

Exp. No. 6393 (115-164)
FINAL REPORT

最 終 報 告 書

1,2-ビス(2-クロロエトキシ)エタンのラットを用いる28日間反復投与毒性試験

試験番号：6393 (115-164)

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1. 要約

1,2-ビス(2-クロロエトキシ)エタンの反復投与毒性を明らかにするため、Crj:CD(SD)IGS 系ラットを用いた 28 日間反復投与毒性試験を実施した。

ラットは 1 群雌雄各 5 匹で 4 試験群、対照群および高用量群には雌雄各 5 匹の回復群を設け、計 60 匹を使用した。

被験物質をコーンオイルに溶解して、0, 50, 100 および 200 mg/kg に相当する量を毎日 1 回、28 日間 (4 週間) 反復経口投与し、一般状態の観察、体重および摂餌量測定、機能観察総合検査 (FOB)、血液学検査、血液凝固能検査、血液生化学検査、尿検査、器官重量測定および病理学検査を行った。なお、回復期間は 2 週間とし、機能観察総合検査 (FOB) を除いて投与終了時と同様の検査を実施した。

投与期間中に、200 mg/kg 群の雄の 1 例が死亡した。

一般状態では、流涎が各投与群で観察されたが、被験物質投与による条件反射と考えられた。また、自発運動低下、削瘦、立毛、被毛の汚れおよび異常呼吸音が 200 mg/kg 群の雄の死亡あるいは切迫解剖した動物に観察された。

体重、摂餌量、飼料効率、血液学検査、血液凝固能検査および尿検査の結果では被験物質の影響と考えられる変化は認められなかった。

血液生化学検査において 200 mg/kg 群の雄で ALT 活性およびカリウム濃度が高値、ナトリウム濃度が低値を示し、被験物質の影響と考えられた。

機能観察総合検査の症状観察では投与群で流涎が観察されたが被験物質の投与に伴う直接的な影響であり、神経毒性を示唆する変化とは考えられなかった。

器官重量測定では 100 および 200 mg/kg 群の雌の肝臓相対重量が高値を示し、被験物質の影響と考えられた。

病理組織学検査では、200 mg/kg 群の雌雄の心臓に心筋細胞の変性・壊死ならびにこれに対する細胞反応が認められたが、回復傾向を有する変化であった。

以上のように、雄では 200 mg/kg 群で死亡例がみられ、心臓に心筋細胞の変性・壊死が観察された。雌では 100 mg/kg 群で肝臓相対重量の高値が認められた。したがって、本試験条件下における 1,2-ビス(2-クロロエトキシ)エタンのラットに対する無影響量は、雄で 100 mg/kg/day、雌で 50 mg/kg/day と判断された。

13. 被験物質

被験物質に関する情報を以下に示した。被験物質の品質試験成績書は『Reference data 1』に示した。

13.1. 被験物質名

1,2-ビス(2-クロロエトキシ)エタン

13.2. CAS No.

112-26-5

13.3. ロット番号

13.4. 純度

99.7 wt%

13.5. 提供元

13.6. 入手年月日

平成 14 年 3 月 11 日

13.7. 保存条件

室温

13.8. 保存場所

安評センター被験物質保管庫 (A-3)

13.9. 化学名

1,2-Bis(2-chloroethoxy)ethane

13.10. 示性式

ClCH2CH2OCH2CH2OCH2CH2Cl

13.11. 分子量

187.07

13.12. 性状

無色透明液体

13.13. 沸点

237°C

13.14. 融点

-32°C

13.15. 溶解性

水：不溶，アセトン：易溶，DMSO：易溶

13.16. 安定性

通常の取り扱い条件では安定

13.17. 取り扱い上の注意

吸入，皮膚への直接接触を避けるため取り扱い時には，マスクおよびゴム手袋を着用すること。

13.18. 被験物質保存および残余被験物質の処理

投与終了後，2 g を保存し，残りは提供元に返却した。

14. 試験材料および方法

14.1. 供試動物

供試したラット Crj:CD(SD)IGS[SPF]は日本チャールス・リバー株式会社 厚木飼育センターから平成 15 年 2 月 19 日に 4 週齢で雌雄各 42 匹、計 84 匹を入荷した。

動物を検収し試験環境に 9 日間馴化後、平成 15 年 2 月 28 日に 5 週齢で投与を開始した。

投与開始時の体重は、雄で 148~170 g、雌で 124~138 g であった。なお、余剰動物は炭酸ガスにより安楽死させた。

14.2. 試験系の選択理由

反復投与試験に繁用されている動物種の一つであるラットを選択した。系統は背景データの保有量、既知化学物質に対する感受性、遺伝的安定性を考慮して選んだ。

14.3. 飼育管理

14.3.1. 飼育環境

動物はバリアシステムの 122 号飼育室 (W 4.2 × D 8.9 × H 2.5 m, 93.5 m³) で飼育し、環境調節の基準値は温度 23±3°C (実測値: 21.9~23.9°C)、湿度 55±20% (実測値: 52~70%)、換気回数 1 時間 20 回、照明 150~300 lx、12 時間 (午前 7 時点灯、午後 7 時消灯) とした。

株式会社東京技研サービスの水洗式飼育機を使用し、アルミ製前面・床ステンレス網目飼育ケージ (W 20.0 × D 28.2 × H 18.0 cm, 10152 cm³) に動物を 1 匹ずつ収容し、飼育ケージは隔週 1 回、給餌器は週 1 回取り換えた。

14.3.2. 飼料

動物には放射線滅菌ラット、マウス固型飼料 CRF-1 (オリエンタル酵母工業株式会社) を飼育期間中、自由に摂取させた。使用した飼料の汚染物質の分析は、ロット番号 (Lot No. 020802, 021105) 毎に財団法人日本食品分析センターに依頼し実施した結果、日本実験動物飼料協会案の許容基準値内であることが確認された。なお、結果を『Reference data 2』に示した。

14.3.3. 給水

動物には水道水を自動給水ノズルより自由に摂取させた。水道水の水質について、水道法に基づく水道水の分析を 3 カ月に 1 回、株式会社エコブ

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ロ・リサーチに依頼し実施した。その結果、飲水中の有害物質量は水道水基準（平成4年12月21日厚生省令第69号および平成14年3月27日厚生労働省令第43号）の基準値内であることが確認された。なお、結果を『Reference data 3』に示した。

14.4. 群分け

群分けは検疫・馴化期間終了時に行った。動物は搬入後、一般状態を観察し、体重測定は搬入時と検疫・馴化期間終了時に測定した。なお、1例に異常が認められたため群分け対象から除外した。

動物はあらかじめ体重によって層別化し、無作為割り付け法により各試験群を構成するように割り付けた。

14.5. 個体識別

動物の個体識別は、機能観察総合検査（Functional Observational Battery : FOB）を盲検法で実施するため以下の方法で行った。動物入荷時に雌雄別に通し番号を割り付け、検疫・馴化期間中に動物の耳介にその通し番号（仮動物番号）を入れ墨した。群分け時に仮動物番号カードと群分け後の動物識別番号カード（IDカード）を用意し、群分け終了時に動物識別番号カードを表にし、対となる仮動物番号カードと重ね、個体別飼育ケージに付けて動物を識別した。機能観察総合検査以外の観察、測定および検査は動物識別番号に基づき実施した。

14.6. 試験群の構成および投与量設定理由

14.6.1. 試験群の構成

| 試験群 | 投与量 (mg/kg) | 性 | 動物数 | 投与期間終了時 解剖動物番号 | 回復期間終了時 解剖動物番号 |
|-----|----------------|---|-----|-------------------|-------------------|
| 1 | 0 | 雄 | 10 | 1001~1005 | 1006~1010 |
| | | 雌 | 10 | 2001~2005 | 2006~2010 |
| 2 | 50 | 雄 | 5 | 1101~1105 | — |
| | | 雌 | 5 | 2101~2105 | — |
| 3 | 100 | 雄 | 5 | 1201~1205 | — |
| | | 雌 | 5 | 2201~2205 | — |
| 4 | 200 | 雄 | 10 | 1301~1305 | 1306~1310 |
| | | 雌 | 10 | 2301~2305 | 2306~2310 |

14.6.2. 投与量設定理由

投与量設定のための2週間反復投与試験を0, 30, 75および150 mg/kgの4用量で実施した結果、150 mg/kg群の雌雄において自発運動低下および

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流涎が観察された。また、150 mg/kg 群の雄で肝臓の絶対重量が高値傾向および相対重量が高値を示した。雌では腎臓相対重量が高値を示した。しかし、いずれも十分な毒性影響の発現ではなかった。そこで、再度 1 週間の投与予備試験を 0, 200, 300 および 500 mg/kg の 4 用量で実施した。

その結果、500 mg/kg 群の雌雄の全例が死亡した。300 mg/kg 群の雌雄においては自発運動低下および流涎が観察され、雌の 3 例中 1 例が死亡した。また、雌雄とも体重増加量が対照群に比較して低値を示した。200 mg/kg 群の雌雄においては自発運動低下および流涎が観察されたが死亡例はみられなかった。したがって、28 日間反復投与毒性試験では被験物質の毒性影響を確認するために最高用量を 200 mg/kg とし、以下公比 2 で除して中用量を 100 mg/kg、低用量を 50 mg/kg と設定した。

14.7. 投与経路選択理由および投与方法

被験物質の投与経路は OECD テストガイドライン (407) に示されている胃ゾンデを用いての強制経口投与とした。

投与液量は体重 100 g 当たり 0.5 mL とし、毎日 1 回投与した。

なお、対照群にはコーンオイルのみを投与した。

14.8. 投与液の調製

被験物質の濃度が 10, 20 および 40 mg/mL となるように、コーンオイル（ナカライトスク株式会社、Lot No. V2P1660）に溶解した。投与液の調製は毎週 1 回実施し、1 日分ずつ小分けして冷蔵庫に保存した。なお、コーンオイル中の被験物質は冷蔵 7 日+室温 24 時間安定であることが急性毒性試験 [試験番号 6391 (115-162)] で確認されている。

14.9. 投与期間

投与期間は、雌雄ともに 28 日間（4 週間）とし、投与期間終了後に対照群および 200 mg/kg 群について 14 日間の回復試験を実施した。

14.10. 投与液中の被験物質濃度分析

被験物質投与群の全ての投与液について適切に調製されていることを確認するため、初回および最終調製時の各投与液の一部 (n=3) を分取し、被験物質濃度分析を行った。初回調製時は設定濃度の 103.1～107.6% および最終調製時は 102.9～109.7% であり、適切に調製されていることが確認された。なお、濃度分析の方法および結果を『Reference data 4』に示した。

15. 観察、測定および検査

15.1. 一般状態の観察

全動物について投与期間は毎日 2 回（投与前および投与後 1 時間以内）、回復期間は午前および午後に観察し、所見を記録した。

15.2. 体重

全動物について投与開始日、投与 3, 7, 10, 14, 17, 21, 24 および 27 日、回復 3, 7, 10 および 13 日に電子天秤 PM3000（メトラー・トレド社）を用いて測定し、記録した。

15.3. 摂餌量

全動物について投与 7, 14, 21 および 27 日、回復 7 および 13 日に残餌量を電子天秤 PM3000（メトラー・トレド社）を用いて測定し、平均摂餌量 (g/day) および飼料効率 (%) を算出した。

15.4. 機能観察総合検査 (FOB)

回復群の動物を除く各群 5 匹の動物について盲検法で行った。以下の FOB の内、詳細な症状観察は投与開始前に 1 回および投与開始後は週 1 回行った。種々の刺激に対する運動感覚反応の観察、握力測定、着地開足幅測定および自発運動測定は投与開始前および投与終了日に行った。なお、投与期間中は投与後 1 時間に検査を行った。

投与開始前の検査は、仮動物番号の若い順に動物を飼育管理者から FOB の実施者に引き渡し、実施した。投与期間中の検査は、飼育管理者が個体別飼育ケージから動物識別番号カード (ID カード) を外し、仮動物番号の若い順に検査の実施者に引き渡し、実施した。飼育管理者は、検査を行わなかった。検査が終了し、検査の実施者が飼育室から退室した後、飼育管理者が仮動物番号と動物標識番号の対比表に基づき、個体別飼育ケージに動物識別番号カードを付けた。

検査項目は次の通りとした。なお、詳細な症状観察および種々の刺激に対する運動感覚反応の観察の結果を総括表および個体別表にまとめる際に使用した用語とその略語は『Reference data 5』に示した。

15.4.1. 詳細な症状観察

ケージ内

| | | |
|------|-----|------|
| 姿勢 | 身悶え | 旋回 |
| 咬み行動 | 痙攣 | 異常発声 |

ケージ外

| | | | |
|------|-------|--------|-----|
| 出し易さ | 扱い易さ | 異常発声 | 筋緊張 |
| 立毛 | 被毛の状態 | 眼瞼状態 | 咬傷 |
| 流涙 | 流涎 | 呼吸 | 眼球 |
| 可視粘膜 | 尿失禁 | カタレプシー | |

オープンフィールド上

| | | | |
|--------|-------|------|------|
| 空中正向反射 | 呼吸 | 協調運動 | 痙攣 |
| 眼瞼状態 | 立ち上がり | 常同行動 | 異常行動 |
| 異常発声 | 移動量 | 覚醒度 | 脱糞 |
| 排尿 | | | |

15.4.2. 種々の刺激に対する運動感覚反応の観察

| | | | | |
|------|------|------|------|------|
| 瞳孔反射 | 接近反応 | 触覚反応 | 聴覚反応 | 痛覚反応 |
|------|------|------|------|------|

15.4.3. 握力（前後肢）

前後肢の握力についてはデジタルパッシュプルゲージ（アイコーベンジニアリング）を用いて投与前は入荷動物全例、投与終了時はFOB実施動物についてそれぞれ2回測定し、平均値を算出した。

15.4.4. 着地開足幅測定

投与前は入荷動物全例、投与終了時はFOB実施動物について行った。動物の左右後肢の裏に耳介插入墨用の墨汁を塗り、30cmの高さから正向位で用紙の上に落下させた。着地した左右足跡間の距離を測定し、2回の平均値を算出した。

15.4.5. 自発運動量測定

CAS（東洋産業株式会社）を用いて投与前は入荷動物全例、投与終了時はFOB実施動物についてFOBの終了後速やかに個別に測定を開始した。データの収集間隔は10分間隔とし、測定時間は1時間とした。測定環境の照明は点灯状態、測定室の騒音レベルはホワイトノイズ発生装置（PA-1、永島医科器械株式会社）でおよそ70dBに保ち、普通騒音計（NA-20、リオン株式会社）を用いて測定し、記録した。

15.5. 臨床検査

血液学検査、血液凝固能検査および血液生化学検査は、投与期間終了時および回復期間終了時の全生存動物について実施した。尿検査については投与期間終了週および回復期間終了週の全生存動物について実施した。

採血するに当たり、動物を絶食させるため検査前日の午後5時に給餌器

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を取り除いた。動物をエーテル麻酔下で開腹し、腹部大動脈から採血した。

15.5.1. 血液学検査

抗凝固剤 (EDTA-2K) 入り採血管インセパック-E (積水化学工業株式会社) に新鮮血を採取し、総合血液学検査装置 ADVIA120 (バイエル社) で下記の項目を測定した。

| 項目名 | 略語名 | 単位 | 測定法 |
|------------|-------------------------------|---------------------------|---------------|
| ヘマトクリット値 | HCT | % | RBC, MCV より算出 |
| ヘモグロビン量 | HGB | g/dL | シアノメトヘモグロビン法 |
| 赤血球数 | RBC | $\times 10^6/\text{mm}^3$ | 暗視野板法 |
| 平均赤血球容積 | MCV | μm^3 | 暗視野板法 |
| 平均赤血球血色素量 | MCH | pg | HGB, RBC より算出 |
| 平均赤血球血色素濃度 | MCHC | % | HGB, HCT より算出 |
| 血小板数 | PLT | $\times 10^3/\text{mm}^3$ | 暗視野板法 |
| 白血球数 | WBC | $\times 10^3/\text{mm}^3$ | フローサイトメトリー |
| 白血球百分率 | Differential leukocyte counts | % | |
| 網赤血球率 | Reticulocyte | % | RNA 染色法 |

15.5.2. 血液凝固能検査

抗凝固剤 (3.13%クエン酸ナトリウム水溶液) 入り採血管ベノジェクトII (テルモ株式会社) に血液を採取した後、3000 r.p.m. で 13 分間遠心分離して得た血漿を検査に用いた。全自動血液凝固線溶測定装置 STA Compact (ロシュ社) を用いて下記の項目を測定した。

| 項目名 | 略語名 | 単位 | 測定法 |
|------------------|------------|-------|----------|
| プロトロンビン時間 | PT | sec. | 粘度変化検知方式 |
| 活性化部分トロンボプラスチン時間 | APTT | sec. | |
| フィブリノーゲン | Fibrinogen | mg/dL | |

15.5.3. 血液生化学検査

採血管インセパック-SQ (積水化学工業株式会社) に血液を採取した後、3000 r.p.m. で 7 分間遠心分離して得た血清を検査に用いた。多項目生化学自動分析装置日立 7170 (株式会社日立製作所) および電解質測定装置 EA06R (株式会社アットウイル) で下記の項目を測定した。

| 項目名 | 英語名 | 単位 | 測定法 |
|-------|------------|------|----------|
| 総蛋白 | T. protein | g/dL | Biuret 法 |
| アルブミン | Albumin | g/dL | BCG 法 |

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| A/G | A/G | - | 計算値 |
|-------------------------|----------------|--------|-----------------------------------|
| 血糖 | Glucose | mg/dL | HK-G-6-PDH 法 |
| 中性脂肪 | Triglyceride | mg/dL | GK-GPO 遊離グリセロール消去法 |
| 総コレステロール | T. cholesterol | mg/dL | コレステロールオキシターゼ HDAOS 法 |
| 尿素窒素 | BUN | mg/dL | ウレアーゼ GLDH 法 |
| クレアチニン | Creatinine | mg/dL | 酵素法 |
| 総ビリルビン | T. bilirubin | mg/dL | バナジン酸酸化法 |
| アスパラギン酸 アミノトランスフェラーゼ | AST | U/L | 酵素-UV 法 (JSCC 準拠) |
| アラニンアミノ トランスフェラーゼ | ALT | U/L | 酵素-UV 法 (JSCC 準拠) |
| アルカリホスファターゼ | ALP | U/L | P-ニトロフェニルリン酸基質法 (JSCC 準拠) |
| γ-グルタミル トランスペプチダーゼ | Gamma-GTP | U/L | L-γ-グルタミル-3-カルボキシ-4NA 法 (JSCC 準拠) |
| カルシウム | Calcium | mg/dL | MXB 法 |
| 無機リン | I. phosphorus | mg/dL | PNP-XDH 法 |
| ナトリウム* | Sodium | mmol/L | イオン選択電極法 |
| カリウム* | Potassium | mmol/L | イオン選択電極法 |
| 塩素* | Chloride | mmol/L | イオン選択電極法 |

*印の項目は EA06R で、他は日立 7170 で測定した。

15.5.4. 尿検査

絶食・絶水の条件下で採尿ケージを用いて一夜尿（午後 4 時から翌日午前 9 時まで）を採取した。採尿に先立ち、水道水を 20 mL/kg 強制経口投与した。

次の項目について検査した。尿浸透圧は、自動浸透圧測定装置 Auto&stat OM-6030 (株式会社アークリイファクトリー) で測定した。

尿を卓上多本架遠心機 LC06-SP (株式会社トミー精工) を用いて、室温、1500 r.p.m. で 5 分間遠心し、上清および残渣に分離した。残渣を用いてステルンハイマー変法により染色を施し、尿沈渣標本を作製して鏡検した。

| 項目名 | 英語名 | 単位 | 測定法 |
|------|------------------|---------|-------|
| 尿量 | Volume | mL | 計量 |
| 色調 | Color | - | 目視 |
| 沈渣 | Sediment | - | 鏡検 |
| 尿浸透圧 | Osmotic Pressure | mOsm/kg | 氷点降下法 |

また、下記の項目は N-マルティスティックス SG (バイエル メディカル

株式会社) を用い、尿分析装置 CLINITEK 500 (バイエル社) で判定した。

| 項目名 | 英語名 | 測定法 |
|----------|--------------|------|
| pH | pH | 試験紙法 |
| 潜血 | Occult Blood | |
| ケトン体 | Keton bodies | |
| 糖 | Glucose | |
| 蛋白 | Protein | |
| ビリルビン | Bilirubin | |
| ウロビリノーゲン | Urobilinogen | |

15.6. 病理学検査

病理学検査では、器官重量測定、肉眼観察および病理組織学検査を行った。動物をエーテル麻酔し、採血した後に解剖した。また、切迫動物は発見後直ちに解剖した。

15.6.1. 器官重量測定

計画解剖動物の心臓、肝臓、脾臓、腎臓、副腎、精巣、卵巣、脳、胸腺、精巣上体および子宮の重量を電子天秤 PE160 (メトラー・トレド社) を用いて測定した。器官重量／体重比 (相対重量) は解剖当日に測定した体重および器官重量から算出した (絶対重量／最終体重 × 100)。

15.6.2. 肉眼観察

解剖では動物の体表、体腔および諸器官について観察し、全ての肉眼所見を記録した。

15.6.3. 固定

リンパ節 (腸間膜、下頸)、骨髓 (大腿骨)、胸腺、気管、肺 (気管支を含む)、心臓、甲状腺、下頸腺、胃、十二指腸、空腸、回腸 (バイエル板を含む)、盲腸、結腸、直腸、脾臓、肝臓、脾臓、腎臓、副腎、膀胱、精嚢、前立腺、精巣、精巣上体、卵巣、子宮、腎、脳、眼球 (視神経を含む)、下垂体、脊髓 (頸部、胸部、腰部)、骨格筋 (大腿部) および坐骨神経を 10% 中性緩衝ホルマリン液で固定した。なお、精巣はホルマリン・酢酸液 (FA 液) で固定した後、10% 中性緩衝ホルマリン液で固定した。

解剖後、保存を要さない屍体残存部は速やかに焼却した。

15.6.4. 病理組織学検査

病理組織標本は全試験群全例の上記の器官・組織について常法に従ってパラフィン包埋、薄切後、ヘマトキシリン・エオジン (H.E.) 染色標本を作製した。なお、脾臓は対照群および 200 mg/kg 群の雌雄のみ病理組織標

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本を作製した。

鏡検では、対照群および高用量群の上記器官および組織について実施し、病変の種類および程度を含む各所見について記録した。なお、200 mg/kg 群の雌雄の心臓に被験物質投与の影響が認められたことから心臓については 50 および 100 mg/kg 群についても観察した。

15.6.5. 電子顕微鏡検査

200 mg/kg 群の雄の死亡動物（動物番号 1303）ならびに投与期間終了時の投与後に切迫解剖した動物（動物番号 1301）では、肝臓に肝細胞の有糸分裂、好酸性小体、脂肪化あるいは肝細胞肥大ならびにうつ血が観察され、うつ血を除けば肝細胞への障害を示す所見と考えられた。しかし、投与終了時、200 mg/kg 群の雌雄の生存動物には肝臓に病理組織学的に特記すべき所見は認められなかった。したがって、死亡動物ならびに切迫解剖動物に認められた肝臓の所見は状態が悪くなった動物あるいは症状が顕著に表れた動物における特異的な変化であり、当被験物質の反復投与による影響ではないと考えられた。よって、肝臓の電子顕微鏡用エポン包埋標本を作製したが、電子顕微鏡観察は行わなかった。

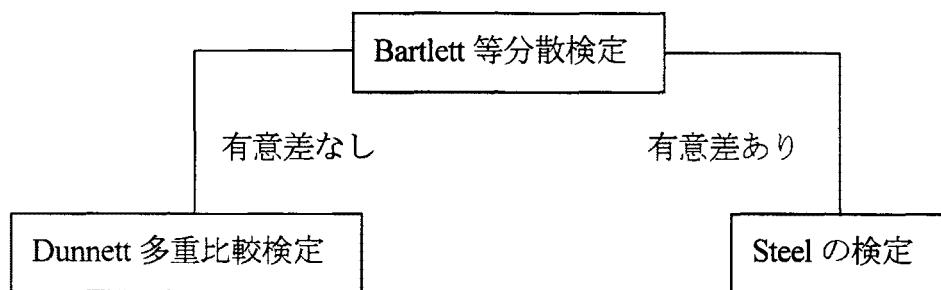
15.7. データ処理

本試験のコンピュータを用いる諸データはコンピュータ・システムを用いて記録し処理した。

15.8. 統計解析

各試験群の体重、摂餌量、飼料効率、FOB 検査値（握力、着地開足幅、自発運動量、立ち上がり回数、脱糞回数、排尿回数）、血液学検査値、血液凝固能検査値、血液生化学検査値、尿検査値（尿量および尿浸透圧）、器官重量および器官重量／体重比は、下記に示した自動判別方式に従い、最初に Bartlett の等分散検定¹⁾を実施した。等分散の場合は Dunnett の多重比較検定²⁾で対照群と各投与群間の有意差を検定した。Bartlett の等分散検定で不等分散の場合は Steel の検定³⁾で対照群と各投与群間の有意差を検定した。上記定量値の有意水準は 5% および 1% の両側検定で実施した。

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また、立ち上がり、脱糞および排尿を除く詳細な症状観察ならびに種々の刺激に対する運動感覚反応の観察の各項目、生存率および病理学検査結果の検定は Fisher の正確検定法⁴⁾を用いた。

16. 試験結果

16.1. 死亡率

生存率を Figure 1 に、生存数および死亡率を Table 1 に示した。

投与期間中、200 mg/kg 群の雄の 1 例（動物番号 1303）が投与後 9 日に死亡した。

回復期間中には対照群および 200 mg/kg 群の雌雄で死亡例は認められなかつた。

16.2. 一般状態の観察

一般状態の観察所見を Table 2 および Appendix 1 に示した。

投与期間中に、流涎が 100 および 200 mg/kg 群の雌雄で投与 1 日以降に、また、50 mg/kg 群の雄で投与 10 日以降、雌で投与 12 日以降に観察された。

発生数は 50, 100 および 200 mg/kg 群の雄で 2, 4 および 10 例、雌で 1, 4 および 10 例であった。死亡動物（動物番号 1303）では自発運動低下が観察された。また、投与期間終了時の投与後に切迫解剖した 1 例（動物番号 1301）では自発運動低下、削瘦、立毛、被毛の汚れおよび異常呼吸音が観察された。生存動物では、外傷が 200 mg/kg 群の雄の 1 例に観察された。

回復期間中、外傷が対照群の雌および 200 mg/kg 群の雄の各 1 例に観察された。

16.3. 体重

体重を Figure 2, Table 3 および Appendix 2 に示した。

対照群に比較して各投与群の雌雄で差がみられなかつた。

16.4. 摂餌量

摂餌量を Figure 3, Table 4 および Appendix 3 に示した。

対照群に比較して各投与群の雌雄で差がみられなかつた。

16.5. 飼料効率

飼料効率を Table 5 および Appendix 4 に示した。

対照群に比較して 200 mg/kg 群の雌が投与 7 日に低値を示したが、投与 14 日以降は差がみられなかつた。

16.6. 機能観察総合検査 (FOB)

16.6.1. 詳細な症状観察および種々の刺激に対する運動感覚反応の観察

詳細な症状観察および種々の刺激に対する運動感覚反応の観察の結果を

Table 6~10 および Appendix 5~9 に示した。

投与 2 および 3 週の検査において 200 mg/kg 群の雄で対照群に比較して軽度な流涎の発生数が高値を示した。また、投与 2, 3 および 4 週の検査において流涎なしの動物数が低値を示した。その他、投与 4 週の検査において 200 mg/kg 群の雌でケージ内で腰を落として座る動物数が高値を示した。投与 1 週の検査において 200 mg/kg 群の雌でつかまり立ちの回数が低値を示した。いずれも神経毒性を示唆するものとは考えられなかった。

16.6.2. 握力（前後肢）

握力の測定結果を Table 11 および Appendix 10 に示した。

投与 4 週の結果において、雌雄の各投与群とも対照群に比較して前肢および後肢の握力に差がみられなかった。

16.6.3. 着地開足幅

着地開足幅の測定結果を Table 12 および Appendix 11 に示した。

投与 4 週の結果において、雌雄の各投与群とも対照群に比較して後肢の着地開足幅に差がみられなかった。

16.6.4. 自発運動量

自発運動量の測定結果を Table 13 および Appendix 12 に示した。

投与開始前の結果において、雌雄の各投与群とも対照群に比較して自発運動量に差がみられなかった。

投与 4 週の結果において、対照群に比較して 200 mg/kg 群の雄で自動運動量の低値が認められた。

16.7. 血液学検査

血液学検査結果を Table 14 および Appendix 13 に示した。

投与期間終了時：対照群に比較して 200 mg/kg 群の雄ではヘマトクリット値が高値および MCHC が低値を示した。また、雌雄で網赤血球率が低値を示した。

回復期間終了時：対照群に比較して 200 mg/kg 群の雄で MCV および血小板数が高値を示した。雌で白血球数および好中球比率が低値およびリンパ球比率が高値を示した。しかし、いずれも軽微な変化であった。

16.8. 血液凝固能検査

血液凝固能検査結果を Table 15 および Appendix 14 に示した。

投与期間終了時：対照群に比較して各投与群の雌雄で差がみられなかつ

た。

回復期間終了時：対照群に比較して雌雄の 200 mg/kg 群で差がみられなかつた。

16.9. 血液生化学検査

血液生化学検査結果を Table 16 および Appendix 15 に示した。

投与期間終了時：対照群に比較して 200 mg/kg 群の雄で ALT 活性およびカリウム濃度が高値、ナトリウム濃度が低値を示した。

回復期間終了時：対照群に比較して 200 mg/kg 群の雄で ALP 活性が、雌で血糖がいずれも低値を示した。

16.10. 尿検査

尿検査結果を Table 17 および Appendix 16 に示した。

投与期間終了時：対照群に比較して 100 mg/kg 群の雌で尿浸透圧が高値を示したが用量に関連しない変化であった。

回復期間終了時：対照群に比較して 200 mg/kg 群の雌で尿浸透圧が低値を示した。

16.11. 病理学検査

16.11.1. 器官重量

器官重量を Table 18 および Appendix 17 に示した。

投与期間終了時：対照群に比較して 100 mg/kg 群の雌で腎臓絶対重量が高値を示したが用量に関連しない変化であった。

回復期間終了時：いずれの器官においても対照群に比較して 200 mg/kg 群で雌雄とも差がみられなかつた。

16.11.2. 器官重量／体重比

器官重量／体重比（相対重量）を Table 19 および Appendix 18 に示した。

投与期間終了時：対照群に比較して 100 および 200 mg/kg 群の雌で肝臓相対重量が高値を示した。また、200 mg/kg 群の雄で腎臓および精巣相対重量が高値を示した。その他、100 mg/kg 群の雌で腎臓相対重量が高値を示したが用量に関連しない変化であった。

回復期間終了時：いずれの器官においても対照群に比較して 200 mg/kg 群で雌雄とも差がみられなかつた。

16.11.3. 肉眼観察

剖検所見を Table 20, 21 および Appendix 19 に示した。

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投与期間終了時：雌雄とも用量に関連した発生を示す所見は認められなかつた。しかし、高用量である 200 mg/kg 群で雄の 1 例（動物番号 1305）に胃の赤色斑点および精嚢の萎縮、雌の 1 例（動物番号 2305）に腎の結節が認められた。加えて、計画解剖日に切迫解剖した雄の 1 例（動物番号 1301）では、削瘦、胃の黒色斑点、脾臓および肝臓の淡色化が観察された。

その他の所見は、対照群のみの発生あるいは用量と関連のない発生であつた。

回復期間終了時：観察された所見は、いずれも対照群のみの発生あるいは用量と関連のない発生であつた。

死亡動物：投与 9 日に死亡した雄の 1 例（動物番号 1303）では、肝臓、肺および胸腺における赤色斑点、肝臓の白色斑点、胸部および下頸リンパ節の赤色化が認められた。

16.11.4. 病理組織学検査

組織所見を Table 22～26 および Appendix 20, 21 に示した。

死亡動物、投与終了時の投与後に切迫解剖した動物、投与終了時の計画解剖動物に共通して心臓に様々な所見が認められ、細胞浸潤以外の所見は当試験における対照群に認められず、さらに同週齢の無処置ラットにも認められない変化であることから被験物質投与の影響と考えられた。したがって、心臓については 50 および 100 mg/kg 群についても検索した。

投与期間終了時：心臓に認められた所見を表 I に示した。200 mg/kg 群では雌雄とも心筋細胞の変性・壊死および細胞浸潤が散見された。加えて、雄の 1 例（動物番号 1305）では線維化も伴っていた。なお、細胞浸潤は、対照群、50 および 100 mg/kg 群ではいずれも軽度であったのに対し、200 mg/kg 群の雄では軽度 1 例、中等度 3 例、同群の雌では中等度 2 例、高度 1 例であった。

50 および 100 mg/kg 群では心臓に被験物質投与の影響は認められなかつた。

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表 I.

| 性別 | 雄 | | | | 雌 | | | |
|-----------|-----------|---|----|-----|-----|---|----|-----|
| | 用量(mg/kg) | 0 | 50 | 100 | 200 | 0 | 50 | 100 |
| 動物数 | 5 | 5 | 5 | 4 | 5 | 5 | 5 | 5 |
| 心臓 | | | | | | | | |
| 心筋変性 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 3 |
| 心筋壞死 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| 細胞浸潤 | 2 | 2 | 1 | 4 | 1 | 2 | 3 | 3 |
| 線維化 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

腎臓の尿細管硝子滴が 200 mg/kg 群の雄のみに 3 例発生した。当病変は、同週齢の無処置ラット雄に発生する α_{2u} グロブリンの再吸収に起因したと考えられているいわゆる好酸性小体とその形態学的特徴（弱好酸性、不整形、周囲にハローを形成、細胞質内に占める割合が大きい）および程度に差はなかった。しかし、当試験の対照群には認められていないことから 200 mg/kg 群で好酸性小体が誘発された可能性も否定できない。

計画解剖時に切迫解剖した 200 mg/kg 群の雄の 1 例（動物番号 1301）では、他の計画解剖動物同様、心臓の中等度的心筋変性および細胞浸潤が観察されたのに加え、肝臓の肝細胞の微小空胞型脂肪化、有糸分裂および好酸性小体、肺の出血およびヘマトイジン結晶沈着、骨髓の赤血球系造血低下、脾臓の白脾髄の萎縮および赤血球系造血低下、下頸リンパ節、腸間膜リンパ節および胸腺のリンパ球の核崩壊、下頸リンパ節のリンパ洞マクロファージの単細胞壊死、十二指腸、空腸および回腸上皮細胞の空胞変性、胰臓のチモーゲン顆粒減少、腎臓の尿細管硝子滴（好酸性小体）および片側性精巣精細管の単細胞壊死ならびに精巣上体の管内細胞残屑が認められた。肺のヘマトイジン結晶沈着は限局性で軽度な病変であり、自然発生することが知られている。腎臓の尿細管硝子滴（好酸性小体）も同様に自然発生病変と特徴ならびに程度に差はなかった。精巣精細管の単細胞壊死ならびに精巣上体の管内細胞残屑については片側性の変化であることから偶発的な病変と考えられた。脾臓の白脾髄萎縮、リンパ節および胸腺におけるリンパ球の核崩壊や胰臓のチモーゲン顆粒減少は一般状態の悪化した動物にみられる非特異的変化であったが、十二指腸、空腸および回腸上皮細胞の空胞変性は本症例のみの発生であり、発現意義は不明であった。

投与終了時の生存動物で肉眼所見の認められた 200 mg/kg 群の雄の 1 例（動物番号 1305）では、前胃の水腫、出血、細胞浸潤および扁平上皮過形性、

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前立腺の単細胞壊死および精囊の分泌減少が認められたが、体重増加抑制のある動物に認められることがある非特異的、かつ軽度な変化であり、被験物質投与の直接的な影響とは考えられなかった。

その他、200 mg/kg 群のみに観察された所見は、一部に限局した軽度な自然発生ないし偶発的と考えられる所見であった。

回復期間終了時：200 mg/kg 群の雄の 1 例（動物番号 1307）の心房に軽度な線維化部位が散見されたが、心筋細胞の変性・壊死は観察されず、同群の他の動物には雌雄とも被験物質投与の影響は認められなかった。

200 mg/kg 群のみに発生した肺のマクロファージ集簇、肝臓の髄外造血および脾臓の腺房細胞の局所萎縮は、いずれも一部に限局した極めて軽度な所見であり、発生個体における系統だった所見ではないことから自然発生ないし偶発的所見と考えられた。

その他に観察された所見は、対照群のみの発生、または対照群を含めて200 mg/kg 群に発生し対照群の病変と程度に差がない所見であった。

死亡動物：心臓の心筋変性および細胞浸潤、肺のうつ血、出血、水腫およびマクロファージの集簇、肝臓の肝細胞肥大、好酸性小体、脂肪化および有糸分裂ならびにうつ血、脾臓の白脾髄萎縮、下顎および腸間膜リンパ節の濾胞萎縮、胸部および下顎リンパ節のうつ血、胸腺および脾臓の出血が観察された。

17. 考察および結論

1,2-ビス(2-クロロエトキシ)エタンを 50, 100 および 200 mg/kg の用量で CD(SD)IGS 系ラットの雌雄に 28 日間にわたって強制経口投与し、その後、14 日間の回復期間を設けた。

投与期間中に、200 mg/kg 群の雄の 1 例が死亡した。

一般状態では、流涎が各投与群で観察された。流涎は被験物質投与による条件反射と考えられた。また、自発運動低下、削瘦、立毛、被毛の汚れおよび異常呼吸音が 200 mg/kg 群の雄の死亡あるいは切迫解剖した動物に観察された。

体重、摂餌量、飼料効率、血液学検査、血液凝固能検査および尿検査の結果では被験物質の影響と考えられる変化は認められなかった。

血液生化学検査において 200 mg/kg 群の雄で ALT 活性およびカリウム濃度が高値、ナトリウム濃度が低値を示し、被験物質の影響と考えられた。

機能観察総合検査の症状観察では投与群で流涎が観察されたが被験物質の投与に伴う直接的な影響であり、神経毒性を示唆する変化とは考えられなかった。

器官重量測定では 100 および 200 mg/kg 群の雌の肝臓相対重量が高値を示した。なお、200 mg/kg 群の雄で腎臓および精巣の相対重量が高値を示したが、この群の体重の低値傾向による二次的変化と考えられた。

病理学検査では、200 mg/kg 群の雌雄の心臓に認められた病変は、心筋細胞の変性・壊死およびこれに引き続いて起こる修復反応であった。これらの投与終了時に観察された病変は投与を中止してから 14 日後には認められず回復傾向を有する変化と考えられた。心筋細胞の変性・壊死病変は散在性にみられたが、発生が 1 細胞単位であり巣状に起こることはなくマクロファージの食作用により処理可能な程度であった。修復範囲が狭かつたために回復期間終了時には病変が認められなかつたものと思われる。

死亡動物では肺にうっ血、出血および水腫が観察されたが、これは急性心不全による続発性変化であり、死因は呼吸不全と考えられた。他の臓器にみられた出血およびうっ血も直接的あるいは間接的に心臓の機能不全に起因するものと思われる。

死亡動物および投与期間終了時の投与後に切迫解剖した動物では、肝臓に肝細胞肥大あるいは有糸分裂など肝細胞への直接的な影響への反応を示す所見が観察されたが、好酸性小体とともにこれらの所見の発現意義は不

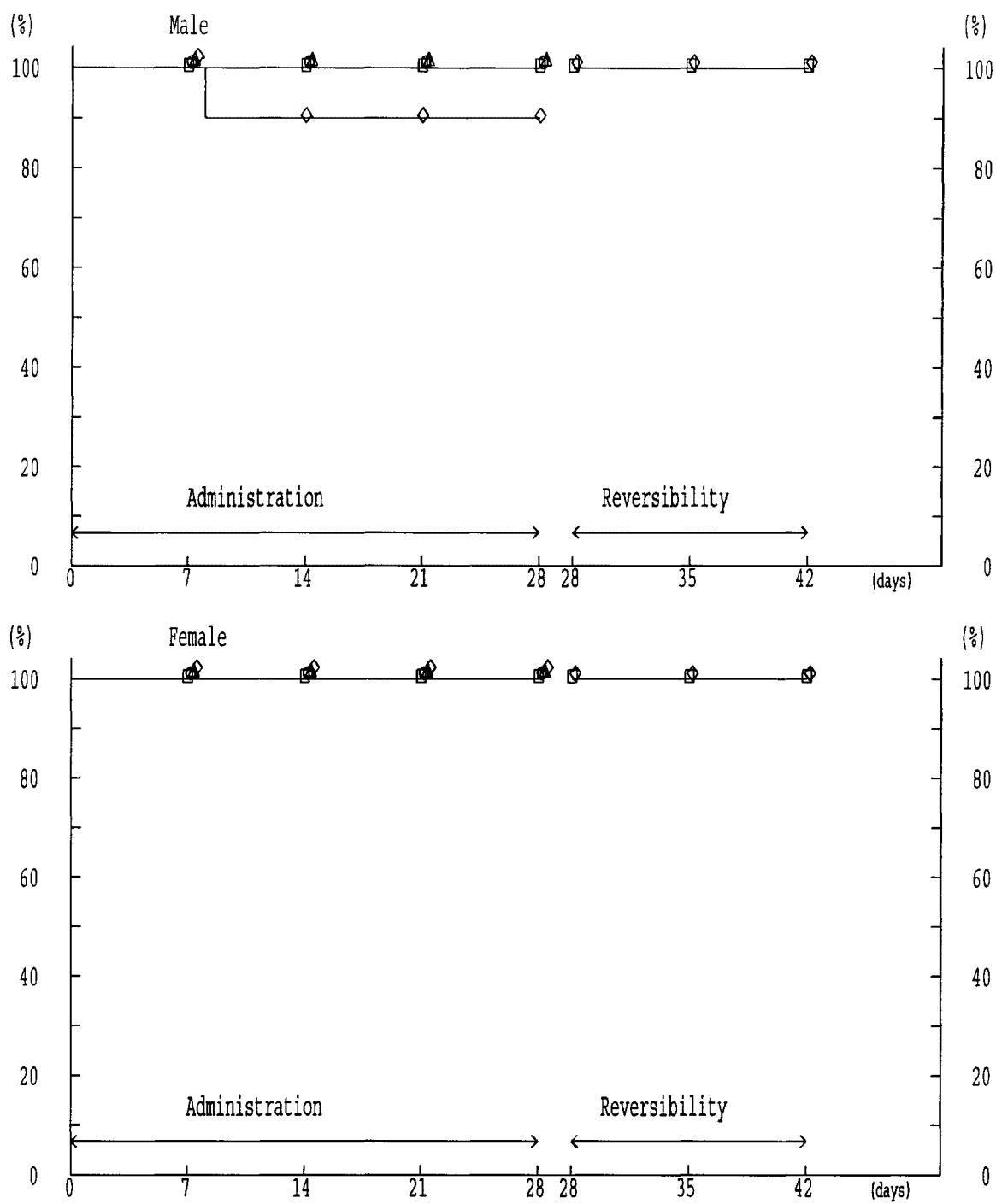
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明である。

以上のように、雄では 200 mg/kg 群で死亡例がみられ、心臓に心筋細胞の変性・壊死が観察された。雌では 100 mg/kg 群で肝臓相対重量の高値が認められた。したがって、本試験条件下における 1,2-ビス(2-クロロエトキシ)エタンのラットに対する無影響量は、雄で 100 mg/kg/day、雌で 50 mg/kg/day と判断された。

18. 参考文献

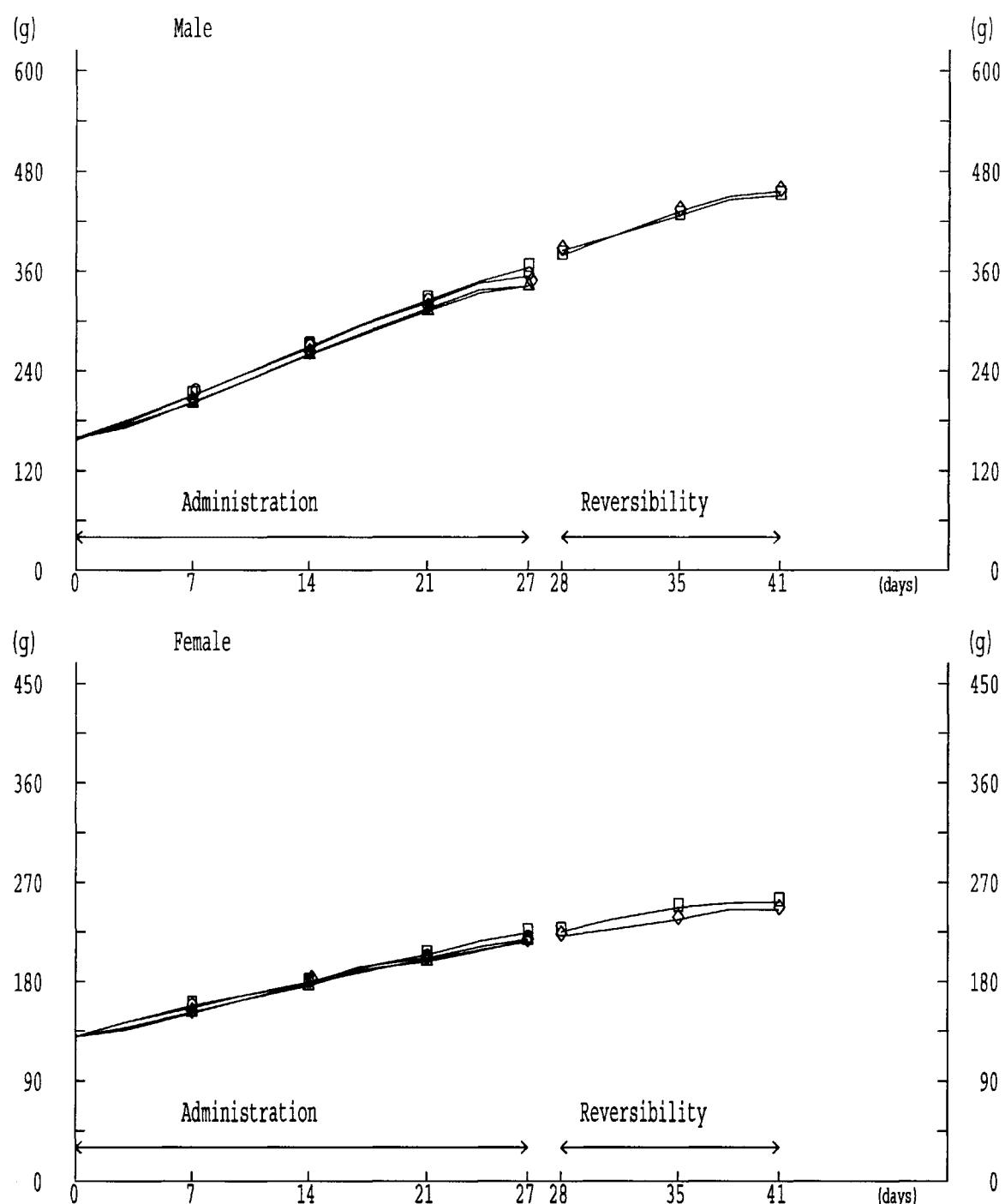
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Exp. No. 6393(115-164)

| Dose level | (mg/kg) |
|------------|---------|
| □ | 0 |
| △ | 50 |
| ▲ | 100 |
| ◇ | 200 |

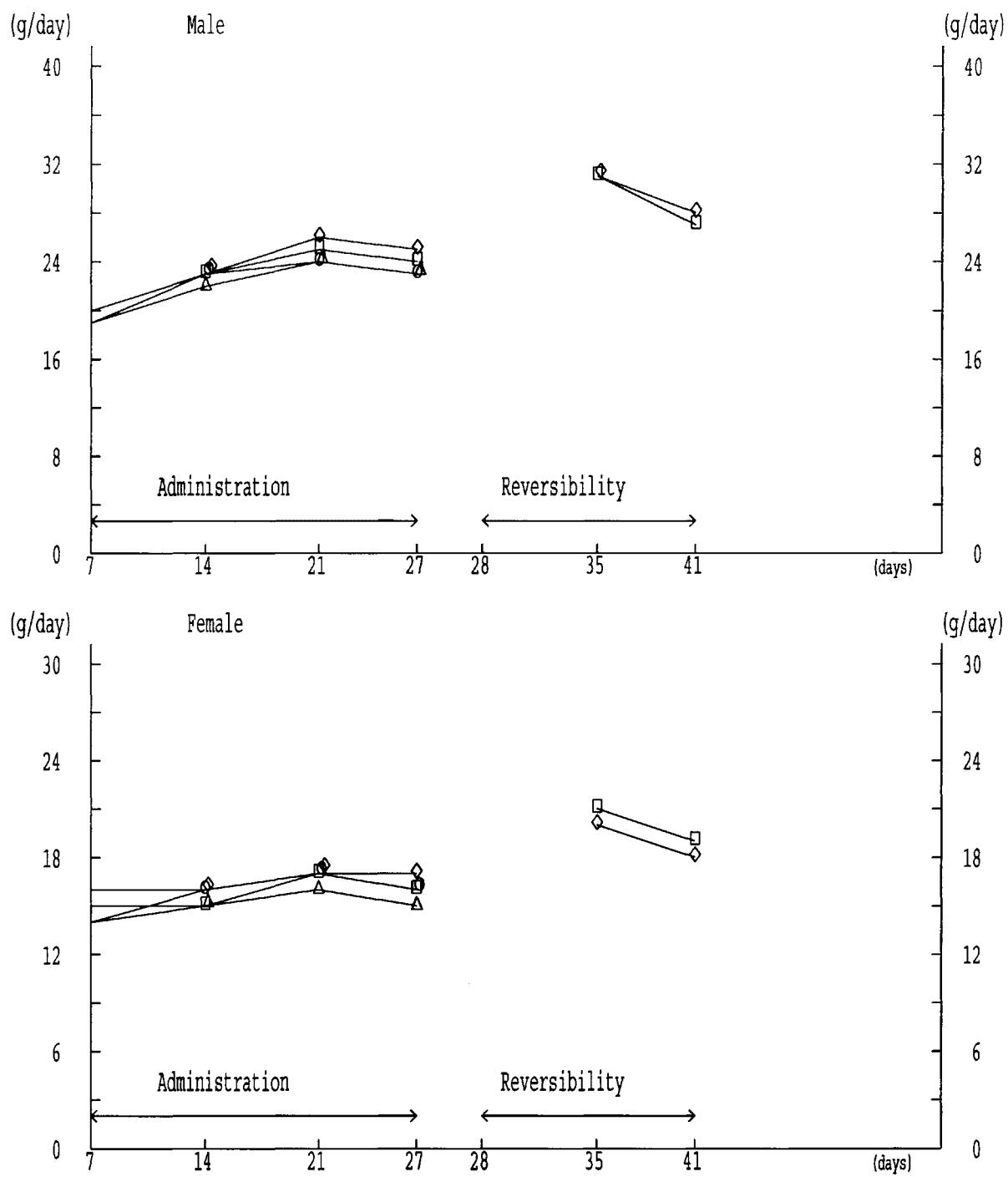
Figure 1. Survival ratio



Exp. No. 6393 (115-164)

| Dose level | (mg/kg) |
|------------|---------|
| □ | 0 |
| ■ | 50 |
| △ | 100 |
| ▲ | 200 |

Figure 2. Body weight



Exp. No. 6393(115-164)

| Dose level (mg/kg) |
|--------------------|
| 0 (□) |
| 50 (○) |
| 100 (△) |
| 200 (◇) |

Figure 3. Food consumption

Table 1. Survival and mortality

Exp. No. 6393 (115-164)

| Sex | Dose level (mg/kg) | Days of experiment | | | | | | | | | | | | |
|--------|-----------------------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| Male | 0 | 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 |
| | 50 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 100 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 200 | 10/10 | 10/10 | 10/10 | 10/10 | 10/10 | 10/10 | 10/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 |
| Female | 0 | 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 |
| | 50 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 100 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 200 | 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 surviving / Number per group.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1001

Table 1. -continued Survival and mortality

Exp. No. 6393 (115-164)

| Sex | Dose level (mg/kg) | Days of experiment | | | | | | | | | | | | |
|--------|-----------------------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| | | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 |
| Male | 0 | 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 |
| | 50 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 100 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 200 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 | 9/10 |
| Female | 0 | 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 |
| | 50 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 100 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 200 | 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 surviving / Number per group.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

T-002

Table 1. -continued Survival and mortality

Exp. No. 6393 (115-164)

| Sex | Dose level (mg/kg) | Days of experiment | | Mortality (%) |
|--------|-----------------------|--------------------|-------|------------------|
| | | 27 | 28 | |
| Male | 0 | 10/10 | 10/10 | 0.0 |
| | 50 | 5/5 | 5/5 | 0.0 |
| | 100 | 5/5 | 5/5 | 0.0 |
| | 200 | 9/10 | 9/10 | 10.0 |
| Female | 0 | 10/10 | 10/10 | 0.0 |
| | 50 | 5/5 | 5/5 | 0.0 |
| | 100 | 5/5 | 5/5 | 0.0 |
| | 200 | 10/10 | 10/10 | 0.0 |

Number surviving / Number per group.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 1. -continued Survival and mortality

Exp. No. 6393 (115-164)

| Sex | Dose level (mg/kg) | Days of experiment | | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |
|--------|-----------------------|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | 28 | 29 | 30 | | | | | | | | | |
| Male | 0 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 200 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| Female | 0 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| | 200 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |

Number surviving / Number per group.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1
0
0
4

Table 1. -continued Survival and mortality

Exp. No. 6393 (115-164)

| Sex | Dose level (mg/kg) | Days of experiment | | Mortality (%) |
|--------|-----------------------|--------------------|-----|------------------|
| | | 41 | 42 | |
| Male | 0 | 5/5 | 5/5 | 0.0 |
| | 200 | 5/5 | 5/5 | |
| Female | 0 | 5/5 | 5/5 | 0.0 |
| | 200 | 5/5 | 5/5 | |

Number surviving / Number per group.
 Significant difference from control group; *: $P \leq 0.05$ **: $P \leq 0.01$

1-005

Table 2. Clinical observation

Exp. No. 6393 (115-164)

Sex : Male

Table 2. -continued Clinical observation

Exp. No. 6393 (115-164)

Sex : Male

| Findings of clinical observation | Dose level (mg/kg) | Days of experiment | | | | | | | | | | | | | |
|----------------------------------|--------------------|--------------------|---|---|---|---|---|---|---|---|----|----|----|----|----|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| trauma/neck | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

Table 2. -continued Clinical observation

Exp. No. 6393 (115-164)

Sex : Male

| Findings of clinical observation | Dose level (mg/kg) | Days of experiment | | | | | | | | | | | | | | Total (1→28) |
|----------------------------------|--------------------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------------|
| | | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | |
| normal/number per group | 0 | 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 |
| | 50 | 3/5 | 4/5 | 4/5 | 3/5 | 3/5 | 3/5 | 3/5 | 3/5 | 5/5 | 3/5 | 3/5 | 4/5 | 3/5 | 3/5 | 3 |
| | 100 | 2/5 | 3/5 | 3/5 | 1/5 | 1/5 | 1/5 | 2/5 | 1/5 | 2/5 | 2/5 | 1/5 | 3/5 | 1/5 | 1/5 | 1 |
| | 200 | 2/9 | 0/9 | 2/9 | 0/9 | 0/9 | 0/9 | 0/9 | 0/9 | 0/9 | 1/9 | 0/9 | 0/9 | 1/9 | 1/9 | 0 |
| wasting | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| piloerection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| dirty hair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| salivation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 2 | 2 |
| | 100 | 3 | 2 | 2 | 4 | 4 | 4 | 3 | 4 | 3 | 3 | 4 | 2 | 4 | 4 | 4 |
| | 200 | 7 | 9 | 7 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 7 | 10 |
| decrease spon. motor act. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| abnormal resp. noise | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |

1-0008

Table 2. -continued Clinical observation

Exp. No. 6393 (115-164)

Sex : Male

| Findings of clinical observation | Dose level (mg/kg) | Days of experiment | | | | | | | | | | | | | | Total (1→28) |
|----------------------------------|--------------------|--------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|--------------|
| | | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | |
| trauma/neck | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| dead | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

Table 2. -continued Clinical observation

Exp. No. 6393 (115-164)

Sex : Female

| Findings of clinical observation | Dose level (mg/kg) | Days of experiment | | | | | | | | | | | | | |
|----------------------------------|-----------------------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| normal/number per group | 0 | 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 |
| | 50 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 4/5 | 5/5 | 5/5 |
| | 100 | 4/5 | 5/5 | 3/5 | 5/5 | 4/5 | 3/5 | 3/5 | 3/5 | 4/5 | 3/5 | 4/5 | 2/5 | 3/5 | 3/5 |
| | 200 | 1/10 | 10/10 | 9/10 | 10/10 | 7/10 | 6/10 | 4/10 | 1/10 | 4/10 | 4/10 | 8/10 | 3/10 | 4/10 | 2/10 |
| salivation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | 100 | 1 | 0 | 2 | 0 | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 3 | 2 | 2 |
| | 200 | 9 | 0 | 1 | 0 | 3 | 4 | 6 | 9 | 6 | 6 | 2 | 7 | 6 | 8 |
| decrease spon. motor act. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

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Table 2. -continued Clinical observation

Exp. No. 6393 (115-164)

Sex : Female

| Findings of clinical observation | Dose level (mg/kg) | Days of experiment | | | | | | | | | | | | | | Total (1→28) |
|----------------------------------|--------------------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------------|
| | | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | |
| normal/number per group | 0 | 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 |
| | 50 | 4/5 | 5/5 | 5/5 | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 4 |
| | 100 | 1/5 | 4/5 | 4/5 | 2/5 | 2/5 | 3/5 | 3/5 | 3/5 | 4/5 | 4/5 | 4/5 | 4/5 | 3/5 | 2/5 | 1 |
| | 200 | 0/10 | 2/10 | 2/10 | 0/10 | 1/10 | 1/10 | 3/10 | 2/10 | 1/10 | 3/10 | 0/10 | 3/10 | 1/10 | 4/10 | 0 |
| salivation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | 100 | 4 | 1 | 1 | 3 | 3 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 3 | 4 |
| | 200 | 10 | 8 | 8 | 10 | 9 | 9 | 7 | 8 | 9 | 7 | 10 | 7 | 9 | 6 | 10 |
| decrease spon. motor act. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

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Table 2. -continued Clinical observation

Exp. No. 6393 (115-164)

Sex : Male

| Findings of clinical observation | Dose level (mg/kg) | Days of experiment | | | | | | | | | | | | | | Total (29→42) |
|----------------------------------|--------------------|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------------------|
| | | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | |
| normal/number per group | 0 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5 |
| | 200 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4 |
| trauma/neck | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 |

1-012

Table 2. -continued Clinical observation

Exp. No. 6393 (115-164)

Sex : Female

| Findings of clinical observation | Dose level (mg/kg) | Days of experiment | | | | | | | | | | | | | | Total (29→42) |
|----------------------------------|--------------------|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---------------|
| | | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | |
| normal/number per group | 0 | 5/5 | 5/5 | 5/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4 |
| | 200 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5 |
| trauma/fore limb | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

1-013

Table 3. Body weight

Exp. No. 6393 (115-164)

(unit : g)

| Sex | Dose level (mg/kg) | Days of experiment | | | | |
|--------|-----------------------|--------------------|----------|----------|----------|----------|
| | | 0 | 3 | 7 | 10 | |
| Male | 0 | 159 ± 9 | 180 ± 11 | 210 ± 17 | 235 ± 20 | 269 ± 27 |
| | 50 | 157 ± 4 | 178 ± 6 | 210 ± 11 | 235 ± 15 | 267 ± 19 |
| | 100 | 158 ± 7 | 175 ± 11 | 201 ± 16 | 226 ± 21 | 259 ± 24 |
| | 200 | 159 ± 7 | 172 ± 11 | 202 ± 15 | 226 ± 18 | 260 ± 24 |
| Female | 0 | 130 ± 5 | 143 ± 6 | 158 ± 9 | 167 ± 10 | 179 ± 12 |
| | 50 | 130 ± 5 | 143 ± 9 | 156 ± 9 | 167 ± 11 | 178 ± 10 |
| | 100 | 130 ± 6 | 138 ± 7 | 152 ± 10 | 163 ± 10 | 176 ± 11 |
| | 200 | 130 ± 3 | 136 ± 5 | 151 ± 7 | 163 ± 8 | 178 ± 10 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

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Table 3. -continued Body weight

Exp. No. 6393 (115-164)

(unit : g)

| Sex | Dose level (mg/kg) | Days of experiment 17 | 21 | 24 | 27 | Gain (0 → 27) |
|--------|-----------------------|--------------------------|----------|----------|----------|------------------|
| Male | 0 | 295 ± 32 | 325 ± 37 | 347 ± 39 | 364 ± 44 | 205 ± 37 |
| | 50 | 294 ± 20 | 322 ± 24 | 345 ± 27 | 354 ± 27 | 197 ± 26 |
| | 100 | 282 ± 30 | 312 ± 35 | 333 ± 37 | 342 ± 36 | 183 ± 30 |
| | 200 | 284 ± 29 | 315 ± 33 | 337 ± 37 | 342 ± 64 | 183 ± 60 |
| Female | 0 | 192 ± 14 | 204 ± 16 | 216 ± 17 | 224 ± 19 | 93 ± 16 |
| | 50 | 193 ± 11 | 201 ± 14 | 211 ± 14 | 218 ± 14 | 89 ± 11 |
| | 100 | 190 ± 11 | 198 ± 11 | 207 ± 11 | 217 ± 11 | 87 ± 7 |
| | 200 | 188 ± 11 | 200 ± 14 | 208 ± 14 | 216 ± 17 | 86 ± 17 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 3. -continued Body weight

Exp. No. 6393 (115-164)

(unit : g)

| Sex | Dose level (mg/kg) | Days of experiment | | | | |
|--------|-----------------------|--------------------|----------|----------|----------|----------|
| | | 28 | 31 | 35 | 38 | 41 |
| Male | 0 | 379 ± 42 | 402 ± 44 | 427 ± 48 | 446 ± 47 | 451 ± 52 |
| | 200 | 385 ± 41 | 402 ± 39 | 432 ± 44 | 450 ± 39 | 456 ± 41 |
| Female | 0 | 225 ± 23 | 236 ± 22 | 247 ± 24 | 251 ± 24 | 252 ± 27 |
| | 200 | 221 ± 22 | 227 ± 22 | 236 ± 23 | 245 ± 26 | 245 ± 30 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

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Table 3. -continued Body weight

Exp. No. 6393 (115-164)

(unit : g)

| Sex | Dose level (mg/kg) | Gain (28 → 41) |
|--------|-----------------------|-------------------|
| Male | 0 | 73 ± 12 |
| | 200 | 71 ± 11 |
| Female | 0 | 28 ± 5 |
| | 200 | 24 ± 10 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 4. Food consumption

Exp. No. 6393 (115-164)

(unit : g/day)

| Sex | Dose level (mg/kg) | Days of experiment | | | | Total (0 → 27) |
|--------|-----------------------|--------------------|---|--------|--------|-------------------|
| | | | 7 | 14 | 21 | |
| Male | 0 | 20 ± 2 | | 23 ± 3 | 25 ± 4 | 24 ± 4N |
| | 50 | 20 ± 2 | | 23 ± 2 | 24 ± 2 | 23 ± 2 |
| | 100 | 19 ± 2 | | 22 ± 2 | 24 ± 3 | 23 ± 2 |
| | 200 | 19 ± 2 | | 23 ± 3 | 26 ± 4 | 25 ± 7 |
| Female | 0 | 15 ± 1 | | 15 ± 1 | 17 ± 1 | 16 ± 2 |
| | 50 | 16 ± 1 | | 16 ± 1 | 17 ± 1 | 16 ± 1 |
| | 100 | 14 ± 2 | | 15 ± 1 | 16 ± 1 | 15 ± 1 |
| | 200 | 14 ± 1 | | 16 ± 1 | 17 ± 1 | 17 ± 2 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

Table 4. -continued Food consumption

Exp. No. 6393 (115-164)

(unit : g/day)

| Sex | Dose level (mg/kg) | Days of experiment | | Total (29 → 41) |
|--------|-----------------------|--------------------|--------|--------------------|
| | | 35 | 41 | |
| Male | 0 | 31 ± 4 | 27 ± 3 | 378 ± 42 |
| | 200 | 31 ± 3 | 28 ± 2 | 385 ± 31 |
| Female | 0 | 21 ± 2 | 19 ± 2 | 257 ± 31 |
| | 200 | 20 ± 3 | 18 ± 3 | 250 ± 36 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1-019

Table 5. Food efficiency

Exp. No. 6393 (115-164)

(unit : %)

| Sex | Dose level (mg/kg) | Days of experiment | | | Mean (0 → 27) |
|--------|-----------------------|--------------------|------------|------------|------------------|
| | | 7 | 14 | 21 | |
| Male | 0 | 35.4 ± 2.6 | 37.3 ± 3.2 | 32.2 ± 2.8 | 32.9 ± 2.0N |
| | 50 | 37.2 ± 3.5 | 35.8 ± 4.8 | 32.1 ± 1.9 | 32.3 ± 2.4 |
| | 100 | 31.3 ± 5.1 | 38.2 ± 2.6 | 30.9 ± 3.2 | 30.8 ± 2.2 |
| | 200 | 32.1 ± 4.0 | 35.4 ± 2.7 | 30.1 ± 3.4 | 28.5 ± 6.0 |
| Female | 0 | 25.6 ± 3.8 | 19.4 ± 5.7 | 21.2 ± 5.4 | 21.7 ± 2.5 |
| | 50 | 24.3 ± 3.1 | 19.9 ± 5.0 | 19.4 ± 5.5 | 20.5 ± 2.3 |
| | 100 | 21.6 ± 3.4 | 22.7 ± 2.7 | 19.1 ± 4.6 | 21.0 ± 0.9 |
| | 200 | 20.9 ± 4.8* | 24.0 ± 3.0 | 18.4 ± 3.8 | 19.8 ± 2.5 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

Table 5. -continued Food efficiency

Exp. No. 6393 (115-164)

(unit : %)

| Sex | Dose level (mg/kg) | Days of experiment 35 | Mean (29 → 41) | |
|--------|-----------------------|--------------------------|-------------------|------------|
| | | | 41 | |
| Male | 0 | 22.5 ± 1.8 | 14.7 ± 1.9 | 19.2 ± 1.6 |
| | 200 | 21.4 ± 3.2 | 14.6 ± 3.1 | 18.4 ± 2.7 |
| Female | 0 | 14.9 ± 3.9 | 5.1 ± 4.6 | 10.8 ± 1.5 |
| | 200 | 10.7 ± 3.0 | 7.8 ± 9.1 | 9.5 ± 3.5 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1-021

Table 6. Detailed clinical observations and sensory reactivity to stimuli of different types

Exp. No. 6393 (115-164)

Sex: Male

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|--------------------|-----------------------|---------------------|---|-----|----|----|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| Number of animals | 0 | 5 | 5 | 5 | 5 | 5 | |
| | 50 | 5 | 5 | 5 | 5 | 5 | |
| | 100 | 5 | 5 | 5 | 5 | 5 | |
| | 200 | 5 | 5 | 4 | 4 | 4 | |
| au/os/pilo/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| au/os/eye/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| au/os/laci/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| au/os/sali/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 3 | 3 | 16 |
| | 100 | 5 | 5 | 3 | 2 | 3 | 13 |
| | 200 | 5 | 3 | 0* | 0* | 1* | 4 |
| au/os/sali/s1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 2 | 2 | 4 |
| | 100 | 0 | 0 | 2 | 3 | 2 | 7 |
| | 200 | 0 | 2 | 4** | 3* | 2 | 11 |
| au/os/sali/profuse | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 1 | 1 | 2 |
| au/os/incon/none | 0 | 2 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 2 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 3 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| au/os/incon/unusu | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 3 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 2 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Male

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-----------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| au/of/palpe/w open | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 3 | 16 |
| au/of/palpe/sl ptosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 1 | 1 |
| au/of/diarrhea/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| au(sr/pupil/norm | 0 | 5 | - | - | - | 5 | 5 |
| | 50 | 5 | - | - | - | 5 | 5 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 5 | - | - | - | 4 | 4 |
| m,p/os/myoto/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| m,p/of/mid/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| se/os/palpe/w open | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| se/os/cata/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| se/os/click/norm | 0 | 5 | - | - | - | 5 | 5 |
| | 50 | 5 | - | - | - | 5 | 5 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 5 | - | - | - | 4 | 4 |

Significant difference from control group;

*: P ≤ 0.05

**: P ≤ 0.01

-: Not examined

Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Male

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-------------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| se/sr/app/no react | 0 | 0 | - | - | - | 0 | 0 |
| | 50 | 0 | - | - | - | 0 | 0 |
| | 100 | 0 | - | - | - | 0 | 0 |
| | 200 | 0 | - | - | - | 1 | 1 |
| se/sr/app/slow app | 0 | 5 | - | - | - | 4 | 4 |
| | 50 | 5 | - | - | - | 5 | 5 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 5 | - | - | - | 3 | 3 |
| se/sr/app/vocal, ener | 0 | 0 | - | - | - | 1 | 1 |
| | 50 | 0 | - | - | - | 0 | 0 |
| | 100 | 0 | - | - | - | 0 | 0 |
| | 200 | 0 | - | - | - | 0 | 0 |
| se/sr/touch/mod react | 0 | 5 | - | - | - | 5 | 5 |
| | 50 | 5 | - | - | - | 5 | 5 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 5 | - | - | - | 4 | 4 |
| se/sr/tail/walk away | 0 | 0 | - | - | - | 0 | 0 |
| | 50 | 0 | - | - | - | 0 | 0 |
| | 100 | 0 | - | - | - | 0 | 0 |
| | 200 | 1 | - | - | - | 0 | 0 |
| se/sr/tail/norm | 0 | 5 | - | - | - | 5 | 5 |
| | 50 | 5 | - | - | - | 5 | 5 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 4 | - | - | - | 4 | 4 |
| ce/hc/posture/curled up | 0 | 1 | 0 | 1 | 0 | 1 | 2 |
| | 50 | 3 | 0 | 0 | 0 | 1 | 1 |
| | 100 | 1 | 1 | 3 | 0 | 1 | 5 |
| | 200 | 2 | 0 | 1 | 0 | 3 | 4 |
| ce/hc/posture/sit | 0 | 2 | 2 | 3 | 0 | 0 | 5 |
| | 50 | 2 | 1 | 4 | 0 | 2 | 7 |
| | 100 | 3 | 1 | 1 | 2 | 1 | 5 |
| | 200 | 3 | 3 | 3 | 2 | 0 | 8 |
| ce/hc/posture/sit/stand | 0 | 2 | 3 | 1 | 5 | 4 | 13 |
| | 50 | 0 | 4 | 1 | 5 | 2 | 12 |
| | 100 | 0 | 3 | 1 | 3 | 3 | 10 |
| | 200 | 0 | 2 | 0 | 2 | 1 | 5 |

Significant difference from control group;

*: P ≤ 0.05

**: P ≤ 0.01

-: Not examined

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Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Male

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-----------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| ce/hc/posture/rear | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 |
| ce/hc/voca/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/hc/repe/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/hc/tonic/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/hc/clonic/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/hc/tremor/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/hc/bite/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 4 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/hc/bite/cage | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 |
| ce/hc/struggling/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Male

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-------------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| ce/os/removal/very easy | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 4 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 1 | 0 | 0 | 0 | 0 | 0 |
| ce/os/removal/easy | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 1 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 4 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 4 | 5 | 4 | 4 | 4 | 17 |
| ce/os/hand/very easy | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 3 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 3 | 0 | 0 | 0 | 0 | 0 |
| ce/os/hand/easy | 0 | 4 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 2 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 2 | 5 | 4 | 4 | 4 | 17 |
| ce/os/vocalization/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/os/bi,wo/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/os/hair/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/os/breath/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/of/tonic/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

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Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Male

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-------------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| ce/of/clonic/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/of/tremor/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/of/coordination/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/of/vocalization/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/of/breath/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/of/ambu/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/of/arousal/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/of/ste/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |
| ce/of/bizarre/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Male

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| ph/os/mucous/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 4 | 4 | 4 | 17 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Female

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|--------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| Number of animals | 0 | 5 | 5 | 5 | 5 | 5 | |
| | 50 | 5 | 5 | 5 | 5 | 5 | |
| | 100 | 5 | 5 | 5 | 5 | 5 | |
| | 200 | 5 | 5 | 5 | 5 | 5 | |
| au/os/pilo/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| au/os/eye/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| au/os/laci/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| au/os/sali/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 4 | 5 | 5 | 17 |
| | 200 | 5 | 4 | 3 | 2 | 2 | 11 |
| au/os/sali/sl | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 1 | 0 | 0 | 3 |
| | 200 | 0 | 1 | 2 | 3 | 3 | 9 |
| au/os/incon/none | 0 | 4 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 3 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 4 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 2 | 5 | 5 | 5 | 5 | 20 |
| au/os/incon/unusu | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 2 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 200 | 3 | 0 | 0 | 0 | 0 | 0 |
| au/of/palpe/w open | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1-029

Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Female

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-----------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| au/of/diarrhea/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| au(sr/pupil/norm | 0 | 5 | - | - | - | 5 | 5 |
| | 50 | 5 | - | - | - | 5 | 5 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 5 | - | - | - | 5 | 5 |
| m,p/os/myoto/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| m,p/of/mid/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| se/os/palpe/w open | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| se/os/cata/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| se/os/click/norm | 0 | 5 | - | - | - | 5 | 5 |
| | 50 | 5 | - | - | - | 5 | 5 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 5 | - | - | - | 5 | 5 |
| se(sr/app/slow app | 0 | 5 | - | - | - | 5 | 5 |
| | 50 | 5 | - | - | - | 5 | 5 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 5 | - | - | - | 5 | 5 |
| se(sr/touch/mod react | 0 | 5 | - | - | - | 5 | 5 |
| | 50 | 5 | - | - | - | 5 | 5 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 5 | - | - | - | 5 | 5 |

Significant difference from control group;

*: P ≤ 0.05

**: P ≤ 0.01

-: Not examined

Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Female

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-------------------------|-----------------------|---------------------|---|---|---|----|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| se/sr/tail/slow turn | 0 | 0 | - | - | - | 0 | 0 |
| | 50 | 1 | - | - | - | 0 | 0 |
| | 100 | 0 | - | - | - | 0 | 0 |
| | 200 | 0 | - | - | - | 0 | 0 |
| se/sr/tail/walk away | 0 | 0 | - | - | - | 0 | 0 |
| | 50 | 0 | - | - | - | 1 | 1 |
| | 100 | 0 | - | - | - | 0 | 0 |
| | 200 | 0 | - | - | - | 3 | 3 |
| se/sr/tail/norm | 0 | 5 | - | - | - | 5 | 5 |
| | 50 | 4 | - | - | - | 4 | 4 |
| | 100 | 5 | - | - | - | 5 | 5 |
| | 200 | 5 | - | - | - | 2 | 2 |
| ce/hc/posture/prone | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 1 | 0 | 0 | 0 | 1 |
| | 200 | 0 | 2 | 0 | 0 | 0 | 2 |
| ce/hc/posture/curled up | 0 | 2 | 1 | 1 | 0 | 3 | 5 |
| | 50 | 0 | 1 | 1 | 0 | 1 | 2 |
| | 100 | 1 | 1 | 0 | 0 | 1 | 2 |
| | 200 | 2 | 2 | 2 | 0 | 0 | 4 |
| ce/hc/posture/sit | 0 | 0 | 1 | 2 | 1 | 0 | 4 |
| | 50 | 5 | 2 | 0 | 0 | 1 | 3 |
| | 100 | 4 | 2 | 4 | 1 | 2 | 9 |
| | 200 | 2 | 1 | 0 | 2 | 4* | 7 |
| ce/hc/posture/sit/stand | 0 | 3 | 1 | 2 | 4 | 2 | 9 |
| | 50 | 0 | 3 | 4 | 5 | 3 | 15 |
| | 100 | 0 | 0 | 1 | 4 | 2 | 7 |
| | 200 | 1 | 0 | 3 | 3 | 1 | 7 |
| ce/hc/posture/rear | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 1 | 0 | 0 | 0 | 1 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 |
| ce/hc/voca/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |

Significant difference from control group;

*: P ≤ 0.05

**: P ≤ 0.01

-: Not examined

Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Female

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-------------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| ce/hc/repe/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/hc/tonic/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/hc/clonic/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/hc/tremor/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/hc/bite/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/hc/struggling/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/os/removal/very easy | 0 | 1 | 0 | 1 | 0 | 1 | 2 |
| | 50 | 0 | 1 | 1 | 0 | 0 | 2 |
| | 100 | 0 | 1 | 0 | 0 | 0 | 1 |
| | 200 | 0 | 2 | 0 | 0 | 2 | 4 |
| ce/os/removal/easy | 0 | 4 | 5 | 3 | 5 | 4 | 17 |
| | 50 | 5 | 3 | 4 | 5 | 5 | 17 |
| | 100 | 5 | 3 | 5 | 5 | 5 | 18 |
| | 200 | 5 | 3 | 5 | 5 | 3 | 16 |
| ce/os/removal/mod diff | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| | 50 | 0 | 1 | 0 | 0 | 0 | 1 |
| | 100 | 0 | 1 | 0 | 0 | 0 | 1 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

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Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Female

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-------------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| ce/os/hand/very easy | 0 | 0 | 2 | 2 | 1 | 0 | 5 |
| | 50 | 1 | 2 | 0 | 0 | 0 | 2 |
| | 100 | 0 | 1 | 1 | 1 | 1 | 4 |
| | 200 | 0 | 3 | 0 | 1 | 3 | 7 |
| ce/os/hand/easy | 0 | 5 | 3 | 2 | 4 | 4 | 13 |
| | 50 | 4 | 2 | 5 | 4 | 4 | 15 |
| | 100 | 5 | 2 | 2 | 3 | 4 | 11 |
| | 200 | 5 | 0 | 3 | 4 | 2 | 9 |
| ce/os/hand/rather easy | 0 | 0 | 0 | 1 | 0 | 1 | 2 |
| | 50 | 0 | 1 | 0 | 1 | 1 | 3 |
| | 100 | 0 | 1 | 2 | 1 | 0 | 4 |
| | 200 | 0 | 2 | 2 | 0 | 0 | 4 |
| ce/os/hand/rather diff | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 50 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 1 | 0 | 0 | 0 | 1 |
| | 200 | 0 | 0 | 0 | 0 | 0 | 0 |
| ce/os/vocalization/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/os/bi,wo/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/os/hair/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/os/breath/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/of/tonic/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Female

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-------------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| ce/of/clonic/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/of/tremor/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/of/coordination/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/of/vocalization/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/of/breath/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/of/ambu/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/of/arousal/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/of/ste/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |
| ce/of/bizarre/none | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

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Table 6. -continued Detailed clinical observations and sensory reactivity to stimuli of different types Exp. No. 6393 (115-164)

Sex: Female

| Signs | Dose level (mg/kg) | Weeks of experiment | | | | | Total (1 → 4) |
|-------------------|-----------------------|---------------------|---|---|---|---|------------------|
| | | 0 | 1 | 2 | 3 | 4 | |
| ph/os/mucous/norm | 0 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 100 | 5 | 5 | 5 | 5 | 5 | 20 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 20 |

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 7. Summary of no. of supported rears

Exp. No. 6393 (115-164)

Sex: male

| Dose level (mg/kg) | Number of animals | Mean no. of supported rears \pm S.D. | | | |
|-----------------------|----------------------|--|------------|--------------------------|--------------------------|
| | | 0 ¹⁾ | 1 | 2 | 3 |
| 0 | 5 | 11 \pm 2 | 9 \pm 7 | 9 \pm 7 | 17 \pm 5 |
| 50 | 5 | 11 \pm 5 | 8 \pm 6 | 9 \pm 7 | 18 \pm 6 |
| 100 | 5 | 11 \pm 6 | 7 \pm 3 | 8 \pm 5 | 14 \pm 6 |
| 200 | 5 | 12 \pm 3 | 14 \pm 5 | 12 \pm 6 ^{a)} | 13 \pm 4 ^{a)} |
| | | | | | 10 \pm 7 ^{a)} |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$ ^{a)}: 4 animals

Table 7. -continued Summary of no. of supported rears

Exp. No. 6393 (115-164)

Sex: female

| Dose level (mg/kg) | Number of animals | 0 ¹⁾ | Mean no. of supported rears \pm S.D. | | | |
|-----------------------|----------------------|-----------------|--|------------|------------|------------|
| | | | 1 | 2 | 3 | 4 |
| 0 | 5 | 15 \pm 7 | 22 \pm 5 | 20 \pm 8 | 20 \pm 6 | 15 \pm 7 |
| 50 | 5 | 17 \pm 5 | 15 \pm 8 | 15 \pm 9 | 19 \pm 8 | 13 \pm 8 |
| 100 | 5 | 14 \pm 5 | 13 \pm 7 | 10 \pm 7 | 15 \pm 7 | 12 \pm 8 |
| 200 | 5 | 10 \pm 5 | 10 \pm 5 * | 12 \pm 9 | 11 \pm 4 | 13 \pm 8 |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$

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Table 8. Summary of no. of unsupported rears

Exp. No. 6393 (115-164)

Sex: male

| Dose level (mg/kg) | Number of animals | Mean no. of unsupported rears \pm S.D. | | | |
|-----------------------|----------------------|--|-----------|-------------------------|-------------------------|
| | | 0 ¹⁾ | 1 | 2 | 3 |
| 0 | 5 | 3 \pm 6 | 0 \pm 1 | 3 \pm 5 | 2 \pm 3 |
| 50 | 5 | 2 \pm 2 | 0 \pm 0 | 0 \pm 1 | 3 \pm 5 |
| 100 | 5 | 1 \pm 1 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 200 | 5 | 1 \pm 1 | 3 \pm 2 | 2 \pm 2 ^{a)} | 8 \pm 9 ^{a)} |
| | | | | | 2 \pm 2 ^{a)} |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$ ^{a)}: 4 animals

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Table 8. -continued Summary of no. of unsupported rears

Exp. No. 6393 (115-164)

Sex: female

| Dose level (mg/kg) | Number of animals | Mean no. of unsupported rears \pm S.D. | | | | |
|-----------------------|----------------------|--|-----------|-----------|-----------|-----------|
| | | 0 ¹⁾ | 1 | 2 | 3 | 4 |
| 0 | 5 | 1 \pm 2 | 2 \pm 1 | 4 \pm 4 | 2 \pm 1 | 4 \pm 5 |
| 50 | 5 | 0 \pm 0 | 1 \pm 1 | 3 \pm 1 | 3 \pm 3 | 2 \pm 3 |
| 100 | 5 | 1 \pm 3 | 1 \pm 1 | 0 \pm 0 | 2 \pm 2 | 2 \pm 4 |
| 200 | 5 | 0 \pm 0 | 0 \pm 0 | 1 \pm 2 | 0 \pm 0 | 0 \pm 0 |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$

Table 9. Summary of no. of pools of urine

Exp. No. 6393 (115-164)

Sex: male

| Dose level (mg/kg) | Number of animals | Mean no. of pools of urine \pm S.D. | | | | |
|-----------------------|----------------------|---------------------------------------|-----------|-------------------------|-------------------------|-------------------------|
| | | 0 ¹⁾ | 1 | 2 | 3 | 4 |
| 0 | 5 | 1 \pm 1 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 50 | 5 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 100 | 5 | 0 \pm 0 | 0 \pm 1 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 200 | 5 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 ^{a)} | 0 \pm 0 ^{a)} | 0 \pm 1 ^{a)} |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$ ^{a)}: 4 animals

)

)

Table 9. -continued Summary of no. of pools of urine

Exp. No. 6393 (115-164)

Sex: female

| Dose level (mg/kg) | Number of animals | Mean no. of pools of urine \pm S.D. | | | | |
|-----------------------|----------------------|---------------------------------------|-----------|-----------|-----------|-----------|
| | | 0 ¹⁾ | 1 | 2 | 3 | 4 |
| 0 | 5 | 0 \pm 1 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 50 | 5 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 1 \pm 0 | 0 \pm 1 |
| 100 | 5 | 1 \pm 1 | 0 \pm 1 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 200 | 5 | 0 \pm 1 | 1 \pm 1 | 1 \pm 1 | 0 \pm 0 | 0 \pm 0 |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$

Table 10. Summary of no. of defecation

Exp. No. 6393 (115-164)

Sex: male

| Dose level (mg/kg) | Number of animals | Mean no. of defecation \pm S.D. | | | | |
|-----------------------|----------------------|-----------------------------------|-----------|-------------------------|-------------------------|-------------------------|
| | | 0 ¹⁾ | 1 | 2 | 3 | 4 |
| 0 | 5 | 1 \pm 1 | 2 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 50 | 5 | 0 \pm 0 | 1 \pm 1 | 0 \pm 1 | 0 \pm 0 | 0 \pm 0 |
| 100 | 5 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 200 | 5 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 ^{a)} | 0 \pm 0 ^{a)} | 0 \pm 0 ^{a)} |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$ ^{a)}: 4 animals

Table 10. -continued Summary of no. of defecation

Exp. No. 6393 (115-164)

Sex: female

| Dose level (mg/kg) | Number of animals | Mean no. of defecation \pm S.D. | | | | |
|-----------------------|----------------------|-----------------------------------|-----------|-----------|-----------|-----------|
| | | 0 ¹⁾ | 1 | 2 | 3 | 4 |
| 0 | 5 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 50 | 5 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 100 | 5 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |
| 200 | 5 | 0 \pm 1 | 0 \pm 1 | 0 \pm 0 | 0 \pm 0 | 0 \pm 0 |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$

Table 11. Summary of grip strength

Exp. No. 6393 (115-164)

Sex: male

| Dose level (mg/kg) | Number of animals | Mean grip strength \pm S.D. (g) | |
|-----------------------|----------------------|-------------------------------------|----------------|
| | | 0 ¹⁾ | 4 |
| 0 | 5 | Forelimb | 341 \pm 99 |
| | | Hindlimb | 186 \pm 50 |
| 50 | 5 | Forelimb | 309 \pm 20 |
| | | Hindlimb | 117 \pm 22 * |
| 100 | 5 | Forelimb | 336 \pm 80 |
| | | Hindlimb | 174 \pm 44 |
| 200 | 5 | Forelimb | 301 \pm 81 |
| | | Hindlimb | 149 \pm 43 |

¹⁾: Week of experimentSignificant difference from control group: *: p \leq 0.05 **: p \leq 0.01^{a)}: 4 animals

Table 11. -continued Summary of grip strength

Exp. No. 6393 (115-164)

Sex: female

| Dose level (mg/kg) | Number of animals | Mean grip strength \pm S.D. (g) | |
|-----------------------|----------------------|-------------------------------------|--------------|
| | | 0 ¹⁾ | 4 |
| 0 | 5 | Forelimb | 217 \pm 36 |
| | | Hindlimb | 173 \pm 66 |
| 50 | 5 | Forelimb | 170 \pm 54 |
| | | Hindlimb | 205 \pm 18 |
| 100 | 5 | Forelimb | 250 \pm 46 |
| | | Hindlimb | 177 \pm 34 |
| 200 | 5 | Forelimb | 172 \pm 39 |
| | | Hindlimb | 152 \pm 33 |

¹⁾: Week of experimentSignificant difference from control group: *: $p \leq 0.05$ **: $p \leq 0.01$

Table 12. Summary of hindlimb foot splay

Exp. No. 6393 (115-164)

Sex: male

| Dose level (mg/kg) | Number of animals | Mean hindlimb foot splay \pm S.D. (cm) | |
|-----------------------|----------------------|--|-----------------------------|
| | | 0 ¹⁾ | 4 |
| 0 | 5 | 4.7 \pm 1.4 | 7.2 \pm 1.6 |
| 50 | 5 | 4.9 \pm 0.7 | 8.8 \pm 1.1 |
| 100 | 5 | 6.0 \pm 2.1 | 8.8 \pm 1.1 |
| 200 | 5 | 4.3 \pm 0.5 | 6.4 \pm 1.1 ^{a)} |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$ ^{a)}: 4 animals

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Table 12. -continued Summary of hindlimb foot splay

Exp. No. 6393 (115-164)

Sex: female

| Dose level (mg/kg) | Number of animals | Mean hindlimb foot splay \pm S.D. (cm) | |
|-----------------------|----------------------|--|---------------|
| | | 0 ¹⁾ | 4 |
| 0 | 5 | 4.5 \pm 1.7 | 5.5 \pm 1.1 |
| 50 | 5 | 4.8 \pm 0.9 | 5.6 \pm 1.2 |
| 100 | 5 | 5.6 \pm 1.5 | 5.3 \pm 1.4 |
| 200 | 5 | 5.8 \pm 1.2 | 6.4 \pm 1.7 |

¹⁾: Week of experimentSignificant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$

Table 13. Summary of motor activity

Exp. No. 6393 (115-164)

1-048

| Week : 0 | Sex: male | | | | | | | | |
|----------|-----------------------|----------------------|--------------------|----------|---------|------------------------------------|---------|-----------|--------------|
| | Dose level (mg/kg) | Number of animals | 0-10 ¹⁾ | 10-20 | 20-30 | Mean motor activity ± S.D. (times) | | 50-60 | Total (0-60) |
| 0 | 5 | 141 ± 43 | 127 ± 36 | 103 ± 20 | 88 ± 37 | 67 ± 41 | 28 ± 43 | 555 ± 155 | |
| 50 | 5 | 151 ± 50 | 106 ± 58 | 98 ± 40 | 84 ± 48 | 52 ± 60 | 19 ± 24 | 511 ± 223 | |
| 100 | 5 | 128 ± 47 | 114 ± 39 | 103 ± 64 | 64 ± 52 | 41 ± 43 | 46 ± 62 | 497 ± 280 | |
| 200 | 5 | 144 ± 51 | 139 ± 45 | 114 ± 63 | 79 ± 45 | 104 ± 61 | 75 ± 44 | 655 ± 239 | |

¹⁾: Time (minutes)Significant difference from control group: *: $p \leq 0.05$ **: $p \leq 0.01$

Table 13. -continued Summary of motor activity

Exp. No. 6393 (115-164)

1-049

| Week : 0 | Sex: female | | | | | | | | |
|----------|-----------------------|----------------------|--------------------|-------------|--|-------------|-------------|---------------|--------------|
| | Dose level (mg/kg) | Number of animals | 0-10 ¹⁾ | | Mean motor activity \pm S.D. (times) | | 50-60 | | Total (0-60) |
| 0 | 5 | 132 \pm 31 | 90 \pm 14 | 60 \pm 47 | 39 \pm 26 | 19 \pm 22 | 43 \pm 43 | 382 \pm 107 | |
| 50 | 5 | 130 \pm 10 | 94 \pm 15 | 55 \pm 25 | 25 \pm 21 | 23 \pm 40 | 34 \pm 31 | 361 \pm 108 | |
| 100 | 5 | 114 \pm 21 | 60 \pm 37 | 43 \pm 14 | 42 \pm 43 | 23 \pm 24 | 19 \pm 27 | 301 \pm 96 | |
| 200 | 5 | 115 \pm 42 | 82 \pm 24 | 45 \pm 14 | 12 \pm 18 | 12 \pm 25 | 1 \pm 2 | 267 \pm 97 | |

¹⁾: Time (minutes)Significant difference from control group; *: $p \leq 0.05$ **: $p \leq 0.01$

Table 13. -continued Summary of motor activity

Exp. No. 6393 (115-164)

| Week : 4 | Sex: male | | | | | | | | |
|----------|-----------------------|----------------------|--------------------|----------|----------|------------------------------------|-----------|-------------|-------|
| | Dose level (mg/kg) | Number of animals | 0-10 ¹⁾ | 10-20 | 20-30 | Mean motor activity ± S.D. (times) | 30-40 | 40-50 | 50-60 |
| 0 | 5 | 189 ± 36 | 152 ± 50 | 116 ± 52 | 124 ± 59 | 109 ± 74 | 115 ± 125 | 806 ± 378 | |
| 50 | 5 | 223 ± 34 | 187 ± 59 | 133 ± 40 | 88 ± 61 | 69 ± 83 | 83 ± 61 | 784 ± 229 | |
| 100 | 5 | 181 ± 49 | 117 ± 45 | 100 ± 62 | 62 ± 57 | 39 ± 19 | 49 ± 51 | 548 ± 177 | |
| 200 | 4 | 102 ± 62 * | 56 ± 44 * | 35 ± 38 | 29 ± 34 | 37 ± 50 | 14 ± 18 | 273 ± 165 * | |

¹⁾: Time (minutes)

Significant difference from control group; *: p ≤ 0.05 **: p ≤ 0.01

1050

Table 13. -continued Summary of motor activity

Exp. No. 6393 (115-164)

1051

| Week : 4 | Sex: female | | | | | | | | |
|----------|-----------------------|----------------------|------------------------------------|---------|---------|---------|---------|-----------|--------------|
| | Dose level (mg/kg) | Number of animals | Mean motor activity ± S.D. (times) | | | | | | Total (0-60) |
| | | | 0-10 ¹⁾ | 10-20 | 20-30 | 30-40 | 40-50 | 50-60 | |
| 0 | 5 | 140 ± 26 | 102 ± 39 | 68 ± 31 | 44 ± 41 | 85 ± 48 | 57 ± 21 | 496 ± 163 | |
| 50 | 5 | 137 ± 8 | 102 ± 39 | 63 ± 30 | 52 ± 42 | 34 ± 30 | 25 ± 32 | 413 ± 138 | |
| 100 | 5 | 124 ± 21 | 65 ± 31 | 51 ± 26 | 26 ± 20 | 36 ± 34 | 32 ± 30 | 333 ± 62 | |
| 200 | 5 | 117 ± 22 | 78 ± 34 | 45 ± 31 | 39 ± 40 | 57 ± 55 | 38 ± 39 | 374 ± 163 | |

¹⁾: Time (minutes)

Significant difference from control group; *: p ≤ 0.05 **: p ≤ 0.01

Table 14. Hematology

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | HCT (%) | HGB (g/dL) | RBC ($\times 10^6/\text{mm}^3$) | MCV (μm^3) | MCH (pg) | MCHC (%) |
|--------|-----------------------|-------------------|-------------|---------------|--------------------------------------|----------------------------|-------------|-------------|
| Male | 0 | 5 | 41.8 ± 1.2 | 14.2 ± 0.6 | 7.79 ± 0.39 | 53.7 ± 1.8 | 18.3 ± 0.7 | 34.0 ± 0.4 |
| | 50 | 5 | 42.9 ± 1.8 | 14.5 ± 0.5 | 7.63 ± 0.43 | 56.3 ± 1.9 | 19.1 ± 0.7 | 33.8 ± 0.4 |
| | 100 | 5 | 43.0 ± 0.7 | 14.4 ± 0.2 | 7.88 ± 0.18 | 54.5 ± 1.6 | 18.3 ± 0.4 | 33.6 ± 0.3 |
| | 200 | 3 | 45.1 ± 1.8* | 15.0 ± 0.6 | 8.20 ± 0.35 | 55.0 ± 1.6 | 18.3 ± 0.4 | 33.3 ± 0.4* |
| Female | 0 | 5 | 43.4 ± 0.7 | 15.2 ± 0.3 | 7.94 ± 0.29 | 54.7 ± 1.3 | 19.1 ± 0.4 | 34.9 ± 0.2 |
| | 50 | 5 | 42.1 ± 1.5 | 14.8 ± 0.4 | 7.72 ± 0.35 | 54.5 ± 0.8 | 19.1 ± 0.5 | 35.1 ± 0.4 |
| | 100 | 5 | 43.2 ± 1.3 | 14.9 ± 0.5 | 8.06 ± 0.14 | 53.5 ± 1.6 | 18.6 ± 0.5 | 34.6 ± 0.4 |
| | 200 | 5 | 43.8 ± 1.5 | 15.2 ± 0.5 | 8.10 ± 0.22 | 54.1 ± 0.6 | 18.7 ± 0.2 | 34.6 ± 0.2 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1-052

Table 14. -continued Hematology

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | PLT ($\times 10^3/\text{mm}^3$) | WBC ($\times 10^3/\text{mm}^3$) | Differential leukocyte counts (%) | | | | | |
|--------|-----------------------|-------------------|--------------------------------------|--------------------------------------|-----------------------------------|---------|-------|-------|-------|-------|
| | | | | | NEUT | LYMPH | MONO | EOSN | BASO | LUC |
| Male | 0 | 5 | 1231 ± 55 | 9.0 ± 1.6 | 13 ± 2 | 84 ± 3 | 1 ± 1 | 1 ± 0 | 0 ± 0 | 1 ± 0 |
| | 50 | 5 | 1301 ± 198 | 9.9 ± 2.2 | 11 ± 2 | 85 ± 2 | 2 ± 1 | 1 ± 0 | 0 ± 0 | 1 ± 0 |
| | 100 | 5 | 1376 ± 137 | 10.5 ± 2.5 | 10 ± 3 | 87 ± 3 | 1 ± 1 | 1 ± 0 | 0 ± 0 | 1 ± 0 |
| | 200 | 3 | 1285 ± 173 | 11.3 ± 3.6 | 11 ± 4 | 85 ± 4 | 2 ± 1 | 1 ± 0 | 0 ± 0 | 1 ± 1 |
| Female | 0 | 5 | 1368 ± 235 | 7.6 ± 1.9 | 8 ± 4 | 89 ± 5N | 1 ± 1 | 1 ± 0 | 0 ± 0 | 1 ± 0 |
| | 50 | 5 | 1480 ± 83 | 7.2 ± 1.8 | 12 ± 8 | 86 ± 9 | 1 ± 0 | 1 ± 0 | 0 ± 0 | 1 ± 0 |
| | 100 | 5 | 1381 ± 178 | 7.6 ± 1.6 | 11 ± 5 | 87 ± 5 | 1 ± 1 | 1 ± 0 | 0 ± 0 | 1 ± 0 |
| | 200 | 5 | 1375 ± 116 | 8.5 ± 2.4 | 9 ± 2 | 87 ± 1 | 2 ± 1 | 1 ± 1 | 0 ± 0 | 1 ± 0 |

NEUT: Neutrophil LYMPH: Lymphocyte MONO: Monocyte EOSN: Eosinophil BASO: Basophil LUC: Large unstained cells
 Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

Table 14. -continued Hematology

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Reticulocyte (%) |
|---------------|-----------------------|-------------------|---------------------|
| Male | 0 | 5 | 2.7 ± 0.3 |
| | 50 | 5 | 2.8 ± 0.6 |
| | 100 | 5 | 2.7 ± 0.2 |
| | 200 | 3 | 1.7 ± 0.8* |
| Female | 0 | 5 | 2.1 ± 0.4 |
| | 50 | 5 | 1.9 ± 0.3 |
| | 100 | 5 | 2.0 ± 0.3 |
| | 200 | 5 | 1.2 ± 0.4** |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

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Table 14. -continued Hematology

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | HCT (%) | HGB (g/dL) | RBC ($\times 10^6/\text{mm}^3$) | MCV (μm^3) | MCH (pg) | MCHC (%) |
|--------|-----------------------|-------------------|-------------|---------------|--------------------------------------|----------------------------|-------------|-------------|
| Male | 0 | 5 | 43.2 ± 1.6N | 14.9 ± 0.6 | 8.31 ± 0.47 | 52.0 ± 1.3 | 17.9 ± 0.6 | 34.5 ± 0.4 |
| | 200 | 5 | 42.5 ± 0.5 | 14.6 ± 0.3 | 7.84 ± 0.15 | 54.3 ± 1.5* | 18.6 ± 0.5 | 34.2 ± 0.6 |
| Female | 0 | 5 | 41.7 ± 1.2 | 14.5 ± 0.5 | 7.89 ± 0.37 | 52.9 ± 2.1 | 18.4 ± 0.5 | 34.9 ± 0.6 |
| | 200 | 5 | 42.0 ± 0.8 | 14.6 ± 0.2 | 8.09 ± 0.31 | 51.9 ± 1.5 | 18.0 ± 0.5 | 34.7 ± 0.3 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

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Table 14. -continued Hematology

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | PLT ($\times 10^3/\text{mm}^3$) | WBC ($\times 10^3/\text{mm}^3$) | Differential leukocyte counts (%) | | | | EOSN | BASO | LUC |
|--------|-----------------------|-------------------|--------------------------------------|--------------------------------------|-----------------------------------|----------|-------|-------|-------|-------|-----|
| | | | | | NEUT | LYMPH | MONO | | | | |
| Male | 0 | 5 | 1144 ± 61 | 9.3 ± 1.6 | 13 ± 3 | 83 ± 4 | 2 ± 1 | 2 ± 0 | 0 ± 0 | 1 ± 1 | |
| | 200 | 5 | 1250 ± 57* | 9.9 ± 2.3 | 13 ± 4 | 84 ± 5 | 2 ± 1 | 1 ± 0 | 0 ± 0 | 1 ± 0 | |
| Female | 0 | 5 | 1302 ± 145 | 6.6 ± 1.6 | 18 ± 6N | 78 ± 5N | 2 ± 1 | 2 ± 1 | 0 ± 0 | 1 ± 1 | |
| | 200 | 5 | 1352 ± 66 | 4.2 ± 0.6* | 12 ± 1* | 85 ± 1** | 1 ± 0 | 1 ± 0 | 0 ± 0 | 1 ± 1 | |

NEUT: Neutrophil LYMPH: Lymphocyte MONO: Monocyte EOSN: Eosinophil BASO: Basophil LUC: Large unstained cells
 Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

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Table 14. -continued Hematology

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Reticulocyte (%) |
|--------|-----------------------|-------------------|---------------------|
| Male | 0 | 5 | 2.4 ± 0.4 |
| | 200 | 5 | 2.9 ± 0.3 |
| Female | 0 | 5 | 2.1 ± 0.5 |
| | 200 | 5 | 2.2 ± 0.2 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

150-1

Table 15. Coagulation

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | PT (sec.) | APTT (sec.) | Fibrinogen (mg/dL) |
|---------------|-----------------------|-------------------|--------------|----------------|-----------------------|
| Male | 0 | 5 | 17.0 ± 0.6 | 22.0 ± 3.1 | 304 ± 21 |
| | 50 | 5 | 17.8 ± 1.2 | 22.2 ± 2.8 | 318 ± 47 |
| | 100 | 5 | 17.4 ± 0.5 | 22.7 ± 1.3 | 352 ± 20 |
| | 200 | 3 | 16.9 ± 0.9 | 22.5 ± 1.9 | 286 ± 46 |
| Female | 0 | 5 | 17.2 ± 0.8 | 18.4 ± 1.5 | 265 ± 36 |
| | 50 | 5 | 17.2 ± 0.5 | 17.7 ± 2.1 | 241 ± 29 |
| | 100 | 5 | 16.8 ± 0.8 | 18.7 ± 1.8 | 261 ± 8 |
| | 200 | 5 | 17.4 ± 0.4 | 18.4 ± 0.8 | 266 ± 34 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

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Table 15. -continued Coagulation

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | PT (sec.) | APTT (sec.) | Fibrinogen (mg/dL) |
|--------|-----------------------|-------------------|--------------|----------------|-----------------------|
| Male | 0 | 5 | 17.2 ± 0.8 | 21.8 ± 1.5 | 318 ± 24 |
| | 200 | 5 | 17.0 ± 0.5 | 21.9 ± 2.8 | 327 ± 30 |
| Female | 0 | 5 | 17.5 ± 0.5 | 20.1 ± 1.2 | 230 ± 32 |
| | 200 | 5 | 17.6 ± 0.4 | 18.6 ± 1.3 | 253 ± 21 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

650-1

Table 16. Blood chemistry

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Glucose (mg/dL) | T.cholesterol (mg/dL) | Triglyceride (mg/dL) |
|--------|-----------------------|-------------------|--------------------|--------------------------|-------------------------|
| Male | 0 | 5 | 142 ± 8 | 65 ± 8 | 45.7 ± 19.0 |
| | 50 | 5 | 156 ± 19 | 66 ± 20 | 44.4 ± 18.7 |
| | 100 | 5 | 151 ± 12 | 67 ± 11 | 39.8 ± 14.9 |
| | 200 | 3 | 140 ± 7 | 57 ± 13 | 27.9 ± 2.2 |
| Female | 0 | 5 | 134 ± 15 | 58 ± 5 | 16.8 ± 11.7 |
| | 50 | 5 | 125 ± 7 | 62 ± 17 | 15.9 ± 8.0 |
| | 100 | 5 | 129 ± 15 | 69 ± 13 | 15.8 ± 8.7 |
| | 200 | 5 | 120 ± 18 | 57 ± 18 | 15.7 ± 5.0 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

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Table 16. -continued Blood chemistry

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | BUN (mg/dL) | Creatinine (mg/dL) | T.bilirubin (mg/dL) | T.protein (g/dL) | Albumin (g/dL) | A/G |
|---------------|-----------------------|-------------------|----------------|-----------------------|------------------------|---------------------|-------------------|--------------|
| Male | 0 | 5 | 9.2 ± 2.2 | 0.24 ± 0.03 | 0.04 ± 0.01 | 5.83 ± 0.16 | 3.30 ± 0.10 | 1.31 ± 0.11 |
| | 50 | 5 | 10.6 ± 1.1 | 0.25 ± 0.04 | 0.03 ± 0.01 | 5.73 ± 0.10 | 3.32 ± 0.10 | 1.38 ± 0.10 |
| | 100 | 5 | 9.7 ± 1.7 | 0.24 ± 0.02 | 0.03 ± 0.01 | 5.75 ± 0.33 | 3.32 ± 0.15 | 1.37 ± 0.08 |
| | 200 | 3 | 12.7 ± 4.3 | 0.24 ± 0.03 | 0.04 ± 0.01 | 5.53 ± 0.32 | 3.14 ± 0.07 | 1.33 ± 0.13 |
| Female | 0 | 5 | 11.4 ± 1.7 | 0.29 ± 0.04 | 0.02 ± 0.00 | 5.74 ± 0.17 | 3.37 ± 0.14 | 1.43 ± 0.15N |
| | 50 | 5 | 12.8 ± 1.0 | 0.27 ± 0.03 | 0.02 ± 0.01 | 5.92 ± 0.27 | 3.51 ± 0.15 | 1.45 ± 0.05 |
| | 100 | 5 | 11.6 ± 2.7 | 0.26 ± 0.04 | 0.03 ± 0.01 | 5.81 ± 0.22 | 3.45 ± 0.11 | 1.46 ± 0.04 |
| | 200 | 5 | 12.4 ± 1.8 | 0.31 ± 0.05 | 0.03 ± 0.01 | 5.72 ± 0.33 | 3.33 ± 0.13 | 1.39 ± 0.08 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

Table 16. -continued Blood chemistry

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Sodium (mmol/L) | Potassium (mmol/L) | Chloride (mmol/L) | Calcium (mg/dL) | I.phosphorus (mg/dL) |
|--------|-----------------------|-------------------|--------------------|-----------------------|----------------------|--------------------|-------------------------|
| Male | 0 | 5 | 144.7 ± 0.9 | 4.43 ± 0.13 | 107.9 ± 1.4 | 9.91 ± 0.10 | 8.04 ± 0.59 |
| | 50 | 5 | 143.7 ± 1.0 | 4.36 ± 0.24 | 107.3 ± 1.2 | 10.06 ± 0.16 | 8.57 ± 0.22 |
| | 100 | 5 | 143.9 ± 1.1 | 4.61 ± 0.22 | 106.6 ± 1.7 | 9.87 ± 0.37 | 8.41 ± 0.53 |
| | 200 | 3 | 142.0 ± 1.8* | 5.09 ± 0.38** | 107.5 ± 0.4 | 9.76 ± 0.40 | 8.68 ± 1.01 |
| Female | 0 | 5 | 143.0 ± 1.0 | 4.45 ± 0.37 | 109.0 ± 1.1 | 9.68 ± 0.31 | 7.29 ± 0.55 |
| | 50 | 5 | 143.2 ± 1.5 | 4.66 ± 0.24 | 108.2 ± 1.3 | 9.90 ± 0.19 | 7.68 ± 0.76 |
| | 100 | 5 | 142.9 ± 0.8 | 4.54 ± 0.18 | 108.9 ± 1.7 | 9.71 ± 0.37 | 7.08 ± 0.34 |
| | 200 | 5 | 141.7 ± 0.9 | 4.76 ± 0.40 | 107.1 ± 1.3 | 9.69 ± 0.17 | 7.95 ± 1.29 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1-062

Table 16. -continued Blood chemistry

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | AST (U/L) | ALT (U/L) | ALP (U/L) | Gamma-GTP (U/L) |
|--------|-----------------------|-------------------|--------------|--------------|--------------|--------------------|
| Male | 0 | 5 | 70 ± 6N | 26 ± 3 | 897 ± 129 | 0.4 ± 0.1 |
| | 50 | 5 | 69 ± 7 | 29 ± 6 | 1038 ± 254 | 0.4 ± 0.1 |
| | 100 | 5 | 65 ± 5 | 31 ± 4 | 1029 ± 133 | 0.4 ± 0.2 |
| | 200 | 3 | 99 ± 34 | 35 ± 2* | 941 ± 254 | 0.5 ± 0.1 |
| Female | 0 | 5 | 75 ± 17N | 25 ± 3 | 479 ± 85 | 0.6 ± 0.3 |
| | 50 | 5 | 69 ± 10 | 21 ± 3 | 532 ± 109 | 0.5 ± 0.1 |
| | 100 | 5 | 69 ± 11 | 23 ± 3 | 509 ± 135 | 0.8 ± 0.1 |
| | 200 | 5 | 118 ± 78 | 31 ± 5 | 592 ± 95 | 1.0 ± 0.3 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

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Table 16. -continued Blood chemistry

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Glucose (mg/dL) | T.cholesterol (mg/dL) | Triglyceride (mg/dL) |
|--------|-----------------------|-------------------|--------------------|--------------------------|-------------------------|
| Male | 0 | 5 | 154 ± 21 | 66 ± 16 | 59.1 ± 7.2 |
| | 200 | 5 | 145 ± 11 | 61 ± 8 | 48.5 ± 16.0 |
| Female | 0 | 5 | 139 ± 14 | 64 ± 11 | 29.7 ± 28.7 |
| | 200 | 5 | 118 ± 13* | 76 ± 15 | 24.5 ± 19.8 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

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Table 16. -continued Blood chemistry

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | BUN (mg/dL) | Creatinine (mg/dL) | T.bilirubin (mg/dL) | T.protein (g/dL) | Albumin (g/dL) | A/G |
|--------|-----------------------|-------------------|----------------|-----------------------|------------------------|---------------------|-------------------|-------------|
| Male | 0 | 5 | 13.1 ± 1.1 | 0.31 ± 0.03 | 0.05 ± 0.02 | 6.06 ± 0.22 | 3.30 ± 0.20 | 1.20 ± 0.08 |
| | 200 | 5 | 12.7 ± 1.0 | 0.27 ± 0.03 | 0.04 ± 0.01 | 6.01 ± 0.11 | 3.31 ± 0.10 | 1.23 ± 0.07 |
| Female | 0 | 5 | 15.1 ± 2.2 | 0.30 ± 0.03 | 0.04 ± 0.01 | 6.24 ± 0.29 | 3.56 ± 0.26 | 1.33 ± 0.17 |
| | 200 | 5 | 14.2 ± 1.7 | 0.29 ± 0.02 | 0.05 ± 0.01 | 6.09 ± 0.36 | 3.52 ± 0.17 | 1.37 ± 0.07 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

100

Table 16. -continued Blood chemistry

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Sodium (mmol/L) | Potassium (mmol/L) | Chloride (mmol/L) | Calcium (mg/dL) | I.phosphorus (mg/dL) |
|--------|-----------------------|-------------------|--------------------|-----------------------|----------------------|--------------------|-------------------------|
| Male | 0 | 5 | 142.4 ± 0.8 | 4.09 ± 0.42 | 105.4 ± 1.1 | 9.90 ± 0.28 | 7.26 ± 0.59 |
| | 200 | 5 | 142.0 ± 0.7 | 4.47 ± 0.22 | 105.3 ± 0.5 | 9.88 ± 0.16 | 7.75 ± 0.48 |
| Female | 0 | 5 | 141.5 ± 1.2 | 4.12 ± 0.16 | 107.8 ± 1.7 | 9.87 ± 0.35 | 5.73 ± 0.94 |
| | 200 | 5 | 142.7 ± 0.8 | 4.25 ± 0.38 | 108.3 ± 0.9 | 9.75 ± 0.21 | 5.67 ± 0.82 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1
0
6

Table 16. -continued Blood chemistry

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | AST (U/L) | ALT (U/L) | ALP (U/L) | Gamma-GTP (U/L) |
|--------|-----------------------|-------------------|--------------|--------------|--------------|--------------------|
| Male | 0 | 5 | 70 ± 4 | 27 ± 2 | 737 ± 102 | 0.7 ± 0.1 |
| | 200 | 5 | 64 ± 5 | 27 ± 2 | 555 ± 85* | 0.6 ± 0.1 |
| Female | 0 | 5 | 70 ± 7 | 22 ± 4 | 317 ± 70 | 0.9 ± 0.2 |
| | 200 | 5 | 63 ± 7 | 23 ± 2 | 329 ± 65 | 1.0 ± 0.2 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1097

Table 17. Urinalysis

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Volume (mL) | Osmotic pressure (mOsm/kg) |
|--------|-----------------------|-------------------|----------------|-------------------------------|
| Male | 0 | 5 | 8.6 ± 3.4 | 918 ± 162 |
| | 50 | 5 | 7.9 ± 2.5 | 881 ± 166 |
| | 100 | 5 | 8.2 ± 2.1 | 853 ± 172 |
| | 200 | 4 | 7.7 ± 2.1 | 1219 ± 525 |
| Female | 0 | 5 | 6.1 ± 1.2 | 818 ± 114N |
| | 50 | 5 | 6.3 ± 2.4 | 1043 ± 410 |
| | 100 | 5 | 5.3 ± 1.5 | 1176 ± 190* |
| | 200 | 5 | 6.2 ± 2.5 | 1312 ± 675 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

Table 17. -continued Urinalysis

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Color | pH | | | | | | | | | | | Occult blood | | | | | | | | | | | | | |
|--------|-----------------------|-------------------|-------|----|---|---|---|---|---|---|---|---|----|----|--------------|-----|---|-----|---|-----|---|-----|-----|---|-----|----|----|----|
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 5 | 5.5 | 6 | 6.5 | 7 | 7.5 | 8 | 8.5 | ≥ 9 | - | +/- | 1+ | 2+ | 3+ |
| Male | 0 | 5 | 5 | | | | | | | | | | | | 1 | 3 | 1 | | | | | | | 4 | 1 | | | |
| | 50 | 5 | 5 | | | | | | | | | | | | 3 | 2 | | | | | | | | 5 | | | | |
| | 100 | 5 | 5 | | | | | | | | | | | | 4 | 1 | | | | | | | | 5 | | | | |
| | 200 | 4 | 4 | | | | | | | | | | | | 3 | | | 1 | | | | | | 3 | | | 1 | |
| Female | 0 | 5 | 5 | | | | | | | | | | | | 4 | 1 | | | | | | | | 5 | | | | |
| | 50 | 5 | 5 | | | | | | | | | | | | 2 | 3 | | | | | | | | 5 | | | | |
| | 100 | 5 | 5 | | | | | | | | | | | | 4 | 1 | | | | | | | | 5 | | | | |
| | 200 | 5 | 5 | | | | | | | | | | | | 5 | | | | | | | | | 5 | | | | |

Color : 1= Colorless, 2= Slight yellow, 3= Yellow-brown, 4= Red, 5= Red-brown, 6= Dark red, 7= Dark brown,
 8= Brown-black 9= Milky white, 10= Fluorescent green, 11= Blue.

1
0
0
6

Table 17. -continued Urinalysis

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Ketone bodies | | | | | Glucose(g/dL) | | | | Protein(mg/dL) | | | | | | |
|---------------|-----------------------|-------------------|---------------|-----|----|----|----|---------------|---|-----|------|----------------|-------|---|-----|----|-----|-------|
| | | | - | +/- | 1+ | 2+ | 3+ | 4+ | - | 0.1 | 0.25 | 0.5 | ≥ 1.0 | - | +/− | 30 | 100 | ≥ 300 |
| Male | 0 | 5 | | 1 | 3 | 1 | | | | 5 | | | | 3 | 2 | | | |
| | 50 | 5 | | | 1 | 4 | | | | 5 | | | | 2 | 3 | | | |
| | 100 | 5 | | | 4 | 1 | | | | 5 | | | | 5 | | | | |
| | 200 | 4 | | | 2 | 2 | | | | 4 | | | | 2 | 1 | 1 | | |
| Female | 0 | 5 | | 4 | 1 | | | | | 5 | | | | 4 | 1 | | | |
| | 50 | 5 | | 4 | 1 | | | | | 5 | | | | 3 | 2 | | | |
| | 100 | 5 | | 3 | 2 | | | | | 5 | | | | 1 | 4 | | | |
| | 200 | 5 | | 5 | | | | | | 5 | | | | 4 | 1 | | | |

10-01

Table 17. -continued Urinalysis

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Bilirubin | Urobilinogen (E.U./dL) | | | | | | | |
|---------------|-----------------------|-------------------|-----------|------------------------|----|----|-----|-----|-----|-----|-----|
| | | | - | 1+ | 2+ | 3+ | 0.1 | 1.0 | 2.0 | 4.0 | 8.0 |
| Male | 0 | 5 | 5 | | | | 5 | | | | |
| | 50 | 5 | 5 | | | | 5 | | | | |
| | 100 | 5 | 5 | | | | 5 | | | | |
| | 200 | 4 | 4 | | | | 4 | | | | |
| Female | 0 | 5 | 5 | | | | 5 | | | | |
| | 50 | 5 | 5 | | | | 5 | | | | |
| | 100 | 5 | 5 | | | | 5 | | | | |
| | 200 | 5 | 5 | | | | 5 | | | | |

1071

Table 17. -continued Urinalysis : Microscopic examination of sediment

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Erythrocytes - 1+ 2+ 3+ | Leukocytes - 1+ 2+ 3+ | Epith. Cells - 1+ 2+ 3+ | Casts - + | Fat glob. - + | M. threads - + | others - + |
|--------|-----------------------|-------------------|----------------------------|--------------------------|----------------------------|--------------|------------------|-------------------|---------------|
| Male | 0 | 5 | 5 | 4 1 | 4 1 | 5 | 5 | 5 | 1 4 |
| | 50 | 5 | 5 | 5 | 5 | 5 | 5 | 4 1 | 2 3 |
| | 100 | 5 | 5 | 5 | 4 1 | 5 | 5 | 3 2 | 3 2 |
| | 200 | 4 | 3 1 | 4 | 2 2 | 3 1 | 4 | 3 1 | 1 3 |
| Female | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 4 1 | 2 3 |
| | 50 | 5 | 5 | 5 | 4 1 | 5 | 5 | 4 1 | 3 2 |
| | 100 | 5 | 5 | 4 1 | 5 | 5 | 5 | 2 3 | 5 |
| | 200 | 5 | 5 | 5 | 1 3 1 | 5 | 5 | 2 3 | 4 1 |

others : Crystals

1-072

Table 17. -continued Urinalysis

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Volume (mL.) | Osmotic pressure (mOsm/kg) |
|--------|-----------------------|-------------------|-----------------|-------------------------------|
| Male | 0 | 5 | 14.2 ± 3.1 | 674 ± 92 |
| | 200 | 5 | 12.6 ± 2.0 | 658 ± 119 |
| Female | 0 | 5 | 6.4 ± 1.4 | 957 ± 127 |
| | 200 | 5 | 8.1 ± 1.6 | 698 ± 206* |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1-073

Table 17. -continued Urinalysis

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Color | pH | | | | | | | | | | | Occult blood | | | | | | | | | | | | | |
|--------|-----------------------|-------------------|-------|----|---|---|---|---|---|---|---|---|----|----|--------------|-----|---|-----|---|-----|---|-----|-----|---|-----|----|----|----|
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 5 | 5.5 | 6 | 6.5 | 7 | 7.5 | 8 | 8.5 | ≥ 9 | - | +/- | 1+ | 2+ | 3+ |
| Male | 0 | 5 | 5 | | | | | | | | | | | | 1 | 4 | | | | | | | | 5 | | | | |
| | 200 | 5 | 5 | | | | | | | | | | | | | | 5 | | | | | | | 4 | 1 | | | |
| Female | 0 | 5 | 5 | | | | | | | | | | | | 1 | 3 | 1 | | | | | | | 4 | 1 | | | |
| | 200 | 5 | 5 | | | | | | | | | | | | 1 | 3 | 1 | | | | | | | 5 | | | | |

Color : 1= Colorless, 2= Slight yellow, 3= Yellow-brown, 4= Red, 5= Red-brown, 6= Dark red, 7= Dark brown,
 8= Brown-black 9= Milky white, 10= Fluorescent green, 11= Blue.

10/4

Table 17. -continued Urinalysis

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Ketone bodies | | | | | Glucose (g/dL) | | | | Protein (mg/dL) | | | | | | |
|--------|-----------------------|-------------------|---------------|-----|----|----|----|----------------|---|-----|------|-----------------|-------|---|-----|----|-----|-------|
| | | | - | +/- | 1+ | 2+ | 3+ | 4+ | - | 0.1 | 0.25 | 0.5 | ≥ 1.0 | - | +/− | 30 | 100 | ≥ 300 |
| Male | 0 | 5 | 2 | 3 | | | | | 5 | | | | | 1 | 3 | 1 | | |
| | 200 | 5 | | 5 | | | | | 5 | | | | | 4 | 1 | | | |
| Female | 0 | 5 | 5 | | | | | | 5 | | | | | 3 | 2 | | | |
| | 200 | 5 | 5 | | | | | | 5 | | | | | 5 | | | | |

570-1

Table 17. -continued Urinalysis

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Bilirubin | Urobilinogen (E.U./dL) | | | | | | | |
|--------|-----------------------|-------------------|-----------|------------------------|----|----|-----|-----|-----|-----|-----|
| | | | - | 1+ | 2+ | 3+ | 0.1 | 1.0 | 2.0 | 4.0 | 8.0 |
| Male | 0 | 5 | 5 | | | | 5 | | | | |
| | 200 | 5 | 5 | | | | 5 | | | | |
| Female | 0 | 5 | 5 | | | | 5 | | | | |
| | 200 | 5 | 5 | | | | 5 | | | | |

Table 17. -continued Urinalysis : Microscopic examination of sediment

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Erythrocytes - 1+ 2+ 3+ | Leukocytes - 1+ 2+ 3+ | Epith. Cells - 1+ 2+ 3+ | Casts - + | Fat glob. - + | M. threads - + | others - + |
|--------|-----------------------|-------------------|----------------------------|--------------------------|----------------------------|--------------|------------------|-------------------|---------------|
| Male | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 4 | 1 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 5 | 3 | 2 |
| Female | 0 | 5 | 5 | 4 1 | 5 | 5 | 5 | 4 | 1 |
| | 200 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 1 4 |

others : Crystals

1-077

Table 18. Organ weight

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Body weight (g) | Brain (g) | Heart (g) | Liver (g) | Kidneys (g) |
|--------|-----------------------|-------------------|--------------------|--------------|--------------|--------------|----------------|
| Male | 0 | 5 | 329 ± 45 | 2.08 ± 0.12 | 1.19 ± 0.14 | 10.65 ± 1.34 | 2.60 ± 0.31 |
| | 50 | 5 | 331 ± 27 | 2.07 ± 0.04 | 1.15 ± 0.09 | 10.75 ± 1.26 | 2.56 ± 0.27 |
| | 100 | 5 | 314 ± 35 | 2.09 ± 0.06 | 1.08 ± 0.15 | 10.58 ± 1.94 | 2.63 ± 0.40 |
| | 200 | 4 | 269 ± 36 | 2.00 ± 0.06 | 1.00 ± 0.06 | 10.11 ± 1.77 | 2.48 ± 0.14 |
| Female | 0 | 5 | 205 ± 14 | 1.90 ± 0.04 | 0.74 ± 0.05 | 6.14 ± 0.50 | 1.58 ± 0.09 |
| | 50 | 5 | 203 ± 15 | 1.86 ± 0.08 | 0.72 ± 0.05 | 6.25 ± 0.46 | 1.58 ± 0.17 |
| | 100 | 5 | 200 ± 9 | 1.90 ± 0.07 | 0.73 ± 0.07 | 6.59 ± 0.32 | 1.77 ± 0.08* |
| | 200 | 5 | 190 ± 10 | 1.86 ± 0.04 | 0.72 ± 0.05 | 6.72 ± 0.47 | 1.64 ± 0.11 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 18. -continued Organ weight

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Spleen (g) | Adrenals (mg) | Testes (g) | Ovaries (mg) | Thymus (mg) |
|--------|-----------------------|-------------------|---------------|------------------|---------------|-----------------|----------------|
| Male | 0 | 5 | 0.58 ± 0.10 | 50 ± 8 | 2.98 ± 0.45N | | 538 ± 61 |
| | 50 | 5 | 0.63 ± 0.08 | 48 ± 9 | 3.12 ± 0.26 | | 565 ± 122 |
| | 100 | 5 | 0.54 ± 0.13 | 47 ± 3 | 2.98 ± 0.09 | | 537 ± 191 |
| | 200 | 4 | 0.43 ± 0.18 | 46 ± 14 | 3.03 ± 0.11 | | 398 ± 55 |
| Female | 0 | 5 | 0.40 ± 0.02 | 59 ± 8 | | 73 ± 6 | 511 ± 90 |
| | 50 | 5 | 0.40 ± 0.06 | 56 ± 7 | | 69 ± 15 | 564 ± 65 |
| | 100 | 5 | 0.37 ± 0.03 | 58 ± 4 | | 69 ± 13 | 433 ± 91 |
| | 200 | 5 | 0.36 ± 0.05 | 55 ± 3 | | 73 ± 6 | 387 ± 62 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

1079

Table 18. -continued Organ weight

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Uterus (mg) | Epididymides (mg) |
|--------|-----------------------|-------------------|----------------|----------------------|
| Male | 0 | 5 | | 614 ± 178N |
| | 50 | 5 | | 670 ± 71 |
| | 100 | 5 | | 660 ± 40 |
| | 200 | 4 | | 562 ± 71 |
| Female | 0 | 5 | 505 ± 208 | |
| | 50 | 5 | 455 ± 213 | |
| | 100 | 5 | 496 ± 187 | |
| | 200 | 5 | 527 ± 291 | |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

1
-
0
8
0

Table 18. -continued Organ weight

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Body weight (g) | Brain (g) | Heart (g) | Liver (g) | Kidneys (g) |
|--------|-----------------------|-------------------|--------------------|--------------|--------------|--------------|----------------|
| Male | 0 | 5 | 419 ± 46 | 2.17 ± 0.08 | 1.30 ± 0.06 | 12.87 ± 1.98 | 2.88 ± 0.35 |
| | 200 | 5 | 425 ± 39 | 2.16 ± 0.07 | 1.38 ± 0.16 | 12.99 ± 1.56 | 3.20 ± 0.44 |
| Female | 0 | 5 | 234 ± 21 | 1.98 ± 0.08 | 0.83 ± 0.08 | 6.83 ± 1.04 | 1.68 ± 0.04 |
| | 200 | 5 | 227 ± 25 | 1.90 ± 0.04 | 0.81 ± 0.06 | 6.67 ± 0.91 | 1.67 ± 0.11 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 18. -continued Organ weight

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Spleen (g) | Adrenals (mg) | Testes (g) | Ovaries (mg) | Thymus (mg) |
|--------|-----------------------|-------------------|---------------|------------------|---------------|-----------------|----------------|
| Male | 0 | 5 | 0.78 ± 0.13 | 61 ± 8 | 3.31 ± 0.27 | | 501 ± 69 |
| | 200 | 5 | 0.77 ± 0.09 | 56 ± 5 | 3.25 ± 0.23 | | 520 ± 75 |
| Female | 0 | 5 | 0.46 ± 0.02N | 62 ± 6 | | 82 ± 7 | 407 ± 51 |
| | 200 | 5 | 0.47 ± 0.08 | 62 ± 10 | | 85 ± 8 | 402 ± 60 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

Table 18. -continued Organ weight

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Uterus (mg) | Epididymides (mg) |
|--------|-----------------------|-------------------|----------------|----------------------|
| Male | 0 | 5 | | 925 ± 44 |
| | 200 | 5 | | 992 ± 111 |
| Female | 0 | 5 | 577 ± 193 | |
| | 200 | 5 | 700 ± 300 | |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

1-083

Table 19. Organ weight per body weight

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Body weight (g) | Brain (%) | Heart (%) | Liver (%) | Kidneys (%) |
|--------|-----------------------|-------------------|--------------------|---------------|---------------|-----------------|----------------|
| Male | 0 | 5 | 329 ± 45 | 0.640 ± 0.062 | 0.362 ± 0.018 | 3.247 ± 0.195N | 0.795 ± 0.050 |
| | 50 | 5 | 331 ± 27 | 0.628 ± 0.040 | 0.347 ± 0.013 | 3.246 ± 0.195 | 0.774 ± 0.051 |
| | 100 | 5 | 314 ± 35 | 0.672 ± 0.063 | 0.342 ± 0.016 | 3.351 ± 0.237 | 0.834 ± 0.045 |
| | 200 | 4 | 269 ± 36 | 0.755 ± 0.113 | 0.376 ± 0.038 | 3.812 ± 0.836 | 0.931 ± 0.099* |
| Female | 0 | 5 | 205 ± 14 | 0.931 ± 0.048 | 0.361 ± 0.017 | 2.995 ± 0.174 | 0.773 ± 0.078 |
| | 50 | 5 | 203 ± 15 | 0.922 ± 0.038 | 0.358 ± 0.014 | 3.086 ± 0.168 | 0.781 ± 0.069 |
| | 100 | 5 | 200 ± 9 | 0.950 ± 0.027 | 0.367 ± 0.029 | 3.303 ± 0.132* | 0.889 ± 0.032* |
| | 200 | 5 | 190 ± 10 | 0.980 ± 0.041 | 0.378 ± 0.023 | 3.529 ± 0.104** | 0.862 ± 0.052 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

1084

Table 19. -continued Organ weight per body weight

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Spleen (%) | Adrenals (%) | Testes (%) | Ovaries (%) | Thymus (%) |
|--------|-----------------------|-------------------|---------------|-----------------|----------------|----------------|---------------|
| Male | 0 | 5 | 0.175 ± 0.010 | 0.015 ± 0.002N | 0.909 ± 0.102 | | 0.166 ± 0.031 |
| | 50 | 5 | 0.190 ± 0.025 | 0.014 ± 0.002 | 0.948 ± 0.087 | | 0.171 ± 0.033 |
| | 100 | 5 | 0.170 ± 0.024 | 0.015 ± 0.002 | 0.955 ± 0.084 | | 0.171 ± 0.055 |
| | 200 | 4 | 0.157 ± 0.050 | 0.017 ± 0.006 | 1.147 ± 0.198* | | 0.150 ± 0.028 |
| Female | 0 | 5 | 0.194 ± 0.008 | 0.029 ± 0.004 | | 0.036 ± 0.003 | 0.249 ± 0.035 |
| | 50 | 5 | 0.198 ± 0.020 | 0.028 ± 0.003 | | 0.034 ± 0.005 | 0.279 ± 0.032 |
| | 100 | 5 | 0.188 ± 0.016 | 0.029 ± 0.002 | | 0.034 ± 0.005 | 0.217 ± 0.045 |
| | 200 | 5 | 0.187 ± 0.027 | 0.029 ± 0.003 | | 0.038 ± 0.004 | 0.203 ± 0.026 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

1
0
8
5

Table 19. -continued Organ weight per body weight

Exp. No. 6393 (115-164)

Day: 28

| Sex | Dose level (mg/kg) | No. of animals | Uterus (%) | Epididymides (%) |
|--------|-----------------------|-------------------|---------------|---------------------|
| Male | 0 | 5 | | 0.187 ± 0.055 |
| | 50 | 5 | | 0.203 ± 0.015 |
| | 100 | 5 | | 0.213 ± 0.031 |
| | 200 | 4 | | 0.211 ± 0.033 |
| Female | 0 | 5 | 0.248 ± 0.102 | |
| | 50 | 5 | 0.224 ± 0.104 | |
| | 100 | 5 | 0.249 ± 0.090 | |
| | 200 | 5 | 0.279 ± 0.158 | |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 19. -continued Organ weight per body weight

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Body weight (g) | Brain (%) | Heart (%) | Liver (%) | Kidneys (%) |
|--------|-----------------------|-------------------|--------------------|---------------|----------------|---------------|----------------|
| Male | 0 | 5 | 419 ± 46 | 0.522 ± 0.039 | 0.312 ± 0.030 | 3.063 ± 0.187 | 0.688 ± 0.039 |
| | 200 | 5 | 425 ± 39 | 0.513 ± 0.061 | 0.324 ± 0.019 | 3.057 ± 0.148 | 0.752 ± 0.051 |
| Female | 0 | 5 | 234 ± 21 | 0.848 ± 0.055 | 0.355 ± 0.008N | 2.909 ± 0.265 | 0.720 ± 0.056 |
| | 200 | 5 | 227 ± 25 | 0.841 ± 0.086 | 0.358 ± 0.030 | 2.929 ± 0.230 | 0.742 ± 0.086 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

N: Non parametric analysis

Table 19. -continued Organ weight per body weight

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Spleen (%) | Adrenals (%) | Testes (%) | Ovaries (%) | Thymus (%) |
|--------|-----------------------|-------------------|---------------|-----------------|---------------|----------------|---------------|
| Male | 0 | 5 | 0.187 ± 0.027 | 0.015 ± 0.002 | 0.794 ± 0.081 | | 0.121 ± 0.021 |
| | 200 | 5 | 0.182 ± 0.015 | 0.013 ± 0.001 | 0.774 ± 0.114 | | 0.122 ± 0.012 |
| Female | 0 | 5 | 0.198 ± 0.020 | 0.026 ± 0.002 | | 0.035 ± 0.005 | 0.176 ± 0.032 |
| | 200 | 5 | 0.206 ± 0.029 | 0.028 ± 0.006 | | 0.038 ± 0.005 | 0.177 ± 0.021 |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 19. -continued Organ weight per body weight

Exp. No. 6393 (115-164)

Day: 42

| Sex | Dose level (mg/kg) | No. of animals | Uterus (%) | Epididymides (%) |
|--------|-----------------------|-------------------|---------------|---------------------|
| Male | 0 | 5 | | 0.222 ± 0.022 |
| | 200 | 5 | | 0.236 ± 0.036 |
| Female | 0 | 5 | 0.244 ± 0.067 | |
| | 200 | 5 | 0.309 ± 0.138 | |

Mean ± S.D.

Significant difference from control group; *: P ≤ 0.05 **: P ≤ 0.01

Table 20.

Summary of gross findings with statistical analysis (sacrificed at 28 Day)

Exp. No. 6393 (115-164)

| Dose level No. of animals necropsied | Organ | Male animals | | | | Female animals | | | |
|---|--|--------------|------|------|------|----------------|------|------|------|
| | | Am 5 | Bm 5 | Cm 5 | Dm 4 | Af 5 | Bf 5 | Cf 5 | Df 5 |
| HEMATOPOIETIC SYSTEM | | | | | | | | | |
| spleen | deformed pale | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| RESPIRATORY SYSTEM | | | | | | | | | |
| lung | red patch/zone | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| DIGESTIVE SYSTEM | | | | | | | | | |
| stomach | black patch/zone red patch/zone | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| liver | cyst hepatodiaphragmatic nodule pale | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| REPRODUCTIVE SYSTEM | | | | | | | | | |
| seminal vesicle | | 0 | 0 | 0 | 1 | - | - | - | - |
| uterus | atrophic dilated lumen | 0 | 0 | 0 | 0 | 2 | 1 | 1 | 1 |
| vagina | nodule | - | - | - | - | 0 | 0 | 0 | 1 |
| OTHERS | | | | | | | | | |
| whole body | wasting | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

Am: 0 Bm: 50 Cm: 100 Dm: 200
 Af: 0 Bf: 50 Cf: 100 Df: 200

Significant difference from control group; * : P ≤ 0.05 ** : P ≤ 0.01

1
0
0

Table 20. -continued Summary of gross findings with statistical analysis (sacrificed at 42 Day) Exp. No. 6393 (115-164)

| Dose level (mg/kg) | No. of animals necropsied | Male animals | | Female animals | |
|-------------------------|---------------------------|--------------|---------|----------------|---------|
| | | Am 5 | Bm 5 | Af 5 | Bf 5 |
| Organ | Findings | | | | |
| RSPIRATORY SYSTEM | | | | | |
| lung | brown patch/zone | 1 | 1 | 0 | 0 |
| DIGESTIVE SYSTEM | | | | | |
| liver | nodule | 0 | 0 | 1 | 0 |
| URINARY SYSTEM | | | | | |
| kidney | dilated pelvis | 1 | 0 | 0 | 0 |
| REPRODUCTIVE SYSTEM | | | | | |
| uterus | dilated lumen | - | - | 1 | 2 |
| INTEGUMENTARY SYSTEM | | | | | |
| skin | wound | 0 | 0 | 1 | 0 |

Am: 0 Bm: 200
 Af: 0 Bf: 200

Significant difference from control group; * : $P \leq 0.05$ ** : $P \leq 0.01$

1
0
6
-

Table 21.

Summary of gross findings (dead or moribund)

Exp. No. 6393 (115-164)

| Dose level No. of animals necropsied | Organ | Male animals | | | | Female animals | | | |
|---|------------------|--------------|---------|---------|---------|----------------|---------|---------|---------|
| | | Am 0 | Bm 0 | Cm 0 | Dm 1 | Af 0 | Bf 0 | Cf 0 | Df 0 |
| HEMATOPOIETIC SYSTEM | | | | | | | | | |
| lymph node | reddish | - | - | - | 1 | - | - | - | - |
| thymus | red patch/zone | - | - | - | 1 | - | - | - | - |
| RESPIRATORY SYSTEM | | | | | | | | | |
| lung | red patch/zone | - | - | - | 1 | - | - | - | - |
| DIGESTIVE SYSTEM | | | | | | | | | |
| liver | red patch/zone | - | - | - | 1 | - | - | - | - |
| | white patch/zone | - | - | - | 1 | - | - | - | - |

Am: 0 Bm: 50 Cm: 100 Dm: 200
 Af: 0 Bf: 50 Cf: 100 Df: 200

T-092

Table 22.

Summary of histological findings with statistical analysis
(sacrificed at 28 Day)

Exp. No. 6393 (115-164)

| Dose level No. of animals necropsied | Organ | Male animals | | | | Female animals | | | |
|---|-----------------------------|--------------|------|------|------|----------------|------|------|------|
| | | Am 5 | Bm 5 | Cm 5 | Dm 4 | Af 5 | Bf 5 | Cf 5 | Df 5 |
| CARDIOVASCULAR SYSTEM | | | | | | | | | |
| heart | | | | | | | | | |
| | edema | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | degeneration of myocardium | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 3 |
| | necrosis | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| | cellular infiltration | 2 | 2 | 1 | 4 | 1 | 2 | 3 | 3 |
| | fibrosis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| HEMATOPOIETIC SYSTEM | | | | | | | | | |
| bone marrow | | | | | | | | | |
| | erythropoiesis, decreased | 0 | - | - | 1 | 0 | - | - | 0 |
| spleen | | | | | | | | | |
| | atrophy, white pulp | 0 | - | - | 1 | 0 | - | - | 0 |
| | erythropoiesis, decreased | 0 | - | - | 1 | 0 | - | - | 0 |
| mesenteric lymph node | | | | | | | | | |
| | karyorrhexis | 0 | - | - | 1 | 0 | - | - | 0 |
| mandibular lymph node | | | | | | | | | |
| | karyorrhexis | 0 | - | - | 1 | 0 | - | - | 0 |
| | single cell necrosis | 0 | - | - | 1 | 0 | - | - | 0 |
| thymus | | | | | | | | | |
| | karyorrhexis | 0 | - | - | 1 | 0 | - | - | 0 |
| RESPIRATORY SYSTEM | | | | | | | | | |
| lung | | | | | | | | | |
| | hemorrhage | 1 | - | - | 1 | 0 | - | - | 0 |
| | accumulation of foamy cells | 1 | - | - | 0 | 0 | - | - | 0 |
| | deposit, hematoidin crystal | 0 | - | - | 1 | 0 | - | - | 0 |
| | osseous metaplasia | 0 | - | - | 0 | 1 | - | - | 0 |
| DIGESTIVE SYSTEM | | | | | | | | | |
| stomach | | | | | | | | | |
| | edema | 0 | - | - | 1 | 0 | - | - | 0 |
| | hemorrhage | 0 | - | - | 1 | 0 | - | - | 0 |
| | cellular infiltration | 0 | - | - | 1 | 0 | - | - | 0 |
| | squamous hyperplasia | 0 | - | - | 1 | 0 | - | - | 0 |
| pancreas | | | | | | | | | |
| | atrophy, focal | 0 | - | - | 0 | 1 | - | - | 0 |

Am: 0 Bm: 50 Cm: 100 Dm: 200

Af: 0 Bf: 50 Cf: 100 Df: 200

Significant difference from control group; * : P ≤ 0.05 ** : P ≤ 0.01

Table 22. -continued Summary of histological findings with statistical analysis
 (sacrificed at 28 Day)

Exp. No. 6393 (115-164)

| Dose level No. of animals necropsied | Organ | Male animals | | | | Female animals | | | |
|---|-----------------------------------|--------------|------|------|------|----------------|------|------|------|
| | | Am 5 | Bm 5 | Cm 5 | Dm 4 | Af 5 | Bf 5 | Cf 5 | Df 5 |
| DIGESTIVE SYSTEM | | | | | | | | | |
| pancreas | decrease, zymogen granules | 0 | - | - | 1 | 0 | - | - | 0 |
| | cellular infiltration, lymphocyte | 0 | - | - | 0 | 0 | - | - | 1 |
| duodenum | degeneration, vacuolar | 0 | - | - | 1 | 0 | - | - | 0 |
| jejunum | degeneration, vacuolar | 0 | - | - | 1 | 0 | - | - | 0 |
| ileum | degeneration, vacuolar | 0 | - | - | 1 | 0 | - | - | 0 |
| liver | congestion | 0 | - | - | 1 | 0 | - | - | 0 |
| | eosinophilic body | 0 | - | - | 1 | 0 | - | - | 0 |
| | fatty change | 1 | - | - | 2 | 4 | - | - | 4 |
| | mitosis | 0 | - | - | 1 | 0 | - | - | 0 |
| | microgranuloma | 5 | - | - | 4 | 5 | - | - | 4 |
| | fibrosis | 1 | - | - | 0 | 0 | - | - | 0 |
| URINARY SYSTEM | | | | | | | | | |
| kidney | edema | 0 | - | - | 1 | 0 | - | - | 0 |
| | basophilic tubules | 5 | - | - | 3 | 3 | - | - | 4 |
| | cyst | 1 | - | - | 0 | 0 | - | - | 0 |
| | hyaline droplet | 0 | - | - | 3* | 0 | - | - | 0 |
| | mineralization | 2 | - | - | 2 | 2 | - | - | 3 |
| | cellular infiltration, lymphocyte | 0 | - | - | 0 | 1 | - | - | 0 |
| | fibrosis | 0 | - | - | 0 | 0 | - | - | 1 |
| urinary bladder | edema | 1 | - | - | 0 | 0 | - | - | 0 |
| | cellular infiltration | 1 | - | - | 0 | 0 | - | - | 0 |
| | transitional cell hyperplasia | 1 | - | - | 0 | 0 | - | - | 0 |
| REPRODUCTIVE SYSTEM | | | | | | | | | |
| testis | single cell necrosis | 0 | - | - | 1 | - | - | - | - |
| epididymis | cell debris, lumen | 0 | - | - | 1 | - | - | - | - |

Am: 0 Bm: 50 Cm: 100 Dm: 200
 Af: 0 Bf: 50 Cf: 100 Df: 200

Significant difference from control group; * : P ≤ 0.05 ** : P ≤ 0.01

Table 22. -continued Summary of histological findings with statistical analysis
(sacrificed at 28 Day)

Exp. No. 6393 (115-164)

| Dose level No. of animals necropsied | Organ | Male animals | | | | Female animals | | | |
|---|-----------------------------------|--------------|---------|---------|---------|----------------|---------|---------|---------|
| | | Am 5 | Bm 5 | Cm 5 | Dm 4 | Af 5 | Bf 5 | Cf 5 | Df 5 |
| REPRODUCTIVE SYSTEM | | | | | | | | | |
| epididymis | cellular infiltration | 0 | - | - | 1 | - | - | - | - |
| prostate | single cell necrosis | 0 | - | - | 1 | - | - | - | - |
| | cellular infiltration, lymphocyte | 1 | - | - | 1 | - | - | - | - |
| seminal vesicle | hyposecretory change | 0 | - | - | 1 | - | - | - | - |
| uterus | dilatation, lumen | - | - | - | - | 2 | - | - | 1 |
| | cellular infiltration | - | - | - | - | 1 | - | - | 0 |
| vagina | epidermal cyst | - | - | - | - | 0 | - | - | 1 |
| ENDOCRINE SYSTEM | | | | | | | | | |
| thyroid gland | ectopic thymus | 0 | - | - | 0 | 1 | - | - | 0 |

Am: 0 Bm: 50 Cm: 100 Dm: 200
 Af: 0 Bf: 50 Cf: 100 Df: 200
 Significant difference from control group; * : P ≤ 0.05 ** : P ≤ 0.01

-
0
5
0

Table 22. -continued Summary of histological findings with statistical analysis
(sacrificed at 42 Day)

Exp. No. 6393 (115-164)

| Dose level (mg/kg) | No. of animals necropsied | Male animals | | Female animals | |
|------------------------------|-----------------------------------|--------------|----|----------------|----|
| | | Am | Bm | Af | Bf |
| Organ | Findings | 5 | 5 | 5 | 5 |
| CARDIOVASCULAR SYSTEM | | | | | |
| heart | | | | | |
| | cellular infiltration | 1 | 2 | 3 | 2 |
| | fibrosis | 0 | 1 | 0 | 0 |
| HEMATOPOIETIC SYSTEM | | | | | |
| bone marrow | | | | | |
| | atrophy, focal | 0 | 0 | 1 | 0 |
| spleen | | | | | |
| | capsulitis | 1 | 0 | 0 | 0 |
| mandibular lymph node | | | | | |
| | ectopic tissue | 0 | 0 | 1 | 0 |
| RESPIRATORY SYSTEM | | | | | |
| lung | | | | | |
| | edema | 1 | 0 | 0 | 0 |
| | hemorrhage | 1 | 1 | 0 | 0 |
| | accumulation of macrophage | 0 | 1 | 0 | 0 |
| | osseous metaplasia | 1 | 0 | 0 | 0 |
| DIGESTIVE SYSTEM | | | | | |
| stomach | | | | | |
| | edema | 1 | 0 | 0 | 0 |
| | cellular infiltration | 1 | 0 | 0 | 0 |
| pancreas | | | | | |
| | atrophy, focal | 0 | 1 | 0 | 1 |
| | cellular infiltration | 1 | 0 | 1 | 0 |
| | cellular infiltration, lymphocyte | 2 | 1 | 0 | 1 |
| | proliferation, duct | 1 | 0 | 0 | 0 |
| rectum | | | | | |
| | microgranuloma | 1 | 0 | 0 | 0 |
| liver | | | | | |
| | deformation | 0 | 0 | 1 | 0 |
| | fatty change | 1 | 0 | 1 | 1 |
| | microgranuloma | 5 | 5 | 4 | 5 |
| | extramedullary hematopoiesis | 0 | 2 | 0 | 0 |

Am: 0 Bm: 200
Af: 0 Bf: 200

Significant difference from control group; * : P ≤ 0.05 ** : P ≤ 0.01

1
0
9

Table 22. -continued Summary of histological findings with statistical analysis
 (sacrificed at 42 Day)

Exp. No. 6393 (115-164)

| Dose level (mg/kg) | No. of animals necropsied | Male animals | | Female animals | |
|-----------------------------|-----------------------------------|--------------|----|----------------|----|
| | | Am | Bm | Af | Bf |
| Organ | Findings | 5 | 5 | 5 | 5 |
| DIGESTIVE SYSTEM | | | | | |
| mandibular gland | ectopic tissue | 3 | 0 | 1 | 2 |
| URINARY SYSTEM | | | | | |
| kidney | basophilic tubules | 4 | 5 | 1 | 2 |
| | hyaline droplet | 2 | 5 | 0 | 0 |
| | mineralization | 4 | 5 | 2 | 3 |
| | cellular infiltration, lymphocyte | 2 | 1 | 0 | 0 |
| | dilatation, renal pelvis | 2 | 0 | 0 | 0 |
| REPRODUCTIVE SYSTEM | | | | | |
| epididymis | cellular infiltration, lymphocyte | 1 | 0 | - | - |
| prostate | cell debris, lumen | 0 | 1 | - | - |
| | cellular infiltration, lymphocyte | 3 | 1 | - | - |
| uterus | dilatation, lumen | - | - | 1 | 3 |
| ENDOCRINE SYSTEM | | | | | |
| pituitary gland | cyst | 1 | 1 | 0 | 0 |
| thyroid gland | cellular infiltration, lymphocyte | 0 | 0 | 1 | 0 |
| | ultimobranchial remnant | 0 | 0 | 0 | 1 |
| SPECIAL SENSE SYSTEM | | | | | |
| eye | foreign body reaction | 1 | 0 | 0 | 0 |
| INTEGUMENTARY SYSTEM | | | | | |
| skin | cellular infiltration | - | - | 1 | - |
| | fibrosis | - | - | 1 | - |
| | squamous hyperplasia | - | - | 1 | - |

Am: 0 Bm: 200
 Af: 0 Bf: 200

Significant difference from control group; * : P ≤ 0.05 ** : P ≤ 0.01

Table 23.

Summary of histological findings (dead or moribund)

Exp. No. 6393 (115-164)

| Dose level (mg/kg) | No. of animals necropsied | Male animals | | | | Female animals | | | |
|------------------------------|---|--------------|---------|---------|---------|----------------|---------|---------|---------|
| | | Am 0 | Bm 0 | Cm 0 | Dm 1 | Af 0 | Bf 0 | Cf 0 | Df 0 |
| Organ | Findings | | | | | | | | |
| CARDIOVASCULAR SYSTEM | | | | | | | | | |
| heart | degeneration of myocardium cellular infiltration | - | - | - | 1 | - | - | - | - |
| HEMATOPOIETIC SYSTEM | | | | | | | | | |
| spleen | atrophy, white pulp | - | - | - | 1 | - | - | - | - |
| lymph node | congestion | - | - | - | 1 | - | - | - | - |
| mesenteric lymph node | atrophy, follicle | - | - | - | 1 | - | - | - | - |
| mandibular lymph node | congestion | - | - | - | 1 | - | - | - | - |
| | atrophy, follicle | - | - | - | 1 | - | - | - | - |
| thymus | hemorrhage | - | - | - | 1 | - | - | - | - |
| RESPIRATORY SYSTEM | | | | | | | | | |
| lung | congestion | - | - | - | 1 | - | - | - | - |
| | edema | - | - | - | 1 | - | - | - | - |
| | hemorrhage | - | - | - | 1 | - | - | - | - |
| | accumulation of macrophage | - | - | - | 1 | - | - | - | - |
| DIGESTIVE SYSTEM | | | | | | | | | |
| pancreas | hemorrhage | - | - | - | 1 | - | - | - | - |
| liver | congestion | - | - | - | 1 | - | - | - | - |
| | eosinophilic body | - | - | - | 1 | - | - | - | - |
| | fatty change | - | - | - | 1 | - | - | - | - |
| | mitosis | - | - | - | 1 | - | - | - | - |
| | hypertrophy, hepatocyte | - | - | - | 1 | - | - | - | - |

Am: 0
Af: 0Bm: 50
Bf: 50Cm: 100
Cf: 100Dm: 200
Df: 200

Table 24.

Summary of histological findings (sacrificed at 28 Day)

Exp. No. 6393 (115-164)

Sex: Male

| Dose level (mg/kg) | 0 | | | 50 | | | 100 | | | 200 | | | |
|--|-----------------------------|-------|---|----|-------|---|-----|-------|---|-----|-------|---|---|
| No. of animals initially in study | 5 | | | 5 | | | 5 | | | 4 | | | |
| No. of animals necropsied | 5 | | | 5 | | | 5 | | | 4 | | | |
| No. of animals examined histologically | 5 | | | 5 | | | 5 | | | 4 | | | |
| Organ | Findings | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| CARDIOVASCULAR SYSTEM | | | | | | | | | | | | | |
| heart | | (5) | | | (5) | | | (5) | | | (4) | | |
| | degeneration of myocardium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| | necrosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| | cellular infiltration | 2 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 0 | 1 | 3 | 0 |
| | fibrosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| HEMATOPOIETIC SYSTEM | | | | | | | | | | | | | |
| bone marrow | | (5) | | | (0) | | | (0) | | | (4) | | |
| | erythropoiesis, decreased | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| spleen | | (5) | | | (0) | | | (0) | | | (4) | | |
| | atrophy, white pulp | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| | erythropoiesis, decreased | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| mesenteric lymph node | | (5) | | | (0) | | | (0) | | | (4) | | |
| | karyorrhexis | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| mandibular lymph node | | (5) | | | (0) | | | (0) | | | (4) | | |
| | karyorrhexis | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| | single cell necrosis | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| thymus | | (5) | | | (0) | | | (0) | | | (4) | | |
| | karyorrhexis | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| RESPIRATORY SYSTEM | | | | | | | | | | | | | |
| lung | | (5) | | | (0) | | | (0) | | | (4) | | |
| | hemorrhage | 1 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| | accumulation of foamy cells | 1 | 0 | 0 | - | - | - | - | - | - | 0 | 0 | 0 |
| | deposit, hematoidin crystal | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | |
| stomach | | (5) | | | (0) | | | (0) | | | (4) | | |
| | edema | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| | hemorrhage | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| | cellular infiltration | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| | squamous hyperplasia | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| pancreas | | (5) | | | (0) | | | (0) | | | (4) | | |
| | decrease, zymogen granules | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |
| duodenum | | (5) | | | (0) | | | (0) | | | (4) | | |
| | degeneration, vacuolar | 0 | 0 | 0 | - | - | - | - | - | - | 1 | 0 | 0 |

1: slight 2: moderate 3: marked

(): No. of animals examined microscopically at this site.

-: Not applicable.

Table 24. -continued Summary of histological findings (sacrificed at 28 Day)

Exp. No. 6393 (115-164)

Sex: Male

| Dose level (mg/kg) | 0 | | | 50 | | | 100 | | | 200 | | | | |
|--|-----------------------------------|---|---|----|-------|---|-----|---|---|-----|-------|---|---|---|
| No. of animals initially in study | 5 | | | 5 | | | 5 | | | 4 | | | | |
| No. of animals necropsied | 5 | | | 5 | | | 5 | | | 4 | | | | |
| No. of animals examined histologically | 5 | | | 5 | | | 5 | | | 4 | | | | |
| Organ | Findings | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | | |
| jejunum | (5) | 0 | 0 | 0 | (0) | - | - | - | - | - | (4) | 1 | 0 | 0 |
| ileum | (5) | 0 | 0 | 0 | (0) | - | - | - | - | - | (4) | 1 | 0 | 0 |
| liver | (5) | 0 | 0 | 0 | (0) | - | - | - | - | - | (4) | 1 | 0 | 0 |
| | congestion | 0 | 0 | 0 | | - | - | - | - | - | | 1 | 0 | 0 |
| | eosinophilic body | 0 | 0 | 0 | | - | - | - | - | - | | 1 | 0 | 0 |
| | fatty change | 1 | 0 | 0 | | - | - | - | - | - | | 1 | 1 | 0 |
| | mitosis | 0 | 0 | 0 | | - | - | - | - | - | | 1 | 0 | 0 |
| | microgranuloma | 5 | 0 | 0 | | - | - | - | - | - | | 4 | 0 | 0 |
| | fibrosis | 1 | 0 | 0 | | - | - | - | - | - | | 0 | 0 | 0 |
| URINARY SYSTEM | | | | | | | | | | | | | | |
| kidney | (5) | 0 | 0 | 0 | (0) | - | - | - | - | - | (4) | 1 | 0 | 0 |
| | edema | 0 | 0 | 0 | | - | - | - | - | - | | 3 | 0 | 0 |
| | basophilic tubules | 5 | 0 | 0 | | - | - | - | - | - | | 0 | 0 | 0 |
| | cyst | 1 | 0 | 0 | | - | - | - | - | - | | 3 | 0 | 0 |
| | hyaline droplet | 0 | 0 | 0 | | - | - | - | - | - | | 2 | 0 | 0 |
| | mineralization | 2 | 0 | 0 | | - | - | - | - | - | | 0 | 0 | 0 |
| urinary bladder | (5) | 0 | 0 | 0 | (0) | - | - | - | - | - | (4) | 0 | 0 | 0 |
| | edema | 1 | 0 | 0 | | - | - | - | - | - | | 0 | 0 | 0 |
| | cellular infiltration | 1 | 0 | 0 | | - | - | - | - | - | | 0 | 0 | 0 |
| | transitional cell hyperplasia | 1 | 0 | 0 | | - | - | - | - | - | | 0 | 0 | 0 |
| REPRODUCTIVE SYSTEM | | | | | | | | | | | | | | |
| testis | (5) | 0 | 0 | 0 | (0) | - | - | - | - | - | (4) | 1 | 0 | 0 |
| epididymis | single cell necrosis | 0 | 0 | 0 | (0) | - | - | - | - | - | (4) | 1 | 0 | 0 |
| | cell debris, lumen | 0 | 0 | 0 | | - | - | - | - | - | | 1 | 0 | 0 |
| | cellular infiltration | 0 | 0 | 0 | | - | - | - | - | - | | 1 | 0 | 0 |
| prostate | (5) | 0 | 0 | 0 | (0) | - | - | - | - | - | (4) | 1 | 0 | 0 |
| | single cell necrosis | 0 | 0 | 0 | | - | - | - | - | - | | 1 | 0 | 0 |
| | cellular infiltration, lymphocyte | 0 | 1 | 0 | | - | - | - | - | - | | 1 | 0 | 0 |
| seminal vesicle | hyposecretory change | 0 | 0 | 0 | | - | - | - | - | - | (4) | 1 | 0 | 0 |

1: slight 2: moderate 3: marked

(): No. of animals examined microscopically at this site.

-: Not applicable.

Table 24. -continued Summary of histological findings (sacrificed at 28 Day)

Exp. No. 6393 (115-164)

Sex: Female

| Dose level (mg/kg) | 0 | 50 | 100 | 200 |
|--|----------|-------|-------|-------|
| No. of animals initially in study | 5 | 5 | 5 | 5 |
| No. of animals necropsied | 5 | 5 | 5 | 5 |
| No. of animals examined histologically | 5 | 5 | 5 | 5 |
| Organ | Findings | 1 | 2 | 3 |
| CARDIOVASCULAR SYSTEM | | | | |
| heart | (5) | 0 0 0 | (5) | 0 0 0 |
| edema | | 0 0 0 | | 1 0 0 |
| degeneration of myocardium | | 0 0 0 | | 0 0 0 |
| necrosis | | 0 0 0 | | 0 0 0 |
| cellular infiltration | | 1 0 0 | 2 0 0 | 3 0 0 |
| RESPIRATORY SYSTEM | | | | |
| lung | (5) | 1 0 0 | (0) | - - - |
| osseous metaplasia | | 1 0 0 | | - - - |
| DIGESTIVE SYSTEM | | | | |
| pancreas | (5) | 1 0 0 | (0) | - - - |
| atrophy, focal | | 1 0 0 | | - - - |
| cellular infiltration, lymphocyte | | 0 0 0 | | - - - |
| liver | (5) | 4 0 0 | (0) | - - - |
| fatty change | | 4 1 0 | | - - - |
| microgranuloma | | | | - - - |
| URINARY SYSTEM | | | | |
| kidney | (5) | 3 0 0 | (0) | - - - |
| basophilic tubules | | 2 0 0 | | - - - |
| mineralization | | 1 0 0 | | - - - |
| cellular infiltration, lymphocyte | | 0 0 0 | | - - - |
| fibrosis | | | | - - - |
| REPRODUCTIVE SYSTEM | | | | |
| uterus | (5) | 2 0 0 | (0) | - - - |
| dilatation, lumen | | 1 0 0 | | - - - |
| cellular infiltration | | | | - - - |
| vagina | (5) | 0 0 0 | (0) | - - - |
| epidermal cyst | | | | - - - |
| ENDOCRINE SYSTEM | | | | |
| thyroid gland | (5) | 1 0 0 | (0) | - - - |
| ectopic thymus | | | | - - - |

1: slight 2: moderate 3: marked

(): No. of animals examined microscopically at this site.

-: Not applicable.

Table 24. -continued Summary of histological findings (sacrificed at 42 Day)

Exp. No. 6393 (115-164)

Sex: Male

| Dose level (mg/kg) | 0 | 50 | 100 | 200 |
|--|----------|-------|-------|-------|
| No. of animals initially in study | 5 | 0 | 0 | 5 |
| No. of animals necropsied | 5 | 0 | 0 | 5 |
| No. of animals examined histologically | 5 | 0 | 0 | 5 |
| Organ | Findings | 1 | 2 | 3 |
| CARDIOVASCULAR SYSTEM | | | | |
| heart | (5) | 1 0 0 | - - - | - - - |
| cellular infiltration | | 0 0 0 | - - - | - - - |
| fibrosis | | | | 2 0 0 |
| HEMATOPOIETIC SYSTEM | | | | |
| spleen | (5) | 1 0 0 | - - - | - - - |
| capsulitis | | | | 0 0 0 |
| RESPIRATORY SYSTEM | | | | |
| lung | (5) | 1 0 0 | - - - | - - - |
| edema | | 1 0 0 | - - - | - - - |
| hemorrhage | | 1 0 0 | - - - | - - - |
| accumulation of macrophage | | 0 0 0 | - - - | - - - |
| osseous metaplasia | | 1 0 0 | - - - | - - - |
| DIGESTIVE SYSTEM | | | | |
| stomach | (5) | 1 0 0 | - - - | - - - |
| edema | | 1 0 0 | - - - | - - - |
| cellular infiltration | | | | 0 0 0 |
| pancreas | (5) | 0 0 0 | - - - | - - - |
| atrophy, focal | | 1 0 0 | - - - | - - - |
| cellular infiltration | | 2 0 0 | - - - | - - - |
| cellular infiltration, lymphocyte | | 1 0 0 | - - - | - - - |
| rectum | (5) | 1 0 0 | - - - | - - - |
| microgranuloma | | 1 0 0 | - - - | - - - |
| liver | (5) | 1 0 0 | - - - | - - - |
| fatty change | | 1 0 0 | - - - | - - - |
| microgranuloma | | 5 0 0 | - - - | - - - |
| extramedullary hematopoiesis | | 0 0 0 | - - - | - - - |
| mandibular gland | (5) | 3 0 0 | - - - | - - - |
| ectopic tissue | | | | 0 0 0 |
| URINARY SYSTEM | | | | |
| kidney | (5) | 4 0 0 | - - - | - - - |
| basophilic tubules | | 1 1 0 | - - - | - - - |
| hyaline droplet | | | | 5 0 0 |
| | | | | 5 0 0 |

1: slight 2: moderate 3: marked

(): No. of animals examined microscopically at this site.

-: Not applicable.

Table 24. -continued Summary of histological findings (sacrificed at 42 Day)

Exp. No. 6393 (115-164)

Sex: Male

| Dose level (mg/kg) | 0 | 50 | 100 | 200 |
|--|----------|----|-----|-----|
| No. of animals initially in study | 5 | 0 | 0 | 5 |
| No. of animals necropsied | 5 | 0 | 0 | 5 |
| No. of animals examined histologically | 5 | 0 | 0 | 5 |
| Organ | Findings | 1 | 2 | 3 |
| | | 1 | 2 | 3 |

| | | | | |
|-----------------------------------|-------|---|---|-------|
| URINARY SYSTEM | | | | |
| kidney | | | | |
| mineralization | 4 | 0 | 0 | |
| cellular infiltration, lymphocyte | 2 | 0 | 0 | |
| dilatation, renal pelvis | 2 | 0 | 0 | |
| REPRODUCTIVE SYSTEM | | | | |
| epididymis | (5) | | | (5) |
| cellular infiltration, lymphocyte | 1 | 0 | 0 | |
| prostate | (5) | | | (5) |
| cell debris, lumen | 0 | 0 | 0 | |
| cellular infiltration, lymphocyte | 2 | 1 | 0 | |
| ENDOCRINE SYSTEM | | | | |
| pituitary gland | (5) | | | (5) |
| cyst | 1 | 0 | 0 | |
| SPECIAL SENSE SYSTEM | | | | |
| eye | (5) | | | (5) |
| foreign body reaction | 1 | 0 | 0 | |

1: slight 2: moderate 3: marked

(): No. of animals examined microscopically at this site.

-: Not applicable.

Table 24. -continued Summary of histological findings (sacrificed at 42 Day)

Exp. No. 6393 (115-164)

Sex: Female

| Dose level (mg/kg) | 0 | 50 | 100 | 200 |
|--|----------|-------|-------|-------------|
| No. of animals initially in study | 5 | 0 | 0 | 5 |
| No. of animals necropsied | 5 | 0 | 0 | 5 |
| No. of animals examined histologically | 5 | 0 | 0 | 5 |
| Organ | Findings | 1 | 2 | 3 |
| CARDIOVASCULAR SYSTEM | | | | |
| heart | (5) | 3 0 0 | - - - | - - - |
| cellular infiltration | | | | (5) 2 0 0 |
| HEMATOPOIETIC SYSTEM | | | | |
| bone marrow | (5) | 1 0 0 | - - - | - - - |
| atrophy, focal | | | | (5) 0 0 0 |
| mandibular lymph node | (5) | 1 0 0 | - - - | - - - |
| ectopic tissue | | | | (5) 0 0 0 |
| DIGESTIVE SYSTEM | | | | |
| pancreas | (5) | 0 0 0 | - - - | - - - |
| atrophy, focal | | | | (5) 1 0 0 |
| cellular infiltration | | | | 0 0 0 |
| cellular infiltration, lymphocyte | | | | 1 0 0 |
| liver | (5) | 1 0 0 | - - - | - - - |
| deformation | | | | (5) 0 0 0 |
| fatty change | | | | 1 0 0 |
| microgranuloma | | | | 5 0 0 |
| mandibular gland | (5) | 4 0 0 | - - - | - - - |
| ectopic tissue | | | | (5) 2 0 0 |
| URINARY SYSTEM | | | | |
| kidney | (5) | 1 0 0 | - - - | - - - |
| basophilic tubules | | | | (5) 2 0 0 |
| mineralization | | | | 3 0 0 |
| REPRODUCTIVE SYSTEM | | | | |
| uterus | (5) | 1 0 0 | - - - | - - - |
| dilatation, lumen | | | | (5) 3 0 0 |
| ENDOCRINE SYSTEM | | | | |
| thyroid gland | (5) | 1 0 0 | - - - | - - - |
| cellular infiltration, lymphocyte | | | | (5) 0 0 0 |
| ultimobranchial remnant | | | | 1 0 0 |

1: slight 2: moderate 3: marked

(): No. of animals examined microscopically at this site.

- : Not applicable.

Table 24. -continued Summary of histological findings (sacrificed at 42 Day)

Exp. No. 6393 (115-164)

Sex: Female

| Dose level (mg/kg) | 0 | 50 | 100 | 200 |
|--|----------|----|-----|-----|
| No. of animals initially in study | 5 | 0 | 0 | 5 |
| No. of animals necropsied | 5 | 0 | 0 | 5 |
| No. of animals examined histologically | 5 | 0 | 0 | 5 |
| Organ | Findings | 1 | 2 | 3 |

INTEGUMENTARY SYSTEM

| skin | (1) | (0) | | |
|-----------------------|-------|-------|---|---|
| cellular infiltration | 1 0 0 | - | - | - |
| fibrosis | 1 0 0 | - | - | - |
| squamous hyperplasia | 1 0 0 | - | - | - |

1: slight 2: moderate 3: marked

(): No. of animals examined microscopically at this site.

-: Not applicable.

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Table 25.

Summary of histological findings (dead or moribund)

Exp. No. 6393 (115-164)

Sex: Male

| Dose level (mg/kg) | 0 | 50 | 100 | 200 |
|--|---|----|-----|-------|
| No. of animals initially in study | 0 | 0 | 0 | 1 |
| No. of animals necropsied | 0 | 0 | 0 | 1 |
| No. of animals examined histologically | 0 | 0 | 0 | 1 |
| Organ Findings | 1 | 2 | 3 | 1 |
| CARDIOVASCULAR SYSTEM | | | | |
| heart | | | | (1) |
| degeneration of myocardium | - | - | - | 0 1 0 |
| cellular infiltration | - | - | - | 1 0 0 |
| HEMATOPOIETIC SYSTEM | | | | |
| spleen | | | | (1) |
| atrophy, white pulp | - | - | - | 1 0 0 |
| lymph node | | | | (1) |
| congestion | - | - | - | 1 0 0 |
| mesenteric lymph node | | | | (1) |
| atrophy, follicle | - | - | - | 1 0 0 |
| mandibular lymph node | | | | (1) |
| congestion | - | - | - | 1 0 0 |
| atrophy, follicle | - | - | - | 1 0 0 |
| thymus | | | | (1) |
| hemorrhage | - | - | - | 1 0 0 |
| RESPIRATORY SYSTEM | | | | |
| lung | | | | (1) |
| congestion | - | - | - | 1 0 0 |
| edema | - | - | - | 1 0 0 |
| hemorrhage | - | - | - | 1 0 0 |
| accumulation of macrophage | - | - | - | 1 0 0 |
| DIGESTIVE SYSTEM | | | | |
| pancreas | | | | (1) |
| hemorrhage | - | - | - | 1 0 0 |
| liver | | | | (1) |
| congestion | - | - | - | 1 0 0 |
| eosinophilic body | - | - | - | 1 0 0 |
| fatty change | - | - | - | 1 0 0 |
| mitosis | - | - | - | 1 0 0 |
| hypertrophy, hepatocyte | - | - | - | 1 0 0 |

1: slight 2: moderate 3: marked

(): No. of animals examined microscopically at this site.

-: Not applicable.

Table 26. Summary of histological findings in dosed and recovery experiments (sacrificed) Exp. No. 6393 (115-164)

Sex: Male

| Dose level Day | (mg/kg) | 0 | | | 200 | | | | | | | | |
|--|-----------|--------|---|---|--------|-------|---|--------|---|-------|--------|---|-------|
| | | 28 day | | | 42 day | | | 28 day | | | 42 day | | |
| No. of animals initially in study | | 5 | | 5 | | 4 | | 5 | | 5 | | 5 | |
| No. of animals necropsied | | 5 | | 5 | | 4 | | 5 | | 5 | | 5 | |
| No. of animals examined histologically | | 5 | | 5 | | 4 | | 5 | | 5 | | 5 | |
| Organ | Findings | T | 1 | 2 | 3 | T | 1 | 2 | 3 | T | 1 | 2 | 3 |
| CARDIOVASCULAR SYSTEM | | | | | | | | | | | | | |
| heart | | (5) | | | | (5) | | | | (4) | | | (5) |
| degeneration of myocardium | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 1 | 0 |
| necrosis | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 1 | 0 |
| cellular infiltration | - | 2 | 0 | 0 | | - | 1 | 0 | 0 | - | 1 | 3 | 0 |
| fibrosis | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| HEMATOPOIETIC SYSTEM | | | | | | | | | | | | | |
| bone marrow | | (5) | | | | (5) | | | | (4) | | | (5) |
| erythropoiesis, decreased | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| spleen | | (5) | | | | (5) | | | | (4) | | | (5) |
| atrophy, white pulp | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| erythropoiesis, decreased | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| capsulitis | - | 0 | 0 | 0 | | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| mesenteric lymph node | | (5) | | | | (5) | | | | (4) | | | (5) |
| karyorrhexis | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| mandibular lymph node | | (5) | | | | (5) | | | | (4) | | | (5) |
| karyorrhexis | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| single cell necrosis | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| thymus | | (5) | | | | (5) | | | | (4) | | | (5) |
| karyorrhexis | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| RESPIRATORY SYSTEM | | | | | | | | | | | | | |
| lung | | (5) | | | | (5) | | | | (4) | | | (5) |
| edema | - | 0 | 0 | 0 | | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| hemorrhage | - | 1 | 0 | 0 | | - | 1 | 0 | 0 | - | 1 | 0 | 0 |
| accumulation of foamy cells | - | 1 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| deposit, hematoidin crystal | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| accumulation of macrophage | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| osseous metaplasia | - | 0 | 0 | 0 | | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | |
| stomach | | (5) | | | | (5) | | | | (4) | | | (5) |
| edema | - | 0 | 0 | 0 | | - | 1 | 0 | 0 | - | 1 | 0 | 0 |
| hemorrhage | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| cellular infiltration | - | 0 | 0 | 0 | | - | 1 | 0 | 0 | - | 1 | 0 | 0 |
| squamous hyperplasia | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |

T: tumor 1: slight 2: moderate 3: marked
 (): No. of animals examined microscopically at this site.

-: Not applicable.

Table 26. -continued Summary of histological findings in dosed and recovery experiments (sacrificed) Exp. No. 6393 (115-164)

Sex: Male

| Dose level Day | | 0 | | | 28 day | | | 42 day | | | 28 day | | | 200 | | | 42 day | | | | |
|--|-----------------------------------|-------|---|---|--------|---|-------|--------|---|---|--------|---|---|-----|-------|---|--------|---|---|---|---|
| | | T | 1 | 2 | 3 | T | 1 | 2 | 3 | T | 1 | 2 | 3 | T | 1 | 2 | 3 | T | 1 | 2 | 3 |
| No. of animals initially in study | | | 5 | | | | 5 | | | | 4 | | | | | 5 | | | | | |
| No. of animals necropsied | | | 5 | | | | 5 | | | | 4 | | | | | 5 | | | | | |
| No. of animals examined histologically | | | 5 | | | | 5 | | | | 4 | | | | | 5 | | | | | |
| Organ | Findings | | | | | | | | | | | | | | | | | | | | |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | |
| pancreas | | (5) | | | | | (5) | | | | (4) | | | | (5) | | | | | | |
| | atrophy, focal | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 | | | |
| | decrease, zymogen granules | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 | | | |
| | cellular infiltration | - | 0 | 0 | 0 | | - | 1 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 | | | |
| | cellular infiltration, lymphocyte | - | 0 | 0 | 0 | | - | 2 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 | | | |
| | proliferation, duct | - | 0 | 0 | 0 | | - | 1 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 | | | |
| duodenum | | (5) | | | | | (5) | | | | (4) | | | | (5) | | | | | | |
| | degeneration, vacuolar | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 | | | |
| jejunum | | (5) | | | | | (5) | | | | (4) | | | | (5) | | | | | | |
| | degeneration, vacuolar | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 | | | |
| ileum | | (5) | | | | | (5) | | | | (4) | | | | (5) | | | | | | |
| | degeneration, vacuolar | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 | | | |
| rectum | | (5) | | | | | (5) | | | | (4) | | | | (5) | | | | | | |
| | microgranuloma | - | 0 | 0 | 0 | | - | 1 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 | | | |
| liver | | (5) | | | | | (5) | | | | (4) | | | | (5) | | | | | | |
| | congestion | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 | | | |
| | eosinophilic body | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 | | | |
| | fatty change | - | 1 | 0 | 0 | | - | 1 | 0 | 0 | - | 1 | 1 | 0 | - | 0 | 0 | 0 | | | |
| | mitosis | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 | | | |
| | microgranuloma | - | 5 | 0 | 0 | | - | 5 | 0 | 0 | - | 4 | 0 | 0 | - | 5 | 0 | 0 | | | |
| | extramedullary hematopoiesis | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 2 | 0 | 0 | | | |
| | fibrosis | - | 1 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 | | | |
| mandibular gland | | (5) | | | | | (5) | | | | (4) | | | | (5) | | | | | | |
| | ectopic tissue | - | 0 | 0 | 0 | | - | 3 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 | | | |
| URINARY SYSTEM | | | | | | | | | | | | | | | | | | | | | |
| kidney | | (5) | | | | | (5) | | | | (4) | | | | (5) | | | | | | |
| | edema | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 | | | |
| | basophilic tubules | - | 5 | 0 | 0 | | - | 4 | 0 | 0 | - | 3 | 0 | 0 | - | 5 | 0 | 0 | | | |
| | cyst | - | 1 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 | | | |
| | hyaline droplet | - | 0 | 0 | 0 | | - | 1 | 1 | 0 | - | 3 | 0 | 0 | - | 5 | 0 | 0 | | | |
| | mineralization | - | 2 | 0 | 0 | | - | 4 | 0 | 0 | - | 2 | 0 | 0 | - | 5 | 0 | 0 | | | |
| | cellular infiltration, lymphocyte | - | 0 | 0 | 0 | | - | 2 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 | | | |
| | dilatation, renal pelvis | - | 0 | 0 | 0 | | - | 2 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 | | | |
| urinary bladder | | (5) | | | | | (5) | | | | (4) | | | | (5) | | | | | | |
| | edema | - | 1 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 | | | |

T: tumor 1: slight 2: moderate 3: marked
 (): No. of animals examined microscopically at this site.

-: Not applicable.

Table 26. -continued Summary of histological findings in dosed and recovery experiments (sacrificed) Exp. No. 6393 (115-164)

Sex: Male

| Dose level Day | (mg/kg) | 0 | | | 200 | | | | | | | | |
|--|-----------------------------------|--------|---|---|--------|-------|---|--------|---|-------|--------|---|-------|
| | | 28 day | | | 42 day | | | 28 day | | | 42 day | | |
| No. of animals initially in study | | 5 | | 5 | | 4 | | 5 | | 4 | | 5 | |
| No. of animals necropsied | | 5 | | 5 | | 4 | | 5 | | 4 | | 5 | |
| No. of animals examined histologically | | 5 | | 5 | | 4 | | 5 | | 4 | | 5 | |
| Organ | Findings | T | 1 | 2 | 3 | T | 1 | 2 | 3 | T | 1 | 2 | 3 |
| URINARY SYSTEM | | | | | | | | | | | | | |
| urinary bladder | | | | | | | | | | | | | |
| cellular infiltration | | - | 1 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| transitional cell hyperplasia | | - | 1 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| REPRODUCTIVE SYSTEM | | | | | | | | | | | | | |
| testis | | (5) | | | | (5) | | | | (4) | | | (5) |
| epididymis | single cell necrosis | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| | | (5) | | | | (5) | | | | (4) | | | (5) |
| | cell debris, lumen | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| | cellular infiltration | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| | cellular infiltration, lymphocyte | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| prostate | | (5) | | | | (5) | | | | (4) | | | (5) |
| | cell debris, lumen | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| | single cell necrosis | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| | cellular infiltration, lymphocyte | - | 0 | 1 | 0 | - | 2 | 1 | 0 | - | 1 | 0 | 0 |
| seminal vesicle | | (5) | | | | (5) | | | | (4) | | | (5) |
| | hyposecretory change | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| | | | | | | | | | | - | 0 | 0 | 0 |
| ENDOCRINE SYSTEM | | | | | | | | | | | | | |
| pituitary gland | | (5) | | | | (5) | | | | (4) | | | (5) |
| cyst | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| SPECIAL SENSE SYSTEM | | | | | | | | | | | | | |
| eye | | (5) | | | | (5) | | | | (4) | | | (5) |
| foreign body reaction | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 |

T: tumor 1: slight 2: moderate 3: marked
 (): No. of animals examined microscopically at this site.

-: Not applicable.

Table 26. -continued Summary of histological findings in dosed and recovery experiments (sacrificed) Exp. No. 6393 (115-164)

Sex: Female

| Dose level Day | (mg/kg) | 0 | | | 200 | | | 42 day | | | | | |
|--|-----------|--------|---|---|--------|-------|---|--------|---|-------|--------|---|-------|
| | | 28 day | | | 42 day | | | 28 day | | | 42 day | | |
| No. of animals initially in study | | 5 | | 5 | | 5 | | 5 | | 5 | | 5 | |
| No. of animals necropsied | | 5 | | 5 | | 5 | | 5 | | 5 | | 5 | |
| No. of animals examined histologically | | 5 | | 5 | | 5 | | 5 | | 5 | | 5 | |
| Organ | Findings | T | 1 | 2 | 3 | T | 1 | 2 | 3 | T | 1 | 2 | 3 |
| CARDIOVASCULAR SYSTEM | | | | | | | | | | | | | |
| heart | | (5) | | | | (5) | | | | (5) | | | (5) |
| degeneration of myocardium | | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 3 | 0 | 0 |
| necrosis | | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 1 | 0 |
| cellular infiltration | | - | 1 | 0 | 0 | - | 3 | 0 | 0 | - | 0 | 2 | 1 |
| HEMATOPOIETIC SYSTEM | | | | | | | | | | | | | |
| bone marrow | | (5) | | | | (5) | | | | (5) | | | (5) |
| atrophy, focal | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| mandibular lymph node | | (5) | | | | (5) | | | | (5) | | | (5) |
| ectopic tissue | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| RESPIRATORY SYSTEM | | | | | | | | | | | | | |
| lung | | (5) | | | | (5) | | | | (5) | | | (5) |
| osseous metaplasia | | - | 1 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | |
| pancreas | | (5) | | | | (5) | | | | (5) | | | (5) |
| atrophy, focal | | - | 1 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| cellular infiltration | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| cellular infiltration, lymphocyte | | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| liver | | (5) | | | | (5) | | | | (5) | | | (5) |
| deformation | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| fatty change | | - | 4 | 0 | 0 | - | 1 | 0 | 0 | - | 4 | 0 | 0 |
| microgranuloma | | - | 4 | 1 | 0 | - | 4 | 0 | 0 | - | 4 | 0 | 0 |
| mandibular gland | | (5) | | | | (5) | | | | (5) | | | (5) |
| ectopic tissue | | - | 0 | 0 | 0 | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| URINARY SYSTEM | | | | | | | | | | | | | |
| kidney | | (5) | | | | (5) | | | | (5) | | | (5) |
| basophilic tubules | | - | 3 | 0 | 0 | - | 1 | 0 | 0 | - | 4 | 0 | 0 |
| mineralization | | - | 2 | 0 | 0 | - | 2 | 0 | 0 | - | 3 | 0 | 0 |
| cellular infiltration, lymphocyte | | - | 1 | 0 | 0 | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| fibrosis | | - | 0 | 0 | 0 | - | 0 | 0 | 0 | - | 1 | 0 | 0 |

T: tumor 1: slight 2: moderate 3: marked

(): No. of animals examined microscopically at this site.

-: Not applicable.

Table 26. -continued Summary of histological findings in dosed and recovery experiments (sacrificed) Exp. No. 6393 (115-164)

Sex: Female

| Dose level Day | | 0 | | | 200 | | | | | | | | |
|--|----------|--------|---|---|--------|-------|---|--------|---|-------|--------|---|-------|
| | | 28 day | | | 42 day | | | 28 day | | | 42 day | | |
| No. of animals initially in study | | 5 | | 5 | | 5 | | 5 | | 5 | | 5 | |
| No. of animals necropsied | | 5 | | 5 | | 5 | | 5 | | 5 | | 5 | |
| No. of animals examined histologically | | 5 | | 5 | | 5 | | 5 | | 5 | | 5 | |
| Organ | Findings | T | 1 | 2 | 3 | T | 1 | 2 | 3 | T | 1 | 2 | 3 |
| REPRODUCTIVE SYSTEM | | | | | | | | | | | | | |
| uterus | (5) | | | | | (5) | | | | (5) | | | (5) |
| dilatation, lumen | - | 2 | 0 | 0 | | - | 1 | 0 | 0 | - | 1 | 0 | 0 |
| cellular infiltration | - | 1 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| vagina | (5) | | | | | (5) | | | | (5) | | | (5) |
| epidermal cyst | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 1 | 0 | 0 |
| ENDOCRINE SYSTEM | | | | | | | | | | | | | |
| thyroid gland | (5) | | | | | (5) | | | | (5) | | | (5) |
| cellular infiltration, lymphocyte | - | 0 | 0 | 0 | | - | 1 | 0 | 0 | - | 0 | 0 | 0 |
| ectopic thymus | - | 1 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| ultimobranchial remnant | - | 0 | 0 | 0 | | - | 0 | 0 | 0 | - | 0 | 0 | 0 |
| INTEGUMENTARY SYSTEM | | | | | | | | | | | | | |
| skin | (0) | | | | | (1) | | | | (0) | | | (0) |
| cellular infiltration | - | - | - | - | | - | 1 | 0 | 0 | - | - | - | - |
| fibrosis | - | - | - | - | | - | 1 | 0 | 0 | - | - | - | - |
| squamous hyperplasia | - | - | - | - | | - | 1 | 0 | 0 | - | - | - | - |

T: tumor 1: slight 2: moderate 3: marked
 (): No. of animals examined microscopically at this site.

-: Not applicable.