	4	5.3	4	20.8						
4102	Male	6	3.0	4	7.1	4	23.1						
	Female	10	3.4	4	6.5	4	22.1						
4103	Male	7	4.6	4	7.5	4	24.6						
	Female	7	5.0	4	7.4	4	24.4						
4104	Male	7	4.4	4	6.6	4	22.6						
	Female	5	3.6	4	6.1	4	21.4						
4105	Male	2	3.6	2	5.3	2	19.3						
	Female	11	3.7	6	6.3	6	20.6						
4106	Male	9	4.5	4	6.6	4	21.4						
	Female	7	3.8	4	6.7	4	21.9						
4107	Male	9	4.1	4	8.3	4	26.1						
	Female	5	4.4	4	8.1	4	26.1						
4108	Male	11	3.6	4	6.3	4	22.3						
	Female	5	3.3	4	5.9	4	20.7						
4109	Male	8	3.4	4	6.6	4	20.6						
	Female	8	2.8	4	6.4	4	21.1						
4110	Male	9	3.1	4	6.5	4	20.6						
	Female	5	3.2	4	6.2	4	19.9						
4111	Male	10	4.1	4	7.0	4	24.8						
	Female	5	4.0	4	6.6	4	23.7						
4112	Male	2	1.2	2	3.0	2	14.6						
	Female	4	1.8	4	3.9	4	17.5						
n	Male	88		44		44							
	Female	81		50		50							
Mean	Male		3.5		6.4		21.8						
	Female		3.5		6.3		21.7						
S.D.	Male		1.0		1.3		3.0						
	Female		0.8		1.0		2.2						

Appendix 19-1

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Externally for gross abnormalities in dead pups

Study No. :

		Dose : Cinchona Bark Extract 0 mg/kg		Species : Rat
Animal No.	Number of pups examined Total (Male + Female)	Findings		
1101	0			
1102	0			
1103	0			
1104	0			
1105	0			
1106	0			
1107	0			
1108	0			
1109	0			
1110	1 (0+1)	NAF		
1111	0			
1112	0			

NAF: No abnormal findings

Appendix 19-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats
Externally for gross abnormalities in dead pups

Study No. :

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Number of pups examined Total (Male + Female)	Findings
2101	0	
2102	0	
2103	0	
2104	0	
2105	0	
2106	0	
2107	0	
2108	0	
2109	0	
2110	0	
2111	0	
2112	0	

			Dose : Cinchona Bark Extract 300 mg/kg	Species : Rat
Animal No.	Number of pups examined Total (Male + Female)		Findings	
3101	0			
3102	1	(0+1)	NAF	
3103	0			
3104	2	(1+1)	NAF	
3105	0			
3106	0			
3107	0			
3108	0			
3109	0			
3110	0			
3111	0			
3112	0			

NAF: No abnormal findings

			Dose : Cinchona Bark Extract 1000 mg/kg	Species : Rat
Animal No.	Number of pups examined Total (Male + Female)		Findings	
4101	0			
4102	0			
4103	0			
4104	1	(1+0)	NAF	
4105	1	(1+0)	NAF	
4106	0			
4107	0			
4108	0			
4109	0			
4110	1	(1+0)	NAF	
4111	0			
4112	0			

NAF: No abnormal findings

Generation : F0

Dose : Cinchona Bark Extract 0 mg/kg

Unit : No.

Days after birth : 13

Species : Rat

Dam No.		Sex	Offspring No. : Nipple retention				Mean	S.D.	n
1101	Male	1101M01 : 0	1101M02 : 0	1101M03 : 0	1101M04 : 0	0.0	0.0	4	
1102	Male	1102M01 : 0	1102M02 : 0	1102M03 : 0	1102M04 : 0	0.0	0.0	4	
1103	Male	1103M01 : 0	1103M02 : 0	1103M03 : 0	1103M04 : 0	0.0	0.0	4	
1104	Male	1104M01 : 0	1104M02 : 0	1104M03 : 0	1104M04 : 0	0.0	0.0	4	
1105	Male	1105M01 : 0	1105M02 : 0	1105M03 : 0	1105M04 : 0	0.0	0.0	4	
1106	Male	1106M01 : 0	1106M02 : 0	1106M03 : 0	1106M04 : 0	0.0	0.0	4	
1107	Male	1107M01 : 0	1107M02 : 0	1107M03 : 0	1107M04 : 0	0.0	0.0	4	
1108	Male	1108M01 : 0	1108M02 : 0	1108M03 : 0	1108M04 : 0	0.0	0.0	4	
1109	Male	1109M01 : 0	1109M02 : 0	1109M03 : 0	1109M04 : 0	0.0	0.0	4	
1110	Male	1110M01 : 0	1110M02 : 0	1110M03 : 0	1110M04 : 0	0.0	0.0	4	
1111	Male	1111M01 : 0	1111M02 : 0	1111M03 : 0	1111M04 : 0	0.0	0.0	4	
1112	Male	1112M01 : 0	1112M02 : 0	1112M03 : 0	1112M04 : 0	0.0	0.0	4	

Nipple retention: Number of nipple / areolae

Appendix 20-2

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Nipple retention of male pups

Study No. : XXXXXXXXXX

Generation : F0

Dose : Cinchona Bark Extract 100 mg/kg

Unit : No.

Days after birth : 13

Species : Rat

Dam No.		Sex	Offspring No. : Nipple retention				Mean	S.D.	n
2101	Male	2101M01 : 0	2101M02 : 0	2101M03 : 0	2101M04 : 0	0.0	0.0	4	
2102	Male	2102M01 : 0	2102M02 : 0	2102M03 : 0	2102M04 : 0	0.0	0.0	4	
2103	Male	2103M01 : 0	2103M02 : 0	2103M03 : 0	2103M04 : 0	0.0	0.0	4	
2104	Male	2104M01 : 0	2104M02 : 0	2104M03 : 0	2104M04 : 0	0.0	0.0	4	
2105	Male	2105M01 : 0	2105M02 : 0	2105M03 : 0	2105M04 : 0	0.0	0.0	4	
2106	Male	2106M01 : 0	2106M02 : 0	2106M03 : 0	2106M04 : 0	0.0	0.0	4	
2107	Male	2107M01 : 0	2107M02 : 0	2107M03 : 0	2107M04 : 0				
		2107M05 : 0	2107M06 : 0			0.0	0.0	6	
2108	Male	2108M01 : 0	2108M02 : 0	2108M03 : 0	2108M04 : 0	0.0	0.0	4	
2109	Male	2109M01 : 0	2109M02 : 0	2109M03 : 0	2109M04 : 0	0.0	0.0	4	
2110	Male	2110M01 : 0	2110M02 : 0	2110M03 : 0	2110M04 : 0	0.0	0.0	4	
2111	Male	2111M01 : 0	2111M02 : 0	2111M03 : 0	2111M04 : 0	0.0	0.0	4	
2112	Male	2112M01 : 0	2112M02 : 0	2112M03 : 0	2112M04 : 0	0.0	0.0	4	

Nipple retention: Number of nipple / areolae

Generation : F0

Dose : Cinchona Bark Extract 300 mg/kg

Unit : No.

Days after birth : 13

Species : Rat

Generation : F0		Dose : Cinchona Bark Extract 500 mg/kg				Unit : No.	Species : Rat			
Dam No.	Sex	Offspring No. :		Nipple retention			Mean	S.D.	n	
3101	Male	3101M01 : 0		3101M02 : 0		3101M03 : 0	3101M04 : 0	0.0	0.0	4
3102	Male	3102M01 : 0		3102M02 : 0		3102M03 : 0	3102M04 : 0	0.0	0.0	4
3103	Male	3103M01 : 0		3103M02 : 0		3103M03 : 0	3103M04 : 0	0.0	0.0	4
3104	Male	3104M01 : 0		3104M02 : 0		3104M03 : 0	3104M04 : 0	0.0	0.0	4
3105	Male	3105M01 : 0		3105M02 : 0		3105M03 : 0	3105M04 : 0	0.0	0.0	4
3106	Male	3106M01 : 0		3106M02 : 0		3106M03 : 0	3106M04 : 0	0.0	0.0	4
3107	Male	3107M01 : 0		3107M02 : 0		3107M03 : 0	3107M04 : 0	0.0	0.0	4
3108	Male	3108M01 : 0		3108M02 : 0		3108M03 : 0	3108M04 : 0	0.0	0.0	4
3109	Male	3109M01 : 0		3109M02 : 0		3109M03 : 0	3109M04 : 0	0.0	0.0	4
3110	Male	3110M01 : 0		3110M02 : 0		3110M03 : 0	3110M04 : 0	0.0	0.0	4
3111	Male	3111M01 : 0		3111M02 : 0		3111M03 : 0	3111M04 : 0	0.0	0.0	4
3112	Male	3112M01 : 0		3112M02 : 0		3112M03 : 0	3112M04 : 0	0.0	0.0	4

Nipple retention: Number of nipple / areolae

Appendix 20-4

Cinchona Bark Extract: An oral combined repeated dose toxicity study
with the reproduction/ developmental toxicity screening test in rats
Nipple retention of male pups

Study No. : [REDACTED]

Generation : F0

Dose : Cinchona Bark Extract 1000 mg/kg

Unit : No.

Days after birth : 13

Species : Rat

Generation : F ₃		Dose : Cichroma Dark Extract 1000 mg/kg				Unit : No.	Species : Rat			
Dam No.	Sex	Offspring No. :		Nipple retention			Mean	S.D.	n	
4101	Male	4101M01 : 0		4101M02 : 0		4101M03 : 0	4101M04 : 0	0.0	0.0	4
4102	Male	4102M01 : 0		4102M02 : 0		4102M03 : 0	4102M04 : 0	0.0	0.0	4
4103	Male	4103M01 : 0		4103M02 : 0		4103M03 : 0	4103M04 : 0	0.0	0.0	4
4104	Male	4104M01 : 0		4104M02 : 0		4104M03 : 0	4104M04 : 0	0.0	0.0	4
4105	Male	4105M01 : 0		4105M02 : 0				0.0	0.0	2
4106	Male	4106M01 : 0		4106M02 : 0		4106M03 : 0	4106M04 : 0	0.0	0.0	4
4107	Male	4107M01 : 0		4107M02 : 0		4107M03 : 0	4107M04 : 0	0.0	0.0	4
4108	Male	4108M01 : 0		4108M02 : 0		4108M03 : 0	4108M04 : 0	0.0	0.0	4
4109	Male	4109M01 : 0		4109M02 : 0		4109M03 : 0	4109M04 : 0	0.0	0.0	4
4110	Male	4110M01 : 0		4110M02 : 0		4110M03 : 0	4110M04 : 0	0.0	0.0	4
4111	Male	4111M01 : 0		4111M02 : 0		4111M03 : 0	4111M04 : 0	0.0	0.0	4
4112	Male	4112M01 : 0		4112M02 : 0				0.0	0.0	2

Nipple retention: Number of nipple / areolae

			Dose : Cinchona Bark Extract 0 mg/kg	Species : Rat
Animal No.	Number of pups examined		Findings	
	Total	(Male + Female)		
1101	8	(4+4)	NAF	
1102	8	(4+4)	NAF	
1103	8	(4+4)	NAF	
1104	8	(4+4)	NAF	
1105	8	(4+4)	NAF	
1106	8	(4+4)	NAF	
1107	8	(4+4)	NAF	
1108	8	(4+4)	NAF	
1109	8	(4+4)	NAF	
1110	8	(4+4)	NAF	
1111	8	(4+4)	NAF	
1112	8	(4+4)	NAF	

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

NAF: No abnormal findings

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Number of pups examined		Findings
	Total	(Male + Female)	
2101	8	(4+4)	NAF
2102	8	(4+4)	NAF
2103	8	(4+4)	NAF
2104	8	(4+4)	NAF
2105	8	(4+4)	NAF
2106	8	(4+4)	NAF
2107	8	(6+2)	NAF
2108	8	(4+4)	NAF
2109	8	(4+4)	NAF
2110	8	(4+4)	NAF
2111	8	(4+4)	NAF
2112	8	(4+4)	NAF

NAF: No abnormal findings

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Number of pups examined		Findings
	Total	(Male + Female)	
3101	8	(4+4)	NAF
3102	8	(4+4)	NAF
3103	8	(4+4)	NAF
3104	8	(4+4)	NAF
3105	8	(4+4)	NAF
3106	8	(4+4)	NAF
3107	8	(4+4)	NAF
3108	8	(4+4)	NAF
3109	8	(4+4)	NAF
3110	8	(4+4)	NAF
3111	8	(4+4)	NAF
3112	8	(4+4)	NAF

NAF: No abnormal findings

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Number of pups examined		Findings	Dose : Cimicifuga Bark Extract 1000 mg/kg	Species : Rat
	Total (Male + Female)				
4101	8	(4+4)	NAF		
4102	8	(4+4)	NAF		
4103	8	(4+4)	NAF		
4104	8	(4+4)	NAF		
4105	8	(2+6)	NAF		
4106	8	(4+4)	NAF		
4107	8	(4+4)	NAF		
4108	8	(4+4)	NAF		
4109	8	(4+4)	NAF		
4110	8	(4+4)	NAF		
4111	8	(4+4)	NAF		
4112	6	(2+4)	NAF		

NAF: No abnormal findings

Organ weight

Stage : After culled (F1 males)

Sex : Male

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Body weight g	Thyroid-RL	
		AB mg	RE mg/100g
1101M01	32.5	3.9	12.0
1102M01	34.3	3.6	10.5
1103M01	40.8	6.0	14.7
1104M01	30.8	5.3	17.2
1105M01	30.2	5.0	16.6
1106M01	32.0	3.5	10.9
1107M01	36.3	3.9	10.7
1108M01	32.9	4.3	13.1
1109M01	32.2	4.8	14.9
1110M01	37.7	5.9	15.6
1111M01	38.6	4.1	10.6
1112M01	32.5	4.0	12.3
n	12	12	12
Mean	34.2	4.5	13.3
S.D.	3.3	0.9	2.5

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : After culled (F1 males)

Sex : Male

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Body weight g	Thyroid-RL	
		AB mg	RE mg/100g
2101M01	39.4	5.1	12.9
2102M01	37.9	5.2	13.7
2103M01	34.1	2.8	8.2
2104M01	35.6	5.4	15.2
2105M01	37.3	5.1	13.7
2106M01	32.9	3.1	9.4
2107M01	37.0	3.9	10.5
2108M01	28.2	3.0	10.6
2109M01	37.4	4.1	11.0
2110M01	30.0	5.9	19.7
2111M01	32.5	3.6	11.1
2112M01	34.6	5.3	15.3
n	12	12	12
Mean	34.7	4.4	12.6
S.D.	3.4	1.1	3.2

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : After culled (F1 males)

Sex : Male

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Body weight g	Thyroid-RL	
		AB mg	RE mg/100g
3101M01	39.0	4.1	10.5
3102M01	34.9	3.3	9.5
3103M01	30.3	4.0	13.2
3104M01	32.1	2.6	8.1
3105M01	34.6	3.8	11.0
3106M01	32.2	3.3	10.2
3107M01	32.9	5.0	15.2
3108M01	29.2	4.2	14.4
3109M01	35.2	3.6	10.2
3110M01	33.2	4.8	14.5
3111M01	39.8	5.6	14.1
3112M01	31.7	6.1	19.2
n	12	12	12
Mean	33.8	4.2	12.5
S.D.	3.2	1.0	3.1

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : After culled (F1 males)

Sex : Male

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Body weight g	Thyroid-RL	
		AB mg	RE mg/100g
4101M01	33.1	5.5	16.6
4102M01	33.8	4.8	14.2
4103M01	34.7	2.2	6.3
4104M01	33.5	4.4	13.1
4105M01	30.9	2.4	7.8
4106M01	32.0	3.3	10.3
4107M01	38.8	6.1	15.7
4108M01	33.7	4.6	13.6
4109M01	30.9	4.9	15.9
4110M01	30.3	3.8	12.5
4111M01	36.0	4.2	11.7
4112M01	23.9	5.0	20.9
n	12	12	12
Mean	32.6	4.3	13.2
S.D.	3.6	1.2	4.0

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : After culled (F1 females)

Sex : Female

Dose : Cinchona Bark Extract 0 mg/kg

Species : Rat

Animal No.	Body weight g	Thyroid-RL	
		AB mg	RE mg/100g
1101F01	34.3	3.3	9.6
1102F01	32.3	5.1	15.8
1103F01	36.2	4.3	11.9
1104F01	29.3	4.8	16.4
1105F01	28.9	6.0	20.8
1106F01	32.3	3.1	9.6
1107F01	35.6	3.8	10.7
1108F01	33.4	4.1	12.3
1109F01	31.1	4.5	14.5
1110F01	36.8	4.9	13.3
1111F01	37.9	4.2	11.1
1112F01	32.9	4.6	14.0
n	12	12	12
Mean	33.4	4.4	13.3
S.D.	2.9	0.8	3.2

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : After culled (F1 females)

Sex : Female

Dose : Cinchona Bark Extract 100 mg/kg

Species : Rat

Animal No.	Body weight g	Thyroid-RL	
		AB mg	RE mg/100g
2101F01	35.0	5.3	15.1
2102F01	33.5	4.5	13.4
2103F01	34.5	2.6	7.5
2104F01	33.9	3.0	8.8
2105F01	38.4	5.0	13.0
2106F01	31.2	4.9	15.7
2107F01	34.6	3.6	10.4
2108F01	28.3	5.1	18.0
2109F01	36.7	5.4	14.7
2110F01	30.6	3.2	10.5
2111F01	32.5	3.5	10.8
2112F01	34.8	4.8	13.8
n	12	12	12
Mean	33.7	4.2	12.6
S.D.	2.7	1.0	3.1

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : After culled (F1 females)

Sex : Female

Dose : Cinchona Bark Extract 300 mg/kg

Species : Rat

Animal No.	Body weight g	Thyroid-RL	
		AB mg	RE mg/100g
3101F01	30.2	6.2	20.5
3102F01	31.2	3.1	9.9
3103F01	29.3	3.6	12.3
3104F01	33.3	3.8	11.4
3105F01	36.2	4.1	11.3
3106F01	32.7	3.2	9.8
3107F01	32.2	6.0	18.6
3108F01	30.6	4.4	14.4
3109F01	30.8	4.4	14.3
3110F01	29.4	4.1	13.9
3111F01	37.6	5.3	14.1
3112F01	32.2	4.7	14.6
n	12	12	12
Mean	32.1	4.4	13.8
S.D.	2.6	1.0	3.2

AB : Absolute weight, RE : Relative weight by body weight

Organ weight

Stage : After culled (F1 females)

Sex : Female

Dose : Cinchona Bark Extract 1000 mg/kg

Species : Rat

Animal No.	Body weight g	Thyroid-RL	
		AB mg	RE mg/100g
4101F01	28.4	5.2	18.3
4102F01	33.1	5.0	15.1
4103F01	34.7	3.0	8.6
4104F01	31.8	5.7	17.9
4105F01	30.2	2.1	7.0
4106F01	33.8	3.3	9.8
4107F01	36.8	4.8	13.0
4108F01	30.8	4.3	14.0
4109F01	30.5	3.5	11.5
4110F01	32.2	4.6	14.3
4111F01	36.4	4.6	12.6
4112F01	27.7	5.5	19.9
n	12	12	12
Mean	32.2	4.3	13.5
S.D.	2.9	1.1	4.0

AB : Absolute weight, RE : Relative weight by body weight

信頼性保証書（1/3）

試験番号：

試験表題： キナ抽出物：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に従って実施されたことを保証致します。

なお、一部委託部分（被験物質のろ過作業及び投与液の濃度分析、ホルモン測定）については各試験場所信頼性保証部門により保証されていることを確認致しております。

- ・ 「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、
環企発第 110331010 号）

なお、調査は下記の通り実施し、報告致しました。

試験の調査

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			
試験計画書変更書（1）			
調製・保存（被験物質）			
試料の発送（投与液）			
群分け			
作業予定表・ コンピュータプロトコール			
改善確認			
膺垢検査、投与・一般状態の観察			
詳細な一般状態の観察			
交配			
尿検査（尿量・色調・定性・沈渣）			
分娩・哺育観察			
摂水量測定			

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
機能検査・握力測定・ 自発運動量測定			
採血（生後 4 日出生児）			
採血・剖検（雄）			
哺育児数調整			
病理組織学検査（切り出し）			
乳頭及び乳輪数の観察			
剖検（生後 13 日出生児）			
剖検（母動物）			
生データ			
図・表・付表			
改善確認			
最終報告書草案			
改善確認			
最終報告書			



信頼性保証書 (3/3)

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				
検疫・馴化				
体重・摂餌量測定				
生体試料の発送				
血液学検査・凝固系 検査・血液化学検査				
病理組織学検査 (包埋・薄切・染色・ 鏡検)				