最 終 報 告 書

2-ニトロ-p-クレゾールのラットを用いる 28 日間反復経口投与毒性試験

（試験番号：06-085）

財団法人 畜産生物科学安全研究所

陳　述　書

試験の表題

2-ニトロ-p-クレゾールのラットを用いる28日間反復経口投与毒性試験

（試験番号：06-085）

本試験は、化審法の試験法ガイドライン「新規化学物質に係る試験の方法について」（平成15年11月21日付け薬食発第1121002号厚生労働省医薬食品局長、平成15・11・13製局第2号経済産業省製造産業局長、環保企初第031121002号環境省総合環境政策局長、連名通知）及び化審法のGLP「新規化学物質等に係わる試験を実施する試験施設に関する基準について」（平成15年11月21日付け薬食発第1121003号厚生労働省医薬食品局長、平成15年・11・17製局第3号経済産業省製造産業局長、環保企発第031121004号環境省総合環境政策局長、連名通知）に定める基準に準拠して実施した。

試験責任者

安全性研究部　首席研究員

[redacted]

平成23年 6月23日

試験の表題

2-ニトロ-p-クレゾールのラットを用いる28日間反復経口投与毒性試験

（試験番号：06-085）

試験委託者

名　　称	厚生労働省 医薬食品局
所 在 地	東京都千代田区霞が関 1-2-2
委託責任者	審査管理課 化学物質安全対策室

試験実施施設

名　　称	財団法人　畜産生物科学安全研究所
所 在 地	神奈川県相模原市橋本台 3-7-11
運営管理者	専務理事
試験責任者	安全性研究部　首席研究員 [redacted]
信頼性保証責任者	信頼性保証室　首席研究員 [redacted]

試験日程

試験開始	平成18年12月28日
動物搬入	平成19年 1 月4日
群分け	平成19年 1 月10日（雄）、1 月11日（雌）
投与開始	平成19年 1 月11日（雄）、1 月12日（雌）
投与終了	平成19年 2 月7日（雄）、2 月8日（雌）
剖検	平成19年 2 月8日（雄）、2 月9日（雌）
回復群剖検	平成19年 2 月22日（雄）、2 月23日（雌）
実験終了	平成21年 2 月28日
試験終了	平成23年 6 月23日

試験成績の信頼性に影響を及ぼす疑いのある事態及び試験計画書からの逸脱

本試験に関し、予見することのできなかった試験成績の信頼性に影響を及ぼす疑いのある事態および試験計画書からの逸脱はなかった。

試資料の保管

次に示す本試験に関する一連の関係試資料は、試験終了後10年間、財団法人 畜産生物科学安全研究所において保管する。その後の処置については、試験委託者と協議して決定する。

1) 試験計画書
2) 被験物質に関する記録およびそのサンプル
3) 供試動物に関する記録
4) 試験結果に関する記録（臨床観察、機能検査、体重、摂餌量、尿検査、血液学検査、血液生化学検査、剖検、器官重量、病理組織学的検査などの生データ）
5) 血液塗抹標本および病理標本（固定器官、包埋ブロック、組織標本）
6) 信頼性保証に関する記録
7) 最終報告書

試験責任者の署名および試験担当者の業務分担

試　験　責　任　者

財団法人　畜産生物科学安全研究所

安全性研究部　首席研究員

氏名 [redacted]　平成23年 6月23日

試験担当者およびその業務分担

検疫責任者 : [redacted]

投与液の調製・分析 :

動物飼育・投与・臨床観察 :

臨床検査 :

病理検査 :

信頼性保証証明書

試験表題 ：2-ニトロ-p-クレゾールのラットを用いる28日間反復経口投与毒性試験

試験番号 ： 06-085

審査・査察実施日	試験責任者への報告日	運営管理者への報告日
1. 試験計画書審査		
平成18年12月28日	平成18年12月28日	平成18年12月28日
2. 試験計画書記載事項変更審査		
(変-1)		
平成20年04月25日	平成20年04月25日	平成20年04月25日
(変-2)		
平成22年07月16日	平成22年07月16日	平成22年07月16日
3. 試験実施状況査察		
動物導入		
平成19年01月04日	平成19年01月04日	平成19年01月04日
検　疫		
平成19年01月05日	平成19年01月05日	平成19年01月05日
被験物質調製		
平成19年01月09日	平成19年01月09日	平成19年01月09日
群分け・個体識別・詳細な臨床観察		
平成19年01月10日	平成19年01月10日	平成19年01月10日
体重測定・投与・症状観察		
平成19年01月11日	平成19年01月11日	平成19年01月11日
餌測定		
平成19年01月15日	平成19年01月15日	平成19年01月15日
体重測定・投与・症状観察・詳細な臨床観察		
平成19年01月24日	平成19年01月24日	平成19年01月24日
尿検査		
平成19年02月02日	平成19年02月02日	平成19年02月02日
餌測定・感覚機能検査・握力測定・自発運動量測定		
平成19年02月06日	平成19年02月06日	平成19年02月06日
解　剖・病理組織標本作製（臓器・組織の固定）・血液検査		
平成19年02月08日	平成19年02月08日	平成19年02月08日
血液生化学検査		
平成19年02月14日	平成19年02月14日	平成19年02月14日
病理組織標本作製(切り出し)		
平成19年03月08日	平成19年03月08日	平成19年03月08日

審査・査察実施日	試験責任者への報告日	運営管理者への報告日
病理組織標本作製(包埋) 平成19年03月12日	平成19年03月12日	平成19年03月12日
病理組織標本作製(染色) 平成19年03月22日	平成19年03月22日	平成19年03月22日
病理組織標本作製(薄切) 平成19年04月02日	平成19年04月02日	平成19年04月02日
4. 生データ査察 平成22年04月26日 ～ 同年04月27日	平成22年04月27日	平成22年04月27日
5. 報告書（草案）審査 平成22年04月27日 ～ 同年04月30日	平成22年04月30日	平成22年04月30日
6. 最終報告書審査 平成23年06月23日	平成23年06月23日	平成23年06月23日

上記の審査・査察により、本試験が「化審法 GLP」に従って実施され、本報告書には、当該試験で使用した方法・手順が忠実に記載され、試験成績には、当該試験の実施過程において得られた生データが正確に反映されていることを確認した。

平成 23 年 6 月 23 日
財団法人　畜産生物科学安全研究所

信頼性保証責任者 [redacted]

目　次

要　約

2-ニトロ-p-クレゾールの 28 日間反復経口投与毒性試験を、SD 系ラットを用いて実施した。投与量は、0（対照：被験物質の溶媒として用いたオリブ油を投与）、15、60、250 および 1000 mg/kg/day とし、対照群および 1000 mg/kg 群は 14 日間の回復群として用いる雌雄各 5 匹を含む雌雄各 10 匹、15、60 および 250 mg/kg 群はそれぞれ雌雄各 5 匹を使用して試験を行った。

250 mg/kg 以上の群で、沈静および眼瞼下垂が雌は投与 1 日のみ、雄は投与 2 日まで認められた。尿検査では、1000 mg/kg 群で雌雄に、尿 pH の有意な低値が認められた。血液学検査では、1000 mg/kg 群で雌雄に、血色素量、ヘマトクリット値および平均赤血球血色素濃度の有意な低値並びに網状赤血球数の有意な高値、さらに雌に活性化部分トロンボプラスチン時間の有意な延長が認められた。血液生化学検査では、1000 mg/kg 群で雄に、アルブミン、A/G 比、総コレステロールおよびカリウム、雌にγ-GTP および総ビリルビンのいずれも有意な高値が認められた。器官重量では、250 mg/kg 群で雌に肝臓の相対重量、1000 mg/kg 群では雌雄に肝臓の絶対および相対重量、雄に腎臓の相対重量並びに脾臓の絶対および相対重量、雌に脾臓の相対重量のいずれも有意な高値が認められた。病理組織学検査では、250 mg/kg 群で雌に肝臓の肝細胞肥大、1000 mg/kg 群で雌雄に肝臓の肝細胞肥大並びに脾臓の髄外造血および褐色色素沈着の増加、雄に腎臓の近位尿細管上皮へのα-2u-グロブリンの沈着による硝子滴の増加が認められ、1000 mg/kg 群の脾臓は、肉眼的に黒色化する傾向にあった。

回復群においては、脾臓の褐色色素沈着の増加およびそれに伴う色調の変化を除き、発現した毒性はいずれも回復しており、可逆的な変化であることが確認された。また、遅発毒性と考えられる変化も認められなかった。

以上の結果から、4-ニトロ-p-クレゾールのラットへの 28 日間反復経口投与により、肝臓および血液等に対する影響並びに関連する血液生化学的変化および脾臓の変化等が認められた。無影響量（NOEL）は雌雄とも 60 mg/kg/day、無毒性量（NOAEL）は雄で 250 mg/kg/day、雌で 60 mg/kg/day と結論された。

目　的

2-ニトロ-p-クレゾールをラットに 28 日間経口投与し、本物質の反復投与毒性について検討した。

材料および方法

1. 被験物質

2-ニトロ-p-クレゾールは、水に難溶、食物油に可溶な淡黄色塊状物である。試験には、東京化成工業株式会社(東京都中央区日本橋本町 4-10-1)より試薬(ロット番号 FBR01、純度 99.8%）を購入し、冷暗所（2～6℃）・密栓下で保管し、使用した。用いた被験物質は投与終了後に分析し、使用期間中安定であったことを確認した（Appendix 1)。本物質の特性は、Appendix 1 に示す。

被験物質の投与液は局方オリブ油（宮澤薬品株式会社，ロット番号 BH17）を溶媒とし、所定の投与用量となる濃度の溶液に調製した。調製した投与液は、1 日の使用量ごとに小分けし、使用時まで冷所（2～6℃）・遮光下で密栓して保管した。冷所遮光下で 7 日間、その後室温遮光下で 1 日保管した投与液中の被験物質は安定であることが確認された（Appendix 2）ので、調製後 7 日以内に使用した。初回に調製された投与液について分析し、所定の濃度で調製されていることを確認した（Appendix 3)。

2. 動物および飼育条件

動物は、SD 系 [Crl : CD(SD)]ラットを用いた。ラットは、日本チャールス・リバー株式会社 厚木飼育センター（神奈川県厚木市下古沢 795）から 4 週齢のものを搬入（雄 42 匹、雌 42 匹）し、雄は 7 日間、雌は 8 日間試験環境に馴化させた。馴化期間中に検疫を行い、発育および一般健康状態が良好なものについて、投与開始前日に体重を測定し、雌雄それぞれ全動物の体重の平均値に近いものから各 35 匹を選び、体重により層別化した後、動物を無作為に各群に振り分け、各群の体重分布が均一となるようにした。試験は 5 週齢で開始した。投与開始時の平均体重(体重範囲)は、雄 161（146～173）g、雌 144（130～154）g であった。ラットは、温度 22±3℃、 湿度 55±10%、換気回数 10 回以上／時（オールフレッシュエアー方式)、照明 12 時間／日(午前 7 時点灯、午後 7 時消灯)に設定したバリアーシステム動物室（第 4 室）で、個体別にステンレス製金

網ケージ〔260W×380D×180 H(mm)〕に収容し、これをステンレス製5段のラックに配置して飼育した。飼料（固型飼料ラボ MR ストック、日本農産工業株式会社、ロット番号 060963、0611164）および飲料水（孔径 1μm のカートリッジフィルターで濾過後紫外線照射した殺菌水道水）は、それぞれ給餌器および自動給水装置または給水瓶（ポリカーボネートケージの場合）により、自由に摂取させた。

動物の個体識別は、ラックおよびケージへの標識札の貼付、並びに耳パンチ法により行った。

飼育期間中、動物室の温度は 22.0～22.6℃、湿度は 55～62%の範囲で推移（Appendix 4）した。また、飼料の分析結果（Appendix 5）は、米国環境保護庁毒性物質規制法の「飼料および媒体の汚染物質限度（1979）」等を参考にして当研究所が設定した許容範囲内にあり、飲料水は水道法に基づく水質基準に適合する（Appendix 6）ことが確認された。したがって、動物の飼育期間を通じて、試験成績の信頼性に影響を及ぼすと思われる環境要因の変化はなかったものと判断された。

本試験は、動物実験を科学的観点および倫理的な配慮の下に実施するために遵守すべき事項等を定めた、「財団法人 畜産生物科学安全研究所の動物実験実施規定」に従い、本施設の動物実験委員会の承認を得て行った。

3. 投与量の設定、試験群の構成および投与方法

投与量設定試験として、1群雌雄各3匹の SD 系 [Crl : CD(SD)]ラットに、本物質を 0（対照：オリブ油投与）、10、30、100、250、500 および 1000 mg/kg/day の用量で、14 日間経口投与した結果、500 mg/kg 以上の群で雌雄に沈静、流涎などの症状および尿の酸性化傾向が認められた。さらに、1000 mg/kg 群では血液学検査で軽度な貧血所見および血液生化学検査で肝機能に対する影響が示唆される変化が認められた。器官重量では、250 mg/kg 以上の群で雌雄に肝臓重量の高値傾向が認められた。

従って、本試験における投与量については、28 日間の反復投与により毒性影響が発現すると予測される 1000 mg/kg/day を最高用量，毒性影響が発現しないと予測される 15 mg/kg/day を最低用量とし，その間に 60 および 250 mg/kg/day の計 4 用量を設定した。

試験群の構成は、①溶媒投与群（以下、対照群）、②被験物質の 15 mg/kg/day 投与

群（15 mg/kg 群）、③同 60 mg/kg/day 投与群（60 mg/kg 群）、④同 250 mg/kg/day 投与群（250 mg/kg 群）、⑤同 1000 mg/kg/day 投与群（1000 mg/kg 群）の 5 群とした。1 群の動物数は雌雄各 5 匹とした。さらに対照群と最高用量群については、現れる変化の回復性を調べるためのサテライト群として、別に雌雄各 5 匹からなる回復群を設けた。

投与方法は、投与液量を体重 1kg 当たり 5 mL とし、テフロン製胃ゾンデを装着した注射筒を用いて、1 日 1 回、28 日間にわたって胃内に投与した。投与は午前中（8：53～10：59）に行った。対照群には、溶媒として用いた局方オリブ油を同様に投与した。各個体の投与液量は、至近日の測定体重を基に算出した。

4. 観察および検査

28 日間の投与期間中あるいは投与期間終了時、および 14 日間の回復期間中あるいは回復期間終了時に、次の観察および検査を行った。

1) 一般状態

全例について、毎日、投与期間においては投与前、投与直後、投与後概ね 30 分～1 時間および 4 時間以降の 4 回、回復期間においては少なくとも 1 日 1 回は主にケージサイドで、動物の生死、外観、行動等について観察した。

2) 機能観察総合検査

(1) 詳細な臨床観察

全例について、投与開始前日およびその後は週 1 回、ケージサイドでの観察に加えて、動物をケージから取り出す時およびケージ外のアルミ製オープンフィールド（370W×560D×40Hmm）で、ケージからの出し易さ、ケージから出す時の扱い易さ、体躯緊張(弛緩～強直)、皮膚（色）、毛並み、立毛、眼瞼閉鎖状態、眼球突出、流涙、眼・鼻分泌物、流涎、下腹部被毛の尿による汚れ、肛門周囲の便による汚れ、発声、呼吸、姿勢、痙攣、振戦、探索行動(覚醒度)、歩行（よろめき）、異常行動（自咬、後ろ向き歩行等）、常同行動（過度の毛繕い、反復旋回運動等）、排尿（回数）および排糞（個数）について観察し、認められた変化を評点（Appendix 6）で記録した。動物には無作為化法で観察番号を付け、 観察者以外の者が群や動物番号を表示したケージの標識札を観察番号のみ表示した標識札に替え、観察者は観察番号順に観察を行うことにより、投与内容が不明な状態で観察した。

(2) 感覚機能検査

投与期間終了時屠殺動物は投与 4 週（雌雄とも投与 27 日）に、回復期間終了時屠殺動物は回復 2 週（雌雄とも回復 13 日）に、聴覚反応（ピンセットで軽くケージを叩く音に対する反応）、視覚反応（顔面に棒を近づけた場合の接近反応）、触覚反応（腰部に触れた場合の反応）、痛覚反応（尾根部をピンセットで摘んだ場合の逃避、発声等の反応）、瞳孔反射（光に対する瞳孔の反応）および正向反射（面上で動物を背臥位にした場合の正常姿勢にもどる反応）を調べ、認められた反応を評点（Appendix 7）で記録した。

(3) 握力および自発運動量

投与期間終了時屠殺動物は、投与 4 週（雌雄とも投与 27 日）に、回復期間終了時屠殺動物は回復 2 週（雌雄とも回復 13 日）に前肢および後肢の握力（ラット・マウス用握力測定装置、MK-380R/FR、室町機械株式会社）並びに自発運動量（自発運動量測定装置、SUPERMEX、室町機械株式会社、動物が発する遠赤外線をセンサーが感知し、測定装置内の区画間の 60 分間における移動回数を測定）の測定を行った。

3) 体重および摂餌量

体重は、投与 1 日（投与開始直前）、7、14、21 および 28 日並びに回復 7 および 14 日に測定し、投与期間中および回復期間中の体重増加量を算出した。また屠殺日に測定し、器官の相対重量の算出に用いた。

摂餌量は、毎週 1 回、雄は投与 5、12、19 および 26 日並びに回復 5 および 12 日、雌は投与 4、11、18 および 25 日並びに回復 4 および 11 日に、それぞれ翌日までの 24 時間の摂餌量（飼料消費量）を測定した。

体重および摂餌量の測定には、電子天秤（FY-3000, GX-2000、エー・アンド・ディ株式会社）を用いた。

4) 尿検査

投与 4 週（雌雄とも投与 22～23 日）に、回復群は回復 2 週（雌雄とも回復 8～9 日）に動物を約 3 時間代謝ケージに収容し、得られた尿について、外観の観察、試験紙法（マルティスティックス、バイエルメディカル株式会社）による pH、タンパク、糖、潜血およびウロビリノーゲンの定性的検査並びに沈渣の検査（URI-CELL 液、ケンブリッジケミカルプロダクト社、で染色して鏡検）を行った。さらに、18 時間収容して得ら

れた尿について、尿量および比重（屈折計、エルマ光学株式会社）を測定した。

5) 血液学検査

投与期間終了時生存動物については最終投与の翌日、回復群については回復期間終了日の翌日に、エーテル麻酔下で開腹して腹大動脈より採血した。動物は前日の午後5時より除餌し、水のみを給与した。採取した血液は3分割し、その一部はEDTA-2Kで凝固阻止処理し、多項目自動血球計数装置（XT-2000iV、シスメックス株式会社）により、赤血球数（電気抵抗検出法）、血色素量（ラウリル硫酸ナトリウム-ヘモグロビン法）、ヘマトクリット値（赤血球パルス高値検出法）、平均赤血球容積、平均赤血球血色素量、平均赤血球血色素濃度（以上、計算値）、血小板数（電気抵抗検出法）、白血球数、網状赤血球数および白血球百分率（以上、フローサイトメトリー法）を測定した。また、血液の一部を3.8%クエン酸ナトリウム液で凝固阻止処理して血漿を得、血液凝固自動測定装置（KC-10A、米国アメルング社）により、プロトロンビン時間（Quick 一段法）および活性化部分トロンボプラスチン時間（エラジン酸活性化法）を測定した。

6) 血液生化学検査

採取した血液の一部から血清を分離し、生化学自動分析装置（JCA-BM8型クリナライザー、日本電子株式会社）により、総タンパク（ビューレット法）、アルブミン（BCG法）、 A/G 比（計算値）、血糖（GluK[1] -G-6-PDH[2] 法）、総コレステロール[（酵素法（CES[3] -COD[4] -POD[5] 系）]、トリグリセライド[酵素法（LPL[6] -GK[7] -GPO[8] -POD[5] 系）]、総ビリルビン（ジアゾ法）、尿素窒素（ウレアーゼ・UV法）、クレアチニン（Jaffe法）、AST、ALT、 ALP、（以上、JSCC[9] 法）、γ-GTP（SSCC[10] 法） LDH（SFBC[11] 法）、カルシウム（OCPC 法）および無機リン[酵素法（PNP[12] -XOD[13] -POD[5] 系）]を、また、電解質自動分析装置（NAKL-132、東亜ディーケーケー株式会社）により、ナトリウム、カリウムおよび塩素（以上、イオン電極法）を測定した。

[1] ：グルコキナーゼ、[2]：グルコース-6-リン酸脱水素酵素、[3]：コレステロールエステラーゼ、[4]：コレステロールオキシダーゼ、[5]：ペルオキシダーゼ、[6]：リポプロテインリパーゼ、 [7]：グリセロールキナーゼ、[8]： L-α-グリセロリン酸オキシダーゼ、[9]：日本臨床化学会、 [10]：スカンジナビア臨床化学会、[11]：フランス臨床生物学会、[12]： プリンヌクレオシドホスフォリラーゼ、 [13]：キサンチンオキシダーゼ

7) 剖検

投与期間終了時生存動物については最終投与の翌日に、回復群については回復期間終

了の翌日にエーテル麻酔下で採血に続いて放血屠殺し、体表、開口部粘膜および内部諸器官を肉眼的に観察した。

8) 器官重量

投与期間終了時生存動物および回復群の脳、胸腺、心臓、肝臓、腎臓、副腎、脾臓、下垂体、甲状腺、さらに雄では精巣、精巣上体、雌では卵巣を秤量（絶対重量）し、屠殺日の体重に基づいて対体重比（相対重量）を算出した。なお、対器官は左右を一括して、下垂体および甲状腺は固定後に秤量した。

9) 病理組織学検査

全例について下記器官・組織を採取し、10%中性リン酸緩衝ホルマリン液で固定（精巣、精巣上体はブアン液で前固定、肺は固定液を注入した後浸漬）して保存した。

脳（大脳，小脳，橋を含む）、下垂体、眼球、甲状腺（上皮小体を含む）、脊髄（頸部、胸部、腰部）、心臓、気管、肺、肝臓、腎臓、胸腺、脾臓、副腎、胃（前胃、腺胃）、腸（十二指腸、空腸、回腸、盲腸、結腸、直腸、パイエル板を含む）、生殖器（精巣又は卵巣）、副生殖器（子宮、膣又は前立腺、精嚢、精巣上体）、膀胱、坐骨神経、リンパ節（下顎リンパ節、腸間膜リンパ節）、骨髄（大腿骨）

病理組織学検査は、対照群と 1000 mg/kg 群の上記器官・組織について実施した。その結果、被験物質の投与に起因する変化が雌雄の肝臓および脾臓並びに雄の腎臓に認められたので、15、60 および 250 mg/kg 群並びに回復群では雌雄の肝臓および脾臓並びに雄の腎臓について検査した。検査は、常法に従ってパラフィン切片を作製し、H-E 染色を施して鏡検を行った。さらに、沈着物を同定するため、対照群と 1000 mg/kg 群について、雌雄とも一部の例の脾臓にベルリンブルー染色、雄の腎臓に α-2u-グロブリン免疫組織化学染色を施した。

5. 統計解析

得られた平均値あるいは頻度について、対照群との有意差（危険率 5%以下）を次の方法で検定した。

(1) パラメトリックデータ

多群間の比較については、Bartlett の分散検定を行った。分散が一様な場合は一元配置の分散分析を行い、その結果有意差を認めた場合、Dunnett の検定法により対照群に

対する各群の比較検定を行った。分散が一様でない場合は、ノンパラメトリックデータに用いる検定法に従った。2 群間の比較については、F 検定を行い、その結果分散が一様な場合は Student の t 検定を、分散が一様でない場合は Aspin-Welch の t 検定を行った。（体重、体重増加量、摂餌量、握力、自発運動量、尿量、尿比重、血液学検査データ、血液生化学検査データ、器官重量）

(2) ノンパラメトリックデータ

多群間の比較については、Kruskal-Wallis の順位検定を行い、その結果有意差を認めた場合、Dunnett 型の検定法により対照群と各群を比較した。2 群間の比較については、Mann-Whitney の U 検定を行った。（尿検査における定性的データ、白血球百分率）

(3) カテゴリカルデータ

Fisher の直接確率法を用いた（一般状態の観察、詳細な臨床観察、感覚機能検査、剖検および病理組織学検査における異常例の発現率）。なお、病理組織学検査所見のうち、グレード分けしたデータについては、Mann-Whitney の U 検定を行った。

結　果

1. 一般状態および死亡（Tables 1、2、Appendices 9、10）

死亡は認められなかった。一般状態の変化については、沈静および眼瞼下垂が 250 mg/kg 以上の群で雌雄の全例に、雄は投与 2 日まで、雌は投与 1 日にのみ認められた。さらに、1000 mg/kg 群で雌雄の全例に、投与直後に認められる一過性の流涎が、投与期間を通じて認められた。また、1000 mg/kg 群で雄に紅涙（1/10 匹）および雌に下腹部の尿による汚れ（2/10 匹）が認められたが、紅涙および尿による汚れは少数の変化であった。回復期間においては、一般状態の変化は認められなかった。

2. 機能観察総合検査

1) 詳細な臨床観察（Tables 3、4、Appendices 11、12）

投与期間中および回復期間中の観察で、各項目に有意な変化は認められなかった。

2) 感覚機能検査（Tables 5、6、Appendices 13、14）

投与期間中および回復期間中の検査で、各項目に変化は認められなかった。

3) 握力および自発運動量（Tables 7、8、Appendices 15、16）

投与期間中の測定において、前後肢の握力および自発運動量に有意な変化は認められなかった。回復期間中の測定においては、回復群の雄の後肢握力に有意な高値および雌の前肢握力に有意な低値が認められた。自発運動量に有意な変化は認められなかった。

3. 体重（Figures 1、2、Tables 9、10、Appendices 17、18）

投与期間および回復期間を通じて、各測定時点の体重および体重増加量に有意な変化は認められなかった。

4. 摂餌量（Tables 11、12、Appendices 19、20）

投与期間において、60 および 250 mg/kg 群で雄の投与 4 週の摂餌量に有意な低値が認められた。しかしながら、1000 mg/kg 群の雄では有意な変化は認められず、用量相関性の認められない変化であった。また、回復期間においては、有意な変化は認められなかった。

5. 尿検査（Tables 13、14、Appendices 21、22）

投与期間中の検査において、250 mg/kg 以上の群で雌雄とも尿の色調が黄色を呈する個体の発現が有意に高かった。さらに、1000 mg/kg 群で雌雄に尿 pH の有意な低値が認められた。回復期間中の検査においては、雄に尿比重の有意な低値が認められた。

6. 血液学検査（Tables 15、16、Appendices 23、24）

投与期間終了時の検査において、1000 mg/kg 群で雌雄に血色素量、ヘマトクリット値および平均赤血球血色素濃度の有意な低値並びに網状赤血球数の有意な高値、さらに雌に活性化部分トロンボプラスチン時間の有意な延長が認められた。

回復期間終了時の検査では、雄に平均赤血球容積および平均赤血球血色素量の有意な高値並びに平均赤血球血色素濃度の有意な低値が認められたが、赤血球数、血色素量およびヘマトクリット値に有意な変化は認められなかった。

7. 血液生化学検査（Tables 17、18、Appendices 25、26）

投与期間終了時の検査において、1000 mg/kg 群で雄にアルブミン、A/G 比、総コレステロールおよびカリウムの有意な高値、雌にγ-GTP および総ビリルビンの有意な高値が認められた。A/G 比の有意な高値は 15 mg/kg 群の雄にも認められたが、1000 mg/kg 群の雄と比べて対照群との変動幅は小さかった。また、60 mg/kg 群の雄に LDH の有意な高値、雌に AST の有意な低値、250 mg/kg 群の雌にナトリウムの有意な高値並びに 1000 mg/kg 群の雌に AST の有意な低値が認められたが、用量相関性が認められず、また対照群との変動幅の小さな変化であった。

回復期間終了時の検査においては、雄にナトリウムの有意な高値が認められた。

8. 剖検（Tables 19、20、Appendices 27、28）

1000 mg/kg 群で脾臓の黒色化が雌雄の全例に認められた。また、1000 mg/kg 群の雌で卵巣および子宮の小さな 1 匹が認められた。回復群では、1000 mg/kg 群で脾臓の黒色化が雄の全例、雌の 4 匹に認められた。

9. 器官重量（Tables 21、22、Appendices 29、30）

投与期間終了時屠殺動物において、250 mg/kg 群で雌に肝臓相対重量の有意な高値が認められた。1000 mg/kg 群では雌雄に肝臓の絶対および相対重量の有意な高値、雄に腎臓相対重量並びに脾臓の絶対および相対重量の有意な高値、下垂体絶対重量の有意な低値、雌に脾臓相対重量の有意な高値が認められた。回復期間終了時屠殺動物においては、変化は認められなかった。

10. 病理組織学検査（Tables 23、24、Appendices 27、28）

投与期間終了時屠殺動物において、肝臓では、小葉中心性肝細胞肥大が 250 mg/kg 群で雌の 2 匹に、1000 mg/kg 群では雄の 3 匹および雌の 5 匹に認められた。また、脾臓では、1000 mg/kg 群で髄外造血の亢進およびベルリンブルー染色陽性でヘモジデリンと考えられる褐色色素の沈着増加が雄の 3 匹および雌の 5 匹に認められ、このうち雌雄各 3 匹にはうっ血も認められた。うっ血は別の雄 2 匹にも認められた。さらに、雄の腎臓では、近位尿細管上皮におけるα-2u-グロブリン免疫染色陽性硝子滴の増加が、1000 mg/kg 群で認められた。

なお、器官重量で変化の認められた下垂体には被験物質の投与に起因する変化は認められなかった。

回復期間終了時屠殺動物においては、投与期間終了時屠殺動物において認められた被験物質の投与に起因する変化のうち、脾臓の増加した褐色色素の沈着と雄の 1 匹に髄外造血の亢進は残存していたものの、それ以外の変化はいずれも認められず、回復していた。

以上の変化の他に、投与期間終了時屠殺動物および回復期間終了時屠殺動物において、対照群のみ、あるいは対照群と被験物質投与群に、肺の泡沫細胞集簇（雄）、肝臓の巣状壊死（雄）、微小肉芽腫（雌雄）および小葉周辺性肝細胞脂肪変性（雌）、腎臓の孤立性嚢胞（雄）、好塩基性尿細管（雌雄）、皮質リンパ球浸潤（雄）および限局性尿細管拡張（雄）、膀胱の粘膜下組織リンパ球浸潤（雄）、前立腺の間質リンパ球浸潤（雄）が認められたが、発現率や変化の程度が被験物質投与群で増強する傾向は認められなかった。また、被験物質投与群にのみ、心臓の心筋変性・線維化（雄）、肝臓の巣状壊死（雌）、小葉周辺性肝細胞脂肪変性（雄）、腎臓の孤立性嚢胞（雌）、胸腺の出血（雄）並びに剖

検で 1000mg/kg 群の雌に認められた小さな卵巣および子宮を有する例には卵巣、子宮および膣の委縮が認められた。しかしながら、これらの変化はいずれも群あたり 1 匹のみの発現で、ラットに背景病変として認められる変化[1]でもあることから、被験物質の投与とは無関係な変化と判断された。

考　察

2-ニトロ-p-クレゾールの反復投与毒性を検討するため、0（対照）、15、60、250 および 1000 mg/kg/day 用量でラットに 28 日間経口投与した。

その結果、主な毒性として、肝臓および血液等に対する影響並びに関連する変化等が認められた。

肝臓に対する影響について、250 mg/kg 群で雌に肝臓の相対重量、1000 mg/kg 群では雌雄に肝臓の絶対および相対重量の高値が認められ、病理組織学検査では、250 mg/kg 群の雌および 1000 mg/kg 群の雌雄に、小葉中心性の肝細胞肥大が観察された。

1000 mg/kg 群の雌に認められたγ-GTP、総ビリルビンおよび活性化部分トロンボプラスチン時間の高値は、肝機能に対する影響を示す変化と考えられる。また、1000 mg/kg 群の雄に認められたアルブミン、A/G 比および総コレステロールの高値も、肝臓に対する影響と関連する変化と考えられる。

血液に対する影響について、1000 mg/kg 群で雌雄に血色素量およびヘマトクリット値の低値が認められ、平均赤血球血色素濃度は低値を示した。

1000 mg/kg 群の雌雄に認められた脾臓の髄外造血亢進および末梢血中網状赤血球数の高値は、貧血に対する造血細胞の反応性変化と考えられる。

本試験で認められた貧血について、ヘモジデリンと思われる赤血球由来色素の沈着増加やうっ血が雌雄の脾臓に認められ、血清カリウムの高値が雄に認められたことから、赤血球の破壊亢進が示唆され、溶血性貧血が発現しているものと考えられた。また、前述の血清総ビリルビンの高値も、肝臓に対する影響に加えて、溶血性貧血と関連した変化である可能性が考えられる。

1000 mg/kg 群の雌雄に認められた脾臓の色調および重量の変化は、これら血液に対する影響と関連した脾臓の病理組織学的変化を反映しているものと考えられる。

一般状態の観察で、沈静および眼瞼下垂が 250 mg/kg 以上の群の雌雄に認められたが、投与 1～2 日のみの変化で、機能観察総合検査で神経機能に対する影響や神経系器官に病理組織学的変化は認められなかった。また、体重や摂餌量に対する影響も認められなかった。

投与直後に認められた一過性の流涎については、被験物質の吸収に伴う毒性影響とは考え難く、投与液の刺激性による変化と判断された。

1000 mg/kg 群の雄で腎臓の相対重量増加が認められ、病理組織学検査では近位尿細管上皮の硝子滴の増加が観察されたが、この硝子滴は雄ラット特有のα-2u-グロブリンの沈着像であることが確認された。

250 mg/kg 以上の群の雌雄に認められた尿の色調変化（黄色尿）は、有害影響とは無関係な被験物質の色調（淡黄色）を反映した変化と考えられ、同様の変化は本被験物質の異性体である 4-ニトロ-m-クレゾールのラットへの投与においても認められている [2]。

また、1000 mg/kg 群の雌雄に認められた尿 pH の低値についても、他に関連する有害影響を伴っていないことから、毒性学的意義は小さいものと考えられる。

血液生化学検査で認められた 15 mg/kg 群の雄の A/G 比、60 mg/kg 群の雄の LDH および 250 mg/kg 群の雌のナトリウムの変化には用量相関性は認められず、いずれも当研究所の背景データにおける基準値（Appendix 33, 34 参照）内の値であった。また、1000 mg/kg 群の雄で認められた下垂体の絶対重量のみの低値についても、下垂体に関連する病理組織学的変化は認められなかった。したがって、これらはいずれも、被験物質の投与とは無関係な偶発的変化と判断された。

このような投与期間中の観察あるいは投与期間終了時の検査で認められた変化のうち、回復群の回復期間中の観察あるいは回復期間終了時の検査では、脾臓の増加した色素沈着およびそれに伴う脾臓の色調変化は残存していたものの、その他の変化はいずれも認められなかった。

なお、回復群では雄に後肢握力および血清ナトリウムの高値、尿比重の低値並びに雌に前肢握力の低値が認められたが、これらの各個体値は、いずれも当研究所の背景データにおける基準値（雄の後肢握力：平均 326, 72～580、雄の血清ナトリウム：Appendix 33 参照、雄の尿比重：平均 1.057, 1.034～1.081、雌の前肢握力：平均 579, 211～946 g）内の値であり、また、投与期間終了時の検査で変化は認められていないことから、投与とは無関係な偶発的なものと判断された。

血液学検査で認められた雄の平均赤血球容積および平均赤血球血色素量の高値並びに平均赤血球血色素濃度の低値については、赤血球数、血色素量およびヘマトクリット値に有意な変化が認められていないことから、遅発的な毒性影響を示唆する変化ではなく、貧血の回復過程における変化と考えられる。

また、脾臓に残存する褐色色素の沈着も、貧血は回復傾向にあることから、主に投

与期間中からの沈着物の残存であり、赤血球の破壊亢進が投与終了後も持続していることを示すものではないと判断される。

したがって、発現した毒性はいずれも可逆的な変化であることが確認された。また、遅発毒性と考えられる変化も認められなかった。

以上の結果から、4-ニトロ-p-クレゾールのラットへの 28 日間反復経口投与により、250 mg/kg 群で雌に肝臓の病理組織学的変化および肝臓重量の変化が認められた。同群の雌雄に一般状態の変化が認められたが、ごく軽度な変化であった。1000 mg/kg 群では、雌雄に肝臓および血液等に対する影響並びに関連する血液生化学的変化および脾臓の変化等が認められた。15 および 60 mg/kg 群では、被験物質の投与に起因する変化は認められなかった。したがって、無影響量（NOEL）は雌雄とも 60 mg/kg/day および無毒性量（NOAEL）は雄で 250 mg/kg/day、雌で 60 mg/kg/day と結論された。

文　献

1) 日本毒性病理学会編，“毒性病理学”，日本毒性病理学会，名古屋，2000.

2) [redacted]，3-メチル-4-ニトロフェノールのラットを用いる経口投与簡易生殖毒性試験，化学物質毒性試験報告，2，157-162，1995.

2-ニトロ-p-クレゾールのラットを用いる28日間反復経口投与毒性試験

(試験番号：06-085)

最終報告書　添付資料A

(図・群別平均値表)

財団法人　畜産生物科学安全研究所

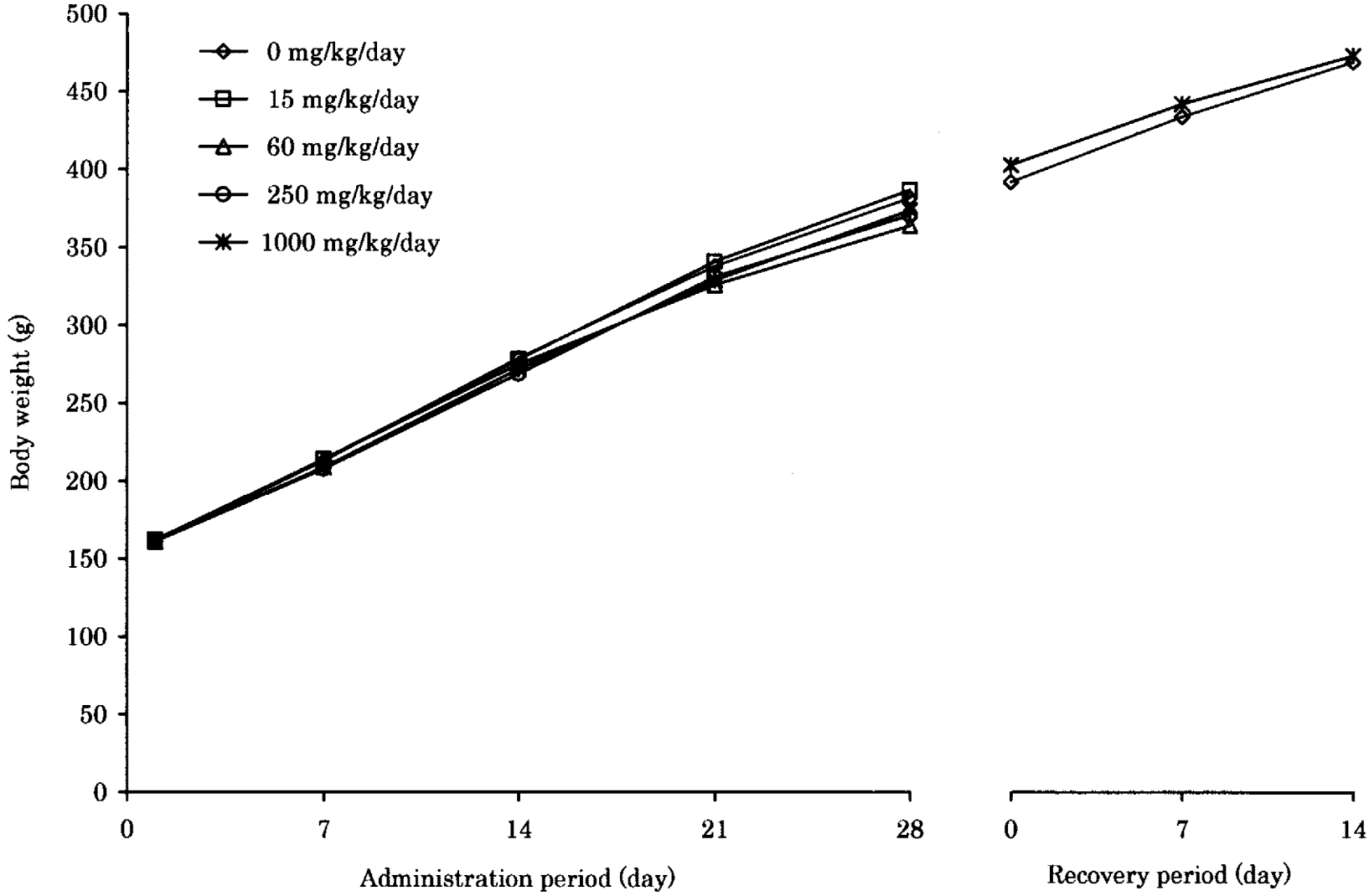


Fig.1 Body weight change of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

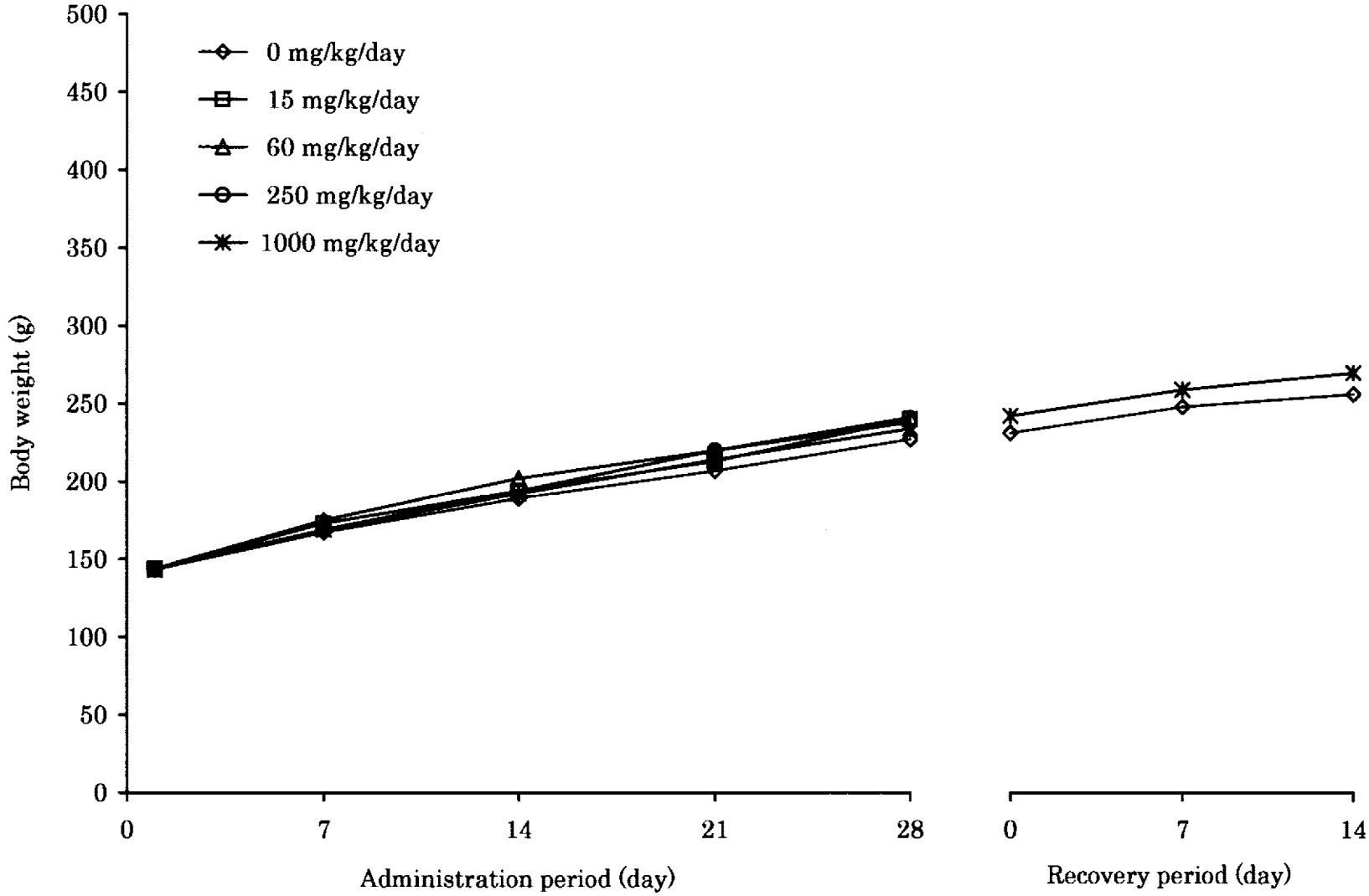


Fig.2 Body weight change of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Table 1 General conditions and mortality of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

General conditions		Dose (mg/kg/day)	Administration period									Recovery period	
			0			15	60	250	1000			0	1000
		Fate	KA	KR	Total	KA	KA	KA	KA	KR	Total	KR	KR
(Clinical signs)	Grade	No. of animals	5	5	10	5	5	5	5	5	10	5	5
Salivation	−		5	5	10	5	5	5	0	0	0	5	5
	+		0	0	0	0	0	0	5	5	10 **	0	0
Sedation	−		5	5	10	5	5	0	0	0	0	5	5
	+		0	0	0	0	0	5 **	5	5	10 **	0	0
Ptosis	−		5	5	10	5	5	0	0	0	0	5	5
	+		0	0	0	0	0	5 **	5	5	10 **	0	0
Reddish tear	−		5	5	10	5	5	5	4	5	9	5	5
	+		0	0	0	0	0	0	1	0	1	0	0
		Mortality (%)	0	0	0	0	0	0	0	0	0	0	0

KA : Killed by design at the end of administration period.
KR : Killed by design at the end of recovery period.
− : Negative. + : Slight.
** : Significantly different from control at 1% level of probability.

Table 2 General conditions and mortality of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

General conditions		Dose (mg/kg/day)	Administration period									Recovery period	
			0			15	60	250	1000			0	1000
		Fate	KA	KR	Total	KA	KA	KA	KA	KR	Total	KR	KR
(Clinical signs)	Grade	No. of animals	5	5	10	5	5	5	5	5	10	5	5
Salivation	−		5	5	10	5	5	5	0	0	0	5	5
	+		0	0	0	0	0	0	5	5	10 **	0	0
Sedation	−		5	5	10	5	5	0	0	0	0	5	5
	+		0	0	0	0	0	5 **	5	5	10 **	0	0
Ptosis	−		5	5	10	5	5	0	0	0	0	5	5
	+		0	0	0	0	0	5 **	5	5	10 **	0	0
Soiled perineal region	−		5	5	10	5	5	5	4	4	8	5	5
	+		0	0	0	0	0	0	1	1	2	0	0
		Mortality (%)	0	0	0	0	0	0	0	0	0	0	0

KA : Killed by design at the end of administration period.
KR : Killed by design at the end of recovery period.
− : Negative. + : Slight.
** : Significantly different from control at 1% level of probability.

Table 3-1 Incidence of clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 Before administration period 〉

Items	Dose(mg/kg/day) / No. of animals	0 / 10	15 / 5	60 / 5	250 / 5	1000 / 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected	10	5	5	5	10
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	10	5	5	5	10
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	10	5	4	4	5
	2 or more	0	0	1	1	5
	Color: Pale yellow	5/5	4/4	2/2	1/1	7/7
Defecation	Not detected or 1	10	2	5	3	6
	2 or more	0	3	0	2	4
	Appearance:Normal	3/3	3/3	-	3/3	4/4

Table 3-2 Incidence of clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of administration period 〉

Items	Dose(mg/kg/day) No. of animals	0 10	15 5	60 5	250 5	1000 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected	10	5	5	5	10
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	10	5	5	5	10
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	10	5	5	5	10
	2 or more	0	0	0	0	0
	Color: Pale yellow	2/2	1/1	2/2	-	6/6
Defecation	Not detected or 1	10	2	4	5	8
	2 or more	0	3	1	0	2
	Appearance:Normal	1/1	3/3	1/1	1/1	5/5

Table 3-3 Incidence of clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of administration period 〉

Items	Dose(mg/kg/day) No. of animals	0 10	15 5	60 5	250 5	1000 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected	10	5	5	5	10
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	10	5	5	5	10
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	8	4	5	5	9
	2 or more	2	1	0	0	1
	Color: Pale yellow	2/2	2/2	-	-	4/4
Defecation	Not detected or 1	9	4	5	5	9
	2 or more	1	1	0	0	1
	Appearance:Normal	1/1	1/1	-	-	2/2

Table 3-4 Incidence of clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 3 of administration period 〉

Items	Dose(mg/kg/day) No. of animals	0 10	15 5	60 5	250 5	1000 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected	10	5	5	5	10
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	10	5	5	5	10
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	10	5	5	5	9
	2 or more	0	0	0	0	1
	Color: Pale yellow	3/3	4/4	-	1/1	5/5
Defecation	Not detected or 1	10	5	5	5	9
	2 or more	0	0	0	0	1
	Appearance:Normal	1/1	2/2	1/1	-	1/1

Table 3-5 Incidence of clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day) No. of animals	0 10	15 5	60 5	250 5	1000 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
	Pale skin	10	5	5	5	10
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected	10	5	5	5	10
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	10	5	5	5	10
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	9	5	5	5	9
	2 or more	1	0	0	0	1
	Color: Pale yellow	3/3	-	-	-	-
	Color: Yellow	-	-	-	1/1	6/6
Defecation	Not detected or 1	9	5	5	5	9
	2 or more	1	0	0	0	1
	Appearance:Normal	1/1	1/1	-	-	2/2

Table 3-6 Incidence of clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of recovery period 〉

Items	Dose(mg/kg/day) No. of animals	0 5	1000 5
Reactivity on removal from the cage	Normal	5	5
Reactivity on handling	Normal	5	5
Muscle tone	Normal	5	5
Skin	Normal	5	5
Fur	Normal	5	5
Piloerection	Not detected	5	5
Eye-nose discharge	Not detected	5	5
Palpebral closure	Not detected	5	5
Exophthalmos	Not detected	5	5
Lacrimation	Not detected	5	5
Salivation	Not detected	5	5
Blotted fur in the lower abdomen with urine	Not detected	5	5
	Slight	0	0
Blotted fur around anus with feces	Not detected	5	5
Vocalization	Not detected	5	5
Breathing	Normal	5	5
Body position	Normal	5	5
Convulsion	Not detected	5	5
Tremor	Not detected	5	5
Exploration	Normal	5	5
Walk	Normal	5	5
Abnormal behavior	Normal	5	5
Stereotypy	Not detected	5	5
Urination	Not detected or 1	4	5
	2 or more	1	0
	Color: Pale yellow	2/2	-
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance:Normal	-	-

Table 3-7 Incidence of clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Items	Dose(mg/kg/day) No. of animals	0 5	1000 5
Reactivity on removal from the cage	Normal	5	5
Reactivity on handling	Normal	5	5
Muscle tone	Normal	5	5
Skin	Normal	5	5
Fur	Normal	5	5
Piloerection	Not detected	5	5
Eye-nose discharge	Not detected	5	5
Palpebral closure	Not detected	5	5
Exophthalmos	Not detected	5	5
Lacrimation	Not detected	5	5
Salivation	Not detected	5	5
Blotted fur in the lower abdomen with urine	Not detected	5	5
Blotted fur around anus with feces	Not detected	5	5
Vocalization	Not detected	5	4
	Temporally in handling	0	1
Breathing	Normal	5	5
Body position	Normal	5	5
Convulsion	Not detected	5	5
Tremor	Not detected	5	5
Exploration	Normal	5	5
Walk	Normal	5	5
Abnormal behavior	Normal	5	5
Stereotypy	Not detected	5	5
Urination	Not detected or 1	5	5
	2 or more	0	0
	Color: Pale yellow	4/4	3/3
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance:Normal	-	-

Table 4-1 Incidence of clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 Before administration period 〉

Items	Dose(mg/kg/day) / No. of animals	0 / 10	15 / 5	60 / 5	250 / 5	1000 / 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected	10	5	5	5	10
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	10	5	5	4	10
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	7	5	5	4	10
	2 or more	3	0	0	1	0
	Color: Pale yellow	3/3	1/1	3/3	2/2	2/2
Defecation	Not detected or 1	10	5	5	4	9
	2 or more	0	0	0	1	1
	Appearance:Normal	1/1	2/2	-	2/2	2/2

Table 4-2 Incidence of clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of administration period 〉

Items	Dose(mg/kg/day) No. of animals	0 10	15 5	60 5	250 5	1000 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected	10	5	5	5	10
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	8	5	5	5	10
	Temporally in handling	2	0	0	0	0
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	8	3	2	4	8
	2 or more	2	2	3	1	2
	Color: Pale yellow	4/4	2/2	4/4	4/4	4/4
Defecation	Not detected or 1	10	5	5	5	8
	2 or more	0	0	0	0	2
	Appearance:Normal	-	-	-	-	2/2

Table 4-3 Incidence of clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of administration period 〉

Items	Dose(mg/kg/day) / No. of animals	0 / 10	15 / 5	60 / 5	250 / 5	1000 / 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected	10	5	5	5	9
	Slight	0	0	0	0	1
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	10	5	5	5	9
	Temporally in handling	0	0	0	0	1
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	10	5	5	4	8
	2 or more	0	0	0	1	2
	Color: Pale yellow	2/2	2/2	-	2/2	5/5
Defecation	Not detected or 1	10	5	5	4	10
	2 or more	0	0	0	1	0
	Appearance:Normal	-	-	-	1/1	1/1

Table 4-4 Incidence of clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 3 of administration period 〉

Items	Dose(mg/kg/day) No. of animals	0 10	15 5	60 5	250 5	1000 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected Slight	10	5	5	5	10
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	10	5	5	5	10
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	9	5	5	5	9
	2 or more	1	0	0	0	1
	Color: Pale yellow	1/1	-	1/1	2/2	1/1
Defecation	Not detected or 1	10	5	5	5	10
	2 or more	0	0	0	0	0
	Appearance:Normal	-	-	-	-	-

Table 4-5 Incidence of clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day) / No. of animals	0 / 10	15 / 5	60 / 5	250 / 5	1000 / 10
Reactivity on removal from the cage	Normal	10	5	5	5	10
Reactivity on handling	Normal	10	5	5	5	10
Muscle tone	Normal	10	5	5	5	10
Skin	Normal	10	5	5	5	10
	Pale skin	0	0	0	0	0
Fur	Normal	10	5	5	5	10
Piloerection	Not detected	10	5	5	5	10
Eye-nose discharge	Not detected	10	5	5	5	10
Palpebral closure	Not detected	10	5	5	5	10
Exophthalmos	Not detected	10	5	5	5	10
Lacrimation	Not detected	10	5	5	5	10
Salivation	Not detected	10	5	5	5	10
Blotted fur in the lower abdomen with urine	Not detected	10	5	5	5	10
Blotted fur around anus with feces	Not detected	10	5	5	5	10
Vocalization	Not detected	9	5	4	4	8
	Temporally in handling	1	0	1	1	2
Breathing	Normal	10	5	5	5	10
Body position	Normal	10	5	5	5	10
Convulsion	Not detected	10	5	5	5	10
Tremor	Not detected	10	5	5	5	10
Exploration	Normal	10	5	5	5	10
Walk	Normal	10	5	5	5	10
Abnormal behavior	Normal	10	5	5	5	10
Stereotypy	Not detected	10	5	5	5	10
Urination	Not detected or 1	10	5	5	3	10
	2 or more	0	0	0	2	0
	Color: Pale yellow	2/2	1/1	2/2	2/2	2/2
Defecation	Not detected or 1	10	5	5	5	10
	2 or more	0	0	0	0	0
	Appearance: Normal	-	-	-	-	1/1

Table 4-6 Incidence of clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of recovery period 〉

Items	Dose(mg/kg/day) No. of animals	0 5	1000 5
Reactivity on removal from the cage	Normal	5	5
Reactivity on handling	Normal	5	5
Muscle tone	Normal	5	5
Skin	Normal	5	5
Fur	Normal	5	5
Piloerection	Not detected	5	5
Eye·nose discharge	Not detected	5	5
Palpebral closure	Not detected	5	5
Exophthalmos	Not detected	5	5
Lacrimation	Not detected	5	5
Salivation	Not detected	5	5
Blotted fur in the lower abdomen with urine	Not detected	5	5
Blotted fur around anus with feces	Not detected	5	5
Vocalization	Not detected	5	5
Breathing	Normal	5	5
Body position	Normal	5	5
Convulsion	Not detected	5	5
Tremor	Not detected	5	5
Exploration	Normal	5	5
Walk	Normal	5	5
Abnormal behavior	Normal	5	5
Stereotypy	Not detected	5	5
Urination	Not detected or 1	5	5
	2 or more	0	0
	Color:Pale yellow	-	1/1
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance:Normal	-	-

Table 4-7 Incidence of clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Items	Dose(mg/kg/day) No. of animals	0 5	1000 5
Reactivity on removal from the cage	Normal	5	5
Reactivity on handling	Normal	5	5
Muscle tone	Normal	5	5
Skin	Normal	5	5
Fur	Normal	5	5
Piloerection	Not detected	5	5
Eye-nose discharge	Not detected	5	5
Palpebral closure	Not detected	5	5
Exophthalmos	Not detected	5	5
Lacrimation	Not detected	5	5
Salivation	Not detected	5	5
Blotted fur in the lower abdomen with urine	Not detected	5	5
Blotted fur around anus with feces	Not detected	5	5
Vocalization	Not detected	5	5
Breathing	Normal	5	5
Body position	Normal	5	5
Convulsion	Not detected	5	5
Tremor	Not detected	5	5
Exploration	Normal	5	5
Walk	Normal	5	5
Abnormal behavior	Normal	5	5
Stereotypy	Not detected	5	5
Urination	Not detected or 1	5	5
	2 or more	0	0
	Color: Pale yellow	-	-
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance:Normal	-	-

Table 5 - 1 Incidence of responses in the sensory/reflex function test of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day)	0	15	60	250	1000
	No. of animals examined	5	5	5	5	5
Eye sight reaction	Normal	5	5	5	5	5
Hearing reaction	Normal	5	5	5	5	5
Sense of touch reaction	Normal	5	5	5	5	5
Pain reaction	Normal	5	5	5	5	5
Pupil reflex	Normal	5	5	5	5	5
Righting reflex	Normal	5	5	5	5	5

Table 5 - 2 Incidence of responses in the sensory/reflex function test of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Items	Dose(mg/kg/day)	0	1000
	No. of animals examined	5	5
Hearing reaction	Normal	5	5
Eye sight reaction	Normal	5	5
Sense of touch reaction	Normal	5	5
Pain reaction	Normal	5	5
Pupil reflex	Normal	5	5
Righting reflex	Normal	5	5

Table 6 - 1 Incidence of responses in the sensory/reflex function test of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day)	0	15	60	250	1000
	No. of animals examined	5	5	5	5	5
Eye sight reaction	Normal	5	5	5	5	5
Hearing reaction	Normal	5	5	5	5	5
Sense of touch reaction	Normal	5	5	5	5	5
Pain reaction	Normal	5	5	5	5	5
Pupil reflex	Normal	5	5	5	5	5
Righting reflex	Normal	5	5	5	5	5

Table 6 - 2 Incidence of responses in the sensory/reflex function test of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Items	Dose(mg/kg/day)	0	1000
	No. of animals examined	5	5
Eye sight reaction	Normal	5	5
Hearing reaction	Normal	5	5
Sense of touch reaction	Normal	5	5
Pain reaction	Normal	5	5
Pupil reflex	Normal	5	5
Righting reflex	Normal	5	5

Table 7 - 1 Mean value of grip strength and motor activity of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Dose (mg/kg/day)	No. of animals	Grip strength (g) Forelimb	Grip strength (g) Hindlimb	Motor activity (counts) 0～60min.
0	5	783 ± 101	269 ± 62	11312 ± 1960
15	5	776 ± 161	259 ± 41	9765 ± 1566
60	5	761 ± 226	248 ± 30	12333 ± 3012
250	5	578 ± 109	318 ± 78	11569 ± 5133
1000	5	735 ± 147	303 ± 34	8572 ± 1715

Each value is exprssed as mean±S.D.

Table 7 - 2 Mean value of grip strength and motor activity of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Dose (mg/kg/day)	No. of animals	Grip strength (g)		Motor activity (counts)
		Forelimb	Hindlimb	0～60min.
0	5	785 ± 232	231 ± 29	13172 ± 1990
1000	5	857 ± 245	283 * ± 36	13983 ± 3318

Each value is exprssed as mean±S.D.

* : Significantly different from control at 5% level of probability.

Table 8 - 1 Mean value of grip strength and motor activity of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Dose (mg/kg/day)	No. of animals	Grip strength (g)		Motor activity (counts)
		Forelimb	Hindlimb	0～60min.
0	5	621 ± 146	279 ± 51	11826 ± 4028
15	5	742 ± 41	261 ± 63	12799 ± 3682
60	5	622 ± 74	271 ± 13	14159 ± 2460
250	5	569 ± 121	318 ± 89	13079 ± 2410
1000	5	566 ± 62	296 ± 65	13411 ± 1811

Each value is exprssed as mean±S.D.

Table 8 - 2 Mean value of grip strength and motor activity of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Dose (mg/kg/day)	No. of animals	Grip strength (g)		Motor activity (counts)
		Forelimb	Hindlimb	0～60min.
0	5	886 ± 104	295 ± 46	10016 ± 3943
1000	5	714 * ± 123	272 ± 31	10385 ± 2616

Each value is exprssed as mean±S.D.

* : Significantly different from control at 5% level of probability.

Table 9 Body weight of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

(g)

Dose (mg/kg/day)	Day	Administration period 1	7	14	21	28	Gain 1～28	Recovery period 0	7	14	Gain 0～14
0		161 ± 6 (10)	213 ± 6 (10)	279 ± 11 (10)	338 ± 17 (10)	382 ± 20 (10)	221 ± 18 (10)	392 ± 19 (5)	434 ± 18 (5)	469 ± 22 (5)	78 ± 4 (5)
15		162 ± 7 (5)	214 ± 13 (5)	278 ± 16 (5)	341 ± 23 (5)	387 ± 27 (5)	225 ± 26 (5)				
60		161 ± 7 (5)	214 ± 14 (5)	275 ± 20 (5)	326 ± 21 (5)	364 ± 30 (5)	203 ± 25 (5)				
250		161 ± 6 (5)	208 ± 3 (5)	269 ± 5 (5)	331 ± 6 (5)	371 ± 11 (5)	211 ± 14 (5)				
1000		161 ± 8 (10)	209 ± 15 (10)	272 ± 22 (10)	329 ± 27 (10)	374 ± 37 (10)	213 ± 30 (10)	403 ± 26 (5)	442 ± 30 (5)	473 ± 35 (5)	71 ± 10 (5)

Each value is expressed as mean±S.D.
(n) : No. of animals

Table 10 Body weight of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

(g)

Dose (mg/kg/day)	Day	Administration period 1	7	14	21	28	Gain 1～28	Recovery period 0	7	14	Gain 0～14
0		143 ± 5 (10)	167 ± 8 (10)	189 ± 9 (10)	207 ± 11 (10)	227 ± 13 (10)	83 ± 11 (10)	231 ± 16 (5)	248 ± 14 (5)	256 ± 15 (5)	25 ± 4 (5)
15		144 ± 5 (5)	173 ± 7 (5)	194 ± 6 (5)	213 ± 10 (5)	240 ± 11 (5)	96 ± 9 (5)				
60		144 ± 6 (5)	175 ± 12 (5)	202 ± 16 (5)	220 ± 18 (5)	241 ± 25 (5)	97 ± 20 (5)				
250		144 ± 6 (5)	169 ± 8 (5)	194 ± 13 (5)	220 ± 18 (5)	238 ± 16 (5)	94 ± 13 (5)				
1000		143 ± 7 (10)	169 ± 10 (10)	192 ± 12 (10)	214 ± 18 (10)	234 ± 18 (10)	91 ± 16 (10)	242 ± 9 (5)	259 ± 15 (5)	270 ± 17 (5)	28 ± 9 (5)

Each value is expressed as mean±S.D.

(n) : No. of animals

Table 11 Food consumption of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

(g/rat/day)

Dose (mg/kg/day)	Week	Administration period 1	2	3	4	Recovery period 1	2
0		26 ± 2 (10)	28 ± 3 (10)	29 ± 3 (10)	32 ± 3 (10)	37 ± 2 (5)	35 ± 1 (5)
15		26 ± 3 (5)	29 ± 2 (5)	29 ± 2 (5)	28 ± 1 (5)		
60		26 ± 3 (5)	27 ± 3 (5)	27 ± 3 (5)	26 * ± 3 (5)		
250		24 ± 1 (5)	27 ± 2 (5)	27 ± 2 (5)	26 ** ± 1 (5)		
1000		27 ± 3 (10)	29 ± 3 (10)	28 ± 4 (10)	29 ± 5 (10)	37 ± 4 (5)	38 ± 4 (5)

Each value is expressed as mean±S.D.
(n) : No. of animals
* : Significantly different from control at 5% level of probability.
** : Significantly different from control at 1% level of probability.

Table 12 Food consumption of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

(g/rat/day)

Dose (mg/kg/day)	Week	Administration period 1	2	3	4	Recovery period 1	2
0		18 ± 3 (10)	19 ± 2 (10)	18 ± 2 (10)	21 ± 2 (10)	22 ± 4 (5)	24 ± 2 (5)
15		18 ± 2 (5)	20 ± 3 (5)	20 ± 2 (5)	20 ± 2 (5)		
60		20 ± 3 (5)	20 ± 2 (5)	20 ± 4 (5)	19 ± 4 (5)		
250		19 ± 2 (5)	20 ± 3 (5)	18 ± 1 (5)	20 ± 3 (5)		
1000		20 ± 2 (10)	22 ± 2 (10)	20 ± 2 (10)	20 ± 3 (10)	24 ± 3 (5)	25 ± 2 (5)

Each value is expressed as mean±S.D.
(n) : No. of animals

Table 13 - 1 Urinary findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Administration period >

Dose (mg/kg/day)	No. of animals	Color		Cloudy		Volume[a] (mL/18hr)	Specific[a] gravity	pH						
		PY	Y	−	+			5.0	6.0	6.5	7.0	7.5	8.0	8.5
0	5	5		5		9.1 ± 3.0	1.058 ± 0.010						1	4
15	5	5		5		6.4 ± 1.1	1.063 ± 0.008							5
60	5	3	2	5		8.0 ± 4.6	1.060 ± 0.016						2	3
250	5	1	4 *	5		10.2 ± 3.2	1.052 ± 0.010						4	1
1000	5		5 **	5		8.5 ± 2.6	1.067 ± 0.011						5 *	

Dose (mg/kg/day)	No. of animals	Protein					Glucose				Occult blood					Urobilinogen			
		−	±	1+	2+	3+	−	1+	2+	3+	−	±	1+	2+	3+	0.1	1	2	4
0	5		1	2	2		5				5					5			
15	5		1	2	2		5				5					5			
60	5			3	2		5				5					5			
250	5			5			5				5					5			
1000	5		3	2			5				5					5			

a) : Mean±S.D.
Color : PY(pale yellow), Y(yellow).
Cloudy : −(negligible), +(cloudy).
Protein : −(negligible), ±(15～30mg/dL), 1+(30mg/dL), 2+(100mg/dL), 3+(300mg/dL).
Glucose : −(negligible), 1+(100mg/dL), 2+(250mg/dL), 3+(500mg/dL).
Occult blood : −(negligible), ±(trace), 1+(slight), 2+(moderate), 3+(marked).
Urobilinogen : Ehrlich unit/dL.
* : Significantly different from control at 5% level of probability.
** : Significantly different from control at 1% level of probability.

Table 13 - 2 Urinary findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Administration period >

Dose (mg/kg/day)	No. of animals	Erythrocytes				Leukocytes				Crystals									
										Mg				Ca			Ams		
		−	1+	2+	3+	−	1+	2+	3+	−	1+	2+	3+	−	1+	2+	−	1+	2+
0	5	5				5				2	1	1	1	4	1		5		
15	5	5				5				4		1		5			5		
60	5	5				5				4	1			4	1		5		
250	5	5				5				2		3		3	2		5		
1000	5	5				5				3	2			5			5		

Dose (mg/kg/day)	No. of animals	Epithelial cells										Casts						Fat globules		
		Sq				R			S			G		H		W				
		−	1+	2+	3+	−	1+	2+	−	1+	2+	−	1+	−	1+	−	1+	−	1+	2+
0	5	2	3			5			5			5		5		5		5		
15	5	2	3			5			5			5		5		5		5		
60	5	5				5			5			5		5		5		5		
250	5	2	3			5			5			5		5		5		5		
1000	5	3	2			5			5			5		5		5		5		

− : Not observed, 1+ : A few in some fields, 2+ : A few in all fields, 3+ : Many in all fields.
Crystals ; Mg (ammonium magnesium phosphate), Ca (calcium carbonate), Ams (amorphous).
Epithelial cells ; Sq (squamous), R (round), S (spindle).
Casts ; G (granule), H (hyaline), W (waxy).

Table 13 - 3 Urinary findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Recovery period >

Dose (mg/kg/day)	No. of animals	Color		Cloudy		Volume[a)] (mL/18hr)	Specific[a)] gravity	pH						
		PY	Y	−	+			5.0	6.0	6.5	7.0	7.5	8.0	8.5
0	5	5		5		10.1 ± 3.4	1.063 ± 0.008						5	
1000	5	5		5		11.2 ± 1.0	1.047 ** ± 0.007					1	4	

Dose (mg/kg/day)	No. of animals	Protein					Glucose				Occult blood					Urobilinogen			
		−	±	1+	2+	3+	−	1+	2+	3+	−	±	1+	2+	3+	0.1	1	2	4
0	5		3	2			5				5					5			
1000	5		2	3			5				5					5			

a) : Mean±S.D.
Color : PY(pale yellow), Y(yellow).
Cloudy : −(negligible), +(cloudy).
Protein : −(negligible), ±(15～30mg/dL), 1+(30mg/dL), 2+(100mg/dL), 3+(300mg/dL).
Glucose : −(negligible), 1+(100mg/dL), 2+(250mg/dL), 3+(500mg/dL).
Occult blood : −(negligible), ±(trace), 1+(slight), 2+(moderate), 3+(marked).
Urobilinogen : Ehrlich unit/dL.
** : Significantly different from control at 1% level of probability.

Table 13 - 4 Urinary findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Recovery period >

Dose (mg/kg/day)	No. of animals	Erythrocytes				Leukocytes				Crystals									
										Mg				Ca			Ams		
		−	1+	2+	3+	−	1+	2+	3+	−	1+	2+	3+	−	1+	2+	−	1+	2+
0	5	5				5					2	2	1	5			5		
1000	5	5				5				2		2	1	5			5		

Dose (mg/kg/day)	No. of animals	Epithelial cells										Casts						Fat globules		
		Sq				R			S			G		H		W				
		−	1+	2+	3+	−	1+	2+	−	1+	2+	−	1+	−	1+	−	1+	−	1+	2+
0	5		5			5			5			5		5		5		5		
1000	5		5			5			5			5		5		5		5		

− : Not observed, 1+ : A few in some fields, 2+ : A few in all fields, 3+ : Many in all fields.
Crystals ; Mg (ammonium magnesium phosphate), Ca (calcium carbonate), Ams (amorphous).
Epithelial cells ; Sq (squamous), R (round), S (spindle).
Casts ; G (granule), H (hyaline), W (waxy).

Table 14 - 1 Urinary findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Administration period >

Dose (mg/kg/day)	No. of animals	Color		Cloudy		Volume[a)] (mL/18hr)	Specific[a)] gravity	pH						
		PY	Y	−	+			5.0	6.0	6.5	7.0	7.5	8.0	8.5
0	5	5		5		5.7 ± 1.3	1.059 ± 0.012						2	3
15	5	5		5		4.0 ± 2.7	1.076 ± 0.021					1	2	2
60	5	5		5		9.0 ± 1.8	1.046 ± 0.008						2	3
250	5		5 **	5		8.6 ± 4.8	1.052 ± 0.017						5	
1000	5		5 **	5		8.1 ± 2.6	1.059 ± 0.012					3	2 *	

Dose (mg/kg/day)	No. of animals	Protein					Glucose				Occult blood					Urobilinogen			
		−	±	1+	2+	3+	−	1+	2+	3+	−	±	1+	2+	3+	0.1	1	2	4
0	5		3	2			5				5					5			
15	5		1	2	2		5				5					5			
60	5			5			5				5					5			
250	5		3	2			5				5					5			
1000	5	2	1	2			5				5					5			

a) : Mean±S.D.
Color : PY(pale yellow), Y(yellow).
Cloudy : −(negligible), +(cloudy).
Protein : −(negligible), ±(15～30mg/dL), 1+(30mg/dL), 2+(100mg/dL), 3+(300mg/dL).
Glucose : −(negligible), 1+(100mg/dL), 2+(250mg/dL), 3+(500mg/dL).
Occult blood : −(negligible), ±(trace), 1+(slight), 2+(moderate), 3+(marked).
Urobilinogen : Ehrlich unit/dL.
* : Significantly different from control at 5% level of probability.
** : Significantly different from control at 1% level of probability.

Table 14 - 2 Urinary findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Administration period >

Dose (mg/kg/day)	No. of animals	Erythrocytes				Leukocytes				Crystals									
										Mg				Ca			Ams		
		−	1+	2+	3+	−	1+	2+	3+	−	1+	2+	3+	−	1+	2+	−	1+	2+
0	5	5				5				1	1	3		5			5		
15	5	5				5				3	1	1		4	1		5		
60	5	5				5				3	2			3	2		5		
250	5	5				5				2	2	1		3	2		5		
1000	5	5				5				3	1		1	5			5		

Dose (mg/kg/day)	No. of animals	Epithelial cells										Casts						Fat globules		
		Sq				R			S			G		H		W				
		−	1+	2+	3+	−	1+	2+	−	1+	2+	−	1+	−	1+	−	1+	−	1+	2+
0	5		5			5			5			5		5		5		5		
15	5	1	4			5			5			5		5		5		5		
60	5	2	3			5			5			5		5		5		5		
250	5	2	3			5			5			5		5		5		5		
1000	5	1	3	1		5			5			5		5		5		5		

− : Not observed, 1+ : A few in some fields, 2+ : A few in all fields, 3+ : Many in all fields.
Crystals ; Mg (ammonium magnesium phosphate), Ca (calcium carbonate), Ams (amorphous).
Epithelial cells ; Sq (squamous), R (round), S (spindle).
Casts ; G (granule), H (hyaline), W (waxy).

Table 14 - 3 Urinary findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Recovery period >

Dose (mg/kg/day)	No. of animals	Color		Cloudy		Volume[a] (mL/18hr)	Specific[a] gravity	pH						
		PY	Y	−	+			5.0	6.0	6.5	7.0	7.5	8.0	8.5
0	5	5		5		8.0 ± 3.5	1.061 ± 0.011						1	4
1000	5	5		5		10.9 ± 5.5	1.047 ± 0.011							5

Dose (mg/kg/day)	No. of animals	Protein					Glucose				Occult blood					Urobilinogen			
		−	±	1+	2+	3+	−	1+	2+	3+	−	±	1+	2+	3+	0.1	1	2	4
0	5	1	2	2			5				5					5			
1000	5	2	2	1			5				5					5			

a) : Mean±S.D.
Color : PY(pale yellow), Y(yellow).
Cloudy : −(negligible), +(cloudy).
Protein : −(negligible), ±(15～30mg/dL), 1+(30mg/dL), 2+(100mg/dL), 3+(300mg/dL).
Glucose : −(negligible), 1+(100mg/dL), 2+(250mg/dL), 3+(500mg/dL).
Occult blood : −(negligible), ±(trace), 1+(slight), 2+(moderate), 3+(marked).
Urobilinogen : Ehrlich unit/dL.

Table 14 - 4 Urinary findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Recovery period >

Dose (mg/kg/day)	No. of animals	Erythrocytes				Leukocytes				Crystals									
										Mg				Ca			Ams		
		−	1+	2+	3+	−	1+	2+	3+	−	1+	2+	3+	−	1+	2+	−	1+	2+
0	5	5				5				1	3	1		5			5		
1000	5	5				5				2	1	1	1	5			5		

Dose (mg/kg/day)	No. of animals	Epithelial cells										Casts						Fat globules		
		Sq				R			S			G		H		W				
		−	1+	2+	3+	−	1+	2+	−	1+	2+	−	1+	−	1+	−	1+	−	1+	2+
0	5	2	3			5			5			5		5		5		5		
1000	5	1	4			5			5			5		5		5		5		

− : Not observed, 1+ : A few in some fields, 2+ : A few in all fields, 3+ : Many in all fields.
Crystals ; Mg (ammonium magnesium phosphate), Ca (calcium carbonate), Ams (amorphous).
Epithelial cells ; Sq (squamous), R (round), S (spindle).
Casts ; G (granule), H (hyaline), W (waxy).

Table 15 - 1 Hematological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	No. of animals	RBC (10^4/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	5	737 ± 45	15.1 ± 0.6	46.9 ± 2.1	64 ± 3	20.6 ± 0.7	32.3 ± 0.4	34.3 ± 6.3	13.2 ± 0.4
15	5	749 ± 33	15.0 ± 0.8	46.4 ± 1.6	62 ± 2	20.0 ± 0.4	32.3 ± 0.7	35.4 ± 3.6	13.3 ± 0.5
60	5	766 ± 43	15.0 ± 0.4	45.7 ± 1.0	60 ± 3	19.6 ± 1.0	32.7 ± 0.3	37.2 ± 6.2	13.1 ± 0.7
250	5	752 ± 27	14.6 ± 0.3	44.6 ± 0.9	59 ± 2	19.4 ± 0.4	32.7 ± 0.5	38.8 ± 5.1	12.7 ± 0.2
1000	5	711 ± 58	13.7 ** ± 0.7	43.8 * ± 2.1	62 ± 3	19.3 ± 0.8	31.3 ** ± 0.3	88.1 ** ± 22.4	12.6 ± 0.2

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. (10^4/μL)	WBC (10^2/μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	21.0 ± 1.1	146 ± 16	82 ± 20	0.0 ± 0.0	0.5 ± 0.3	14.7 ± 5.0	81.7 ± 5.0	3.1 ± 0.3
15	5	20.4 ± 0.9	138 ± 10	59 ± 11	0.0 ± 0.0	0.7 ± 0.2	14.9 ± 5.9	81.3 ± 5.2	3.1 ± 1.3
60	5	20.3 ± 2.2	140 ± 10	67 ± 18	0.0 ± 0.0	0.8 ± 0.2	15.9 ± 3.4	79.9 ± 4.6	3.4 ± 1.5
250	5	20.3 ± 1.9	134 ± 14	66 ± 19	0.0 ± 0.0	0.5 ± 0.2	13.8 ± 2.5	83.0 ± 2.2	2.6 ± 0.4
1000	5	20.5 ± 1.3	138 ± 23	63 ± 6	0.0 ± 0.0	0.5 ± 0.2	17.5 ± 3.0	79.8 ± 3.4	2.2 ± 0.9

Each value is expressed as mean±S.D.

* : Significantly different from control at 5% level of probability.

** : Significantly different from control at 1% level of probability.

Table 15 - 2 Hematological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	No. of animals	RBC (10^4/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	5	813 ± 24	14.8 ± 0.4	44.5 ± 1.0	55 ± 1	18.2 ± 0.3	33.3 ± 0.2	29.2 ± 6.4	13.3 ± 0.5
1000	5	796 ± 20	15.0 ± 0.5	46.0 ± 1.7	58 * ± 2	18.8 * ± 0.4	32.7 * ± 0.4	34.2 ± 4.0	13.0 ± 0.4

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. (10^4/μL)	WBC (10^2/μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	21.2 ± 1.3	147 ± 15	75 ± 13	0.0 ± 0.0	0.9 ± 0.7	15.5 ± 5.8	80.5 ± 6.5	3.2 ± 0.9
1000	5	22.3 ± 1.8	134 ± 9	71 ± 13	0.0 ± 0.0	0.8 ± 0.2	13.3 ± 4.4	83.0 ± 5.2	2.9 ± 0.8

Each value is expressed as mean±S.D.

* : Significantly different from control at 5% level of probability.

Table 16 - 1 Hematological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	No. of animals	RBC (10^4/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	5	779 ± 82	15.1 ± 1.1	45.1 ± 3.2	58 ± 3	19.4 ± 0.8	33.4 ± 0.3	21.6 ± 4.7	13.3 ± 0.5
15	5	712 ± 31	13.9 ± 0.5	42.3 ± 1.2	60 ± 1	19.6 ± 0.3	32.9 ± 0.3	23.4 ± 2.7	12.6 ± 0.6
60	5	738 ± 34	14.7 ± 0.7	44.3 ± 2.4	60 ± 2	19.9 ± 0.5	33.1 ± 0.5	21.3 ± 3.0	13.1 ± 0.7
250	5	776 ± 26	14.6 ± 0.4	44.6 ± 1.6	58 ± 2	18.8 ± 0.5	32.7 ± 0.6	25.8 ± 5.3	13.2 ± 0.4
1000	5	684 * ± 45	13.0 ** ± 0.7	40.2 ** ± 1.7	59 ± 2	19.0 ± 0.5	32.3 ** ± 0.5	64.9 ** ± 12.4	13.2 ± 0.4

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. (10^4/μL)	WBC (10^2/μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	16.7 ± 0.5	131 ± 18	55 ± 19	0.0 ± 0.0	1.2 ± 0.3	10.6 ± 5.3	85.5 ± 5.4	2.7 ± 0.6
15	5	18.2 ± 1.6	140 ± 23	47 ± 9	0.0 ± 0.0	1.1 ± 0.6	13.2 ± 3.8	83.2 ± 4.1	2.5 ± 0.5
60	5	17.4 ± 0.4	145 ± 7	62 ± 11	0.0 ± 0.0	0.7 ± 0.3	10.4 ± 4.2	86.1 ± 4.9	2.8 ± 1.1
250	5	16.9 ± 0.8	139 ± 19	48 ± 10	0.0 ± 0.0	1.3 ± 0.8	13.7 ± 4.1	81.8 ± 3.1	3.2 ± 1.1
1000	5	20.6 ** ± 0.9	141 ± 20	49 ± 20	0.0 ± 0.0	0.9 ± 0.4	11.7 ± 4.5	85.6 ± 5.8	1.8 ± 1.3

Each value is expressed as mean±S.D.

* : Significantly different from control at 5% level of probability.

** : Significantly different from control at 1% level of probability.

Table 16 - 2 Hematological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	No. of animals	RBC (10^4/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	5	765 ± 46	14.5 ± 0.7	42.9 ± 2.3	56 ± 1	18.9 ± 0.5	33.7 ± 0.2	27.8 ± 7.9	13.3 ± 0.3
1000	5	780 ± 28	15.2 ± 0.7	45.4 ± 1.9	58 ± 3	19.5 ± 0.8	33.4 ± 0.5	24.9 ± 3.2	13.5 ± 0.3

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. (10^4/μL)	WBC (10^2/μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	18.0 ± 2.3	126 ± 9	52 ± 15	0.0 ± 0.0	1.3 ± 0.7	16.6 ± 3.6	79.8 ± 3.8	2.2 ± 0.6
1000	5	17.7 ± 1.5	129 ± 12	53 ± 11	0.0 ± 0.0	0.9 ± 0.3	16.2 ± 3.5	79.8 ± 4.2	3.1 ± 1.0

Each value is expressed as mean±S.D.

Table 17 - 1 Blood biochemical findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	No. of animals	LDH (IU/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	γ-GTP (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Cho. (mg/dL)	T.G. (mg/dL)
0	5	193 ± 83	61 ± 6	31 ± 6	725 ± 131	0.60 ± 0.12	5.82 ± 0.15	2.82 ± 0.10	0.94 ± 0.03	65 ± 8	60 ± 35
15	5	214 ± 51	61 ± 6	31 ± 6	756 ± 144	0.50 ± 0.19	5.80 ± 0.17	2.95 ± 0.14	1.04 ** ± 0.06	65 ± 12	56 ± 11
60	5	381 ** ± 98	71 ± 7	32 ± 3	747 ± 149	0.49 ± 0.10	5.78 ± 0.20	2.86 ± 0.12	0.98 ± 0.02	61 ± 9	70 ± 33
250	5	200 ± 56	64 ± 8	32 ± 5	790 ± 74	0.54 ± 0.14	5.84 ± 0.14	2.90 ± 0.11	0.99 ± 0.06	73 ± 12	63 ± 24
1000	5	192 ± 58	64 ± 8	37 ± 3	664 ± 127	1.12 ± 0.42	6.20 ± 0.42	3.38 ** ± 0.25	1.20 ** ± 0.04	99 ** ± 23	68 ± 36

Dose (mg/kg/day)	No. of animals	Glu. (mg/dL)	BUN (mg/dL)	Crea. (mg/dL)	T-Bil. (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	5	152 ± 11	12.2 ± 1.7	0.38 ± 0.03	0.35 ± 0.07	9.6 ± 0.1	7.8 ± 0.6	147 ± 2	4.80 ± 0.33	106 ± 2
15	5	151 ± 13	11.1 ± 1.0	0.34 ± 0.03	0.35 ± 0.03	9.5 ± 0.2	8.3 ± 0.2	147 ± 1	4.95 ± 0.38	106 ± 1
60	5	150 ± 13	11.1 ± 1.5	0.34 ± 0.04	0.39 ± 0.02	9.4 ± 0.4	8.2 ± 0.7	146 ± 1	5.17 ± 0.29	106 ± 2
250	5	160 ± 10	10.8 ± 1.0	0.39 ± 0.02	0.36 ± 0.03	9.4 ± 0.2	7.4 ± 0.5	146 ± 1	4.89 ± 0.24	106 ± 1
1000	5	159 ± 14	10.7 ± 1.6	0.39 ± 0.02	0.40 ± 0.04	9.8 ± 0.5	8.0 ± 0.5	147 ± 2	5.65 ** ± 0.25	104 ± 2

Each value is expressed as mean±S.D.

** : Significantly different from control at 1% level of probability.

Table 17 - 2 Blood biochemical findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	No. of animals	LDH (IU/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	γ-GTP (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Cho. (mg/dL)	T.G. (mg/dL)
0	5	327 ± 114	73 ± 5	38 ± 5	579 ± 75	0.73 ± 0.09	5.90 ± 0.21	2.79 ± 0.13	0.91 ± 0.09	67 ± 8	62 ± 8
1000	5	269 ± 120	74 ± 11	40 ± 4	545 ± 111	0.87 ± 0.24	5.97 ± 0.12	2.94 ± 0.07	0.97 ± 0.06	65 ± 21	55 ± 22

Dose (mg/kg/day)	No. of animals	Glu. (mg/dL)	BUN (mg/dL)	Crea. (mg/dL)	T-Bil. (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	5	156 ± 16	14.4 ± 2.2	0.40 ± 0.08	0.33 ± 0.04	9.5 ± 0.4	7.2 ± 0.6	145 ± 1	4.98 ± 0.21	106 ± 1
1000	5	143 ± 10	14.5 ± 2.6	0.41 ± 0.06	0.33 ± 0.03	9.6 ± 0.3	7.8 ± 0.6	147 * ± 1	4.79 ± 0.23	104 ± 2

Each value is expressed as mean±S.D.

* : Significantly different from control at 5% level of probability.

Table 18 - 1 Blood biochemical findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	No. of animals	LDH (IU/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	γ-GTP (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Cho. (mg/dL)	T.G. (mg/dL)
0	5	363 ± 186	73 ± 11	28 ± 3	530 ± 107	0.42 ± 0.37	5.99 ± 0.21	3.17 ± 0.27	1.13 ± 0.16	67 ± 10	29 ± 18
15	5	296 ± 154	67 ± 3	25 ± 3	533 ± 64	1.17 ± 0.45	5.95 ± 0.26	3.03 ± 0.32	1.04 ± 0.14	68 ± 21	31 ± 15
60	5	268 ± 67	62 * ± 6	25 ± 6	433 ± 90	0.59 ± 0.48	6.01 ± 0.13	3.26 ± 0.22	1.19 ± 0.15	82 ± 14	30 ± 21
250	5	294 ± 74	65 ± 7	29 ± 6	479 ± 93	0.64 ± 0.31	6.20 ± 0.27	3.39 ± 0.32	1.21 ± 0.14	67 ± 10	40 ± 24
1000	5	341 ± 93	59 * ± 4	29 ± 6	460 ± 125	2.14 ** ± 0.90	6.16 ± 0.17	3.36 ± 0.14	1.21 ± 0.13	96 ± 29	31 ± 16

Dose (mg/kg/day)	No. of animals	Glu. (mg/dL)	BUN (mg/dL)	Crea. (mg/dL)	T-Bil. (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	5	129 ± 22	15.2 ± 1.6	0.43 ± 0.06	0.24 ± 0.02	9.3 ± 0.3	7.3 ± 0.6	146 ± 1	5.01 ± 0.27	108 ± 1
15	5	129 ± 6	12.8 ± 1.6	0.43 ± 0.03	0.24 ± 0.01	9.3 ± 0.3	7.4 ± 0.3	147 ± 0	4.52 ± 0.25	107 ± 1
60	5	122 ± 13	13.2 ± 2.3	0.40 ± 0.02	0.24 ± 0.03	9.6 ± 0.4	7.3 ± 0.8	147 ± 1	4.79 ± 0.36	108 ± 3
250	5	138 ± 15	13.5 ± 1.8	0.44 ± 0.03	0.27 ± 0.02	9.8 ± 0.3	7.3 ± 0.7	148 * ± 1	5.07 ± 0.59	108 ± 2
1000	5	146 ± 17	12.2 ± 1.8	0.39 ± 0.02	0.34 ** ± 0.03	9.5 ± 0.1	6.7 ± 0.7	145 ± 3	5.17 ± 0.38	106 ± 3

Each value is expressed as mean±S.D.

* : Significantly different from control at 5% level of probability.

** : Significantly different from control at 1% level of probability.

Table 18 - 2 Blood biochemical findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	No. of animals	LDH (IU/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	γ-GTP (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Cho. (mg/dL)	T.G. (mg/dL)
0	5	330 ± 60	73 ± 15	29 ± 2	330 ± 94	0.84 ± 0.44	6.32 ± 0.61	3.45 ± 0.50	1.20 ± 0.14	82 ± 16	36 ± 21
1000	5	305 ± 48	91 ± 49	33 ± 9	391 ± 178	0.54 ± 0.31	6.34 ± 0.16	3.54 ± 0.19	1.27 ± 0.10	89 ± 10	40 ± 9

Dose (mg/kg/day)	No. of animals	Glu. (mg/dL)	BUN (mg/dL)	Crea. (mg/dL)	T-Bil. (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	5	131 ± 10	16.0 ± 3.1	0.48 ± 0.02	0.27 ± 0.02	9.9 ± 0.3	6.2 ± 0.7	146 ± 2	5.01 ± 0.31	108 ± 3
1000	5	137 ± 10	17.7 ± 2.3	0.50 ± 0.06	0.24 ± 0.03	9.9 ± 0.3	6.9 ± 0.7	147 ± 1	4.73 ± 0.21	109 ± 1

Each value is expressed as mean±S.D.

Table 19 Incidence of necropsy findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Organ	: Findings	Dose(mg/kg/day)	At the end of administration period					At the end of recovery period[a)]	
			0	15	60	250	1000	0	1000
		No. of animals	5	5	5	5	5	5	5
Spleen	: Blackish	-	5	5	5	5	0	5	1
		+	0	0	0	0	5**	0	4*

a) : Satellite group.
- : Negative, + : Slight.
* : Significantly different from control at 5% level of probability.
** : Significantly different from control at 1% level of probability.

Table 20 Incidence of necropsy findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Organ	: Findings	Dose(mg/kg/day)	At the end of administration period					At the end of recovery period[a)]	
			0	15	60	250	1000	0	1000
		No. of animals	5	5	5	5	5	5	5
Spleen	: Blackish	-	5	5	5	5	0	5	0
		+	0	0	0	0	5**	0	5**
Ovary/ Uterus	: Small	-	5	5	5	5	4	5	5
		+++	0	0	0	0	1	0	0

a) : Satellite group.
- : Negative, + : Slight, +++ : Severe.
** : Significantly different from control at 1% level of probability.

Table 21 - 1 Absolute and relative organ weights of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of administration period>

	Dose (mg/kg/day)	No.of Animals	Body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland (mg)	Spleen (g)	Testis (g)	Epididy-mis (g)	Pituitary gland (mg)	Thyroid gland (mg)
Absolute	0	5	338 ±17	1.93 ±0.11	0.56 ±0.11	1.14 ±0.09	10.97 ±1.58	2.49 ±0.22	61.8 ±14.4	0.68 ±0.09	3.16 ±0.38	0.76 ±0.05	12.5 ±0.9	23.5 ±3.8
	15	5	353 ±28	1.90 ±0.05	0.55 ±0.04	1.19 ±0.11	10.99 ±1.02	2.64 ±0.24	56.2 ±6.9	0.74 ±0.08	3.22 ±0.27	0.86 ±0.11	12.2 ±1.1	23.0 ±1.9
	60	5	333 ±27	1.86 ±0.08	0.43 ±0.08	1.14 ±0.09	10.36 ±1.35	2.48 ±0.31	58.5 ±2.2	0.62 ±0.09	3.15 ±0.20	0.80 ±0.07	11.0 ±1.2	22.6 ±2.4
	250	5	341 ±10	1.93 ±0.06	0.49 ±0.09	1.14 ±0.05	11.37 ±0.72	2.61 ±0.07	51.1 ±4.0	0.65 ±0.05	3.13 ±0.27	0.75 ±0.05	11.2 ±0.8	26.3 ±3.7
	1000	5	315 ±16	1.91 ±0.09	0.47 ±0.09	1.09 ±0.09	14.10 ** ±2.14	2.67 ±0.12	47.2 ±5.8	0.89 * ±0.16	3.13 ±0.19	0.76 ±0.07	10.8 * ±0.6	26.4 ±7.8
Relative @	0	5	338 ±17	0.57 ±0.03	0.16 ±0.03	0.33 ±0.02	3.24 ±0.39	0.73 ±0.03	18.2 ±4.1	0.20 ±0.03	0.94 ±0.11	0.23 ±0.02	3.7 ±0.3	6.9 ±1.0
	15	5	353 ±28	0.54 ±0.03	0.16 ±0.02	0.34 ±0.01	3.11 ±0.07	0.75 ±0.06	16.0 ±2.3	0.21 ±0.01	0.91 ±0.08	0.25 ±0.04	3.5 ±0.3	6.5 ±0.5
	60	5	333 ±27	0.56 ±0.03	0.13 ±0.03	0.34 ±0.01	±3.10 ±0.20	0.74 ±0.06	17.7 ±1.5	0.19 ±0.03	0.95 ±0.08	0.24 ±0.02	3.3 ±0.2	6.8 ±1.1
	250	5	341 ±10	0.57 ±0.02	0.15 ±0.03	0.33 ±0.02	3.34 ±0.18	0.76 ±0.03	15.0 ±1.2	0.19 ±0.01	0.92 ±0.10	0.22 ±0.02	3.3 ±0.2	7.7 ±1.0
	1000	5	315 ±16	0.61 ±0.01	0.15 ±0.03	0.35 ±0.01	4.47 * ±0.60	0.85 ** ±0.01	15.0 ±2.1	0.28 ** ±0.04	0.99 ±0.02	0.24 ±0.02	3.4 ±0.2	8.3 ±2.3

Each value is expressed as mean ± S.D.
@ : Relative organ weight per 100g body weight.
* : Significantly different from control at 5% level of probability.
** : Significantly different from control at 1% level of probability.

Table 21 - 2 Absolute and relative organ weights of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study <At the end of recovery period>

	Dose (mg/kg/day)	No.of Animals	Body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland (mg)	Spleen (g)	Testis (g)	Epididy-mis (g)	Pituitary gland (mg)	Thyroid gland (mg)
Absolute	0	5	428 ±22	2.04 ±0.10	0.50 ±0.10	1.45 ±0.09	12.16 ±0.94	2.86 ±0.09	63.5 ±5.5	0.72 ±0.11	3.31 ±0.10	1.04 ±0.05	13.4 ±0.7	28.0 ±2.8
	1000	5	429 ±31	1.99 ±0.06	0.44 ±0.12	1.38 ±0.06	12.86 ±1.60	3.08 ±0.22	66.9 ±5.4	0.82 ±0.16	3.29 ±0.48	1.07 ±0.13	13.3 ±1.4	28.1 ±1.1
Relative @	0	5	428 ±22	0.48 ±0.01	0.12 ±0.03	0.34 ±0.03	2.84 ±0.15	0.67 ±0.04	14.9 ±1.3	0.17 ±0.03	0.77 ±0.04	0.24 ±0.01	3.1 ±0.1	6.5 ±0.8
	1000	5	429 ±31	0.47 ±0.03	0.10 ±0.02	0.32 ±0.02	2.99 ±0.23	0.72 ±0.09	15.6 ±1.3	0.19 ±0.02	0.77 ±0.10	0.25 ±0.03	3.1 ±0.4	6.6 ±0.6

Each value is expressed as mean ± S.D.
@ : Relative organ weight per 100g body weight.

Table 22 - 1 Absolute and relative organ weights of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of administration period>

	Dose (mg/kg/day)	No.of Animals	Body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland (mg)	Spleen (g)	Ovary (mg)	Pituitary gland (mg)	Thyroid gland (mg)
Absolute	0	5	203 ±14	1.80 ±0.11	0.50 ±0.15	0.76 ±0.04	5.84 ±0.58	1.58 ±0.07	65.0 ±2.0	0.44 ±0.08	82.2 ±9.2	13.7 ±2.4	18.1 ±3.3
	15	5	220 ±10	1.81 ±0.04	0.47 ±0.06	0.76 ±0.02	6.95 ±0.49	1.72 ±0.10	68.2 ±11.4	0.51 ±0.07	92.9 ±19.1	15.0 ±2.9	19.6 ±2.6
	60	5	223 ±22	1.84 ±0.09	0.49 ±0.12	0.84 ±0.10	6.77 ±0.77	1.76 ±0.17	59.9 ±5.4	0.51 ±0.12	85.0 ±8.9	14.2 ±2.2	19.5 ±2.7
	250	5	217 ±13	1.81 ±0.08	0.43 ±0.11	0.77 ±0.04	7.01 ±0.65	1.71 ±0.18	67.6 ±11.0	0.49 ±0.09	98.0 ±7.1	13.1 ±1.6	19.8 ±0.9
	1000	5	209 ±23	1.77 ±0.07	0.49 ±0.12	0.77 ±0.08	8.17 ** ±0.93	1.72 ±0.08	66.0 ±6.4	0.62 ±0.07	76.6 ±40.0	13.1 ±1.2	21.6 ±2.6
Relative @	0	5	203 ±14	0.89 ±0.03	0.25 ±0.08	0.37 ±0.03	2.87 ±0.16	0.78 ±0.03	32.2 ±2.5	0.22 ±0.04	40.5 ±3.7	6.7 ±0.9	9.0 ±1.6
	15	5	220 ±10	0.83 ±0.05	0.21 ±0.02	0.35 ±0.01	3.16 ±0.15	±0.78 ±0.06	31.0 ±4.9	0.23 ±0.02	42.2 ±7.7	6.8 ±1.4	8.9 ±1.0
	60	5	223 ±22	0.83 ±0.05	0.21 ±0.03	0.38 ±0.03	3.04 ±0.10	0.79 ±0.04	27.0 ±2.2	0.23 ±0.04	38.2 ±0.9	6.4 ±0.9	8.7 ±0.4
	250	5	217 ±13	0.84 ±0.06	0.20 ±0.04	0.35 ±0.02	3.24 * ±0.26	0.79 ±0.05	31.1 ±3.8	0.23 ±0.04	45.3 ±3.2	6.0 ±0.7	9.2 ±0.6
	1000	5	209 ±23	0.86 ±0.08	0.24 ±0.04	0.37 ±0.02	3.93 ** ±0.18	0.83 ±0.05	31.9 ±2.3	0.30 ** ±0.02	38.4 ±20.2	6.3 ±0.5	10.4 ±1.1

Each value is expressed as mean ± S.D.
@ : Relative organ weight per 100g body weight.
* : Significantly different from control at 5% level of probability.
** : Significantly different from control at 1% level of probability.

Table 22 - 2 Absolute and relative organ weights of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study <At the end of recovery period>

	Dose (mg/kg/day)	No.of Animals	Body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland (mg)	Spleen (g)	Ovary (mg)	Pituitary gland (mg)	Thyroid gland (mg)
Absolute	0	5	236 ±9	1.77 ±0.07	0.41 ±0.08	0.84 ±0.05	6.50 ±0.62	1.73 ±0.19	71.1 ±9.5	0.48 ±0.03	77.3 ±19.4	15.5 ±1.7	20.9 ±3.6
	1000	5	248 ±12	1.82 ±0.04	0.39 ±0.04	0.87 ±0.07	7.13 ±0.22	1.65 ±0.12	66.2 ±5.6	0.52 ±0.03	88.2 ±15.8	14.6 ±1.6	21.8 ±2.2
Relative @	0	5	236 ±9	0.75 ±0.02	0.17 ±0.03	0.35 ±0.03	2.75 ±0.28	0.74 ±0.09	30.1 ±3.8	0.21 ±0.01	32.7 ±8.0	6.6 ±0.8	8.9 ±1.7
	1000	5	248 ±12	0.73 ±0.03	0.16 ±0.01	0.35 ±0.02	2.88 ±0.08	0.67 ±0.03	26.8 ±2.5	0.21 ±0.01	35.6 ±6.2	5.9 ±0.5	8.8 ±1.2

Each value is expressed as mean ± S.D.
@ : Relative organ weight per 100g body weight.

Table 23-1 Incidence of histopathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Organs	: Findings	Grade	At the end of administration period						At the end of recovery period[a)]	
		Dose(mg/kg/day)	0	15	60	250	1000		0	1000
		No. of animals	5	5	5	5	5		5	5
Lung	: Accumulation, foam cell	-	4	#	#	#	4		#	#
		+	1	#	#	#	1		#	#
Heart	: Myocardial degeneration/fibrosis	-	5	#	#	#	4		#	#
		+	0	#	#	#	1		#	#
Liver	: Hypertrophy, hepatocyte, centrilobular	-	5	5	5	5	2		5	5
		+	0	0	0	0	2		0	0
		++	0	0	0	0	1		0	0
	Degeneration, fatty, hepatocyte, peripheral	-	5	5	4	5	5		5	5
		+	0	0	1	0	0		0	0
	Necrosis, focal	-	3	5	5	4	3		4	5
		+	2	0	0	1	2		1	0
	Microgranuloma	-	4	4	4	4	3		4	4
		+	1	1	1	1	2		1	1
Kidney	: Hyaline droplet, proximal tubular epithelium	-	0	0	0	0	0		0	0
		+	5	5	4	4	0		4	3
		++	0	0	1	1	3		1	2
		+++	0	0	0	0	2	**	0	0
	Basophilic tubule	-	3	3	3	3	4		4	3
		+	2	2	2	2	1		1	2
	Cyst, solitary	-	4	5	5	5	5		5	5
		+	1	0	0	0	0		0	0

a) : Satellite group.

Grade, - : Negative, + : Slight, ++ : Moderate, +++ : Severe, # : Not examined.

** : Significantly different from control at 1% level of probability.

Table 23-2 Incidence of histopathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Organs	Findings	Grade	At the end of administration period						At the end of recovery period[a)]	
		Dose(mg/kg/day)	0	15	60	250	1000		0	1000
		No. of animals	5	5	5	5	5		5	5
Kidney	Cellular infiltration, lymphocyte, cortex, unilateral	-	5	5	5	5	4		4	5
		+	0	0	0	0	1		1	0
	Dilatation, tubular, focal	-	5	5	5	5	5		4	4
		+	0	0	0	0	0		1	1
Urinary bladder	Cellular infiltration, lymphocyte, submucosal layer	-	4	#	#	#	5		#	#
		+	1	#	#	#	0		#	#
Thymus	Hemorrhage	-	5	#	#	#	4		#	#
		+	0	#	#	#	1		#	#
Spleen	Congestion	-	5	5	5	5	0		5	5
		+	0	0	0	0	5	**	0	0
	Hematopoiesis, extramedullary	+	5	5	5	5	2		5	4
		++	0	0	0	0	3		0	1
	Deposit, pigment, brown	+	5	5	5	5	2		5	2
		++	0	0	0	0	3		0	3
Prostate	Cellular infiltration, lymphocyte, interstitium	-	4	#	#	#	5		#	#
		+	1	#	#	#	0		#	#

a) : Satellite group.

Grade, - : Negative, + : Slight, ++ : Moderate, # : Not examined.

** : Significantly different from control at 1% level of probability.

No abnormalities were detected in the brain, pituitary, thyroid, parathyroid, trachea, stomach, small intestine, large intestine, adrenal, testis, epididymis, seminal vesicle, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball from animals of control and 1000mg/kg groups.

Table 24-1 Incidence of histopathological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Organs	: Findings	Grade	At the end of administration period						At the end of recovery period[a)]	
		Dose(mg/kg/day)	0	15	60	250	1000		0	1000
		No. of animals	5	5	5	5	5		5	5
Liver	: Hypertrophy, hepatocyte, centrilobular	-	5	5	5	3	0		5	5
		+	0	0	0	2	4		0	0
		++	0	0	0	0	1	**	0	0
	Degeneration, fatty, hepatocyte, perilpheral	-	3	4	4	4	4		5	5
		+	2	1	1	1	1		0	0
	Necrosis, focal	-	5	5	5	4	4		5	5
		+	0	0	0	1	1		0	0
	Microgranuloma	-	4	4	4	3	5		4	3
		+	1	1	1	2	0		1	2
Kidney	: Basophilic tubule	-	4	#	#	#	5		#	#
		+	1	#	#	#	0		#	#
	Cyst, solitary	-	5	#	#	#	4		#	#
		+	0	#	#	#	1		#	#

a) : Satellite group.

Grade, - : Negative, + : Slight, ++ : Moderate, # : Not examined.

** : Significantly different from control at 1% level of probability.

Table 24-2 Incidence of histopathological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Organs	Findings	Grade	At the end of administration period						At the end of recovery period[a)]		
		Dose(mg/kg/day)	0	15	60	250	1000		0	1000	
		No. of animals	5	5	5	5	5		5	5	
Spleen	Congestion	-	5	5	5	5	2		5	5	
		+	0	0	0	0	3		0	0	
	Hematopoiesis, extramedullary	+	5	5	5	5	0		5	5	
		++	0	0	0	0	5	**	0	0	
	Deposit, pigment, brown	+	5	5	5	5	0		5	0	
		++	0	0	0	0	5	**	0	5	**
Ovary/ Uterus/Vagina	Atrophy	-	5	5	5	5	4		5	5	
		+++	0	0	0	0	1		0	0	

a) : Satellite group.
Grade, - : Negative, + : Slight, ++ : Moderate, +++ : Severe, # : Not examined.
** : Significantly different from control at 1% level of probability.

No abnormalities were detected in the the brain, pituitary, parathyroid, thymus, trachea, lung, heart, stomach, small intestine, large intestine, adrenal, urinary bladder, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball l from animals of control and 1000mg/kg groups.

2-ニトロ-p-クレゾールのラットを用いる28日間反復経口投与毒性試験

(試験番号：06-085)

最終報告書　添付資料B

(個体別表等)

財団法人　畜産生物科学安全研究所

Appendix 1 Test item characterization

被験物質の特性

名　　称　：2-ニトロ-p-クレゾール

ロット番号　：FBR01

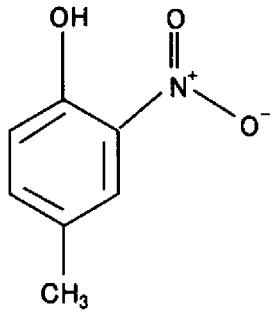
CAS 番号　：119-33-5

入 手 先　：東京化成工業株式会社（東京都中央区日本橋本町 4-10-1）より試薬を購入

入 手 日　：2006 年 8 月 31 日

純　　度　：99.8%（GC 法，分析：東京化成工業株式会社))

構 造 式　：



性状（常温）：淡黄色塊

溶 解 性　：水溶性

平均分子量　：153.14

融点　：32℃

溶解性　：油溶性

安定性　：安定〔実験終了後、(財)畜産生物科学安全研究所において保管した残余被験物質の純度を測定（GC 法）した結果、99.9%（2007 年 4 月 13 日分析）であり、実験開始前の分析値と比べて変化はなく、実験期間中被験物質は安定であったことを確認した。分析は、東京化成工業株式会社に委託して実施した。〕

保管条件　：冷暗所（2～6℃）で密栓

Appendix 2 Stability of the test article in the dosing solutions

被験物質の投与形態での安定性

「2-ニトロ-p-クレゾールのラットを用いる28日間反復経口投与毒性試験（試験番号：06-085)」を実施するに当たり、被験物質の投与形態での安定性を調べるため、溶媒として局方オリブ油（宮澤薬品株式会社、ロット番号 BH17）を用いて 2-ニトロ-p-クレゾール（ロット番号 FBR01）の 0.2 w/v%および 20 w/v%濃度の溶解液を調製し、3 日間および 7 日間冷暗所保存（2～6℃）し、さらに、それぞれ室温・遮光下で 1 日保存したものについて、上、中および下層よりサンプリングし、濃度を分析（GC 法）した。得られた結果は、次表に示す。

調製濃度 (%)	分析時点	分析値（%）			
		上層	中層	下層	平均値
0.2	調製直後	0.22	0.22	0.22	0.22
	4 日後	0.24	0.26	0.25	0.25
	8 日後	0.25	0.25	0.24	0.25
20	調製直後	19.6	19.5	19.5	19.5
	4 日後	18.7	18.9	18.9	18.9
	8 日後	18.1	17.8	18.4	18.1

以上の結果、局方オリブ油に溶解した 2-ニトロ-p-クレゾールの 0.2 および 20 w/v%液において、3 日間および 7 日間冷暗所保存（2～6℃）し、さらに、それぞれ室温・遮光下で 1 日保存したものについて、均一、かつ安定であると判断された。

Appendix 3 Analysis of concentrations of the test article in the dosing solutions

投与液中の被験物質濃度の確認

「2-ニトロ-p-クレゾールのラットを用いる28日間反復経口投与毒性試験（試験番号：06-085）」のための被験物質投与液について、所定の濃度で調製されていることを確認するため、初回に調製された2-ニトロ-p-クレゾールの局方オリブ油による溶液（15 mg/kg群用：3 mg/mL(0.3 w/v%)、60 mg/kg群用：12 mg/mL(1.2 w/v%)、250 mg/kg群用：50 mg/mL(5 w/v%)、1000 mg/kg群用：200 mg/mL(20 w/v%)）について、それぞれ調製直後に上、中、下層より各n=1でサンプリングし、分析（GC法）した。得られた結果は、次表に示す。

調製濃度	分析値（%）			
(%)	①	②	③	平均値
0.3	0.32	0.33	0.33	0.33
1.2	1.24	1.21	1.20	1.22
5	5.0	5.0	5.0	5.0
20	20.1	19.9	20.1	20.0

以上の結果から、被験物質投与液は、所定の濃度で調製されていることが確認された。

Appendix 4-1　Environmental conditions of animal room

動物室(4室)の温度・湿度の測定結果

年 月 日	温度(℃)	湿度(%)	備 考	
平成19年1月4日	22.1 - 22.4	58	動物搬入	
1月5日	22.2 - 22.4	57		
1月6日	22.2 - 22.4	57 - 58		
1月7日	22.4 - 22.5	57		
1月8日	22.3 - 22.4	57 - 58		
1月9日	22.3 - 22.4	57 - 58		
1月10日	22.3 - 22.5	57 - 58	雄 群分け	
1月11日	22.2 - 22.4	57 - 58	雌 群分け	雄投与開始
1月12日	22.2 - 22.4	58 - 62		雌投与開始
1月13日	22.3 - 22.4	57 - 59		
1月14日	22.2 - 22.5	57 - 58		
1月15日	22.1 - 22.5	58 - 59		
1月16日	22.1 - 22.4	57 - 58		
1月17日	22.2 - 22.4	58 - 59		
1月18日	22.4 - 22.5	57 - 58		
1月19日	22.2 - 22.3	57 - 58		
1月20日	22.2 - 22.3	58 - 59		
1月21日	22.2 - 22.4	58 - 59		
1月22日	22.1 - 22.4	58 - 60		
1月23日	22.1 - 22.2	58 - 59		
1月24日	22.1 - 22.4	55		
1月25日	22.1 - 22.3	58 - 59		
1月26日	22.0 - 22.4	57 - 62		
1月27日	22.3 - 22.5	58 - 59		
1月28日	22.1 - 22.4	58 - 59		
1月29日	22.2	59 - 60		
1月30日	22.1 - 22.4	57 - 60		
1月31日	22.2 - 22.5	58 - 59		
2月1日	22.2 - 22.3	58 - 59		
2月2日	22.1 - 22.4	57 - 59		
2月3日	22.1 - 22.4	58 - 59		
2月4日	22.1 - 22.2	58 - 60		
2月5日	22.0 - 22.4	58 - 60		
2月6日	22.1 - 22.6	57 - 59		
2月7日	22.1 - 22.2	58 - 59		雄投与終了
2月8日	22.0 - 22.4	58 - 59	雄 解剖(投与群)	雌投与終了
2月9日	22.1 - 22.4	57 - 58	雌 解剖(投与群)	

Appendix 4-2 Environmental conditions of animal room

動物室(4室)の温度・湿度の測定結果

年 月 日	温度(℃)	湿度(%)	備 考
平成19年2月10日	22.4 - 22.5	57	
2月11日	22.2 - 22.4	56 - 57	
2月12日	22.1 - 22.4	57	
2月13日	22.1 - 22.5	56 - 57	
2月14日	22.2	57 - 58	
2月15日	22.3 - 22.4	56 - 57	
2月16日	22.1 - 22.3	57	
2月17日	22.0 - 22.3	57	
2月18日	22.1 - 22.3	57 - 58	
2月19日	22.1 - 22.4	58 - 61	
2月20日	22.0 - 22.2	57 - 58	
2月21日	22.1 - 22.4	57 - 58	
2月22日	22.0 - 22.4	56 - 58	雄 解剖(回復群)
2月23日	22.2 - 22.3	56 - 57	雌 解剖(回復群)

TOKYO KENBIKYO-IN FOUNDATION

Institute for Food and Environment Sciences

IMAS-HAKOZAKI BLDG., 44-1, Nihonbashi hakozaki-cho, Chuo-Ku, Tokyo 103-0015, JAPAN
TEL: 03(3663)9681 FAX: 03(3663)9685

Date : December 19, 2006

CERTIFICATE

Applicant	: NIHON NOSAN KOGYO K.K
Samples	: LABO MR-STOCK, Lot No.061164
Date of Application	: November 28 , 2006
Date of Examination	: November 28 , 2006 ~ December 19 , 2006
Examination No.	: 260611-0041

As a result of tests carried out on the sample submitted under the above mentioned name on November 28, 2006, we herewith report as follows :

RESULTS

Aflatoxin B_1	not detected	(detection limit 5 ppb)
Aflatoxin B_2	not detected	(detection limit 5 ppb)
Aflatoxin G_1	not detected	(detection limit 5 ppb)
Aflatoxin G_2	not detected	(detection limit 5 ppb)
Arsenic(As)	0.18 ppm	(detection limit 0.01 ppm)
Lead(Pb)	0.2 ppm	(detection limit 0.1 ppm)
Cadmium(Cd)	0.07 ppm	(detection limit 0.01 ppm)
Chromium(Cr)	1.1 ppm	(detection limit 0.1 ppm)
Mercury(Hg)	not detected	(detection limit 0.01 ppm)
Polychlorinatedbiphenyl(PCBs)	not detected	(detection limit 0.01 ppm)
Total BHC*[1]	not detected	(detection limit 0.05 ppm)
Parathion	not detected	(detection limit 0.05 ppm)
Malathion	not detected	(detection limit 0.05 ppm)
Total DDT*[2]	not detected	(detection limit 0.05 ppm)

*[1] Expressed as total amounts of α-BHC, β-BHC, γ-BHC and δ-BHC

*[2] Expressed as total amounts of op'-DDT , pp'-DDT ,op'-DDD , pp-DDD , op'-DDE and pp'-DDE

continued.

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TEL: 03(3663)9681 FAX: 03(3663)9685

Heptachlor ·····	not detected	(detection limit 0.01 ppm)
Dieldrin ·····	not detected	(detection limit 0.01 ppm)
Aldrin ·····	not detected	(detection limit 0.01 ppm)
N-Nitrosodimethylamine ·····	not detected	(detection limit 10 ppb)
N-Nitrosodiethylamine ·····	not detected	(detection limit 10 ppb)

[redacted]

[redacted],D.V.M.,Ph.D.
Director
Institute for Food and Environment Sciences
TOKYO KENBIKYO-IN FOUNDATION

NOSAN

DATE Nov 24. 2006

MICROBIOLOGICAL INSPECTION

Customer
RESEARCH INSTITUTE FOR ANIMAL SCIENCE
IN BIOCHEMISTORY AND TOXICOLOGY
Sample Designation
LABO MR STOCK
Lot No.06.11.64

S.P.C.	8.1×10^{3} CFU/g
Coliform Group	Negative
Salmonella	Negative
Molds	<20 CFU/g

NOSAN CORPORATION
R & D Center
Safety & QC Station
5246 TAKURA, TSUKUBASHI, 300-2615 JAPAN

[redacted] Director

TOKYO KENBIKYO-IN FOUNDATION

Institute for Food and Environment Sciences

IMAS-HAKOZAKI BLDG., 44-1, Nihonbashi hakozaki-cho, Chuo-Ku, Tokyo 103-0015, JAPAN

TEL: 03(3663)9681 FAX: 03(3663)9685

Date : January 12, 2007

CERTIFICATE

Applicant	: NIHON NOSAN KOGYO K.K
Samples	: LABO MR-STOCK, Lot No.061255
Date of Application	: December 13 , 2006
Date of Examination	: December 13 , 2006 ~ January 12 , 2007
Examination No.	: 260612-0020

As a result of tests carried out on the sample submitted under the above mentioned name on December 13, 2006, we herewith report as follows :

RESULTS

Aflatoxin B_1	not detected	(detection limit 5 ppb)
Aflatoxin B_2	not detected	(detection limit 5 ppb)
Aflatoxin G_1	not detected	(detection limit 5 ppb)
Aflatoxin G_2	not detected	(detection limit 5 ppb)
Arsenic(As)	0.12 ppm	(detection limit 0.01 ppm)
Lead(Pb)	0.2 ppm	(detection limit 0.1 ppm)
Cadmium(Cd)	0.06 ppm	(detection limit 0.01 ppm)
Chromium(Cr)	0.9 ppm	(detection limit 0.1 ppm)
Mercury(Hg)	not detected	(detection limit 0.01 ppm)
Polychlorinatedbiphenyl(PCBs)	not detected	(detection limit 0.01 ppm)
Total BHC*1	not detected	(detection limit 0.05 ppm)
Parathion	not detected	(detection limit 0.05 ppm)
Malathion	0.13 ppm	(detection limit 0.05 ppm)
Total DDT*2	not detected	(detection limit 0.05 ppm)

*1 Expressed as total amounts of α-BHC, β-BHC, γ-BHC and δ-BHC

*2 Expressed as total amounts of op'-DDT , pp'-DDT ,op'-DDD , pp-DDD , op'-DDE and pp'-DDE

continued.

TOKYO KENBIKYO-IN FOUNDATION

Institute for Food and Environment Sciences

IMAS-HAKOZAKI BLDG., 44-1, Nihonbashi hakozaki-cho, Chuo-Ku, Tokyo 103-0015, JAPAN

TEL: 03(3663)9681 FAX: 03(3663)9685

Heptachlor ·····	not detected	(detection limit 0.01 ppm)
Dieldrin ·····	not detected	(detection limit 0.01 ppm)
Aldrin ·····	not detected	(detection limit 0.01 ppm)
N-Nitrosodimethylamine ·····	not detected	(detection limit 10 ppb)
N-Nitrosodiethylamine ·····	not detected	(detection limit 10 ppb)

[redacted]

[redacted], D.V.M., Ph.D.
Director
Institute for Food and Environment Sciences
TOKYO KENBIKYO-IN FOUNDATION

NOSAN

DATE Dec 15. 2006

MICROBIOLOGICAL INSPECTION

Customer
RESEARCH INSTITUTE FOR ANIMAL SCIENCE
IN BIOCHEMISTORY AND TOXICOLOGY
Sample Designation
LABO MR STOCK
Lot No.06.12.55

S.P.C.	9.9×10^{3} CFU/g
Coliform Group	Negative
Salmonella	Negative
Molds	<20 CFU/g

NOSAN CORPORATION
R & D Center
Safety & QC Station
5246 TAKURA, TSUKUBASHI, 300-2615 JAPAN

[redacted], Director

Analytical Certificate of Tap water

Issue no. D-070158
Date: 9 Mar. 2007

Messrs. The CHIKUSAN SEIBUTU KAGAKU KENKYUSHO Foundati[redacted]

TOKYO TECHNICAL·SERV[redacted]
8-Chome-20-20 Nishikasai Edogawa[redacted]
Tel: 03(3688)3284, Fax: 03(3877)53[redacted]
Registered No.:170
(Analyst registered to Ministry of health,labour and welfare)
Registered No.:Tokyo 56water-327
(Analyst of Drinking water in buil. facilities)
Director of analysis : [redacted]
Sampling by : [redacted]

Sample: Tap water
Sampling spot: Clean room
Date of sampling: 27. Feb. 2007 14:50
Purpose of analysis: Suitability inspection according to the Criteria of the Ministry of health,labour and welfare Waterworks Bureau (10 Items)

No.	Items	Unit	Results	*Criteria*
1	Bacteria	count/1ml	0	*less than 100*
2	Escherichia. Coli	—	Non-detected	*Non-detected*
3	Nitrogen(as nitrite&nitrate)	mg/l	1.3	*less than 10*
4	Chlorine	mg/l	7.8	*less than 200*
5	Organic substance(as Total organic carbons)	mg/l	0.6	*less than 5*
6	p H	—	7.5	*5.8~8.6*
7	Taste	—	normal	*Not abnormal*
8	Odor	—	normal	*Not abnormal*
9	Color	degree	Below 1	*less than 5*
10	Turbidity	degree	Below 1	*less than 2*

Methods of analysis are based on the Ministry of Health, Labour and Welfare Order No.101 (2003)

The result of above-mentioned items of tap water suits the criteria of the Ministry of Health, Labour and Welfare Waterworks Bureau

Appendix 7 Scoring lists for clinical signs in detailed observation of rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

ケージからの出し易さ Reactivity on removal from the cage	1.取り出し簡単 2.やや困難 3.困難 4.不可能に近い 5.凶暴・不可能
ケージから出す時の扱い易さ Reactivity on handling	1.従順で簡単 2.やや抵抗 3.抵抗しやや困難 4.逃避し困難 5.ハンドリング困難
体躯緊張 Muscle tone	1.弛緩 2.やや弛緩 3.正常 4.やや硬直 5.硬直
皮膚 Skin	1.正常 2.やや赤い 3.赤い 4.退色 5.蒼白
毛並み Fur	1.正常 2.軽度悪い 3.中等度 4.重度
立毛 Piloerection	1.なし 2.頭部周辺軽度 3.頭背部周辺軽度 4.ほぼ全身 5.全身
眼・鼻分泌物 Eye-nose discharge	1.なし 2.少しあり 3.あり 4.かなりあり 5.付着し閉鎖
眼瞼閉鎖状態 Palpebral closure	1.なし 2. 1/4 3. 1/2 4. 3/4 4.閉鎖
眼球突出 Exophthalmos	1.なし 2.僅か 3.やや 4.かなりあり 5.重度
流涙 Lacrimation	1.なし 2.眼周囲やや湿潤 3.湿潤 4.かなり湿潤 5.流涙
流涎 Salivation	1.なし 2.口周囲やや湿潤 3.湿潤 4.かなり湿潤 5.流涎
下腹部被毛の尿による汚れ Blotted fur in the lower abdomen with urine	1.なし 2.少しあり 3.あり 4.かなりあり
肛門周囲の便による汚れ Blotted fur around anus with feces	1.なし 2.少しあり 3.あり 4.かなりあり
発声 Vocalization	1.なし 2.保定時の一時的 3.やや持続的 4.持続的 5.中断なし
呼吸 Breathing	1.正常 2.軽度の不全:速く浅い 3.中等度の不全:浅く呼吸困難 4.重度の不全:開口呼吸 5.努力呼吸
姿勢 Body position	1.正常 2.腰高 3.横臥 4.伏臥 5.背臥
痙攣 Convulsion	1.なし 2.間歇的 3.やや持続的 4.持続的 5.中断なし
振戦 Tremor	1.なし 2.間歇的 3.やや持続的 4.持続的 5.中断なし
探索行動 Exploration	1.行動せず 2.やや行動 3.通常 4.かなり行動 5.頻繁に行動
歩行 Walk	1.異常なし 2.ややよろめく 3.よろめく
異常行動 Abnormal behavior	1.異常なし 2.やや繰り返す 3.繰り返す 4.かなり繰り返す 5.頻繁に繰り返す
常同行動 Stereotypy	1なし 2.たまにあり 3.よくあり 4.頻繁に
排尿 Urination	回数・性状及び色等
排糞 Defecation	回数・性状及び色等

Appendix 8 Scoring lists for sensory/reflex function tests of rats

Eye sight reaction	1: Normal; 2: Slightly late reaction for avoidance; 3: Late reaction for avoidance; 4: No reaction for avoidance
Hearing reaction	1: Normal; 2: Slight insensitivity; 3: Insensitivity; 4: No reaction
Sense of touch reaction	1: No reaction; 2: Slight reaction; 3: Normal; 4: Slight hypersensitivity; 5: Hypersensitivity
Pain reaction	1: Normal (immediate reaction for avoidance); 2: Slightly late reaction for avoidance; 3: Late reaction for avoidance; 4: No reaction
Pupil reflex (Reaction to light)	1: Normal (immedeate miosis); 2: No reflex
Righting reflex	1: Normal (immedeate reflex); 2: Slightly late reflex; 3: Late reflex; 4: No reflex

Appendix 9-1 Individual general conditions of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
0	001	KA	29	NAD
	002	KA	29	NAD
	003	KA	29	NAD
	004	KA	29	NAD
	005	KA	29	NAD
	006	KR	43	NAD
	007	KR	43	NAD
	008	KR	43	NAD
	009	KR	43	NAD
	010	KR	43	NAD
15	011	KA	29	NAD
	012	KA	29	NAD
	013	KA	29	NAD
	014	KA	29	NAD
	015	KA	29	NAD
60	016	KA	29	NAD
	017	KA	29	NAD
	018	KA	29	NAD
	019	KA	29	NAD
	020	KA	29	NAD

KA : Killed by design at the end of administration period. KR : Killed by design at the end of recovery period.
a : Day after initiation of administration.
NAD : No abnormalities were detected. + : Slight.

Appendix 9-2 Individual general conditions of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
250	021	KA	29	Sedation : +(1-2)[b] Ptosis : + (1-2)[b]
	022	KA	29	Sedation : +(1-2)[b] Ptosis : + (1-2)[b]
	023	KA	29	Sedation : +(1-2)[b] Ptosis : + (1-2)[b]
	024	KA	29	Sedation : +(1-2)[b] Ptosis : + (1-2)[b]
	025	KA	29	Sedation : +(1-2)[b] Ptosis : + (1-2)[b]

KA : Killed by design at the end of administration period.

a : Day after initiation of administration. b : Experimental day when the sign was observed.

+ : Slight.

Appendix 9-3 Individual general conditions of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
1000	026	KA	29	Salivation : + (1-2, 4, 7-11, 13, 15-28)[b]
				Sedation : +(1-2)[b]
				Ptosis : + (1-2)[b]
	027	KA	29	Salivation : + (1-3, 7-10, 13-28)[b]
				Sedation : +(1-2)[b]
				Ptosis : + (1-2)[b]
				Reddish tear : +(1-2)[b]
	028	KA	29	Salivation : + (1, 5, 7-10, 12-17, 19-24, 26-28)[b]
				Sedation : +(1-2)[b]
				Ptosis : + (1-2)[b]
	029	KA	29	Salivation : + (8-11, 13-15, 17, 20-23, 27-28)[b]
				Sedation : +(1-2)[b]
				Ptosis : + (1-2)[b]
	030	KA	29	Salivation : + (1, 4-5, 7-9, 11-14, 16-22, 27-28)[b]
				Sedation : +(1-2)[b]
				Ptosis : + (1-2)[b]

KA : Killed by design at the end of administration period.

a : Day after initiation of administration. b : Experimental day when the sign was observed.

+ : Slight.

Appendix 9-4 Individual general conditions of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
1000	031	KR	43	Salivation : + (3-5, 8-9, 11-15, 19-21, 24-28)[b] Sedation : +(1-2)[b] Ptosis : + (1-2)[b]
	032	KR	43	Salivation : + (1-2, 4-5, 7-9, 11-28)[b] Sedation : +(1-2)[b] Ptosis : + (1-2)[b]
	033	KR	43	Salivation : + (2, 4-5, 7-9, 13, 15-16, 18-25, 27-28)[b] Sedation : +(1-2)[b] Ptosis : + (1-2)[b]
	034	KR	43	Salivation : + (1, 3, 6-9, 11-21, 23-24, 27-28)[b] Sedation : +(1-2)[b] Ptosis : + (1-2)[b]
	035	KR	43	Salivation : + (1-2, 4, 7-9, 12-13, 16-24, 26-28)[b] Sedation : +(1-2)[b] Ptosis : + (1-2)[b]

KR : Killed by design at the end of recovery period.

a : Day after initiation of administration. b : Experimental day when the sign was observed.

+ : Slight.

Appendix 10-1 Individual general conditions of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
0	501	KA	29	NAD
	502	KA	29	NAD
	503	KA	29	NAD
	504	KA	29	NAD
	505	KA	29	NAD
	506	KR	43	NAD
	507	KR	43	NAD
	508	KR	43	NAD
	509	KR	43	NAD
	510	KR	43	NAD
15	511	KA	29	NAD
	512	KA	29	NAD
	513	KA	29	NAD
	514	KA	29	NAD
	515	KA	29	NAD
60	516	KA	29	NAD
	517	KA	29	NAD
	518	KA	29	NAD
	519	KA	29	NAD
	520	KA	29	NAD

KA : Killed by design at the end of administration period. KR : Killed by design at the end of recovery period.
a : Day after initiation of administration.
NAD : No abnormalities were detected. + : Slight.

Appendix 10-2 Individual general conditions of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
250	521	KA	29	Sedation : + (1)[b] Ptosis : + (1)[b]
	522	KA	29	Sedation : + (1)[b] Ptosis : + (1)[b]
	523	KA	29	Sedation : + (1)[b] Ptosis : + (1)[b]
	524	KA	29	Sedation : + (1)[b] Ptosis : + (1)[b]
	525	KA	29	Sedation : + (1)[b] Ptosis : + (1)[b]

KA : Killed by design at the end of administration period.
a : Day after initiation of administration. b : Experimental day when the sign was observed.
+ : Slight.

Appendix 10-3 Individual general conditions of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
1000	526	KA	29	Salivation : + (3-5, 10-14, 17-23, 26-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b]
	527	KA	29	Salivation : + (1, 4, 6-13, 16-21, 23-24, 26-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b]
	528	KA	29	Salivation : + (2, 4, 6, 8-10, 12-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b] Soiled perineal region : + (10, 12, 17-20)[b]
	529	KA	29	Salivation : + (1, 6, 12, 15, 18-24, 26-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b]
	530	KA	29	Salivation : + (1-3, 6, 11-24, 26-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b]

KA : Killed by design at the end of administration period.

a : Day after initiation of administration. b : Experimental day when the sign was observed.

+ : Slight.

Appendix 10-4 Individual general conditions of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
1000	531	KR	43	Salivation : + (6-7, 9, 11-14, 16, 18-23, 26-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b] Soiled perineal region : + (2-5)[b]
	532	KR	43	Salivation : + (1-2, 6-7, 9, 11-14, 16-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b]
	533	KR	43	Salivation : + (1, 6-9, 11-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b]
	534	KR	43	Salivation : + (4, 6, 9, 11-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b]
	535	KR	43	Salivation : + (3, 6, 9, 11-28)[b] Sedation : + (1)[b] Ptosis : + (1)[b]

KA : Killed by design at the end of administration period. KR : Killed by design at the end of recovery period.
a : Day after initiation of administration. b : Experimental day when the sign was observed.
+ : Slight.

Appendix 11 - 1 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 Before administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		001	002	003	004	005	006	007	008	009	010
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	1	1	1	1	0	1
	: tone of color	-	-	-	-	PY	PY	PY	PY	-	PY
Defecatio	: count	1	0	0	0	1	1	0	0	0	0
	: appearance	N	-	-	-	N	N	-	-	-	-

PY : Pale yellow; N : Normal.

Appendix 11 - 2 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 Before administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	1	0	1	1	1	0	1	2	0	0	0	2	0	0	0
	: tone of color	PY	-	PY	PY	PY	-	PY	PY	-	-	-	PY	-	-	-
Defecatio	: count	0	0	3	4	2	0	0	0	0	0	0	3	0	1	4
	: appearance	-	-	N	N	N	-	-	-	-	-	-	N	-	N	N

PY : Pale yellow; N : Normal.

Appendix 11 - 3 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 Before administration period 〉

Items	Dose(mg/kg/day) / Animal number	1000									
		026	027	028	029	030	031	032	033	034	035
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	2	1	0	2	2	0	0	1	2	2
	: tone of color	PY	PY	-	PY	PY	-	-	PY	PY	PY
Defecatio	: count	0	0	0	0	3	0	0	5	2	5
	: appearance	-	-	-	-	N	-	-	N	N	N

PY : Pale yellow; N : Normal.

Appendix 11 - 4 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		001	002	003	004	005	006	007	008	009	010
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	1	0	1	0	0	0	0	0
	: tone of color	-	-	PY	-	PY	-	-	-	-	-
Defecatio	: count	0	0	0	0	1	0	0	0	0	0
	: appearance	-	-	-	-	N	-	-	-	-	-

PY : Pale yellow; N : Normal.

Appendix 11 - 5 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	1	0	0	0	0	0	1	0	1	0	0	0	0	0	0
	: tone of color	PY	-	-	-	-	-	PY	-	PY	-	-	-	-	-	-
Defecatio	: count	5	0	4	3	0	0	0	0	2	0	0	0	0	0	1
	: appearance	N	-	N	N	-	-	-	-	N	-	-	-	-	-	N

PY : Pale yellow; N : Normal.

Appendix 11 - 6 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	1000									
		026	027	028	029	030	031	032	033	034	035
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	1	0	1	1	0	0	1	1	1
	: tone of color	-	PY	-	PY	PY	-	-	PY	PY	PY
Defecatic	: count	0	0	0	1	1	0	0	2	1	2
	: appearance	-	-	-	N	N	-	-	N	N	N

PY : Pale yellow; N : Normal.

Appendix 11・7 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		001	002	003	004	005	006	007	008	009	010
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	2	0	0	0	2	0
	: tone of color	-	-	-	-	PY	-	-	-	PY	-
Defecatio	: count	0	0	0	0	0	0	0	0	3	0
	: appearance	-	-	-	-	-	-	-	-	N	-

PY : Pale yellow; N : Normal.

Appendix 11 - 8 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	1	0	0	3	0	0	0	0	0	0	0	0	0	0	0
	: tone of color	PY	-	-	PY	-	-	-	-	-	-	-	-	-	-	-
Defecatio	: count	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	N	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow; N : Normal.

Appendix 11 - 9 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	1000									
		026	027	028	029	030	031	032	033	034	035
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	1	0	1	0	0	0	0	2	1
	: tone of color	-	PY	-	PY	-	-	-	-	PY	PY
Defecatio	: count	0	1	0	0	0	0	0	0	3	0
	: appearance	-	N	-	-	-	-	-	-	N	-

PY : Pale yellow; N : Normal.

Appendix 11 - 10 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 3 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		001	002	003	004	005	006	007	008	009	010
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	1	0	1	1	0	0	0	0	0
	: tone of color	-	PY	-	PY	PY	-	-	-	-	-
Defecatic	: count	0	0	0	0	0	0	0	0	0	1
	: appearance	-	-	-	-	-	-	-	-	-	N

PY : Pale yellow; N : Normal.

Appendix 11 - 11 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 3 of administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	1	1	0	1	1	0	0	0	0	0	1	0	0	0	0
	: tone of color	PY	PY	-	PY	PY	-	-	-	-	-	PY	-	-	-	-
Defecatio	: count	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0
	: appearance	N	-	-	-	N	-	-	-	N	-	-	-	-	-	-

PY : Pale yellow; N : Normal.

Appendix 11 - 12 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 3 of administration period 〉

Items	Dose(mg/kg/day) Animal number	1000									
		026	027	028	029	030	031	032	033	034	035
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	1	0	2	0	0	1	1	0	1
	: tone of color	-	PY	-	PY	-	-	PY	PY	-	PY
Defecatio	: count	0	0	0	0	0	0	0	2	0	0
	: appearance	-	-	-	-	-	-	-	N	-	-

PY : Pale yellow; N : Normal.

Appendix 11 - 13 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		001	002	003	004	005	006	007	008	009	010
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	2	0	0	1	0	0	1	0	0
	: tone of color	-	PY	-	-	PY	-	-	PY	-	-
Defecation	: count	0	0	0	0	0	0	0	0	2	0
	: appearance	-	-	-	-	-	-	-	-	N	-

PY : Pale yellow; N : Normal.

Appendix 11・14 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
	: tone of color	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-
Defecatio	: count	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	N	-	-	-	-	-	-	-	-	-	-

Y : Yellow; N : Normal.

Appendix 11 - 15 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day) Animal number	1000									
		026	027	028	029	030	031	032	033	034	035
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	1	1	2	0	0	1	1	1	0
	: tone of color	-	Y	Y	Y	-	-	Y	Y	Y	-
Defecatio	: count	0	3	0	0	0	0	0	1	0	0
	: appearance	-	N	-	-	-	-	-	N	-	-

Y : Yellow; N : Normal.

Appendix 11 - 16 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of recovery period 〉

Items	Dose(mg/kg/day)	0					1000				
	Animal number	006	007	008	009	010	031	032	033	034	035
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	1	0	2	0	0	0	0	0	0	0
	: tone of color	PY	-	PY	-	-	-	-	-	-	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 11 - 17 Individual clinical signs in detailed observation of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Items	Dose(mg/kg/day)	0					1000				
	Animal number	006	007	008	009	010	031	032	033	034	035
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatior	: count	1	1	1	1	0	1	0	0	1	1
	: tone of color	PY	PY	PY	PY	-	PY	-	-	PY	PY
Defecatio	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 12 - 1 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 Before administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		501	502	503	504	505	506	507	508	509	510
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	3	0	0	3	3	0	0	0	0	0
	: tone of color	PY	-	-	PY	PY	-	-	-	-	-
Defecatio	: count	0	0	0	0	0	0	1	0	0	0
	: appearance	-	-	-	-	-	-	N	-	-	-

PY : Pale yellow; N : Normal.

Appendix 12 - 2 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 Before administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	1	0	1	1	0	1	0	0	1	0	2
	: tone of color	-	-	-	-	PY	-	PY	PY	-	PY	-	-	PY	-	PY
Defecatio	: count	1	1	0	0	0	0	0	0	0	0	2	0	0	0	1
	: appearance	N	N	-	-	-	-	-	-	-	-	N	-	-	-	N

PY : Pale yellow; N : Normal.

Appendix 12 - 3 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 Before administration period 〉

Items	Dose(mg/kg/day) / Animal number	1000									
		526	527	528	529	530	531	532	533	534	535
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	0	1	1	0	0	0
	: tone of color	-	-	-	-	-	PY	PY	-	-	-
Defecatio	: count	0	1	0	0	0	0	0	0	0	3
	: appearance	-	N	-	-	-	-	-	-	-	N

PY : Pale yellow; N : Normal.

Appendix 12 - 4 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		501	502	503	504	505	506	507	508	509	510
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	2	1	2	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	3	0	0	3	0	0	1	0	0	1
	: tone of color	PY	-	-	PY	-	-	PY	-	-	PY
Defecatio	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 12 - 5 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	3	2	0	0	0	2	2	1	2	1	1	0	2	1
	: tone of color	-	PY	PY	-	-	-	PY	PY	PY	PY	PY	PY	-	PY	PY
Defecatio	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 12 - 6 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	1000									
		526	527	528	529	530	531	532	533	534	535
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	1	0	0	0	2	0	1	2	0
	: tone of color	-	PY	-	-	-	PY	-	PY	PY	-
Defecatio	: count	0	3	0	0	0	0	0	4	0	0
	: appearance	-	N	-	-	-	-	-	N	-	-

PY : Pale yellow; N : Normal.

Appendix 12 - 7 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		501	502	503	504	505	506	507	508	509	510
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	1	0	0	0	0	0	1	0	0	0
	: tone of color	PY	-	-	-	-	-	PY	-	-	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow

Appendix 12 - 8 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	1	1	0	0	0	0	0	0	0	2	0	0	1	0
	: tone of color	-	PY	PY	-	-	-	-	-	-	-	PY	-	-	PY	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
	: appearance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	N

PY : Pale yellow; N : Normal.

Appendix 12 - 9 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of administration period 〉

Items	Dose(mg/kg/day) Animal number	1000									
		526	527	528	529	530	531	532	533	534	535
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	2	1	1	1	1	1	1	1
Vocalization		2	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	1	0	1	2	3	1
	: tone of color	-	-	-	-	PY	-	PY	PY	PY	PY
Defecatio	: count	0	0	0	1	0	0	0	0	0	0
	: appearance	-	-	-	N	-	-	-	-	-	-

PY : Pale yellow; N : Normal.

Appendix 12 - 10 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 3 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		501	502	503	504	505	506	507	508	509	510
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	5	0	0	0	0	0	0	0	0	0
	: tone of color	PY	-	-	-	-	-	-	-	-	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 12 - 11 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 3 of administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0
	: tone of color	-	-	-	-	-	-	-	-	PY	-	PY	-	PY	-	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 12 - 12 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 3 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	1000									
		526	527	528	529	530	531	532	533	534	535
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	0	0	0	2	0	0
	: tone of color	-	-	-	-	-	-	-	PY	-	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 12・13 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	0									
		501	502	503	504	505	506	507	508	509	510
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	2	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	1	1	0	0	0	0	0
	: tone of color	-	-	-	PY	PY	-	-	-	-	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 12・14 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day)	15					60					250				
	Animal number	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	2	1	1	1	1	1	2
Breathing		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	1	1	0	0	1	0	3	2	0	0	0
	: tone of color	-	-	-	-	PY	PY	-	-	PY	-	PY	PY	-	-	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 12 - 15 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Items	Dose(mg/kg/day) / Animal number	1000									
		526	527	528	529	530	531	532	533	534	535
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		2	1	1	1	2	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	1	0	0	1	0	0
	: tone of color	-	-	-	-	PY	-	-	PY	-	-
Defecatio	: count	0	0	0	0	0	1	0	0	0	0
	: appearance	-	-	-	-	-	N	-	-	-	-

PY : Pale yellow; N : Normal.

Appendix 12 - 16 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 1 of recovery period 〉

Items	Dose(mg/kg/day) / Animal number	0					1000				
		506	507	508	509	510	531	532	533	534	535
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	0	0	0	1	0	0
	: tone of color	-	-	-	-	-	-	-	PY	-	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Appendix 12 - 17 Individual clinical signs in detailed observation of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Items	Dose(mg/kg/day) / Animal number	0					1000				
		506	507	508	509	510	531	532	533	534	535
Reactivity on removal from the cage		1	1	1	1	1	1	1	1	1	1
Reactivity on handling		1	1	1	1	1	1	1	1	1	1
Muscle tone		3	3	3	3	3	3	3	3	3	3
Skin		1	1	1	1	1	1	1	1	1	1
Fur		1	1	1	1	1	1	1	1	1	1
Piloerection		1	1	1	1	1	1	1	1	1	1
Eye-nose discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exophthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	1	1	1	1	1	1	1	1
Blotted fur in the lower abdomen with urine		1	1	1	1	1	1	1	1	1	1
Blotted fur around anus with feces		1	1	1	1	1	1	1	1	1	1
Vocalization		1	1	1	1	1	1	1	1	1	1
Breathing		1	1	1	1	1	1	1	1	1	1
Body position		1	1	1	1	1	1	1	1	1	1
Convulsion		1	1	1	1	1	1	1	1	1	1
Tremor		1	1	1	1	1	1	1	1	1	1
Exploration		3	3	3	3	3	3	3	3	3	3
Walk		1	1	1	1	1	1	1	1	1	1
Abnormal behavior		1	1	1	1	1	1	1	1	1	1
Stereotypy		1	1	1	1	1	1	1	1	1	1
Urinatio	: count	0	0	0	0	0	0	0	0	0	0
	: tone of color	-	-	-	-	-	-	-	-	-	-
Defecatio	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

Appendix 13 - 1 Individual sensory/reflex function data of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Dose (mg/kg/day)	Animal No.	Eye sight reaction	Hearing reaction	Sense of touch reaction	Pain reaction	Pupil reflex	Righting reflex
0	001	1	1	3	1	1	1
	002	1	1	3	1	1	1
	003	1	1	3	1	1	1
	004	1	1	3	1	1	1
	005	1	1	3	1	1	1
15	011	1	1	3	1	1	1
	012	1	1	3	1	1	1
	013	1	1	3	1	1	1
	014	1	1	3	1	1	1
	015	1	1	3	1	1	1
60	016	1	1	3	1	1	1
	017	1	1	3	1	1	1
	018	1	1	3	1	1	1
	019	1	1	3	1	1	1
	020	1	1	3	1	1	1
250	021	1	1	3	1	1	1
	022	1	1	3	1	1	1
	023	1	1	3	1	1	1
	024	1	1	3	1	1	1
	025	1	1	3	1	1	1
1000	026	1	1	3	1	1	1
	027	1	1	3	1	1	1
	028	1	1	3	1	1	1
	029	1	1	3	1	1	1
	030	1	1	3	1	1	1

1 or 3 : Normal.
Criterions for scoring are shown in appendix 8.

Appendix 13 - 2 Individual sensory/reflex function data of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of reccovery period 〉

Dose (mg/kg/day)	Animal No.	Eye sight reaction	Hearing reaction	Sense of touch reaction	Pain reaction	Pupil reflex	Righting reflex
0	006	1	1	3	1	1	1
	007	1	1	3	1	1	1
	008	1	1	3	1	1	1
	009	1	1	3	1	1	1
	010	1	1	3	1	1	1
1000	031	1	1	3	1	1	1
	032	1	1	3	1	1	1
	033	1	1	3	1	1	1
	034	1	1	3	1	1	1
	035	1	1	3	1	1	1

1 or 3 : Normal.
Criterions for scoring are shown in appendix 8.

Appendix 14 - 1 Individual sensory/reflex function data of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Dose (mg/kg/day)	Animal No.	Eye sight reaction	Hearing reaction	Sense of touch reaction	Pain reaction	Pupil reflex	Righting reflex
0	501	1	1	3	1	1	1
	502	1	1	3	1	1	1
	503	1	1	3	1	1	1
	504	1	1	3	1	1	1
	505	1	1	3	1	1	1
15	511	1	1	3	1	1	1
	512	1	1	3	1	1	1
	513	1	1	3	1	1	1
	514	1	1	3	1	1	1
	515	1	1	3	1	1	1
60	516	1	1	3	1	1	1
	517	1	1	3	1	1	1
	518	1	1	3	1	1	1
	519	1	1	3	1	1	1
	520	1	1	3	1	1	1
250	521	1	1	3	1	1	1
	522	1	1	3	1	1	1
	523	1	1	3	1	1	1
	524	1	1	3	1	1	1
	525	1	1	3	1	1	1
1000	526	1	1	3	1	1	1
	527	1	1	3	1	1	1
	528	1	1	3	1	1	1
	529	1	1	3	1	1	1
	530	1	1	3	1	1	1

1 or 3 : Normal.
Criterions for scoring are shown in appendix 8.

Appendix 14 - 2 Individual sensory/reflex function data of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of reccovery period 〉

Dose (mg/kg/day)	Animal No.	Eye sight reaction	Hearing reaction	Sense of touch reaction	Pain reaction	Pupil reflex	Righting reflex
0	506	1	1	3	1	1	1
	507	1	1	3	1	1	1
	508	1	1	3	1	1	1
	509	1	1	3	1	1	1
	510	1	1	3	1	1	1
1000	531	1	1	3	1	1	1
	532	1	1	3	1	1	1
	533	1	1	3	1	1	1
	534	1	1	3	1	1	1
	535	1	1	3	1	1	1

1 or 3 : Normal.
Criterions for scoring are shown in appendix 8.

Appendix 15 - 1 Individual grip strength and motor activity data of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Dose (mg/kg/day)	Animal number	Grip strength (g) Fore-limb	Grip strength (g) Hind-limb	Motor activity (counts) 0～60min.
0	001	797	218	14347
	002	626	241	9377
	003	890	227	10822
	004	847	290	10010
	005	755	367	12003
	Mean	783	269	11312
15	011	973	277	10498
	012	650	223	8244
	013	625	249	8724
	014	924	320	9229
	015	707	225	12128
	Mean	776	259	9765
60	016	555	210	11431
	017	579	290	14132
	018	687	240	12335
	019	1080	261	7895
	020	906	241	15873
	Mean	761	248	12333
250	021	541	273	17813
	022	430	352	11132
	023	722	423	15569
	024	632	325	5642
	025	563	217	7687
	Mean	578	318	11569
1000	026	892	326	11381
	027	635	328	8700
	028	533	247	6808
	029	788	316	8164
	030	827	297	7808
	Mean	735	303	8572

Appendix 15 - 2 Individual grip strength and motor activity data of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Dose (mg/kg/day)	Animal number	Grip strength (g) Fore-limb	Grip strength (g) Hind-limb	Motor activity (counts) $0\sim60_{min.}$
0	006	778	202	13821
	007	549	211	10739
	008	906	220	14550
	009	1107	251	15314
	010	583	271	11435
	Mean	785	231	13172
1000	031	714	274	12478
	032	1004	273	18468
	033	715	346	12733
	034	636	258	16166
	035	1217	262	10069
	Mean	857	283	13983

Appendix 16 - 1 Individual grip strength and motor activity data of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 4 of administration period 〉

Dose (mg/kg/day)	Animal number	Grip strength (g) Fore-limb	Grip strength (g) Hind-limb	Motor activity (counts) 0~60min.
0	501	407	272	15192
	502	544	243	6208
	503	655	258	15795
	504	755	369	9424
	505	743	255	12513
	Mean	621	279	11826
15	511	803	304	7477
	512	697	210	10974
	513	727	197	13265
	514	761	248	15983
	515	723	346	16296
	Mean	742	261	12799
60	516	592	284	11995
	517	526	273	14290
	518	724	278	17252
	519	655	249	11463
	520	613	269	15794
	Mean	622	271	14159
250	521	553	219	15715
	522	442	320	13693
	523	728	456	10914
	524	652	330	14842
	525	469	266	10231
	Mean	569	318	13079
1000	526	638	232	11669
	527	508	273	15725
	528	626	402	12337
	529	512	309	14975
	530	545	265	12350
	Mean	566	296	13411

Appendix 16 - 2 Individual grip strength and motor activity data of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

〈 On week 2 of recovery period 〉

Dose (mg/kg/day)	Animal number	Grip strength (g) Fore-limb	Grip strength (g) Hind-limb	Motor activity (counts) $0 \sim 60_{min.}$
0	506	761	248	11584
	507	810	331	10284
	508	986	356	7136
	509	875	265	5497
	510	996	274	15578
	Mean	886	295	10016
1000	531	846	299	9016
	532	832	296	7183
	533	656	279	11614
	534	683	263	10037
	535	555	223	14074
	Mean	714	272	10385

Appendix 17 Individual body weight of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

(g)

Dose (mg/kg/day)	Animal number	Day	Administration period 1	7	14	21	28	Gain 1~28	Recovery period 0	7	14	Gain 0~14
0	001		150	209	272	334	379	229	--	--	--	--
	002		158	204	262	308	346	188	--	--	--	--
	003		157	203	268	327	361	204	--	--	--	--
	004		159	221	292	352	387	228	--	--	--	--
	005		161	212	278	340	390	229	--	--	--	--
	006		163	218	289	346	389	226	389	434	464	75
	007		164	212	269	318	364	200	364	408	438	74
	008		170	220	294	361	412	242	412	448	495	83
	009		164	212	283	358	406	242	406	454	486	80
	010		167	218	281	338	388	221	388	426	464	76
	Mean		161	213	279	338	382	221	392	434	469	78
15	011		155	195	252	304	343	188	--	--	--	--
	012		155	205	273	340	392	237	--	--	--	--
	013		161	225	293	365	417	256	--	--	--	--
	014		164	221	287	353	399	235	--	--	--	--
	015		173	224	285	345	384	211	--	--	--	--
	Mean		162	214	278	341	387	225	--	--	--	--
60	016		153	199	251	298	334	181	--	--	--	--
	017		156	207	269	325	353	197	--	--	--	--
	018		162	211	271	316	348	186	--	--	--	--
	019		167	217	277	334	373	206	--	--	--	--
	020		168	236	306	356	411	243	--	--	--	--
	Mean		161	214	275	326	364	203	--	--	--	--
250	021		151	208	269	338	380	229	--	--	--	--
	022		159	203	262	331	374	215	--	--	--	--
	023		162	210	272	330	376	214	--	--	--	--
	024		163	208	269	322	353	190	--	--	--	--
	025		168	212	274	333	374	206	--	--	--	--
	Mean		161	208	269	331	371	211	--	--	--	--
1000	026		146	181	240	287	317	171	--	--	--	--
	027		153	198	258	307	351	198	--	--	--	--
	028		157	198	254	314	360	203	--	--	--	--
	029		158	203	254	310	347	189	--	--	--	--
	030		160	206	267	320	353	193	--	--	--	--
	031		166	228	312	375	429	263	429	470	500	71
	032		164	209	271	326	365	201	365	398	420	55
	033		165	218	291	358	420	255	420	464	504	84
	034		169	228	289	358	412	243	412	452	484	72
	035		173	222	283	338	388	215	388	424	459	71
	Mean		161	209	272	329	374	213	403	442	473	71

Appendix 18 Individual body weight of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

(g)

Dose (mg/kg/day)	Animal number	Day	Administration period 1	7	14	21	28	Gain 1~28	Recovery period 0	7	14	Gain 0~14
0	501		137	159	179	198	217	80	--	--	--	--
	502		140	168	191	211	218	78	--	--	--	--
	503		136	166	189	204	232	96	--	--	--	--
	504		141	163	181	194	211	70	--	--	--	--
	505		147	175	199	221	232	85	--	--	--	--
	506		142	160	182	200	215	73	215	232	244	29
	507		142	162	184	197	223	81	223	246	252	29
	508		148	160	183	202	221	73	221	236	241	20
	509		151	181	201	228	246	95	246	259	268	22
	510		150	177	204	214	250	100	250	265	275	25
	Mean		143	167	189	207	227	83	231	248	256	25
15	511		139	163	189	198	224	85	--	--	--	--
	512		138	169	186	207	239	101	--	--	--	--
	513		145	174	198	223	240	95	--	--	--	--
	514		147	178	200	221	255	108	--	--	--	--
	515		150	179	199	214	240	90	--	--	--	--
	Mean		144	173	194	213	240	96	--	--	--	--
60	516		137	159	179	197	209	72	--	--	--	--
	517		140	167	194	209	233	93	--	--	--	--
	518		148	181	213	238	258	110	--	--	--	--
	519		144	177	203	222	231	87	--	--	--	--
	520		151	191	220	236	273	122	--	--	--	--
	Mean		144	175	202	220	241	97	--	--	--	--
250	521		138	167	186	223	242	104	--	--	--	--
	522		140	162	187	203	225	85	--	--	--	--
	523		146	174	201	231	246	100	--	--	--	--
	524		143	163	183	202	220	77	--	--	--	--
	525		154	181	213	243	259	105	--	--	--	--
	Mean		144	169	194	220	238	94	--	--	--	--
1000	526		136	153	178	201	211	75	--	--	--	--
	527		141	171	203	238	260	119	--	--	--	--
	528		130	152	169	177	202	72	--	--	--	--
	529		144	172	196	216	235	91	--	--	--	--
	530		143	165	182	196	223	80	--	--	--	--
	531		144	172	201	223	243	99	243	259	281	38
	532		144	173	197	229	250	106	250	266	274	24
	533		146	173	197	214	234	88	234	244	254	20
	534		151	181	207	232	252	101	252	280	291	39
	535		154	178	191	212	231	77	231	247	252	21
	Mean		143	169	192	214	234	91	242	259	270	28

Appendix 19 Individual food consumption of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

(g/rat/day)

Dose (mg/kg/day)	Animal number	Week	Administration period 1	2	3	4	Recovery period 1	2
0	001		26	28	29	33	--	--
	002		23	24	25	27	--	--
	003		23	28	27	29	--	--
	004		28	31	32	31	--	--
	005		27	29	29	35	--	--
	006		28	29	30	34	37	35
	007		26	25	24	29	35	35
	008		28	33	34	34	39	36
	009		27	29	30	34	37	34
	010		27	28	30	31	35	33
	Mean		26	28	29	32	37	35
15	011		22	26	28	26	--	--
	012		23	28	28	29	--	--
	013		28	30	31	29	--	--
	014		30	28	31	27	--	--
	015		26	31	29	29	--	--
	Mean		26	29	29	28	--	--
60	016		22	22	22	24	--	--
	017		25	28	28	27	--	--
	018		25	27	28	25	--	--
	019		25	28	28	24	--	--
	020		31	31	31	32	--	--
	Mean		26	27	27	26	--	--
250	021		23	27	28	25	--	--
	022		23	26	27	28	--	--
	023		25	28	25	26	--	--
	024		23	25	28	24	--	--
	025		26	29	29	26	--	--
	Mean		24	27	27	26	--	--
1000	026		23	25	25	24	--	--
	027		24	28	22	28	--	--
	028		23	26	27	28	--	--
	029		26	26	26	26	--	--
	030		24	26	26	24	--	--
	031		32	32	32	31	34	36
	032		29	27	30	29	34	35
	033		30	35	37	40	43	44
	034		30	33	31	33	38	36
	035		28	30	28	30	36	40
	Mean		27	29	28	29	37	38

Appendix 20 Individual food consumption of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

(g/rat/day)

Dose (mg/kg/day)	Animal number	Week	Administration period 1	2	3	4	Recovery period 1	2
0	501		18	20	15	19	--	--
	502		20	20	19	23	--	--
	503		14	20	20	21	--	--
	504		18	18	16	19	--	--
	505		22	15	19	25	--	--
	506		19	21	18	21	19	22
	507		13	19	19	20	20	23
	508		19	17	20	22	25	25
	509		20	20	15	19	19	25
	510		20	24	20	17	28	27
	Mean		18	19	18	21	22	24
15	511		15	20	17	21	--	--
	512		19	19	20	19	--	--
	513		19	17	19	18	--	--
	514		18	22	22	21	--	--
	515		17	24	22	23	--	--
	Mean		18	20	20	20	--	--
60	516		16	18	15	16	--	--
	517		19	20	21	16	--	--
	518		22	20	24	22	--	--
	519		22	19	18	18	--	--
	520		19	23	23	25	--	--
	Mean		20	20	20	19	--	--
250	521		21	22	17	24	--	--
	522		17	20	18	19	--	--
	523		21	15	19	19	--	--
	524		16	20	18	17	--	--
	525		20	22	18	19	--	--
	Mean		19	20	18	20	--	--
1000	526		19	19	16	21	--	--
	527		20	25	19	21	--	--
	528		19	18	17	16	--	--
	529		17	21	21	19	--	--
	530		20	22	20	21	--	--
	531		21	24	19	21	26	24
	532		20	21	19	16	23	24
	533		23	22	22	22	20	27
	534		21	20	23	25	26	22
	535		22	24	19	18	25	28
	Mean		20	22	20	20	24	25

Appendix 21 - 1 Individual urinary findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Administration period >

Dose (mg/kg/day)	Animal number	Color	Cloudy	Volume (mL/18hr)	Specific gravity	pH	Protein	Glucose	Occult blood	Urobilinogen
0	001	PY	−	9.2	1.054	8.5	2+	−	−	0.1
	002	PY	−	7.6	1.058	8.5	2+	−	−	0.1
	003	PY	−	5.6	1.070	8.5	1+	−	−	0.1
	004	PY	−	13.8	1.044	8.0	±	−	−	0.1
	005	PY	−	9.1	1.062	8.5	1+	−	−	0.1
15	011	PY	−	6.5	1.062	8.5	1+	−	−	0.1
	012	PY	−	4.6	1.074	8.5	2+	−	−	0.1
	013	PY	−	6.8	1.060	8.5	2+	−	−	0.1
	014	PY	−	7.5	1.052	8.5	±	−	−	0.1
	015	PY	−	6.4	1.066	8.5	1+	−	−	0.1
60	016	PY	−	8.7	1.052	8.5	1+	−	−	0.1
	017	Y	−	4.6	1.072	8.0	1+	−	−	0.1
	018	Y	−	3.5	1.080	8.5	2+	−	−	0.1
	019	PY	−	15.2	1.040	8.0	1+	−	−	0.1
	020	PY	−	7.8	1.056	8.5	2+	−	−	0.1
250	021	Y	−	13.2	1.048	8.0	1+	−	−	0.1
	022	Y	−	13.5	1.046	8.0	1+	−	−	0.1
	023	Y	−	10.1	1.044	8.0	1+	−	−	0.1
	024	PY	−	7.2	1.056	8.5	1+	−	−	0.1
	025	Y	−	6.9	1.068	8.0	1+	−	−	0.1
1000	026	Y	−	5.9	1.076	8.0	±	−	−	0.1
	027	Y	−	8.2	1.068	8.0	±	−	−	0.1
	028	Y	−	12.0	1.054	8.0	1+	−	−	0.1
	029	Y	−	10.2	1.058	8.0	±	−	−	0.1
	030	Y	−	6.3	1.080	8.0	1+	−	−	0.1

Color : PY(pale yellow), Y(yellow).
Cloudy : −(negligible).
Protein : −(negligible), ±(15～30mg/dL), 1+(30mg/dL), 2+(100mg/dL).
Glucose : −(negligible).
Occult blood : −(negligible).
Urobilinogen : Ehrlich unit/dL.

Appendix 21 -2 Individual urinary findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Administration period >

Dose (mg/kg/day)	Animal number	Erythro-cytes	Leuko-cytes	Crystals			Epithelial cells			Casts			Fat globules
				Mg	Ca	Ams	Sq	R	S	G	H	W	
0	001	—	—	2+	—	—	1+	—	—	—	—	—	—
	002	—	—	3+	—	—	1+	—	—	—	—	—	—
	003	—	—	—	1+	—	—	—	—	—	—	—	—
	004	—	—	—	—	—	—	—	—	—	—	—	—
	005	—	—	1+	—	—	1+	—	—	—	—	—	—
15	011	—	—	—	—	—	1+	—	—	—	—	—	—
	012	—	—	—	—	—	—	—	—	—	—	—	—
	013	—	—	—	—	—	—	—	—	—	—	—	—
	014	—	—	—	—	—	1+	—	—	—	—	—	—
	015	—	—	2+	—	—	1+	—	—	—	—	—	—
60	016	—	—	—	—	—	—	—	—	—	—	—	—
	017	—	—	—	—	—	—	—	—	—	—	—	—
	018	—	—	—	1+	—	—	—	—	—	—	—	—
	019	—	—	1+	—	—	—	—	—	—	—	—	—
	020	—	—	—	—	—	—	—	—	—	—	—	—
250	021	—	—	2+	1+	—	1+	—	—	—	—	—	—
	022	—	—	2+	1+	—	1+	—	—	—	—	—	—
	023	—	—	—	—	—	—	—	—	—	—	—	—
	024	—	—	—	—	—	—	—	—	—	—	—	—
	025	—	—	2+	—	—	1+	—	—	—	—	—	—
1000	026	—	—	—	—	—	—	—	—	—	—	—	—
	027	—	—	1+	—	—	—	—	—	—	—	—	—
	028	—	—	1+	—	—	1+	—	—	—	—	—	—
	029	—	—	—	—	—	—	—	—	—	—	—	—
	030	—	—	—	—	—	1+	—	—	—	—	—	—

— : Not observed, 1+ : A few in some fields, 2+ : A few in all fields, 3+ : Many in all fields.
Crystals ; Mg (ammonium magnesium phosphate), Ca (calcium carbonate), Ams (amorphous).
Epithelial cells ; Sq (squamous), R (round), S (spindle).
Casts ; G (granule), H (hyaline), W (waxy).

Appendix 21 - 3 Individual urinary findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Recovery period >

Dose (mg/kg/day)	Animal number	Color	Cloudy	Volume (mL/18hr)	Specific gravity	pH	Protein	Glucose	Occult blood	Urobilinogen
0	006	PY	−	11.3	1.060	8.0	±	−	−	0.1
	007	PY	−	8.7	1.066	8.0	±	−	−	0.1
	008	PY	−	13.1	1.058	8.0	±	−	−	0.1
	009	PY	−	4.7	1.076	8.0	1+	−	−	0.1
	010	PY	−	12.5	1.056	8.0	1+	−	−	0.1
1000	031	PY	−	12.4	1.054	8.0	±	−	−	0.1
	032	PY	−	11.2	1.054	8.0	1+	−	−	0.1
	033	PY	−	9.8	1.046	7.5	1+	−	−	0.1
	034	PY	−	10.9	1.042	8.0	1+	−	−	0.1
	035	PY	−	11.8	1.038	8.0	±	−	−	0.1

Color : PY(pale yellow).
Cloudy : −(negligible).
Protein : ±(15～30mg/dL), 1+(30mg/dL).
Glucose : −(negligible).
Occult blood : −(negligible).
Urobilinogen : Ehrlich unit/dL.

Appendix 21 - 4 Individual urinary findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Recovery period >

Dose (mg/kg/day)	Animal number	Erythro-cytes	Leuko-cytes	Crystals			Epithelial cells			Casts			Fat globules
				Mg	Ca	Ams	Sq	R	S	G	H	W	
0	006	—	—	1+	—	—	1+	—	—	—	—	—	—
	007	—	—	3+	—	—	1+	—	—	—	—	—	—
	008	—	—	2+	—	—	1+	—	—	—	—	—	—
	009	—	—	1+	—	—	1+	—	—	—	—	—	—
	010	—	—	2+	—	—	1+	—	—	—	—	—	—
1000	031	—	—	—	—	—	1+	—	—	—	—	—	—
	032	—	—	2+	—	—	1+	—	—	—	—	—	—
	033	—	—	3+	—	—	1+	—	—	—	—	—	—
	034	—	—	2+	—	—	1+	—	—	—	—	—	—
	035	—	—	—	—	—	1+	—	—	—	—	—	—

— : Not observed, 1+ : A few in some fields, 2+ : A few in all fields, 3+ : Many in all fields.
Crystals ; Mg (ammonium magnesium phosphate), Ca (calcium carbonate), Ams (amorphous).
Epithelial cells ; Sq (squamous), R (round), S (spindle).
Casts ; G (granule), H (hyaline), W (waxy).

Appendix 22 - 1 Individual urinary findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Administration period >

Dose (mg/kg/day)	Animal number	Color	Cloudy	Volume (mL/18hr)	Specific gravity	pH	Protein	Glucose	Occult blood	Urobilinogen
0	501	PY	−	5.2	1.044	8.5	±	−	−	0.1
	502	PY	−	4.6	1.070	8.0	±	−	−	0.1
	503	PY	−	7.7	1.056	8.0	1+	−	−	0.1
	504	PY	−	6.4	1.054	8.5	±	−	−	0.1
	505	PY	−	4.6	1.072	8.5	1+	−	−	0.1
15	511	PY	−	7.8	1.052	8.0	1+	−	−	0.1
	512	PY	−	2.1	1.096	7.5	2+	−	−	0.1
	513	PY	−	2.2	1.080	8.5	±	−	−	0.1
	514	PY	−	2.1	1.096	8.0	2+	−	−	0.1
	515	PY	−	6.0	1.056	8.5	1+	−	−	0.1
60	516	PY	−	9.7	1.040	8.5	1+	−	−	0.1
	517	PY	−	8.5	1.054	8.5	1+	−	−	0.1
	518	PY	−	9.9	1.042	8.5	1+	−	−	0.1
	519	PY	−	10.9	1.038	8.0	1+	−	−	0.1
	520	PY	−	6.1	1.054	8.0	1+	−	−	0.1
250	521	Y	−	13.4	1.040	8.0	±	−	−	0.1
	522	Y	−	10.1	1.046	8.0	1+	−	−	0.1
	523	Y	−	12.3	1.034	8.0	±	−	−	0.1
	524	Y	−	4.3	1.062	8.0	1+	−	−	0.1
	525	Y	−	2.8	1.076	8.0	±	−	−	0.1
1000	526	Y	−	6.2	1.068	7.5	1+	−	−	0.1
	527	Y	−	5.3	1.076	8.0	−	−	−	0.1
	528	Y	−	8.8	1.050	8.0	−	−	−	0.1
	529	Y	−	12.1	1.048	7.5	±	−	−	0.1
	530	Y	−	8.2	1.052	7.5	1+	−	−	0.1

Color : PY(pale yellow), Y(yellow).
Cloudy : −(negligible).
Protein : −(negligible), ±(15～30mg/dL), 1+(30mg/dL), 2+(100mg/dL).
Glucose : −(negligible).
Occult blood : −(negligible).
Urobilinogen : Ehrlich unit/dL.

Appendix 22 - 2 Individual urinary findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Administration period >

Dose (mg/kg/day)	Animal number	Erythro-cytes	Leuko-cytes	Crystals			Epithelial cells			Casts			Fat globules
				Mg	Ca	Ams	Sq	R	S	G	H	W	
0	501	—	—	1+	—	—	1+	—	—	—	—	—	—
	502	—	—	—	—	—	1+	—	—	—	—	—	—
	503	—	—	2+	—	—	1+	—	—	—	—	—	—
	504	—	—	2+	—	—	1+	—	—	—	—	—	—
	505	—	—	2+	—	—	1+	—	—	—	—	—	—
15	511	—	—	—	1+	—	1+	—	—	—	—	—	—
	512	—	—	—	—	—	—	—	—	—	—	—	—
	513	—	—	2+	—	—	1+	—	—	—	—	—	—
	514	—	—	—	—	—	1+	—	—	—	—	—	—
	515	—	—	1+	—	—	1+	—	—	—	—	—	—
60	516	—	—	—	—	—	—	—	—	—	—	—	—
	517	—	—	—	—	—	—	—	—	—	—	—	—
	518	—	—	1+	1+	—	1+	—	—	—	—	—	—
	519	—	—	—	1+	—	1+	—	—	—	—	—	—
	520	—	—	1+	—	—	1+	—	—	—	—	—	—
250	521	—	—	1+	1+	—	1+	—	—	—	—	—	—
	522	—	—	2+	—	—	1+	—	—	—	—	—	—
	523	—	—	—	—	—	—	—	—	—	—	—	—
	524	—	—	1+	1+	—	1+	—	—	—	—	—	—
	525	—	—	—	—	—	—	—	—	—	—	—	—
1000	526	—	—	—	—	—	1+	—	—	—	—	—	—
	527	—	—	—	—	—	—	—	—	—	—	—	—
	528	—	—	1+	—	—	1+	—	—	—	—	—	—
	529	—	—	3+	—	—	1+	—	—	—	—	—	—
	530	—	—	—	—	—	2+	—	—	—	—	—	—

— : Not observed, 1+ : A few in some fields, 2+ : A few in all fields, 3+ : Many in all fields.
Crystals ; Mg (ammonium magnesium phosphate), Ca (calcium carbonate), Ams (amorphous).
Epithelial cells ; Sq (squamous), R (round), S (spindle).
Casts ; G (granule), H (hyaline), W (waxy).

Appendix 22 - 3 Individual urinary findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Recovery period >

Dose (mg/kg/day)	Animal number	Color	Cloudy	Volume (mL/18hr)	Specific gravity	pH	Protein	Glucose	Occult blood	Urobilinogen
0	506	PY	−	6.3	1.066	8.0	1+	−	−	0.1
	507	PY	−	4.7	1.072	8.5	±	−	−	0.1
	508	PY	−	6.8	1.064	8.5	1+	−	−	0.1
	509	PY	−	8.2	1.060	8.5	±	−	−	0.1
	510	PY	−	13.9	1.042	8.5	−	−	−	0.1
1000	531	PY	−	11.8	1.048	8.5	1+	−	−	0.1
	532	PY	−	12.7	1.042	8.5	±	−	−	0.1
	533	PY	−	5.3	1.056	8.5	−	−	−	0.1
	534	PY	−	18.7	1.032	8.5	−	−	−	0.1
	535	PY	−	5.9	1.058	8.5	±	−	−	0.1

Color : PY(pale yellow).
Cloudy : −(negligible).
Protein : −(negligible), ±(15~30mg/dL), 1+(30mg/dL).
Glucose : −(negligible).
Occult blood : −(negligible).
Urobilinogen : Ehrlich unit/dL.

Appendix 22 - 4 Individual urinary findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< Recovery period >

Dose (mg/kg/day)	Animal number	Erythro-cytes	Leuko-cytes	Crystals			Epithelial cells			Casts			Fat globules
				Mg	Ca	Ams	Sq	R	S	G	H	W	
0	506	—	—	2+	—	—	1+	—	—	—	—	—	—
	507	—	—	1+	—	—	—	—	—	—	—	—	—
	508	—	—	1+	—	—	1+	—	—	—	—	—	—
	509	—	—	—	—	—	—	—	—	—	—	—	—
	510	—	—	1+	—	—	1+	—	—	—	—	—	—
1000	531	—	—	3+	—	—	1+	—	—	—	—	—	—
	532	—	—	—	—	—	1+	—	—	—	—	—	—
	533	—	—	2+	—	—	1+	—	—	—	—	—	—
	534	—	—	—	—	—	—	—	—	—	—	—	—
	535	—	—	1+	—	—	1+	—	—	—	—	—	—

— : Not observed, 1+ : A few in some fields, 2+ : A few in all fields, 3+ : Many in all fields.
Crystals ; Mg (ammonium magnesium phosphate), Ca (calcium carbonate), Ams (amorphous).
Epithelial cells ; Sq (squamous), R (round), S (spindle).
Casts ; G (granule), H (hyaline), W (waxy).

Appendix 23 - 1 Individual hematological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	RBC (10^4/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	001	799	15.7	48.2	60	19.6	32.6	28.4	13.4
	002	680	14.2	43.4	64	20.9	32.7	35.4	12.7
	003	744	15.1	47.2	63	20.3	32.0	36.7	13.1
	004	751	15.6	48.5	65	20.8	32.2	28.0	13.7
	005	709	15.1	47.4	67	21.3	31.9	43.1	13.3
	Mean	737	15.1	46.9	64	20.6	32.3	34.3	13.2
15	011	766	15.2	47.5	62	19.8	32.0	40.8	14.0
	012	739	14.3	44.4	60	19.4	32.2	35.1	12.7
	013	731	14.7	45.6	62	20.1	32.2	36.4	13.3
	014	712	14.5	45.9	65	20.4	31.6	31.1	13.0
	015	798	16.2	48.5	61	20.3	33.4	33.6	13.5
	Mean	749	15.0	46.4	62	20.0	32.3	35.4	13.3
60	016	793	14.8	44.9	57	18.7	33.0	37.1	13.4
	017	763	15.5	47.0	62	20.3	33.0	31.2	14.0
	018	756	15.1	46.0	61	20.0	32.8	33.4	12.0
	019	816	14.9	46.2	57	18.3	32.3	36.7	12.9
	020	701	14.5	44.6	64	20.7	32.5	47.4	13.0
	Mean	766	15.0	45.7	60	19.6	32.7	37.2	13.1
250	021	725	14.5	44.1	61	20.0	32.9	30.5	12.7
	022	740	14.5	45.2	61	19.6	32.1	44.0	12.7
	023	773	14.7	44.0	57	19.0	33.4	40.0	12.8
	024	734	14.2	43.9	60	19.3	32.3	41.2	12.8
	025	787	15.0	45.9	58	19.1	32.7	38.4	12.3
	Mean	752	14.6	44.6	59	19.4	32.7	38.8	12.7
1000	026	686	13.5	43.1	63	19.7	31.3	91.2	12.9
	027	765	14.6	46.6	61	19.1	31.3	82.2	12.5
	028	666	12.7	41.0	62	19.1	31.0	123.2	12.6
	029	657	13.5	43.4	66	20.5	31.1	82.0	12.8
	030	780	14.3	45.1	58	18.3	31.7	61.9	12.4
	Mean	711	13.7	43.8	62	19.3	31.3	88.1	12.6

Appendix 23 - 2 Individual hematological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	APTT (sec)	Plat. (10^4/μL)	WBC (10^2/μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	001	20.0	151	111	0.0	0.2	15.1	81.8	2.9
	002	20.6	148	84	0.0	0.2	13.0	83.8	3.0
	003	21.1	154	88	0.0	0.5	8.7	87.3	3.5
	004	22.8	159	65	0.0	0.9	14.4	81.8	2.9
	005	20.3	119	60	0.0	0.7	22.4	73.7	3.2
	Mean	21.0	146	82	0.0	0.5	14.7	81.7	3.1
15	011	21.2	128	59	0.0	1.0	21.0	76.0	2.0
	012	20.9	152	49	0.0	0.4	10.8	86.0	2.8
	013	20.7	134	48	0.0	0.8	9.2	84.7	5.3
	014	18.9	143	69	0.0	0.7	11.9	84.6	2.8
	015	20.5	133	72	0.0	0.8	21.4	75.4	2.4
	Mean	20.4	138	59	0.0	0.7	14.9	81.3	3.1
60	016	20.9	145	95	0.0	0.6	14.3	83.1	2.0
	017	23.4	126	45	0.0	0.9	16.3	80.3	2.5
	018	17.9	136	61	0.0	0.8	17.1	77.0	5.1
	019	20.7	144	63	0.0	1.0	11.4	85.2	2.4
	020	18.6	151	69	0.0	0.7	20.6	73.9	4.8
	Mean	20.3	140	67	0.0	0.8	15.9	79.9	3.4
250	021	19.1	116	79	0.0	0.4	12.6	84.6	2.4
	022	23.5	124	50	0.0	0.6	11.5	84.9	3.0
	023	20.2	150	67	0.0	0.3	14.0	83.3	2.4
	024	20.1	143	45	0.0	0.7	13.1	83.1	3.1
	025	18.6	137	91	0.0	0.7	17.9	79.3	2.1
	Mean	20.3	134	66	0.0	0.5	13.8	83.0	2.6
1000	026	21.3	147	67	0.0	0.3	15.0	82.9	1.8
	027	20.9	112	60	0.0	0.7	22.3	75.0	2.0
	028	20.9	171	71	0.0	0.7	17.4	78.2	3.7
	029	21.4	123	56	0.0	0.5	17.6	80.1	1.8
	030	18.2	135	59	0.0	0.5	15.0	83.0	1.5
	Mean	20.5	138	63	0.0	0.5	17.5	79.8	2.2

Appendix 23 - 3 Individual hematological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	RBC (10^4/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	006	842	15.5	46.1	55	18.4	33.6	22.3	13.7
	007	819	14.9	44.5	54	18.2	33.5	39.5	12.5
	008	824	14.6	44.0	53	17.7	33.2	27.0	13.2
	009	778	14.5	43.4	56	18.6	33.4	30.3	13.2
	010	803	14.6	44.3	55	18.2	33.0	26.8	13.8
	Mean	813	14.8	44.5	55	18.2	33.3	29.2	13.3
1000	031	828	15.6	47.1	57	18.8	33.1	37.6	13.6
	032	784	15.0	46.7	60	19.1	32.1	34.7	12.8
	033	779	14.6	44.8	58	18.7	32.6	31.8	12.9
	034	802	15.5	47.6	59	19.3	32.6	28.8	12.5
	035	789	14.4	43.6	55	18.3	33.0	38.2	13.0
	Mean	796	15.0	46.0	58	18.8	32.7	34.2	13.0

Appendix 23 - 4 Individual hematological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	APTT (sec)	Plat. (10^4/μL)	WBC (10^2/μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	006	22.6	157	88	0.0	1.5	14.5	79.4	4.6
	007	19.8	157	87	0.0	0.3	6.5	90.9	2.3
	008	20.1	137	60	0.0	0.3	15.6	80.8	3.3
	009	21.0	160	78	0.0	0.5	18.5	78.0	3.0
	010	22.3	125	64	0.0	1.9	22.2	73.2	2.7
	Mean	21.2	147	75	0.0	0.9	15.5	80.5	3.2
1000	031	22.1	123	74	0.0	0.7	7.8	89.6	1.9
	032	20.7	138	61	0.0	1.0	15.8	79.4	3.8
	033	24.4	135	74	0.0	0.8	10.2	86.3	2.7
	034	20.4	129	90	0.0	0.6	13.6	83.2	2.6
	035	24.0	147	58	0.0	0.9	19.0	76.5	3.6
	Mean	22.3	134	71	0.0	0.8	13.3	83.0	2.9

Appendix 24 - 1 Individual hematological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	RBC (10^4/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	501	767	15.4	45.8	60	20.1	33.6	25.4	13.4
	502	876	16.3	49.0	56	18.6	33.3	17.7	13.0
	503	652	13.3	40.2	62	20.4	33.1	28.0	12.8
	504	814	15.4	45.6	56	18.9	33.8	18.9	13.4
	505	788	15.0	45.0	57	19.0	33.3	18.2	14.0
	Mean	779	15.1	45.1	58	19.4	33.4	21.6	13.3
15	511	692	13.6	42.0	61	19.7	32.4	25.1	13.2
	512	686	13.4	40.9	60	19.5	32.8	25.7	12.2
	513	761	14.6	44.1	58	19.2	33.1	18.9	12.6
	514	696	13.9	41.9	60	20.0	33.2	24.1	12.0
	515	726	14.2	42.8	59	19.6	33.2	23.3	13.2
	Mean	712	13.9	42.3	60	19.6	32.9	23.4	12.6
60	516	712	14.5	43.0	60	20.4	33.7	24.6	14.2
	517	780	15.5	47.0	60	19.9	33.0	20.8	12.8
	518	739	15.1	46.6	63	20.4	32.4	18.3	13.0
	519	762	14.6	43.6	57	19.2	33.5	18.5	12.4
	520	698	13.7	41.5	60	19.6	33.0	24.2	13.2
	Mean	738	14.7	44.3	60	19.9	33.1	21.3	13.1
250	521	787	14.4	43.3	55	18.3	33.3	18.7	12.7
	522	748	14.3	44.5	60	19.1	32.1	22.8	13.3
	523	761	14.2	42.8	56	18.7	33.2	31.0	13.7
	524	770	15.0	45.8	60	19.5	32.8	25.8	12.9
	525	816	15.0	46.7	57	18.4	32.1	30.7	13.4
	Mean	776	14.6	44.6	58	18.8	32.7	25.8	13.2
1000	526	644	12.3	38.7	60	19.1	31.8	82.9	13.1
	527	712	13.4	40.8	57	18.8	32.8	57.1	13.6
	528	748	14.0	42.7	57	18.7	32.8	61.2	13.6
	529	664	12.5	38.7	58	18.8	32.3	51.7	13.0
	530	650	12.9	40.3	62	19.8	32.0	71.4	12.8
	Mean	684	13.0	40.2	59	19.0	32.3	64.9	13.2

Appendix 24 - 2 Individual hematological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	APTT (sec)	Plat. (10^4/μL)	WBC (10^2/μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	501	16.2	161	81	0.0	1.7	7.2	88.9	2.2
	502	17.3	116	66	0.0	1.1	7.2	88.4	3.3
	503	16.4	121	38	0.0	0.8	13.9	82.9	2.4
	504	17.0	132	35	0.0	1.1	18.3	77.2	3.4
	505	16.4	126	56	0.0	1.1	6.4	90.3	2.2
	Mean	16.7	131	55	0.0	1.2	10.6	85.5	2.7
15	511	17.9	141	48	0.0	0.8	10.7	85.4	3.1
	512	20.8	168	52	0.0	0.8	13.9	83.0	2.3
	513	16.9	146	58	0.0	1.0	8.2	88.9	1.9
	514	16.9	104	39	0.0	0.8	17.3	79.6	2.3
	515	18.4	142	38	0.0	2.1	16.0	79.0	2.9
	Mean	18.2	140	47	0.0	1.1	13.2	83.2	2.5
60	516	17.0	145	53	0.0	0.9	6.3	90.7	2.1
	517	17.5	155	65	0.0	0.3	5.9	90.9	2.9
	518	17.3	137	57	0.0	1.2	14.7	79.5	4.6
	519	17.1	148	57	0.0	0.7	10.8	85.7	2.8
	520	18.0	139	80	0.0	0.6	14.1	83.5	1.8
	Mean	17.4	145	62	0.0	0.7	10.4	86.1	2.8
250	521	17.2	112	38	0.0	0.5	18.8	78.4	2.3
	522	17.1	147	62	0.0	1.1	9.2	86.1	3.6
	523	17.5	160	46	0.0	2.2	9.9	83.6	4.3
	524	17.2	129	55	0.0	0.7	16.0	81.5	1.8
	525	15.5	146	41	0.0	2.2	14.6	79.3	3.9
	Mean	16.9	139	48	0.0	1.3	13.7	81.8	3.2
1000	526	19.0	164	53	0.0	1.1	7.9	88.6	2.4
	527	21.1	138	78	0.0	0.5	8.0	91.0	0.5
	528	21.0	110	41	0.0	0.5	12.8	85.2	1.5
	529	20.8	153	22	0.0	1.4	18.9	76.0	3.7
	530	20.9	140	49	0.0	0.8	10.9	87.3	1.0
	Mean	20.6	141	49	0.0	0.9	11.7	85.6	1.8

Appendix 24 - 3 Individual hematological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	RBC ($10^4/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	506	697	13.7	40.4	58	19.7	33.9	23.6	13.4
	507	802	15.2	44.9	56	19.0	33.9	34.5	13.7
	508	755	14.2	42.0	56	18.8	33.8	20.4	12.8
	509	814	15.3	45.7	56	18.8	33.5	22.4	13.3
	510	759	14.0	41.7	55	18.4	33.6	38.1	13.4
	Mean	765	14.5	42.9	56	18.9	33.7	27.8	13.3
1000	531	768	14.1	42.7	56	18.4	33.0	27.3	13.5
	532	775	15.8	47.1	61	20.4	33.5	23.5	13.6
	533	813	15.3	44.8	55	18.8	34.2	20.6	13.5
	534	742	14.9	45.1	61	20.1	33.0	28.7	13.8
	535	803	15.7	47.4	59	19.6	33.1	24.5	13.1
	Mean	780	15.2	45.4	58	19.5	33.4	24.9	13.5

Appendix 24 - 4 Individual hematological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	APTT (sec)	Plat. (10^4/μL)	WBC (10^2/μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	506	22.0	127	69	0.0	0.7	17.2	80.5	1.6
	507	16.4	111	50	0.0	1.0	20.2	76.8	2.0
	508	17.4	128	40	0.0	1.0	18.4	77.8	2.8
	509	17.0	135	66	0.0	1.4	10.7	86.1	1.8
	510	17.3	130	37	0.0	2.5	16.7	77.8	3.0
	Mean	18.0	126	52	0.0	1.3	16.6	79.8	2.2
1000	531	19.1	134	50	0.0	1.0	21.6	73.6	3.8
	532	15.2	108	69	0.0	0.4	17.0	80.3	2.3
	533	18.7	136	51	0.0	0.8	15.1	81.1	3.0
	534	17.6	128	57	0.0	0.9	11.9	85.3	1.9
	535	17.7	139	39	0.0	1.3	15.6	78.7	4.4
	Mean	17.7	129	53	0.0	0.9	16.2	79.8	3.1

Appendix 25 - 1 Individual blood biochemical findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	LDH (IU/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	γ-GTP (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Cho. (mg/dL)	T.G. (mg/dL)
0	001	165	63	35	888	0.67	5.81	2.84	0.96	73	68
	002	333	71	39	767	0.71	5.67	2.70	0.91	66	18
	003	200	56	32	678	0.69	5.95	2.84	0.91	53	52
	004	126	58	25	760	0.50	6.01	2.96	0.97	64	51
	005	142	57	24	532	0.44	5.68	2.74	0.93	71	113
	Mean	193	61	31	725	0.60	5.82	2.82	0.94	65	60
15	011	298	62	35	769	0.39	5.72	2.99	1.10	62	68
	012	228	58	32	768	0.58	5.69	2.95	1.08	82	55
	013	182	55	25	732	0.55	5.91	2.99	1.02	69	50
	014	178	57	23	552	0.73	5.64	2.73	0.94	63	43
	015	186	71	38	958	0.23	6.04	3.11	1.06	50	66
	Mean	214	61	31	756	0.50	5.80	2.95	1.04	65	56
60	016	350	66	34	800	0.61	5.78	2.87	0.99	59	44
	017	414	65	27	814	0.38	5.91	2.89	0.96	48	58
	018	231	70	31	653	0.39	5.90	2.96	1.01	72	99
	019	421	73	31	543	0.54	5.88	2.91	0.98	63	38
	020	491	82	36	924	0.54	5.43	2.65	0.95	64	112
	Mean	381	71	32	747	0.49	5.78	2.86	0.98	61	70
250	021	128	64	30	752	0.49	5.90	2.99	1.03	72	68
	022	263	57	26	706	0.40	5.61	2.83	1.02	58	83
	023	236	62	33	774	0.54	5.89	2.77	0.89	80	77
	024	218	77	37	900	0.49	5.82	2.88	0.98	67	22
	025	157	62	36	819	0.77	5.98	3.04	1.03	88	66
	Mean	200	64	32	790	0.54	5.84	2.90	0.99	73	63
1000	026	279	72	37	622	0.56	5.84	3.24	1.25	91	35
	027	119	57	41	722	0.83	6.89	3.80	1.23	98	118
	028	200	69	37	856	1.47	6.18	3.37	1.20	94	90
	029	173	69	37	535	1.53	5.91	3.16	1.15	74	33
	030	191	55	33	585	1.22	6.16	3.32	1.17	137	63
	Mean	192	64	37	664	1.12	6.20	3.38	1.20	99	68

Appendix 25 - 2 Individual blood biochemical findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Glu. (mg/dL)	BUN (mg/dL)	Crea. (mg/dL)	T-Bil. (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	001	167	12.7	0.39	0.34	9.6	7.8	145	5.30	105
	002	137	9.8	0.36	0.37	9.6	7.0	146	4.44	109
	003	151	11.3	0.42	0.30	9.6	7.4	146	4.73	106
	004	150	13.3	0.38	0.28	9.7	8.3	147	4.61	105
	005	156	14.1	0.35	0.45	9.4	8.4	149	4.93	105
	Mean	152	12.2	0.38	0.35	9.6	7.8	147	4.80	106
15	011	150	9.9	0.35	0.37	9.1	8.1	146	5.29	106
	012	158	11.6	0.34	0.31	9.7	8.4	146	4.45	104
	013	164	10.7	0.36	0.32	9.5	8.1	147	4.86	106
	014	152	12.5	0.36	0.36	9.5	8.4	147	4.77	108
	015	130	10.9	0.28	0.39	9.7	8.6	147	5.37	105
	Mean	151	11.1	0.34	0.35	9.5	8.3	147	4.95	106
60	016	130	13.4	0.36	0.42	9.2	7.2	146	5.18	107
	017	144	9.7	0.34	0.40	9.5	8.7	146	5.06	104
	018	161	11.9	0.40	0.38	10.1	9.0	148	4.81	104
	019	156	10.0	0.29	0.38	9.2	7.7	146	5.61	107
	020	160	10.5	0.32	0.38	9.0	8.4	146	5.17	107
	Mean	150	11.1	0.34	0.39	9.4	8.2	146	5.17	106
250	021	169	10.7	0.41	0.39	9.5	7.3	146	4.62	104
	022	145	11.9	0.37	0.40	9.2	6.9	146	5.08	106
	023	157	11.3	0.39	0.34	9.5	7.7	145	5.18	106
	024	161	9.3	0.41	0.34	9.2	7.1	147	4.84	108
	025	170	10.8	0.39	0.34	9.6	8.1	146	4.71	106
	Mean	160	10.8	0.39	0.36	9.4	7.4	146	4.89	106
1000	026	149	9.8	0.38	0.44	9.5	7.7	148	5.32	104
	027	173	10.8	0.42	0.36	10.7	8.7	151	5.91	101
	028	171	10.4	0.38	0.39	9.5	7.5	146	5.55	105
	029	142	9.0	0.38	0.44	9.5	7.9	145	5.89	106
	030	160	13.3	0.38	0.37	9.9	8.1	146	5.59	104
	Mean	159	10.7	0.39	0.40	9.8	8.0	147	5.65	104

Appendix 25 - 3 Individual blood biochemical findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	LDH (IU/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	γ-GTP (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Cho. (mg/dL)	T.G. (mg/dL)
0	006	253	69	37	632	0.81	5.99	2.83	0.90	74	70
	007	199	66	34	530	0.81	6.13	2.93	0.92	77	52
	008	313	76	35	683	0.62	5.68	2.89	1.04	61	69
	009	492	73	36	535	0.77	6.03	2.66	0.79	65	57
	010	376	79	47	513	0.64	5.66	2.66	0.89	59	62
	Mean	327	73	38	579	0.73	5.90	2.79	0.91	67	62
1000	031	395	90	43	452	1.03	6.18	2.93	0.90	83	41
	032	394	81	46	732	0.78	5.90	2.86	0.94	48	42
	033	165	65	36	554	0.62	5.89	2.94	1.00	58	69
	034	148	68	40	501	0.70	5.94	3.05	1.06	44	88
	035	243	66	36	486	1.20	5.95	2.92	0.96	90	36
	Mean	269	74	40	545	0.87	5.97	2.94	0.97	65	55

Appendix 25 - 4 Individual blood biochemical findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	Glu. (mg/dL)	BUN (mg/dL)	Crea. (mg/dL)	T-Bil. (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	006	155	10.5	0.34	0.29	10.0	7.6	145	4.82	107
	007	141	15.4	0.46	0.35	9.7	7.1	146	5.00	107
	008	149	15.2	0.29	0.33	9.6	6.3	144	5.19	106
	009	151	15.2	0.41	0.28	9.2	7.7	145	5.17	106
	010	183	15.9	0.48	0.38	9.0	7.1	146	4.70	106
	Mean	156	14.4	0.40	0.33	9.5	7.2	145	4.98	106
1000	031	136	18.5	0.51	0.34	9.5	8.1	148	4.83	104
	032	153	12.6	0.37	0.30	9.2	7.1	145	4.89	105
	033	144	13.9	0.40	0.35	9.5	8.1	147	4.44	104
	034	150	15.2	0.41	0.37	10.0	8.4	149	4.72	100
	035	130	12.1	0.35	0.31	9.6	7.3	147	5.06	106
	Mean	143	14.5	0.41	0.33	9.6	7.8	147	4.79	104

Appendix 26 - 1 Individual blood biochemical findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	LDH (IU/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	γ-GTP (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Cho. (mg/dL)	T.G. (mg/dL)
0	501	287	63	27	423	0.41	5.75	2.96	1.06	61	44
	502	340	88	33	702	0.97	6.29	3.55	1.30	67	17
	503	210	63	26	521	0.57	6.08	3.15	1.08	82	17
	504	685	79	30	538	0.10	5.84	3.30	1.30	56	54
	505	293	74	26	464	0.07	6.00	2.89	0.93	68	15
	Mean	363	73	28	530	0.42	5.99	3.17	1.13	67	29
15	511	255	68	25	553	1.26	5.69	2.72	0.92	76	51
	512	431	64	21	622	0.98	6.37	3.47	1.20	62	30
	513	482	63	29	446	0.53	5.96	3.21	1.17	101	40
	514	176	69	23	523	1.73	5.93	2.97	1.00	53	14
	515	136	70	25	521	1.36	5.81	2.76	0.90	49	18
	Mean	296	67	25	533	1.17	5.95	3.03	1.04	68	31
60	516	302	69	34	433	0.44	5.88	3.16	1.16	62	11
	517	336	62	25	312	0.30	6.04	3.42	1.31	90	63
	518	158	58	21	527	0.52	6.22	3.45	1.25	90	39
	519	265	53	19	381	0.24	5.91	3.33	1.29	73	26
	520	280	66	26	512	1.43	6.00	2.93	0.95	94	13
	Mean	268	62	25	433	0.59	6.01	3.26	1.19	82	30
250	521	389	64	36	378	0.69	6.42	3.66	1.33	78	50
	522	288	67	30	391	0.38	6.40	3.58	1.27	58	77
	523	205	63	26	589	0.50	5.77	2.92	1.02	64	23
	524	344	57	21	492	0.47	6.28	3.59	1.33	77	34
	525	243	76	30	543	1.16	6.13	3.19	1.09	56	17
	Mean	294	65	29	479	0.64	6.20	3.39	1.21	67	40
1000	526	259	53	24	354	2.09	6.14	3.48	1.31	92	51
	527	250	57	38	617	2.96	5.98	3.17	1.13	141	42
	528	326	59	34	512	2.50	6.01	3.48	1.38	60	12
	529	466	65	26	313	2.51	6.29	3.41	1.18	99	31
	530	403	60	24	504	0.62	6.38	3.28	1.06	90	21
	Mean	341	59	29	460	2.14	6.16	3.36	1.21	96	31

Appendix 26 - 2 Individual blood biochemical findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Glu. (mg/dL)	BUN (mg/dL)	Crea. (mg/dL)	T-Bil. (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	501	162	16.4	0.39	0.24	9.2	6.6	145	5.30	107
	502	125	16.1	0.51	0.26	9.8	7.9	147	4.63	107
	503	122	16.0	0.48	0.22	9	8.1	146	4.85	110
	504	134	12.5	0.38	0.26	9.5	7.1	146	5.21	109
	505	101	15.1	0.37	0.21	9.1	7.0	145	5.08	108
	Mean	129	15.2	0.43	0.24	9.3	7.3	146	5.01	108
15	511	136	12.0	0.39	0.23	9.3	7.3	146	4.72	108
	512	128	15.3	0.46	0.25	9.6	7.6	147	4.67	106
	513	123	13.3	0.41	0.26	9.7	7.3	147	4.68	106
	514	135	12.3	0.47	0.24	9	7.8	147	4.13	106
	515	125	11.1	0.41	0.23	9	7.0	147	4.40	108
	Mean	129	12.8	0.43	0.24	9.3	7.4	147	4.52	107
60	516	116	14.0	0.42	0.21	9.2	7.5	148	4.75	112
	517	132	13.0	0.40	0.24	9.7	6.2	148	4.67	109
	518	124	16.3	0.38	0.26	10	8.2	148	5.42	104
	519	103	12.6	0.37	0.27	9.8	7.0	145	4.52	106
	520	134	10.0	0.42	0.22	9.3	7.7	148	4.60	108
	Mean	122	13.2	0.40	0.24	9.6	7.3	147	4.79	108
250	521	155	15.6	0.47	0.24	9.5	6.7	148	4.61	108
	522	139	11.1	0.46	0.26	9.6	6.7	147	4.68	110
	523	122	14.8	0.45	0.29	9.7	7.4	147	5.01	107
	524	149	12.3	0.42	0.27	9.9	7.4	148	4.99	109
	525	124	13.9	0.39	0.27	10	8.5	149	6.07	105
	Mean	138	13.5	0.44	0.27	9.8	7.3	148	5.07	108
1000	526	132	12.4	0.36	0.39	9.6	5.6	146	5.34	107
	527	167	13.5	0.39	0.35	9.5	7.3	140	5.61	102
	528	156	9.9	0.41	0.30	9.4	6.7	147	4.57	109
	529	150	14.3	0.40	0.34	9.6	6.6	147	5.11	106
	530	126	11.1	0.37	0.33	9.6	7.2	145	5.24	108
	Mean	146	12.2	0.39	0.34	9.5	6.7	145	5.17	106

Appendix 26 - 3 Individual blood biochemical findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	LDH (IU/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	γ-GTP (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Cho. (mg/dL)	T.G. (mg/dL)
0	506	300	54	30	176	0.20	7.38	4.30	1.40	105	71
	507	355	77	30	406	0.79	6.00	3.33	1.25	73	21
	508	348	95	29	382	1.30	6.30	3.43	1.20	64	22
	509	403	68	28	380	1.19	5.93	2.99	1.02	79	38
	510	245	70	26	306	0.73	6.01	3.19	1.13	87	26
	Mean	330	73	29	330	0.84	6.32	3.45	1.20	82	36
1000	531	354	68	25	648	0.90	6.31	3.59	1.32	84	47
	532	258	67	33	393	0.50	6.29	3.57	1.31	105	47
	533	250	73	29	461	0.16	6.45	3.69	1.34	84	42
	534	321	70	29	196	0.35	6.12	3.21	1.10	79	41
	535	342	179	48	257	0.80	6.52	3.66	1.28	91	24
	Mean	305	91	33	391	0.54	6.34	3.54	1.27	89	40

Appendix 26 - 4 Individual blood biochemical findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	Glu. (mg/dL)	BUN (mg/dL)	Crea. (mg/dL)	T-Bil. (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	506	136	14.5	0.44	0.29	10.4	5.3	146	4.58	105
	507	132	20.6	0.49	0.26	9.8	6.9	146	5.45	109
	508	123	14.5	0.50	0.24	9.8	5.8	143	4.97	106
	509	144	17.6	0.47	0.27	9.7	6.8	147	5.07	109
	510	120	13.0	0.48	0.27	9.6	6.0	148	4.99	112
	Mean	131	16.0	0.48	0.27	9.9	6.2	146	5.01	108
1000	531	131	14.9	0.48	0.24	9.6	7.1	146	4.75	108
	532	147	19.2	0.57	0.20	10.0	7.2	146	4.80	108
	533	137	18.4	0.51	0.24	10.4	7.8	147	4.36	109
	534	146	15.7	0.41	0.24	9.7	6.0	148	4.90	110
	535	124	20.3	0.53	0.28	9.7	6.4	146	4.83	109
	Mean	137	17.7	0.50	0.24	9.9	6.9	147	4.73	109

Appendix 27-1 Individual pathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
0	001	NAD	a	Lung	: Accumulation, foam cell +
				Liver	: Microgranuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
					(Immuno-histochemistry with α 2U-globulin antibody:Positive)
					Basophilic tubule +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown + (Berlin blue stain: Positive)
	002	NAD	a	Liver	: Necrosis, focal +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
					(Immuno-histochemistry with α 2U-globulin antibody:Positive)
					Cyst, solitary, unilateral +
				Urinary bladder	: Cellular infiltration, lymphocyte, submucosal layer +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown + (Berlin blue stain: Positive)
	003	NAD	a	Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
				Prostate	: Cellular infiltration, lymphocyte, interstitium +
	004	NAD	a	Liver	: Necrosis, focal +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	005	NAD	a	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +

NAD : No abnormalities were detected, + : Slight.

a : Organs of the brain, pituitary, thyroid, parathyroid, thymus, trachea, lung, heart, stomach, small intestine, large intestine, liver, spleen, kidney, adrenal, urinary bladder, testis, epididymis, prostate, seminal vesicle, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball were examined.

Appendix 27-2 Individual pathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
15	011	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	012	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	013	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	014	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	015	NAD	c	Liver	: Microgranuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +

NAD : No abnormalities were detected, + : Slight.
c : The organs of liver, kidney and spleen were examind.

Appendix 27-3 Individual pathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
60	016	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	017	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	018	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	019	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	020	NAD	c	Liver	: Degeneration, fatty, hepatocyte, peripheral +
					Microgranuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium ++
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +

NAD : No abnormalities were detected, + : Slight, ++ : Moderate.
c : The organs of liver, kidney and spleen were examind.

Appendix 27-4 Individual pathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
250	021	NAD	c	Liver	: Necrosis, focal +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule, unilateral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	022	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule, unilateral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	023	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	024	NAD	c	Liver	: Microgranuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	025	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium ++
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +

NAD : No abnormalities were detected, + : Slight, ++ : Moderate.
c : The organs of liver, kidney and spleen were examind.

Appendix 27-5 Individual pathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy		Histology	
1000	026	Spleen : Blackish +	a	Heart	: Myocardial degeneration/fibrosis +
				Liver	: Microgranuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium +++ (Immuno-histochemistry with α 2U-globulin antibody:Positive)
				Spleen	: Congestion + Hematopoiesis, extramedullary ++ Deposit, pigment, brown ++ (Berlin blue stain: Positive)
				Parathyroid	: Not in section
	027	Spleen : Blackish +	a	Liver	: Hypertrophy, hepatocyte, centrilobular ++
				Kidney	: Hyaline droplet, proximal tubular epithelium ++ (Immuno-histochemistry with α 2U-globulin antibody:Positive)
				Spleen	: Congestion + Hematopoiesis, extramedullary ++ Deposit, pigment, brown ++ (Berlin blue stain: Positive)
	028	Spleen : Blackish +	a	Lung	: Accumulation, foam cell +
				Liver	: Hypertrophy, hepatocyte, centrilobular + Necrosis, focal +
				Kidney	: Hyaline droplet, proximal tubular epithelium +++
				Thymus	: Hemorrhage +
				Spleen	: Congestion + Hematopoiesis, extramedullary ++ Deposit, pigment, brown ++

NAD : No abnormalities were detected, + : Slight, ++ : Moderate, +++ : Severe.

a : Organs of the brain, pituitary, thyroid, parathyroid, thymus, trachea, lung, heart, stomach, small intestine, large intestine, liver, spleen, kidney, adrenal, urinary bladder, testis, epididymis, prostate, seminal vesicle, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball were examined.

Appendix 27-6 Individual pathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
	029	Spleen : Blackish +	a	Liver	: Necrosis, focal +
					Microgranuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium ++
				Spleen	: Congestion +
					Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	030	Spleen : Blackish +	a	Liver	: Hypertrophy, hepatocyte, centrilobular +
				Kidney	: Hyaline droplet, proximal tubular epithelium ++
					Basophilic tubule, unilateral +
					Cellular infiltration, lymphocyte, cortex, unilateral +
				Spleen	: Congestion +
					Hematopoiesis, extramedullary +
					Deposit, pigment, brown +

NAD : No abnormalities were detected, + : Slight, ++ : Moderate.

a : Organs of the brain, pituitary, thyroid, parathyroid, thymus, trachea, lung, heart, stomach, small intestine, large intestine, liver, spleen, kidney, adrenal, urinary bladder, testis, epididymis, prostate, seminal vesicle, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball were examined.

Appendix 27-7 Individual pathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
0	006	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Cellular infiltration, lymphocyte, cortex, unilateral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	007	NAD	c	Liver	: Microgranuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium ++
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	008	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	009	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule, unilateral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	010	NAD	c	Liver	: Necrosis, focal +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
					Dilatation, tubular, focal, unilateral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +

NAD : No abnormalities were detected, + : Slight, ++ : Moderate.
c : The organs of liver, kidney and spleen were examind.

Appendix 27-8 Individual pathological findings of male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
1000	031	Spleen : Blackish +	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Dilatation, tubular, focal, unilateral +
				Spleen	: Hematopoiesis, extramedullary ++
					Deposit, pigment, brown +
	032	Spleen : Blackish +	c	Liver	: Microgranuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium ++
					Basophilic tubule, unilateral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown ++
	033	NAD	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule, unilateral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	034	Spleen : Blackish +	c	Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown ++
	035	Spleen : Blackish +	c	Kidney	: Hyaline droplet, proximal tubular epithelium ++
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown ++

NAD : No abnormalities were detected, + : Slight, ++ : Moderate.
c : The organs of liver, kidney and spleen were examind.

Appendix 28-1 Individual pathological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
0	501	NAD	b	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown + (Berlin blue stain: Positive)
	502	NAD	b	Kidney Spleen	: Basophilic tubule + : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	503	NAD	b	Liver Spleen	: Degeneration, fatty, hepatocyte, peripheral + : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	504	NAD	b	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown + (Berlin blue stain: Positive)
	505	NAD	b	Liver Spleen	: Degeneration, fatty, hepatocyte, peripheral + Microgranuloma + : Hematopoiesis, extramedullary + Deposit, pigment, brown +

NAD : No abnormalities were detected, + : Slight.

b : Organs of the brain, pituitary, thyroid, parathyroid, thymus, trachea, lung, heart, stomach, small intestine, large intestine, liver, spleen, kidney, adrenal, urinary bladder, ovary, uterus, vagina, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball were examined.

Appendix 28-2 Individual pathological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
15	511	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +
	512	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +
	513	NAD	d	Liver Spleen	: Microgranuloma + : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	514	NAD	d	Liver Spleen	: Degeneration, fatty, hepatocyte, peripheral + : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	515	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +
60	516	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +
	517	NAD	d	Liver Spleen	: Microgranuloma + : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	518	NAD	d	Liver Spleen	: Degeneration, fatty, hepatocyte, peripheral + : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	519	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +
	520	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +

NAD : No abnormalities were detected, + : Slight.
d : The organs of liver and spleen were examind.

Appendix 28-3 Individual pathological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
250	521	NAD	d	Liver	: Hypertrophy, hepatocyte, centrilobular +
					Degeneration, fatty, hepatocyte, peripheral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	522	NAD	d	Liver	: Hypertrophy, hepatocyte, centrilobular +
					Necrosis, focal +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	523	NAD	d	Liver	: Microgranuloma +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	524	NAD	d	Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	525	NAD	d	Liver	: Microgranuloma +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +

NAD : No abnormalities were detected, + : Slight.
d : The organs of liver and spleen were examind.

Appendix 28-4 Individual pathological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
1000	526	Spleen : Blackish +	b	Liver	: Hypertrophy, hepatocyte, centrilobular +
				Kidney	: Cyst, solitary, unilateral +
				Spleen	: Congestion +
					Hematopoiesis, extramedullary ++
					Deposit, pigment, brown ++ (Berlin blue stain: Positive)
	527	Spleen : Blackish +	b	Liver	: Hypertrophy, hepatocyte, centrilobular +
		Ovary : Small +++		Spleen	: Hematopoiesis, extramedullary ++
		Uterus : Small +++			Deposit, pigment, brown ++ (Berlin blue stain: Positive)
				Ovary	: Atrophy +++
				Uterus	: Atrophy +++
				Vagina	: Atrophy +++
	528	Spleen : Blackish +	b	Liver	: Hypertrophy, hepatocyte, centrilobular +
				Spleen	: Hematopoiesis, extramedullary ++
					Deposit, pigment, brown ++
	529	Spleen : Blackish +	b	Liver	: Hypertrophy, hepatocyte, centrilobular ++
					Necrosis, focal +
				Spleen	: Congestion +
					Hematopoiesis, extramedullary ++
					Deposit, pigment, brown ++
	530	Spleen : Blackish +	b	Liver	: Hypertrophy, hepatocyte, centrilobular +
					Degeneration, fatty, hepatocyte, peripheral +
				Spleen	: Congestion +
					Hematopoiesis, extramedullary ++
					Deposit, pigment, brown ++
				Parathyroid	: Not in section

NAD : No abnormalities were detected, + : Slight, ++ : Moderate, +++ : Severe.

b : Organs of the brain, pituitary, thyroid, parathyroid, thymus, trachea, lung, heart, stomach, small intestine, large intestine, liver, spleen, kidney, adrenal, urinary bladder, ovary, uterus, vagina, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball were examined.

Appendix 28-5 Individual pathological findings of female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	Necropsy			Histology
0	506	NAD	d	Liver Spleen	: Microgranuloma + : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	507	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +
	508	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +
	509	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +
	510	NAD	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown +
1000	531	Spleen : Blackish +	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown ++
	532	Spleen : Blackish +	d	Liver Spleen	: Microgranuloma + : Hematopoiesis, extramedullary + Deposit, pigment, brown ++
	533	Spleen : Blackish +	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown ++
	534	Spleen : Blackish +	d	Spleen	: Hematopoiesis, extramedullary + Deposit, pigment, brown ++
	535	Spleen : Blackish +	d	Liver Spleen	: Microgranuloma + : Hematopoiesis, extramedullary + Deposit, pigment, brown ++

NAD : No abnormalities were detected, + : Slight, ++ : Moderate.
d : The organs of liver and spleen were examind.

Appendix 29 - 1 Absolute organ weights of individual male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of administration period>

Dose (mg/kg/day)	Animal numbers	Body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland (mg)	Spleen (g)	Testis (g)	Epididy-mis (g)	Pituitary gland (mg)	Thyroid gland (mg)
0	001	342	2.03	0.66	1.19	10.23	2.51	53.9	0.74	3.71	0.72	13.9	28.3
	002	319	1.88	0.45	1.06	8.95	2.18	47.5	0.64	2.73	0.80	11.8	20.8
	003	323	1.82	0.59	1.08	11.40	2.37	70.9	0.67	3.35	0.73	12.3	20.5
	004	353	1.85	0.67	1.28	13.24	2.69	82.4	0.79	3.04	0.74	11.5	20.9
	005	355	2.06	0.44	1.08	11.03	2.70	54.1	0.55	2.98	0.83	12.8	26.8
	Mean	338	1.93	0.56	1.14	10.97	2.49	61.8	0.68	3.16	0.76	12.5	23.5
15	011	309	1.82	0.51	1.01	9.51	2.27	57.8	0.61	3.05	0.89	11.4	21.3
	012	356	1.90	0.59	1.27	11.35	2.81	45.2	0.73	2.85	0.71	12.1	25.5
	013	383	1.94	0.50	1.23	12.11	2.63	63.9	0.80	3.25	0.80	12.3	24.1
	014	371	1.92	0.59	1.27	11.55	2.62	55.7	0.74	3.53	0.94	14.1	23.3
	015	348	1.90	0.56	1.17	10.43	2.89	58.4	0.80	3.40	0.97	11.2	21.0
	Mean	353	1.90	0.55	1.19	10.99	2.64	56.2	0.74	3.22	0.86	12.2	23.0
60	016	307	1.83	0.39	1.06	8.63	2.22	61.4	0.70	3.31	0.74	11.0	22.1
	017	321	1.90	0.50	1.07	9.83	2.61	55.6	0.55	3.06	0.88	10.4	25.1
	018	322	1.75	0.33	1.12	10.70	2.08	57.9	0.52	2.90	0.71	9.7	25.1
	019	339	1.87	0.53	1.16	10.30	2.68	57.9	0.73	3.09	0.81	11.1	20.2
	020	377	1.95	0.40	1.28	12.34	2.81	59.8	0.62	3.38	0.86	12.8	20.3
	Mean	333	1.86	0.43	1.14	10.36	2.48	58.5	0.62	3.15	0.80	11.0	22.6
250	021	351	1.85	0.58	1.15	11.76	2.68	49.5	0.70	2.87	0.73	10.9	27.3
	022	342	1.94	0.49	1.19	10.55	2.66	46.2	0.63	2.93	0.71	10.3	24.4
	023	342	1.94	0.57	1.18	12.15	2.58	56.6	0.69	3.49	0.84	11.0	28.2
	024	325	1.89	0.35	1.08	10.66	2.61	49.8	0.57	3.35	0.74	11.2	20.9
	025	343	2.01	0.47	1.08	11.75	2.50	53.6	0.66	3.00	0.74	12.5	30.5
	Mean	341	1.93	0.49	1.14	11.37	2.61	51.1	0.65	3.13	0.75	11.2	26.3
1000	026	289	1.77	0.41	0.96	11.33	2.51	50.2	0.68	2.85	0.70	9.9	19.2
	027	313	1.87	0.54	1.10	16.75	2.59	37.9	0.85	3.02	0.81	11.3	24.2
	028	331	2.01	0.34	1.21	14.18	2.83	46.1	1.04	3.27	0.69	10.9	29.0
	029	320	1.92	0.55	1.11	12.79	2.69	48.6	1.07	3.22	0.77	11.5	38.6
	030	321	1.97	0.49	1.09	15.47	2.73	53.1	0.82	3.29	0.84	10.5	21.0
	Mean	315	1.91	0.47	1.09	14.10	2.67	47.2	0.89	3.13	0.76	10.8	26.4

Appendix 29 - 2 Relative organ weights of individual male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of administration period>

Dose (mg/kg/day)	Animal numbers	Body weight (g)	Brain (%)	Thymus (%)	Heart (%)	Liver (%)	Kidney (%)	Adrenal gland (mg%)	Spleen (%)	Testis (%)	Epididy-mis (%)	Pituitary gland (mg%)	Thyroid gland (mg%)
0	001	342	0.59	0.19	0.35	2.99	0.73	15.8	0.22	1.08	0.21	4.1	8.3
	002	319	0.59	0.14	0.33	2.81	0.68	14.9	0.20	0.86	0.25	3.7	6.5
	003	323	0.56	0.18	0.33	3.53	0.73	22.0	0.21	1.04	0.23	3.8	6.3
	004	353	0.52	0.19	0.36	3.75	0.76	23.3	0.22	0.86	0.21	3.3	5.9
	005	355	0.58	0.12	0.30	3.11	0.76	15.2	0.15	0.84	0.23	3.6	7.5
	Mean	338	0.57	0.16	0.33	3.24	0.73	18.2	0.20	0.94	0.23	3.7	6.9
15	011	309	0.59	0.17	0.33	3.08	0.73	18.7	0.20	0.99	0.29	3.7	6.9
	012	356	0.53	0.17	0.36	3.19	0.79	12.7	0.21	0.80	0.20	3.4	7.2
	013	383	0.51	0.13	0.32	3.16	0.69	16.7	0.21	0.85	0.21	3.2	6.3
	014	371	0.52	0.16	0.34	3.11	0.71	15.0	0.20	0.95	0.25	3.8	6.3
	015	348	0.55	0.16	0.34	3.00	0.83	16.8	0.23	0.98	0.28	3.2	6.0
	Mean	353	0.54	0.16	0.34	3.11	0.75	16.0	0.21	0.91	0.25	3.5	6.5
60	016	307	0.60	0.13	0.35	2.81	0.72	20.0	0.23	1.08	0.24	3.6	7.2
	017	321	0.59	0.16	0.33	3.06	0.81	17.3	0.17	0.95	0.27	3.2	7.8
	018	322	0.54	0.10	0.35	3.32	0.65	18.0	0.16	0.90	0.22	3.0	7.8
	019	339	0.55	0.16	0.34	3.04	0.79	17.1	0.22	0.91	0.24	3.3	6.0
	020	377	0.52	0.11	0.34	3.27	0.75	15.9	0.16	0.90	0.23	3.4	5.4
	Mean	333	0.56	0.13	0.34	3.10	0.74	17.7	0.19	0.95	0.24	3.3	6.8
250	021	351	0.53	0.17	0.33	3.35	0.76	14.1	0.20	0.82	0.21	3.1	7.8
	022	342	0.57	0.14	0.35	3.08	0.78	13.5	0.18	0.86	0.21	3.0	7.1
	023	342	0.57	0.17	0.35	3.55	0.75	16.5	0.20	1.02	0.25	3.2	8.2
	024	325	0.58	0.11	0.33	3.28	0.80	15.3	0.18	1.03	0.23	3.4	6.4
	025	343	0.59	0.14	0.31	3.43	0.73	15.6	0.19	0.87	0.22	3.6	8.9
	Mean	341	0.57	0.15	0.33	3.34	0.76	15.0	0.19	0.92	0.22	3.3	7.7
1000	026	289	0.61	0.14	0.33	3.92	0.87	17.4	0.24	0.99	0.24	3.4	6.6
	027	313	0.60	0.17	0.35	5.35	0.83	12.1	0.27	0.96	0.26	3.6	7.7
	028	331	0.61	0.10	0.37	4.28	0.85	13.9	0.31	0.99	0.21	3.3	8.8
	029	320	0.60	0.17	0.35	4.00	0.84	15.2	0.33	1.01	0.24	3.6	12.1
	030	321	0.61	0.15	0.34	4.82	0.85	16.5	0.26	1.02	0.26	3.3	6.5
	Mean	315	0.61	0.15	0.35	4.47	0.85	15.0	0.28	0.99	0.24	3.4	8.3

Appendix 29 - 3 Absolute organ weights of individual male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of recovery period>

Dose (mg/kg/day)	Animal numbers	Body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland (mg)	Spleen (g)	Testis (g)	Epididy-mis (g)	Pituitary gland (mg)	Thyroid gland (mg)
0	006	421	2.07	0.38	1.45	11.22	2.93	63.4	0.56	3.42	1.06	12.9	24.2
	007	401	1.88	0.66	1.49	11.85	2.85	65.7	0.80	3.17	0.98	12.9	29.0
	008	454	2.08	0.49	1.40	13.73	2.97	63.9	0.73	3.24	0.99	14.6	27.3
	009	446	2.14	0.46	1.33	12.06	2.73	69.7	0.67	3.38	1.06	13.6	27.4
	010	419	2.01	0.53	1.57	11.92	2.84	54.8	0.82	3.35	1.10	12.9	32.0
	Mean	428	2.04	0.50	1.45	12.16	2.86	63.5	0.72	3.31	1.04	13.4	28.0
1000	031	458	2.07	0.55	1.41	13.01	2.81	72.1	0.97	3.83	1.20	11.3	27.0
	032	382	1.94	0.34	1.32	10.61	3.06	62.5	0.56	2.72	0.94	13.2	29.1
	033	450	1.93	0.44	1.38	14.03	3.06	60.0	0.86	2.96	0.92	13.8	29.1
	034	440	1.96	0.56	1.32	14.62	3.05	71.6	0.90	3.23	1.13	13.0	28.6
	035	417	2.04	0.29	1.45	12.01	3.43	68.3	0.82	3.72	1.14	15.2	26.8
	Mean	429	1.99	0.44	1.38	12.86	3.08	66.9	0.82	3.29	1.07	13.3	28.1

Appendix 29 - 4 Relative organ weights of individual male rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of recovery period>

Dose (mg/kg/day)	Animal numbers	Body weight (g)	Brain (%)	Thymus (%)	Heart (%)	Liver (%)	Kidney (%)	Adrenal gland (mg%)	Spleen (%)	Testis (%)	Epididy-mis (%)	Pituitary gland (mg%)	Thyroid gland (mg%)
0	006	421	0.49	0.09	0.34	2.67	0.70	15.1	0.13	0.81	0.25	3.1	5.7
	007	401	0.47	0.16	0.37	2.96	0.71	16.4	0.20	0.79	0.24	3.2	7.2
	008	454	0.46	0.11	0.31	3.02	0.65	14.1	0.16	0.71	0.22	3.2	6.0
	009	446	0.48	0.10	0.30	2.70	0.61	15.6	0.15	0.76	0.24	3.0	6.1
	010	419	0.48	0.13	0.37	2.84	0.68	13.1	0.20	0.80	0.26	3.1	7.6
	Mean	428	0.48	0.12	0.34	2.84	0.67	14.9	0.17	0.77	0.24	3.1	6.5
1000	031	458	0.45	0.12	0.31	2.84	0.61	15.7	0.21	0.84	0.26	2.5	5.9
	032	382	0.51	0.09	0.35	2.78	0.80	16.4	0.15	0.71	0.25	3.5	7.6
	033	450	0.43	0.10	0.31	3.12	0.68	13.3	0.19	0.66	0.20	3.1	6.5
	034	440	0.45	0.13	0.30	3.32	0.69	16.3	0.20	0.73	0.26	3.0	6.5
	035	417	0.49	0.07	0.35	2.88	0.82	16.4	0.20	0.89	0.27	3.6	6.4
	Mean	429	0.47	0.10	0.32	2.99	0.72	15.6	0.19	0.77	0.25	3.1	6.6

Appendix 30 - 1 Absolute organ weights of individual female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of administration period>

Dose (mg/kg/day)	Animal numbers	Body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland (mg)	Spleen (g)	Ovary (mg)	Pituitary gland (mg)	Thyroid gland (mg)
0	501	193	1.70	0.73	0.72	5.54	1.50	62.2	0.41	83.7	11.2	14.4
	502	200	1.81	0.47	0.82	5.94	1.52	67.3	0.52	80.7	15.3	16.6
	503	214	1.80	0.38	0.76	6.62	1.65	64.6	0.37	96.1	16.4	16.6
	504	187	1.70	0.36	0.73	5.06	1.56	66.4	0.37	70.7	11.3	20.6
	505	221	1.97	0.58	0.75	6.04	1.66	64.7	0.54	79.6	14.2	22.5
	Mean	203	1.80	0.50	0.76	5.84	1.58	65.0	0.44	82.2	13.7	18.1
15	511	205	1.82	0.43	0.76	6.27	1.72	57.2	0.42	70.5	12.8	18.9
	512	216	1.87	0.45	0.75	7.16	1.64	79.8	0.50	101.5	19.9	16.0
	513	224	1.80	0.53	0.73	7.39	1.68	55.3	0.55	111.0	13.3	20.6
	514	231	1.75	0.53	0.79	7.33	1.66	71.2	0.60	107.5	13.4	23.0
	515	223	1.80	0.41	0.77	6.60	1.90	77.4	0.49	74.2	15.5	19.4
	Mean	220	1.81	0.47	0.76	6.95	1.72	68.2	0.51	92.9	15.0	19.6
60	516	192	1.72	0.37	0.71	5.57	1.48	58.9	0.38	74.8	14.6	16.0
	517	215	1.80	0.46	0.79	6.76	1.82	53.5	0.54	79.1	10.9	19.2
	518	242	1.85	0.64	0.99	7.20	1.81	65.1	0.42	92.0	15.7	21.1
	519	217	1.85	0.39	0.86	6.69	1.78	56.3	0.52	83.1	13.3	18.3
	520	247	1.96	0.58	0.85	7.62	1.92	65.7	0.68	96.1	16.3	23.1
	Mean	223	1.84	0.49	0.84	6.77	1.76	59.9	0.51	85.0	14.2	19.5
250	521	217	1.74	0.33	0.78	7.78	1.65	64.0	0.35	108.2	11.6	18.8
	522	204	1.76	0.39	0.73	6.99	1.65	51.4	0.46	95.9	11.5	20.3
	523	225	1.76	0.47	0.74	6.79	1.75	72.9	0.58	94.4	15.2	21.1
	524	204	1.88	0.36	0.75	6.08	1.49	68.5	0.48	89.8	13.6	19.4
	525	234	1.92	0.61	0.83	7.43	1.99	81.0	0.56	101.8	13.5	19.6
	Mean	217	1.81	0.43	0.77	7.01	1.71	67.6	0.49	98.0	13.1	19.8
1000	526	195	1.79	0.47	0.76	7.78	1.72	61.8	0.61	88.0	11.8	22.1
	527	241	1.81	0.66	0.83	9.10	1.83	69.3	0.67	6.2	13.7	21.4
	528	182	1.65	0.38	0.66	7.14	1.60	56.8	0.51	93.1	12.4	18.4
	529	219	1.76	0.39	0.86	9.21	1.74	71.3	0.67	105.5	15.0	25.5
	530	202	1.84	0.56	0.75	7.61	1.69	70.9	0.62	90.4	12.8	20.5
	Mean	209	1.77	0.49	0.77	8.17	1.72	66.0	0.62	76.6	13.1	21.6

Appendix 30 - 2 Relative organ weights of individual female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of administration period>

Dose (mg/kg/day)	Animal numbers	Body weight (g)	Brain (%)	Thymus (%)	Heart (%)	Liver (%)	Kidney (%)	Adrenal gland (mg%)	Spleen (%)	Ovary (mg%)	Pituitary gland (mg%)	Thyroid gland (mg%)
0	501	193	0.88	0.38	0.37	2.87	0.78	32.2	0.21	43.4	5.8	7.5
	502	200	0.91	0.24	0.41	2.97	0.76	33.7	0.26	40.4	7.7	8.3
	503	214	0.84	0.18	0.36	3.09	0.77	30.2	0.17	44.9	7.7	7.8
	504	187	0.91	0.19	0.39	2.71	0.83	35.5	0.20	37.8	6.0	11.0
	505	221	0.89	0.26	0.34	2.73	0.75	29.3	0.24	36.0	6.4	10.2
	Mean	203	0.89	0.25	0.37	2.87	0.78	32.2	0.22	40.5	6.7	9.0
15	511	205	0.89	0.21	0.37	3.06	0.84	27.9	0.20	34.4	6.2	9.2
	512	216	0.87	0.21	0.35	3.31	0.76	36.9	0.23	47.0	9.2	7.4
	513	224	0.80	0.24	0.33	3.30	0.75	24.7	0.25	49.6	5.9	9.2
	514	231	0.76	0.23	0.34	3.17	0.72	30.8	0.26	46.5	5.8	10.0
	515	223	0.81	0.18	0.35	2.96	0.85	34.7	0.22	33.3	7.0	8.7
	Mean	220	0.83	0.21	0.35	3.16	±0.78	31.0	0.23	42.2	6.8	8.9
60	516	192	0.90	0.19	0.37	2.90	0.77	30.7	0.20	39.0	7.6	8.3
	517	215	0.84	0.21	0.37	3.14	0.85	24.9	0.25	36.8	5.1	8.9
	518	242	0.76	0.26	0.41	2.98	0.75	26.9	0.17	38.0	6.5	8.7
	519	217	0.85	0.18	0.40	3.08	0.82	25.9	0.24	38.3	6.1	8.4
	520	247	0.79	0.23	0.34	3.09	0.78	26.6	0.28	38.9	6.6	9.4
	Mean	223	0.83	0.21	0.38	3.04	0.79	27.0	0.23	38.2	6.4	8.7
250	521	217	0.80	0.15	0.36	3.59	0.76	29.5	0.16	49.9	5.3	8.7
	522	204	0.86	0.19	0.36	3.43	0.81	25.2	0.23	47.0	5.6	10.0
	523	225	0.78	0.21	0.33	3.02	0.78	32.4	0.26	42.0	6.8	9.4
	524	204	0.92	0.18	0.37	2.98	0.73	33.6	0.24	44.0	6.7	9.5
	525	234	0.82	0.26	0.35	3.18	0.85	34.6	0.24	43.5	5.8	8.4
	Mean	217	0.84	0.20	0.35	3.24	0.79	31.1	0.23	45.3	6.0	9.2
1000	526	195	0.92	0.24	0.39	3.99	0.88	31.7	0.31	45.1	6.1	11.3
	527	241	0.75	0.27	0.34	3.78	0.76	28.8	0.28	2.6	5.7	8.9
	528	182	0.91	0.21	0.36	3.92	0.88	31.2	0.28	51.2	6.8	10.1
	529	219	0.80	0.18	0.39	4.21	0.79	32.6	0.31	48.2	6.8	11.6
	530	202	0.91	0.28	0.37	3.77	0.84	35.1	0.31	44.8	6.3	10.1
	Mean	209	0.86	0.24	0.37	3.93	0.83	31.9	0.30	38.4	6.3	10.4

Appendix 30 - 3 Absolute organ weights of individual female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of recovery period>

Dose (mg/kg/day)	Animal numbers	Body weight (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland (mg)	Spleen (g)	Ovary (mg)	Pituitary gland (mg)	Thyroid gland (mg)
0	506	226	1.67	0.37	0.89	7.17	1.98	69.5	0.45	50.6	17.4	21.7
	507	231	1.76	0.41	0.75	5.53	1.50	68.7	0.47	75.9	15.9	26.6
	508	234	1.82	0.31	0.84	6.54	1.72	65.8	0.48	101.4	13.8	17.0
	509	243	1.84	0.51	0.85	6.39	1.85	87.7	0.50	89.2	13.7	20.0
	510	247	1.77	0.45	0.86	6.86	1.62	64.0	0.52	69.5	16.5	19.0
	Mean	236	1.77	0.41	0.84	6.50	1.73	71.1	0.48	77.3	15.5	20.9
1000	531	252	1.82	0.42	0.90	7.17	1.66	66.9	0.50	76.2	15.3	19.6
	532	251	1.78	0.36	0.92	7.04	1.55	57.0	0.55	92.1	14.8	19.2
	533	233	1.82	0.35	0.75	6.99	1.53	66.1	0.50	68.1	14.4	23.1
	534	264	1.88	0.45	0.88	7.49	1.82	71.1	0.55	97.9	16.3	22.9
	535	239	1.78	0.38	0.88	6.95	1.68	70.1	0.49	106.6	12.0	24.1
	Mean	248	1.82	0.39	0.87	7.13	1.65	66.2	0.52	88.2	14.6	21.8

Appendix 30 - 4 Relative organ weights of individual female rats treated with 2-nitro-p-cresol in the repeated dose 28-day oral toxicity study
<At the end of recovery period>

Dose (mg/kg/day)	Animal numbers	Body weight (g)	Brain (%)	Thymus (%)	Heart (%)	Liver (%)	Kidney (%)	Adrenal gland (mg%)	Spleen (%)	Ovary (mg%)	Pituitary gland (mg%)	Thyroid gland (mg%)
0	506	226	0.74	0.16	0.39	3.17	0.88	30.8	0.20	22.4	7.7	9.6
	507	231	0.76	0.18	0.32	2.39	0.65	29.7	0.20	32.9	6.9	11.5
	508	234	0.78	0.13	0.36	2.79	0.74	28.1	0.21	43.3	5.9	7.3
	509	243	0.76	0.21	0.35	2.63	0.76	36.1	0.21	36.7	5.6	8.2
	510	247	0.72	0.18	0.35	2.78	0.66	25.9	0.21	28.1	6.7	7.7
	Mean	236	0.75	0.17	0.35	2.75	0.74	30.1	0.21	32.7	6.6	8.9
1000	531	252	0.72	0.17	0.36	2.85	0.66	26.5	0.20	30.2	6.1	7.8
	532	251	0.71	0.14	0.37	2.80	0.62	22.7	0.22	36.7	5.9	7.6
	533	233	0.78	0.15	0.32	3.00	0.66	28.4	0.21	29.2	6.2	9.9
	534	264	0.71	0.17	0.33	2.84	0.69	26.9	0.21	37.1	6.2	8.7
	535	239	0.74	0.16	0.37	2.91	0.70	29.3	0.21	44.6	5.0	10.1
	Mean	248	0.73	0.16	0.35	2.88	0.67	26.8	0.21	35.6	5.9	8.8

Appendix 31 Historical background data of the Crl:CD(SD) strain male rats on the hematological and biochemical parameters

Parameters	Mean		Normal range[a)]	
	A	B	A	B
Hematological parameters				
① Erythrocyte count ($10^4/\mu L$)	742 (108)	799 (103)	632 ~ 852	670 ~ 928
② Hemoglobin concentration (g/dL)	15.0 (108)	15.4 (103)	13.5 ~ 16.4	13.9 ~ 16.8
③ Hematocrit value (%)	46.0 (108)	46.6 (103)	41.6 ~ 50.4	43.1 ~ 50.1
④ Mean corpuscular volume (fL)	62 (108)	59 (103)	55 ~ 69	50 ~ 67
⑤ Mean corpuscular hemoglobin (pg)	20.2 (108)	19.3 (103)	18.5 ~ 21.9	17.2 ~ 21.3
⑥ Mean corpuscular hemoglobin concentration (%)	32.5 (108)	33.0 (103)	30.8 ~ 34.3	31.4 ~ 34.5
⑦ Reticulocyte count (‰)	48.0 (108)	34.0 (103)	9.0 ~ 86.9	1.0 ~ 67.1
⑧ Prothrombin time (sec)	15.9 (15)	15.2 (10)	12.2 ~ 19.5	14.1 ~ 16.3
⑨ Activated partial thromboplastin time (sec)	18.6 (15)	16.9 (10)	12.9 ~ 24.2	14.5 ~ 19.2
⑩ Total leukocyte count ($10^2/\mu L$)	66 (108)	74 (103)	24 ~ 107	35 ~ 114
⑪ Platelet count ($10^4/\mu L$)	141 (108)	137 (103)	106 ~ 175	103 ~ 171
⑫ Baso	0.0 (108)	0.0 (103)	0.0 0.0	0.0 0.0
⑬ Eosin	0.7 (108)	1.0 (103)	0.1 ~ 1.3	0.1 ~ 1.8
⑭ Seg	15.2 (108)	14.6 (103)	6.0 ~ 24.4	6.8 ~ 22.4
⑮ Lymph	81.4 (108)	81.5 (103)	71.7 ~ 91.2	73.0 ~ 89.9
⑯ Mono	2.6 (108)	3.0 (103)	0.9 ~ 4.4	0.7 ~ 5.2
Biochemical parameters				
① Lactate dehydrogenase (IU/L)	327 (181)	331 (176)	65 ~ 588	62 ~ 599
② Aspartate aminotransferase (IU/L)	74 (181)	74 (176)	54 ~ 94	53 ~ 95
③ Alanine aminotransferase (IU/L)	33 (181)	35 (176)	23 ~ 44	22 ~ 47
④ Alkaline phosphatase (IU/L)	965 (181)	873 (176)	428 ~ 1502	212 ~ 1533
⑤ γ-Glutamyl transpeptidase (IU/L)	0.57 (181)	0.58 (176)	0.01 ~ 1.13	0.06 ~ 1.21
⑥ Cholinesterase (IU/L)	54 (181)	48 (176)	16 ~ 93	16 ~ 80
⑦ Total protein (g/dL)	5.60 (181)	5.64 (176)	5.10 ~ 6.09	4.94 ~ 6.35
⑧ Albumin (g/dL)	2.78 (181)	2.79 (176)	2.40 ~ 3.16	2.36 ~ 3.23
⑨ A/G ratio	0.99 (181)	0.99 (176)	0.81 ~ 1.17	0.73 ~ 1.25
⑩ Total cholesterol (mg/dL)	73 (181)	74 (176)	40 ~ 107	42 ~ 106
⑪ Triglyceride (mg/dL)	50 (181)	57 (176)	9 ~ 90	3 ~ 110
⑫ Glucose (mg/dL)	138 (181)	140 (176)	97 ~ 179	96 ~ 184
⑬ Urea nitrogen (mg/dL)	12.8 (181)	13.6 (176)	7.5 ~ 18.1	8.0 ~ 19.2
⑭ Creatinine (mg/dL)	0.37 (181)	0.38 (176)	0.26 ~ 0.48	0.27 ~ 0.50
⑮ Total bilirubin (mg/dL)	0.36 (181)	0.35 (176)	0.24 ~ 0.47	0.25 ~ 0.46
⑯ Calcium (mg/dL)	9.9 (181)	9.9 (176)	9.0 ~ 10.8	8.8 ~ 10.9
⑰ Inorganic phosphorus (mg/dL)	8.7 (181)	8.4 (176)	7.2 ~ 10.3	6.6 ~ 10.3
⑱ Sodium (mEq/L)	145 (181)	145 (176)	142 ~ 148	141 ~ 149
⑲ Potassium (mEq/L)	4.87 (181)	4.89 (176)	4.10 ~ 5.63	4.16 ~ 5.63
⑳ Chloride (mEq/L)	105 (181)	105 (176)	102 ~ 109	102 ~ 109

a) : (mean−2S.D.) ~ (mean+2S.D.) .

( ) : Number of animals.

* : Calculated from log-transformed data.

A : 9~10-week-old rat.

B : 11~12-week-old rat.

Appendix 32 Historical background data of the Crl:CD(SD) strain female rats on the hematological and biochemical parameters

Parameters	Mean		Normal range[a)]	
	A	B	A	B
Hematological parameters				
① Erythrocyte count (10^4/μL)	750 (109)	771 (103)	662 ~ 839	687 ~ 855
② Hemoglobin concentration (g/dL)	14.8 (109)	14.8 (103)	13.2 ~ 16.4	13.4 ~ 16.3
③ Hematocrit value (%)	44.2 (109)	44.2 (103)	39.6 ~ 48.8	40.0 ~ 48.3
④ Mean corpuscular volume (fL)	59 (109)	57 (103)	54 ~ 64	52 ~ 62
⑤ Mean corpuscular hemoglobin (pg)	19.7 (109)	19.3 (103)	18.5 ~ 20.9	18.0 ~ 20.5
⑥ Mean corpuscular hemoglobin concentration (%)	33.4 (109)	33.6 (103)	31.5 ~ 35.3	32.1 ~ 35.1
⑦ Reticulocyte count (‰)	31.4 (109)	27.4 (103)	11.5 ~ 51.3	8.4 ~ 46.4
⑧ Prothrombin time (sec)	16.2 (15)	17.0 (10)	14.8 ~ 17.7	12.3 ~ 21.6
⑨ Activated partial thromboplastin time (sec)	16.3 (15)	17.1 (10)	15.0 ~ 17.6	14.1 ~ 20.0
⑩ Total leukocyte count (10^2/μL)	49 (109)	51 (103)	17 ~ 82	21 ~ 82
⑪ Platelet count (10^4/μL)	137 (109)	131 (103)	100 ~ 175	96 ~ 167
⑫ Baso	0.0 (109)	0.0 (103)	0.0 0.0	0.0 0.0
⑬ Eosin	1.2 (109)	1.3 (103)	0.0 ~ 2.3	0.0 ~ 2.6
⑭ Seg	14.9 (109)	14.5 (103)	1.5 ~ 28.2	3.2 ~ 25.9
⑮ Lymph	81.6 (109)	81.5 (103)	67.6 ~ 95.5	69.4 ~ 93.6
⑯ Mono	2.4 (109)	2.6 (103)	0.5 ~ 4.3	0.5 ~ 4.8
Biochemical parameters				
① Lactate dehydrogenase (IU/L)	454 (181)	423 (176)	79 ~ 829	69 ~ 777
② Aspartate aminotransferase (IU/L)	76 (181)	77 (176)	55 ~ 97	48 ~ 105
③ Alanine aminotransferase (IU/L)	28 (181)	29 (176)	12 ~ 44	10 ~ 49
④ Alkaline phosphatase (IU/L)	620 (181)	555 (176)	241 ~ 998	93 ~ 1017
⑤ γ-Glutamyl transpeptidase (IU/L)	0.85 (181)	0.85 (176)	0.10 ~ 1.81	0.06 ~ 1.75
⑥ Cholinesterase (IU/L)	340 (181)	356 (176)	4 ~ 676	35 ~ 678
⑦ Total protein (g/dL)	5.85 (181)	5.92 (176)	5.16 ~ 6.53	5.16 ~ 6.68
⑧ Albumin (g/dL)	3.05 (181)	3.10 (176)	2.47 ~ 3.63	2.48 ~ 3.71
⑨ A/G ratio	1.09 (181)	1.10 (176)	0.85 ~ 1.34	0.84 ~ 1.36
⑩ Total cholesterol (mg/dL)	75 (181)	77 (176)	37 ~ 113	38 ~ 116
⑪ Triglyceride (mg/dL)	28 (181)	28 (176)	4 ~ 89	6 ~ 62
⑫ Glucose (mg/dL)	126 (181)	127 (176)	95 ~ 157	94 ~ 161
⑬ Urea nitrogen (mg/dL)	13.9 (181)	14.9 (176)	8.5 ~ 19.3	9.0 ~ 20.8
⑭ Creatinine (mg/dL)	0.40 (181)	0.42 (176)	0.27 ~ 0.54	0.29 ~ 0.56
⑮ Total bilirubin (mg/dL)	0.26 (181)	0.26 (176)	0.18 ~ 0.33	0.17 ~ 0.35
⑯ Calcium (mg/dL)	9.9 (181)	9.9 (176)	9.1 ~ 10.8	8.9 ~ 10.8
⑰ Inorganic phosphorus (mg/dL)	8.1 (181)	7.7 (176)	6.3 ~ 9.9	5.6 ~ 9.9
⑱ Sodium (mEq/L)	146 (181)	145 (176)	142 ~ 149	142 ~ 149
⑲ Potassium (mEq/L)	4.72 (181)	4.72 (176)	3.83 ~ 5.61	3.80 ~ 5.64
⑳ Chloride (mEq/L)	107 (181)	107 (176)	103 ~ 111	102 ~ 111

a) : (mean−2S.D.) ~ (mean+2S.D.) .

( ) : Number of animals.

* : Calculated from log-transformed data.

A : 9~10-week-old rat.

B : 11~12-week-old rat.

Photo 1. Liver (0 mg/kg group, male, No. 001, H·E stain, ×264)
No abnormalities

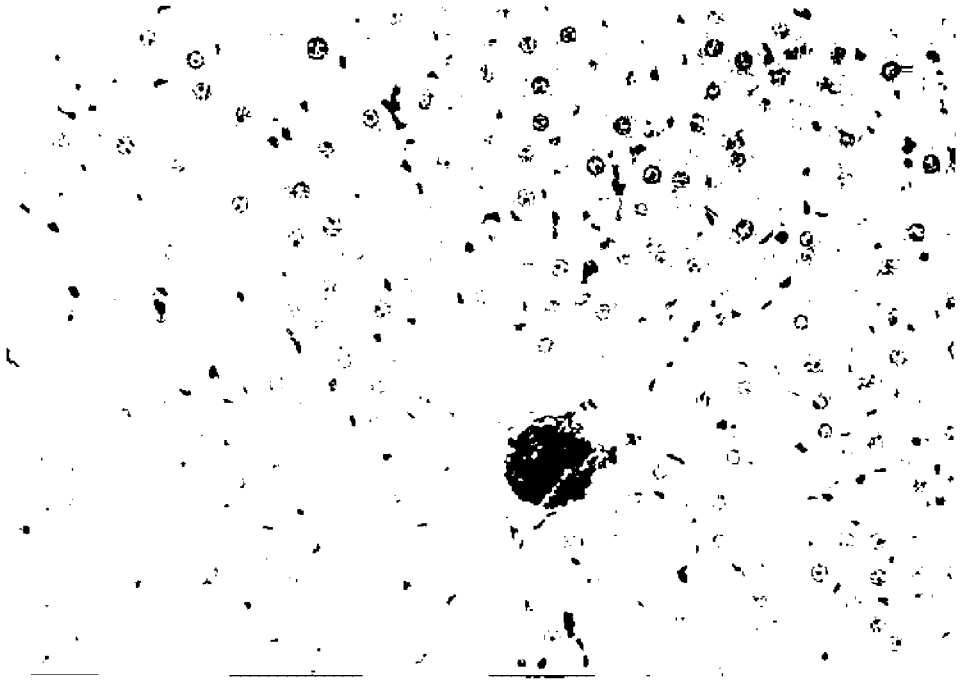

Photo 2. Liver (1000 mg/kg group, male, No. 027, H·E stain, ×264)
Centrilobular hypertrophy of the hepatocyte

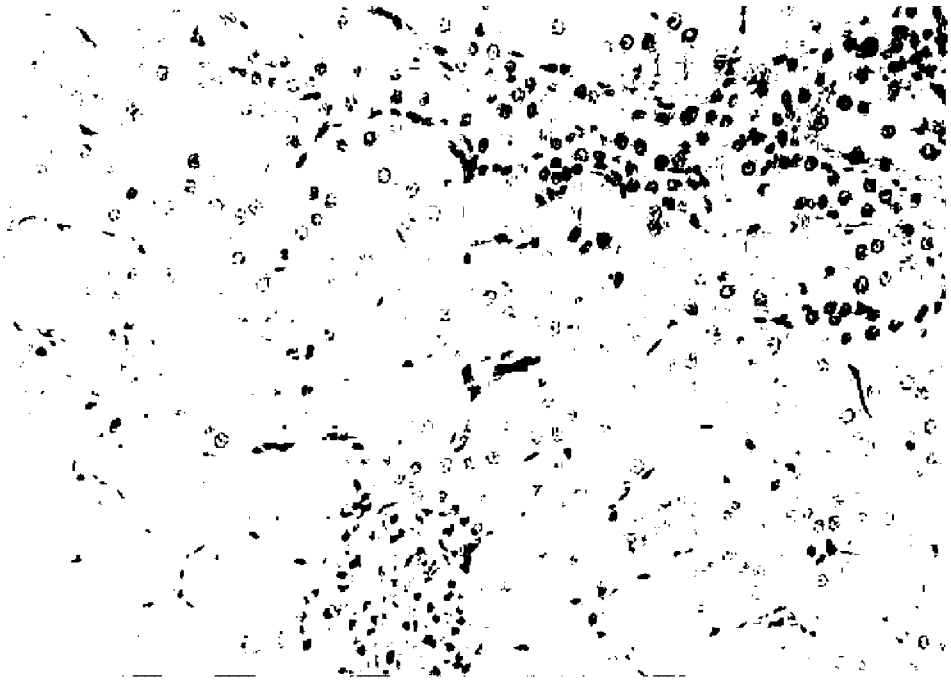

Photo 3. Kidney (0 mg/kg group, male, No. 001, H·E stain, ×264)
No abnormalities

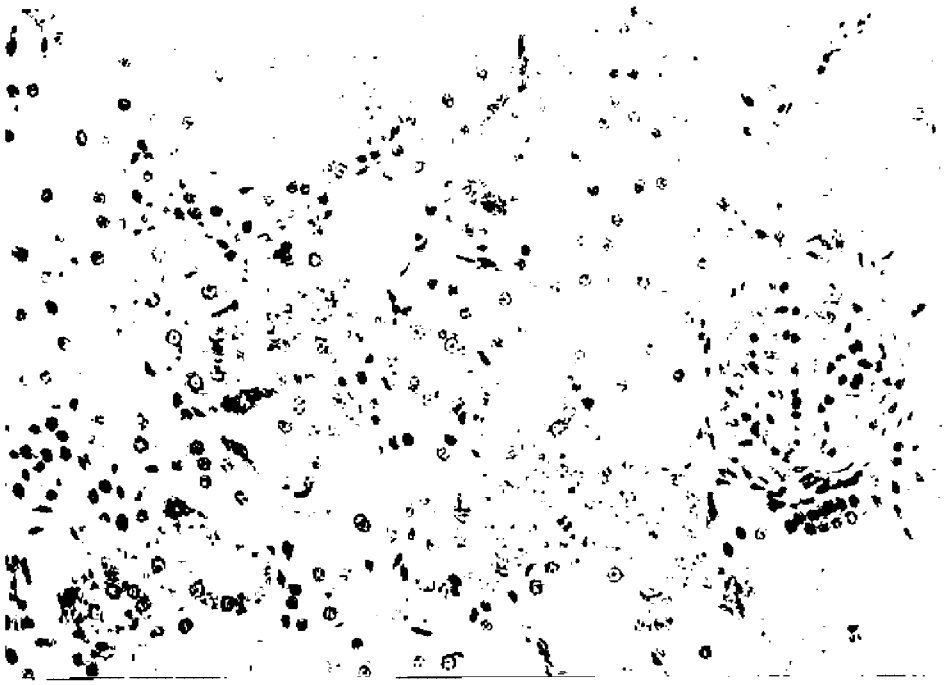

Photo 4. Kidney (1000 mg/kg group, male, No. 026, H·E stain, ×264)
Increased hyaline droplets in the proximal tubular epithelium

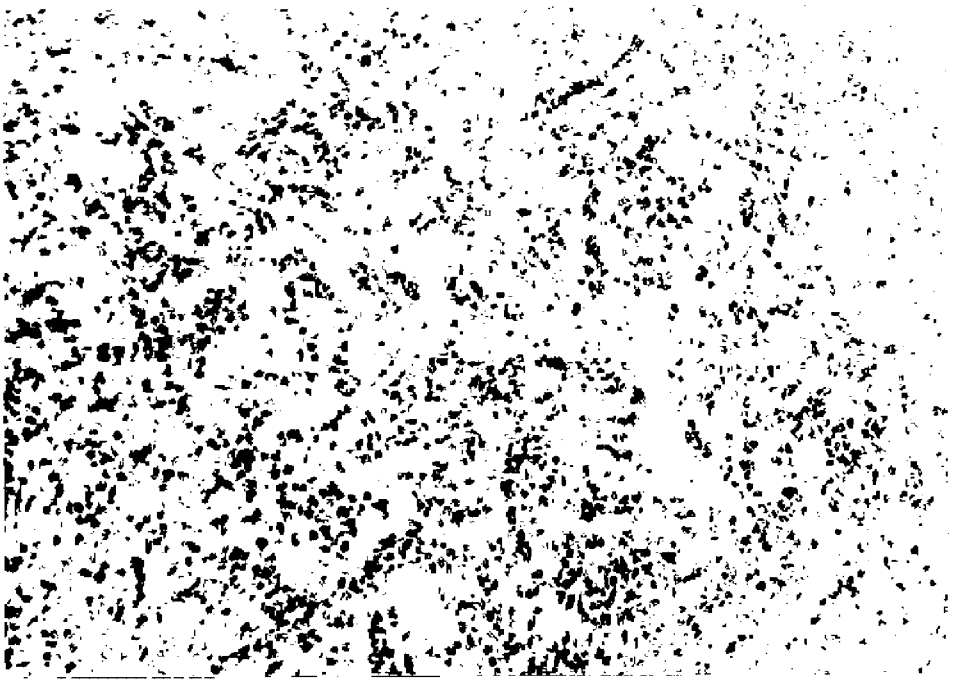

Photo 5. Spleen (0 mg/kg group, female, No. 501, H·E stain, ×264)
No abnormalities

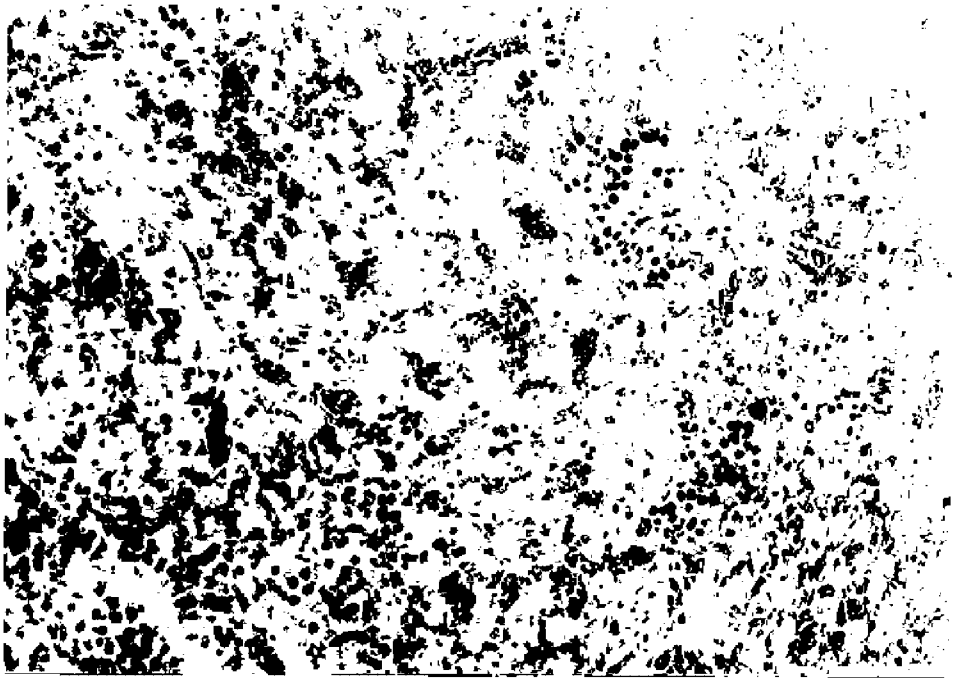

Photo 6. Spleen (1000 mg/kg group, female, No. 529, H·E stain, ×264)
Congestion, increased extramedullary hematopoiesis and deposits of brown pigment