最 終 報 告 書

ジフェニレンオキシドのラットを用いる 28 日間反復経口投与毒性試験
（試験番号：05-232）

財団法人 畜産生物科学安全研究所

陳　述　書

試験の表題

ジフェニレンオキシドのラットを用いる28日間反復経口投与毒性試験

（試験番号：05-232）

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　主任研究員

[redacted]

平成22年11月22日

試験の表題

ジフェニレンオキシドのラットを用いる28日間反復経口投与毒性試験

(試験番号：05-232)

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	神奈川県相模原市緑区橋本台 3-7-11	
運営管理者	専務理事	[redacted]
試験責任者	安全性研究部	
	主任研究員	[redacted]
信頼性保証	信頼性保証室	
責任者	首席研究員	[redacted]

試験日程

試験開始日		平成18年　7月　3日
動物入荷日		平成18年　7月　6日
群分け	雄	平成18年　7月12日
	雌	平成18年　7月13日
投与開始	雄	平成18年　7月13日（実験開始）
	雌	平成18年　7月14日
投与終了	雄	平成18年　8月　9日
	雌	平成18年　8月10日
解　　剖	雄	平成18年　8月10日（投与終了時）
		平成18年　8月24日（回復終了時）
	雌	平成18年　8月11日（投与終了時）

	平成 18 年　8 月 25 日（回復終了時）
検査終了	平成 20 年 11 月 30 日（実験終了）
報告書草案	平成 20 年 12 月 24 日
試験終了	平成 22 年 11 月 22 日（最終報告書作成）

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

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（一般状態，詳細な臨床観察，感覚反射機能検査，握力，自発運動量，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，病理組織学検査などの生データ）
5) 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　主任研究員

氏名 [redacted]　　平成22年11月22日

試験担当者およびその業務分担

被験物質の分析　：

投与液の調製　：

動物飼育・投与・臨床観察/ 測定：

臨床検査　：

病理検査　：

統計　：

[redacted]

信頼性保証証明書

試験表題 ： ジフェニレンオキシドのラットを用いる28日間反復経口投与毒性試験

試験番号 ： 05-232

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07月03日	平成18年07月03日	平成18年07月03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18年07月06日	平成18年07月06日	平成18年07月06日
検　疫		
平成18年07月07日	平成18年07月07日	平成18年07月07日
被験物質調製・群分け・個体識別・詳細な臨床観察		
平成18年07月12日	平成18年07月12日	平成18年07月12日
体重測定・投与・症状観察		
平成18年07月13日	平成18年07月13日	平成18年07月13日
餌測定		
平成18年07月18日	平成18年07月18日	平成18年07月18日
体重測定・投与・症状観察・詳細な臨床観察		
平成18年07月26日	平成18年07月26日	平成18年07月26日
尿検査		
平成18年08月04日	平成18年08月04日	平成18年08月04日
被験物質調製		
平成18年08月07日	平成18年08月07日	平成18年08月07日
餌測定・感覚機能検査・握力測定・自発運動量測定		
平成18年08月08日	平成18年08月08日	平成18年08月08日
解　剖・病理組織標本作製（臓器・組織の固定）・血液検査		
平成18年08月10日	平成18年08月10日	平成18年08月10日
血液生化学検査		
平成18年08月16日	平成18年08月16日	平成18年08月16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18年08月30日	平成18年08月30日	平成18年08月30日
病理組織標本作製(切り出し) 平成18年08月21日	平成18年08月21日	平成18年08月21日
病理組織標本作製(薄切) 平成18年09月04日	平成18年09月04日	平成18年09月04日
病理組織標本作製(染色) 平成18年09月05日	平成18年09月05日	平成18年09月05日
病理組織標本作製(脱灰) 平成18年09月26日	平成18年09月26日	平成18年09月26日
4. 生データ査察 平成20年07月14日 ～ 同年07月15日	平成20年07月15日	平成20年07月15日
5. 報告書（草案）審査 平成20年07月16日 ～ 同年07月22日	平成20年07月22日	平成20年07月22日
平成21年12月21日 ～ 同年12月22日	平成21年12月24日	平成21年12月24日
6. 最終報告書審査 平成22年11月22日	平成22年11月22日	平成22年11月22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 22 年 11 月 22 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

添付資料

A 図・群別平均値表

B. 個体別表等

要　約

ジフェニレンオキシドの反復投与毒性を検討するため，本物質を 1 群雌雄各 5 匹の SD 系ラットに，0（被験物質の溶媒として用いたオリブ油のみ投与），10，40，150 および 600 mg/kg/day の用量で 28 日間経口投与した。現れる変化の可逆性を調べるため，0 および 600 mg/kg/day では，投与終了後 14 日間の回復期間を設けたサテライト群を別に設けた。

150 mg/kg 群で雄に自発運動低下が投与 1 日のみに認められた。600 mg/kg 群では，雌雄に自発運動低下が投与 1 日ないし 2 日までにのみ認められたほか，尿による下腹部の汚れが雌に，体重の低値が雄に認められた。尿検査では，600 mg/kg 群で雌に尿量の高値，尿比重の低値およびタンパク濃度の低下が認められた。血液学検査では 40 mg/kg 以上で群の雄にいずれも軽度な赤血球数，血色素量およびヘマトクリット値の低値，600 mg/kg 群では雌にも血色素量の低値が認められた。また，150 およぼ 600 mg/kg 群で雄にプロトロンビン時間の延長が認められた。血液生化学検査では，600 mg/kg 群で雌雄に ALT および総コレステロール，さらに雄にγ-GTP，雌にアルブミン，トリグリセライド，総ビリルビンおよびカルシウムのいずれも高値が認められた。器官重量では，150 mg/kg 以上の群で雄に肝臓相対重量および腎臓相対重量の高値，600 mg/kg 群ではさらに雌に肝臓に絶対および相対重量並びに腎臓相対重量の高値が認められた。病理組織学検査では，肝臓の小葉中心性肝細胞肥大が 150 mg/kg 群の雄および 600 mg/kg 群の雌雄に，また，腎臓の皮質尿細管の拡張および皮質尿細管上皮の空胞変性が 600 mg/kg の雌に認められた。

回復期間あるいは回復期間終了時においては，これら投与期間中あるいは投与期間終了時の認められた変化のうち，雌の血清アルブミン，A/G 比および総コレステロール並びに肝臓相対重量の高値に回復傾向が認められ，またその他の変化はいずれも回復し，ジフェニレンオキシドの毒性は可逆的であることが確認された。

以上の結果から，ジフェニレンオキシドのラットへの 28 日間反復経口投与において，肝臓および腎臓に対する毒性が認められた。また，血液に対する軽度な影響も認められた。無影響量（NOEL）は雄で 10 mg/kg/day，雌で 40 mg/kg/day，並びに無毒性量（NOAEL）は，雌雄とも 40 mg/kg/day と推定された。

目　的

ジフェニレンオキシドをラットに 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

被験物質として用いたジフェニレンオキシド(CAS 番号 132-64-9)は，分子量 168.20 の，水に難溶，エタノール，アセトン，エーテルに可溶な，白色の結晶および小塊を成す物質である。試験には，東京化成株式会社（東京都日本橋本町 4-10-2）から試薬としてロット番号 KNIKD（純度 99.9%）を入手して，冷暗所（2～6℃），密封下で保管し，使用した。保管した被験物質は投与終了後に，東京化成株式会社に委託して分析（GC 法）し，安定であったことを確認した。本物質の特性は，Appendix 1 に示す。

被験物質は，局方オリブ油（宮澤薬品株式会社，ロット番号 BA26）を用いて，所定の投与用量になる濃度に溶解し，投与液とした。被験物質調製液の安定性を調べた結果，冷暗所で 7 日間，続いて室温遮光下で 1 日の保存条件下で安定であることが確認された(Appendix 2)ので，投与液は週 1 回調製して 1 日の使用量に小分けして密栓し，使用時まで冷暗所(2~6℃)で保管した。初回に調製したそれぞれ 0.2, 0.8, 3.0 および 12 w/v% 溶液について，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（雌雄各 42 匹）し，雄で 7 日間，雌で 8 日間試験環境に馴化させ，その間に検疫を行い，発育が順調で，一般健康状態が良好な雌雄各 35 匹を，5 週齢で試験に用いた。

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 060453，060659）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 22.2～23.5℃，湿度は 55～62%の範囲で推移（Appendix 4）し，また飼料および飲料水の汚染物質の分析結果（Appendices 5，6）は，いずれも当研究所で設定した許容範囲内にあることが確認された。従って，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などを定めた，「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 4 匹のラットに，被験物質を 0（溶媒対照，オリブ油），50，100，500 および 1000 mg/kg/day で 14 日間経口投与し，一般状態の観察，体重および摂餌量の測定，尿検査，血液学検査，血液生化学検査，剖検，器官重量の測定を行った。その結果，500 mg/kg 群以上の雌雄に自発運動の低下（投与 1 日のみ）および流涎が認められた。1000 mg/kg の雌の 1 匹が死亡した。尿検査では，500 mg/kg 以上の群の雌雄でタンパクおよびケトン体濃度の低値傾向が認められた。血液学検査では，1000 mg/kg 群で雌雄に活性化部分トロンボプラスチン時間の遅延傾向が認められた。血液生化学検査では，1000 mg/kg 群で雌雄に ALT およびγ-GTP，雌にトリグリセライド，総コレステロールおよび総ビリルビンのいずれも高値傾向が認められた。総コレステロールの高値傾向は 500 mg/kg 群の雌にも認められた。器官重量では，100 mg/kg 群以上の雄および 500 mg/kg 群以上の雌で肝臓重量の増加傾向が認められた。以上の結果から，本試験における投与量については，確実に反復投与毒性が発現すると予測される 600 mg/kg/day を最高用量，毒性影響が発現しないと予測される 10 mg/kg/day を最低用量とし，これらの用量の間に 40 および 150 mg/kg/day の計 4 用量を設定した。また，対照と 600 mg/kg/day の両群には，投与終了後 14 日間の回復試験

を行なうためのサテライト群を別に設けた。

試験群の構成は，①溶媒投与群（以下，対照群），②対照群の回復群（サテライト群），③被験物質の 10 mg/kg/day 投与群（10 mg/kg 群），④同 40 mg/kg/day 投与群（40 mg/kg 群），⑤同 150 mg/kg/day 投与群（150 mg/kg 群），⑥同 600 mg/kg/day 投与群（600 mg/kg 群）および⑦600 mg/kg 群の回復群（サテライト群）の 7 群で，各群の動物数は雌雄各 5 匹とした。

動物の群分けは，投与開始前日に行った。健常と判断された動物について，雌雄それぞれ全動物の体重の平均値に近いものから必要数を選別し，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。投与開始時の平均体重（体重範囲）は，雄で 162(152～172g)，雌で 137(128～148g)であった。

投与方法は，投与液量を体重 1kg 当たり 5mL とし，テフロン製胃ゾンデを装着した注射筒を用いて，投与液を胃内に，1 日 1 回（午前中 9：00～11：45），28 日間にわたって経口投与した。各個体の投与液量は，至近日の測定体重を基に算出した。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。

4. 観察および検査

観察期間は，投与開始前日から投与期間の 28 日間およびサテライト群ではそれに続く回復期間の 14 日間とし，次の観察および検査を実施した。

1)一般状態観察

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 回，動物の生死，外観，行動などについて観察した。

2)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，眼分泌物，眼瞼閉鎖状態，眼球突出，流涙，口鼻分泌物（汚れ），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），警戒性，自発運動（活動性），歩行（よろめき），異常行動（自咬，後ろ向き歩行など），常同（過度の毛繕い，反復旋回運動など），意識不全（混迷，カタレプシー，昏睡），四

肢筋緊張度，排尿および排糞について，ケージサイドに加えて，ケージから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）で観察し，認められた変化を評点（Appendix 7）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。

3)感覚機能検査

投与期間終了時解剖動物は投与 4 週およびサテライト群については回復 2 週に，視覚反応（顔面に棒を近づけた場合の接近反応），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），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，発声などの反応），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 8）で記録した。

4)握力および自発運動量

投与期間終了時解剖動物は投与 4 週およびサテライト群については回復 2 週に，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）を測定した。

5)体重および摂餌量

体重は，投与 1（投与開始直前），7，14，21 および 28 日，回復 7 日および 14 日並びに屠殺日に測定し，投与期間中の体重増加量を算出した。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，翌日までの 24 時間の摂餌量（飼料消費量）を測定した。

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

6)尿検査

投与期間終了時解剖動物は投与 4 週およびサテライト群では回復 2 週に実施した。ま

ず腰部を刺激して新鮮尿を採取し，色調および濁度の観察，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，潜血，タンパク，糖，ケトン体，ビリルビンおよびウロビリノーゲンの定性的検査を行った。また，代謝ケージに約 3 時間収容して得られた蓄尿について尿沈渣の検査[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]を行い，さらに 18 時間収容して得られた尿について尿量（メスシリンダー）および比重（屈折計，エルマ光学株式会社）を測定した。

7)血液学検査

投与期間および回復期間終了の翌日に，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遠心分離し，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。

8)血液生化学検査

採取した血液の一部から血清を遠心分離し，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[酵素法（GluK[1]-G-6-PDH[2]-UV 系）]，総コレステロール[（酵素法（CES[3]-CO[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 法[10]），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，東亜電波工業株式会社）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。

測定法の注釈；[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

9)剖検および器官重量

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。また，脳，胸腺，心臓，肝臓，腎臓，副腎，脾臓さらに雄では精巣，精巣上体，雌では卵巣（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秤量した。

10)病理組織学検査

全例について下記器官を採取し，10%中性リン酸緩衝ホルマリン液（精巣，精巣上体はブアン液で前固定）で固定し，保存した。

脳（大脳，小脳，橋を含む），眼球，下垂体，甲状腺（上皮小体を含む），脊髄（頸部，胸部，腰部），心臓，気管および肺（固定液を注入後浸漬），肝臓，腎臓，胸腺，脾臓，副腎，胃および腸（十二指腸から直腸，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，精巣上体，精嚢），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，対照群および 600 mg/kg 群の上記の器官・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肝臓および腎臓に認められたので，10 mg/kg 群，40 mg/kg，150 mg/kg およびサテライト群の雌雄については，肝臓および腎臓の検査を実施した。検査は，常法に従ってパラフィン切片を作製し，H-E 染色を施して鏡検した。

5. 統計解析

パラメトリックデータ（握力・自発運動量・体重・体重増加量・摂餌量・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）については，群ごとに平均値および標準偏差を求めた。また，試験群が 3 群以上の場合は，Bartlett の分散検定を行い，その結果分散が一様な場合は一元配置の分散分析を行った。分散が一様でない場合並びにノンパラメトリックデータ（白血球百分率・尿の定性的検査）は Kruskal-Wallis

の順位検定を行った。それらの結果有意差を認めた場合，Dunnett ないし Dunnett 型の検定法により多比重比較を行った。試験群が 2 群の場合は，パラメトリックデータについて 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，一様でない場合は Aspin-Welch の t 検定を行った。また，ノンパラメトリックデータは，Mann-Whitney の U 検定を行った。カテゴリカルデータ（一般状態の観察・詳細な臨床観察・感覚機能検査・剖検・病理組織学検査における異常例の発現率）には Fisher の直接確率法を用いた。有意水準は，いずれの検定法も 5%とした。

結　果

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

投与期間および回復期間中において，死亡は認められなかった。

一般状態の変化として，投与 1 日あるいは投与 1 日および 2 日のみ，自発運動の低下が 150 mg/kg 群で雄の 1 匹，600 mg/kg 群でサテライト群を含む雄の 10 匹，雌の 6 匹に認められた。また投与期間を通じて，投与直後から発現する一過性の流涎が 150 mg/kg で雄の 4 匹，雌の 5 匹および 600 mg/kg で雌雄各 10 匹に，さらに投与 9 日以降において，尿による下腹部の汚れが，600 mg/kg 群で雌の 3 匹に認められた。600 mg/kg 群の雌雄の自発運動の低下並びに 150 および 600 mg/kg 群の雌雄の流涎の発現率には，対照群と比べて有意差が認められた。

これらの変化は回復期間においては認められなかった。

また死亡は，投与および回復期間を通じて認められなかった。

2. 詳細な臨床観察（Tables 3，4，Appendices 11，12）

投与期間中の観察において，600 mg/kg 群で雌に下腹部被毛の尿による汚れが，投与 2 週の検査で 3 匹，投与 3 週の検査で 2 匹，投与 4 週で 1 匹に認められた。

回復期間中の観察で，被験物質の投与に起因する変化は認められなかった。

3. 感覚機能検査（Tables 5，6，Appendices 13，14）

投与および回復期間中の検査において，各項目に有意な変化は認められなかった。

4. 握力および自発運動量（Tables 7，8，Appendices 15，16）

投与期間中の検査において，10 mg/kg 群で雌に前肢握力の有意な低値が認められたが，用量相関性は認められなかった。後肢握力および自発運動量には有意な変化は認められなかった。

回復期間中の検査では，10 mg/kg 群の雌に前肢握力に変化は認められなかった。600 mg/kg で雄の自発運動量の有意が認められたが，投与期間の検査では認められなかった変化であった。

5. 体重（Figures 1, 2, Tables 9, 10, Appendices 17, 18）

投与期間中において，600 mg/kg 群の雄で，投与 7 日の体重に有意な低値が認められ，投与期間中の体重増加量も低値傾向にあった。

回復期間においては，600 mg/kg 群の雄の体重増加量は対照群を上回る傾向を示した。

6. 摂餌量（Tables 11, 12, Appendices 19, 20）

投与期間中および回復期間中の各測定時点とも，有意な変化は認められなかった。

7. 尿検査（Tables 13, 14, Appendices 21, 22）

投与期間中の検査において，600 mg/kg 群の雌で尿量の有意な高値，尿比重の有意な低値およびタンパク濃度の有意な低下が認められた。

回復期間中の検査においては，有意な変化は認められなかった。

8. 血液学検査（Tables 15, 16, Appendices 23, 24, 背景データ Appendices 33, 34）

投与期間終了時において，40 mg/kg 以上の群で雄に，赤血球数，血色素量およびヘマトクリット値の有意な低値（150 mg/kg 群の赤血球数のみは有意が認められず）が認められた。一方，雌においては 600 mg/kg 群の血色素量にのみ有意な低値が認められた。また，150 および 600 mg/kg 群の雄にプロトロンビン時間の有意な延長が認められた。600 mg/kg 群の雌のプロトロンビン時間は雄とは逆に有意な短縮を示した。

回復期間終了時においては，投与期間終了時の検査で認められた変化は認められなかった。600 mg/kg 群の雄に血小板数の有意な高値が認められたが，投与期間終了時の検査では認められなかった変化であった。

9. 血液生化学検査（Tables 17, 18, Appendices 25, 26, 背景データ Appendices 33, 34）

投与期間終了時において，600 mg/kg 群で雌雄に，ALT および総コレステロール，さらに雄でγ-GTP，雌でアルブミン，トリグリセライド，総ビリルビンおよびカルシウムのいずれも有意な高値が認められた。

回復期間終了時において，600 mg/kg 群で雌のアルブミンおよび総コレステロールの

有意な高値は残ったが，投与期間終了時と比べて変化の程度は軽減する傾向が認められ，また，その他の変化については回復した。なお，投与期間終了時の検査では認めらなかったが，600 mg/kg 群で雌に A/G 比の有意な高値が認められた。

10.剖検（Tables 19，20，Appendices 27，28）

投与期間終了時および回復期間終了時とも，各器官・組織に変化は認められなかった。

11.器官重量（Tables 21，22，Appendices 29～32）

投与期間終了時において，150 mg/kg 以上の群で，雄に肝臓相対重量および腎臓相対重量の有意な高値が認められた。600 mg/kg 群においては，雌においても肝臓の絶対および相対重量並びに腎臓相対重量の有意な高値が認められた。

回復期間終了時において，600 mg/kg 群の雌に肝臓相対重量の有意な高値は認められたものの，変化の程度は投与期間終了時と比べて軽減し，雄の肝臓重量および雌雄の腎臓重量の高値は回復していた。雄の腎臓の相対重量は逆に有意な低値を示した，なお，600 mg/kg 群の雌に胸腺の絶対重量並びに脾臓の絶対および相対重量の有意な低値が認められたが，これらの変化は投与期間終了時には認められなかった。

12.病理組織学検査（Tables 23，24，Appendices 27，28）

被験物質の投与に起因する変化が，雄で肝臓，雌で肝臓および腎臓に認められた。

肝細胞肥大が 150mg/kg 群で雄 2 匹に，600 mg/kg 群では雄 5 匹および雌 5 匹に認められ，600mg/kg 群の発現率には有意差が認められた。肥大した肝細胞は小葉中心帯に限局する変化であったが，600 mg/kg 群の変化は 150 mg/kg のそれよりも重度化し，用量相関性が認められた。回復群では，雌雄とも変化は認められず，回復傾向が認められた。

腎臓において，600 mg/kg 群の雌で，皮質尿細管の拡張が 4 匹に，皮質尿細管上皮の空胞変性が 4 匹に認められ，いずれの発現率にも有意差が認められた。回復群では，この変化は認められなかった。

被験物質の投与とは無関係な自然発生病変と判断された所見として，肺の泡沫細胞集簇巣および動脈壁鉱質沈着，心臓の心筋変性・線維化並びに胸腺の出血が対照群と 600

mg/kg 群に共通して，あるいはどちらかの群に 1 匹のみ認められた。雌雄全群で検査した，肝臓の巣状壊死，門脈域肝細胞脂肪変性および微小肉芽腫，腎臓の好塩基性尿細管，リンパ球皮質浸潤，硝子円柱，孤立性嚢胞，皮質線維化および皮髄境界部の鉱質沈着がいずれも低い発現率で認められた。

また，雄の腎臓の近位尿細管上皮硝子滴並びに雌雄の脾臓の髄外造血および褐色色素沈着がいずれも高い発現率で認められたが，600 mg/kg 群における発現率や変化の程度に対照群と差は認められなかった。これらはいずれも，被験物質の投与とは無関係な自然発生病変と判断された。

考　察

ジフェニレンオキシドをラットに 0, 10, 40, 150 および 600 mg/kg/day の用量で 28 日間経口投与し，本物質の反復投与毒性を検討した結果，肝臓および腎臓に対する毒性が認められた。また，血液に対する軽度な影響が認められた。

肝臓に対する毒性について，病理組織学検査で，小葉中心性の肝細胞肥大が 150 mg/kg 群の雄および 600 mg/kg 群の雌雄に観察された。150 mg/kg 群の雄および 600 mg/kg の雌雄で認められた肝臓重量の高値は，病理組織学検査で認められた肝細胞の変化と関連するものと考えられる。また，600mg/kg 群で認められた雌雄の ALT および総コレステロールの高値，雄のγ-GTP の高値，雌のトリグリセライドおよび総ビリルビンの高値，並びに 150 および 600 mg/kg 群で認められた雄の血液プロトロンビン時間の延長も，肝臓に対する影響と関連する変化と考えられる。

なお 600 mg/kg 群の雌のプロトロンビン時間は雄とは逆に低値を示したが，変動幅はごく軽度なものであった。また，600 mg/kg 群の雌で認められたカルシウムの高値については，軽度な変化でカルシウム代謝と関連する変化を伴っていないことから，アルブミンの高値に伴う二次的変化と考えられる。

腎臓に対する毒性について，病理組織学検査で 600 mg/kg 群の雌に，皮質尿細管の拡張および皮質尿細管上皮の空胞変性が観察され，関連する変化として同群の雌に腎臓の相対重量の高値および尿量の増加が認められた。尿比重およびタンパクの低値も認められたが，これらは尿量の増加に伴う二次的な変化と考えられる。雄では腎臓に対する影響は認められなかった。

本被験物質と類似した化学構造を有するジフェニレンジオキシドを 5000 および 10000 ppm 濃度の飼料添加によりラットに 100-117 週間投与した試験で，雌雄の肝臓に肝細胞の脂肪変性および壊死並びに雌の腎臓に尿細管の拡張が認められている [1]。

ジフェニレンオキシドもジフェニレンジオキシドと類似して雌雄の肝臓および雌の腎臓に毒性影響が確認された。

血液に対する影響について，雄は 600 mg/kg 群で血色素量，雌は 40, 150 および 600 mg/kg 群で赤血球数，血色素量およびヘマトクリット値（150 mg/kg 群の赤血球数を除く）のいずれも低値が認められた。

しかしながら，これら貧血所見は雌では 40 mg/kg 群から認められたものの，用量相

関的に増強する傾向は認められず，雌雄とも軽度な変化で，600 mg/kg 群の雄の 1 匹の血色素量並びに 600 mg/kg 群の雌の 1 匹の血色素量およびヘマトクリット値が当研究所の背景データにおける基準値をわずかに下回ったほかは，いずれも基準値（雄の血色素量：13.4～15.5 g/dL，雌の赤血球数：671～800×10^4/μL，雌の血色素量：13.5～15.9 g/dL，およびヘマトクリット値：41.2～47.9%）内の変化であった。また，出血や赤血球破壊亢進並びに造血能低下や貧血に対する反応性の変化など，貧血と関連する変化は認められなかった。

これらの変化は被験物質の投与と関連性があるものと考えられるが，有害性の観点からは，問題とならないごく軽度な影響と判断された。

600 mg/kg 群で認められた雄の体重の低値および雌の尿による下腹部の汚れ並びに 150 mg/kg 群の雄および 600 mg/kg 群の雌雄に認められた自発運動の低下は，被験物質の投与による毒性影響と考えられる。

詳細な臨床観察，感覚反射機能検査，握力，自発運動量，神経系器官の病理組織学検査所見において，神経毒性を示唆する変化は認められなかった。150 mg/kg 以上の群の雌雄に認められた流涎は，投与直後に一過性に認められた変化で，神経毒性などの全身毒性を示す変化とは考え難く，投与液に対する忌避反応を解せられる。また，10 mg/kg 群の雌に認められた握力の低値には用量相関性が認められず，被験物質の投与とは無関係な偶発的変化と判断された。

回復期間中あるいは回復期間終了時においては，これら投与期間中および投与期間終了時に認められた変化のうち，雌の血清アルブミンおよび総コレステロール並びに肝臓相対重量の高値に回復傾向が認められ，またその他の変化はいずれも回復し，ジフェニレンオキシドの毒性は可逆的であることが確認された。

回復期間中あるいは回復期間終了時の検査で雄に認められた血小板数の高値，自発運動量および腎臓相対重量の低値，雌に認められた胸腺の絶対重量並びに脾臓の絶対および相対重量の低値については，投与期間中あるいは投与期間終了時の検査では認められなかった変化であり，ほかに関連する変化も認められなかったことから，被験物質の投与とは無関係な偶発的変化と考えられた。

以上の結果から，ジフェニレンオキシドのラットへの 28 日間反復経口投与において，肝臓および腎臓に対する毒性が認められた。また，血液に対する軽度な影響も認められ

た。無影響量（NOEL）は雄で 10 mg/kg/day，雌で 40 mg/kg/day，並びに無毒性量（NOAEL）は，雌雄とも雌で 40 mg/kg/day と推定された。

文　献

1) EPA working group: Environmental Protection Agency Vol:EPA/600/8-88/026(1987)26p.

ジフェニレンオキシドのラットを用いる28日間反復経口投与毒性試験

(試験番号：05-232)

最終報告書　添付資料B

(個体別表・写真等)

財団法人　畜産生物科学安全研究所

Appendix 1 Test article characterization

被験物質の特性

名　　称　ジフェニレンオキシド（Diphenylene oxide）

別　　称　ジベンゾフラン（Dibenzofuran）

CAS 番号　132-64-9

ロット番号　KNIKD

純　　度　99.9%

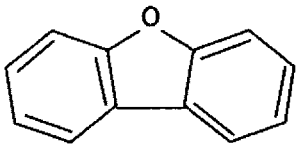
入 手 先　東京化成工業株式会社（東京都中央区日本橋本町 4-10-2）
　　試薬として購入

入手日（量）　平成 18 年 4 月 27 日 (470g)

物 性 等

分子式　$C_{12}H_8O$

構造式



分子量　168.20

性　状　白色結晶及び小塊

融　点　83～86℃

沸　点　287℃

蒸気圧　0.00248mm Hg

オクタノール／水分配係数
　　Log Pow 4.12

溶解性　水に難溶，エタノール，アセトン，エーテルに可溶

溶解度　水に対して 3.1 mg/L(25℃)

保管条件　冷暗所（2～6℃），密栓

安定性

試験期間中の被験物質の安定性を確認するため，試験に用いたジフェニレンオキシド（ロット番号 KNIKD）を試験開始前および投与終了後に分析した。分析は入手先の東京化成工業株式会社に委託して実施した。得られた結果は，次表に示す。

	ジフェニレンオキシド分析値（GC 法）
試験開始前（試薬購入時）	99.9%
投与終了後（平成 19 年 5 月 8 日分析）	99.9%

以上の結果より，ジフェニレンオキシドは試験期間中安定であったことが確認された。

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

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 BA26）を用いてジフェニレンオキシド（ロット番号 KNIKD）の 0.5%及び 20.0%濃度の溶解液を調製し，調製後冷暗所（2～6℃）・密栓下で 3 日および 7 日間，続いてそれぞれ室温暗所・密栓下で 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（%）				変動係数 (%)
		上層	中層	下層	平均値	
0.20	調製直後	0.21	0.22	0.20	0.21	4.8
	4日後	0.20	0.20	0.20	0.20	0
	8日後	0.20	0.20	0.20	0.20	0
20.0	調製直後	21.7	20.9	21.6	21.4	2.1
	4日後	21.2	20.6	19.9	20.6	3.2
	8日後	20.4	20.3	20.0	20.2	1.0

以上の結果から，局方オリブ油に懸濁したジフェニレンオキシドは，冷暗所（2～6℃）・密栓下で 3 日および 7 日間，続いてそれぞれ室温暗所・密栓下で 1 日の保存において，均一，かつ安定であることが確認された。

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

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，初回に調製されたジフェニレンオキシドの局方オリブ油による 0.2（10mg/kg 用量），0.8（40mg/kg 用量），3.0（150mg/kg 用量）および 12%（600mg/kg 用量）液について，それぞれ上，中および下層よりサンプリングし，分析（GC 法）を行った。得られた結果は，次表に示す。

調製濃度	分析値（%）				変動係数
(%)	上層	中層	下層	平均値	(%)
0.2	0.20	0.20	0.19	0.20	2.90
0.8	0.80	0.74	0.78	0.77	4.0
3.0	3.01	2.99	3.00	3.00	0.33
12.0	12.3	11.4	12.4	12.0	4.6

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

Result of temperature and relative humidity at animal room No.4

Permissible level : Temperature ; 22±3℃, Humidity ; 55±10%

Date	Temperature(℃)	Humidity(%)	Note	
2006/7/6	22.3 - 22.6	57 - 58	Arrival of animals	
2006/7/7	22.5 - 22.6	58		
2006/7/8	22.5 - 22.6	57 - 62		
2006/7/9	22.5	58 - 59		
2006/7/10	22.4 - 22.5	58 - 59		
2006/7/11	22.4 - 22.5	58 - 59		
2006/7/12	22.4 - 22.5	59 - 60	Grouping of male	
2006/7/13	22.5 - 22.8	58 - 60	Grouping of female	Start of administration
2006/7/14	22.7 - 23.0	58 - 59		↓
2006/7/15	22.6 - 22.8	57 - 59		↓
2006/7/16	22.5	59 - 60		↓
2006/7/17	22.4 - 22.5	60 - 62		↓
2006/7/18	22.3 - 22.5	59 - 60		↓
2006/7/19	22.4	60		↓
2006/7/20	22.3 - 22.4	60		↓
2006/7/21	22.2 - 22.4	60		↓
2006/7/22	22.4 - 22.5	60 - 62		↓
2006/7/23	22.4 - 22.5	59 - 61		↓
2006/7/24	22.4 - 22.5	59 - 60		↓
2006/7/25	22.4 - 22.5	59 - 61		↓
2006/7/26	22.4 - 22.8	59 - 60		↓
2006/7/27	22.5	60 - 61		↓
2006/7/28	22.4 - 22.7	59		↓
2006/7/29	22.4 - 22.6	59 - 60		↓
2006/7/30	22.5 - 22.6	59 - 61		↓
2006/7/31	22.4 - 22.7	59 - 60		↓
2006/8/1	22.3 - 22.5	59 - 61		↓
2006/8/2	22.4	60 - 61		↓
2006/8/3	22.5 - 23.0	58 - 61		↓
2006/8/4	22.7 - 23.3	55 - 61		↓
2006/8/5	22.6 - 23.2	56 - 60		↓
2006/8/6	22.7 - 23.2	57 - 62		↓
2006/8/7	22.6 - 23.3	55 - 60		↓
2006/8/8	22.4 - 22.9	60		↓
2006/8/9	22.4 - 22.5	60 - 61		↓
2006/8/10	22.5 - 22.7	57 - 61	Necropsy of male[a]	End of administration
2006/8/11	22.4 - 22.6	58	Necropsy of female[a]	

a:At the end of administration period

Appendix 4-2 Environmental conditions of animal room

Result of temperature and relative humidity at animal room No.4

Permissible level : Temperature ; 22±3℃, Humidity ; 55±10%

Date	Temperature(℃)	Humidity(%)	Note
2006/8/12	22.5	57 - 58	
2006/8/13	22.5 - 22.7	57 - 58	
2006/8/14	22.5	57 - 58	
2006/8/15	22.3 - 22.5	58 - 59	
2006/8/16	22.3 - 22.5	59	
2006/8/17	22.4 - 22.6	58 - 59	
2006/8/18	22.5 - 22.8	55 - 58	
2006/8/19	22.6 - 22.9	55 - 60	
2006/8/20	22.5 - 22.7	56 - 58	
2006/8/21	22.6 - 23.5	56 - 58	
2006/8/22	22.3 - 22.5	57 - 59	
2006/8/23	22.5	58	
2006/8/24	22.4 - 22.7	57 - 58	Necropsy of male[b]
2006/8/25	22.2 - 22.4	58 - 59	Necropsy of female[b]

b:At the end of recovery period

分析試験成績書

依頼者　日本農産工業株式会社　殿

東顕食発　第　260604-0041　号
2006年5月24日

2006年4月27日　当センターに依頼された供試品について試験した結果は下記のとおりです。

財団法人 東京顕[redacted]
食と環[redacted]ター
日本橋研究所 東京都[redacted]44-1

試験品名称	ラボMRストック（060453）
表記事項	----------

分析試験結果

(1) ラボMRストック（060453）

試験項目	結果	検出限界	試験法	脚注
アフラトキシンB_1	検出せず	5 ppb	飼料分析基準注解	
アフラトキシンB_2	検出せず	5 ppb	飼料分析基準注解	
アフラトキシンG_1	検出せず	5 ppb	飼料分析基準注解	
アフラトキシンG_2	検出せず	5 ppb	飼料分析基準注解	
ヒ素	0.17 ppm		飼料分析基準注解	
鉛	0.3 ppm		飼料分析基準注解	
カドミウム	0.08 ppm		飼料分析基準注解	
クロム	0.6 ppm		飼料分析基準注解	
総水銀	検出せず	0.01 ppm	飼料分析基準注解	
PCB	検出せず	0.01 ppm	飼料分析基準注解	
総BHC	検出せず	0.05 ppm	飼料分析基準注解	
パラチオン	検出せず	0.05 ppm	飼料分析基準注解	
マラチオン	0.18 ppm		飼料分析基準注解	
総DDT	検出せず	0.05 ppm	ECD－ガスクロマトグラフ法	
ヘプタクロル	検出せず	0.01 ppm	ECD－ガスクロマトグラフ法	
ディルドリン	検出せず	0.01 ppm	ECD－ガスクロマトグラフ法	
アルドリン	検出せず	0.01 ppm	ECD－ガスクロマトグラフ法	
N－ニトロソジエチルアミン	検出せず	10 ppb	TEA－ガスクロマトグラフ法	
N－ニトロソジメチルアミン	検出せず	10 ppb	TEA－ガスクロマトグラフ法	

NOSAN

報告書No. 06－10995
2006年5月2日

バイオ部 バイオ第1G　御中

日本農産工業株式[redacted]
研究開発セ[redacted]
安全QCステー[redacted]

検査報告書

受付年月日	2006年4月27日
依頼事業所	バイオ部
担当部署	バイオ第1G
担当者氏名	[redacted]
検査名	サルモネラ分離検査、細菌検査、真菌数
検体内容	製品 ラボMRストック(Lot. 060453)

以上の検体の検査結果をご報告します。

検体名	一般生菌数 (CFU/g)	大腸菌群	サルモネラ	真菌数 (CFU/g)
ラボMRストック	8.2×10^{3}	－	－	<20

＋:陽性　－:陰性　NT:検査せず

以上

分析試験成績書

東顕食発　第　260606-0018　号
2006年7月13日

依頼者　日本農産工業株式会社　殿

2006年6月21日　当センターに依頼された供試品について試験した結果は下記のとおりです。

財団法人 東京顕[redacted]
食と環[redacted]
日本橋研究所 東京都中[redacted]4-1

試験品名称	ラボMRストック（060659）
表記事項	――――――――――――――――――――――――――――――――

分析試験結果

(1) ラボMRストック（060659）

試験項目	結果	検出限界	試験法	脚注
アフラトキシンB_1	検出せず	5 ppb	飼料分析基準注解	
アフラトキシンB_2	検出せず	5 ppb	飼料分析基準注解	
アフラトキシンG_1	検出せず	5 ppb	飼料分析基準注解	
アフラトキシンG_2	検出せず	5 ppb	飼料分析基準注解	
ヒ素	0.16 ppm	0.01 ppm	飼料分析基準注解	
鉛	0.2 ppm	0.1 ppm	飼料分析基準注解	
カドミウム	0.11 ppm	0.01 ppm	飼料分析基準注解	
クロム	0.8 ppm	0.1 ppm	飼料分析基準注解	
総水銀	検出せず	0.01 ppm	飼料分析基準注解	
PCB	検出せず	0.01 ppm	飼料分析基準注解	
総BHC	検出せず	0.05 ppm	飼料分析基準注解	
パラチオン	検出せず	0.05 ppm	飼料分析基準注解	
マラチオン	0.38 ppm	0.05 ppm	飼料分析基準注解	
総DDT	検出せず	0.05 ppm	ECD－ガスクロマトグラフ法	
ヘプタクロル	検出せず	0.01 ppm	ECD－ガスクロマトグラフ法	
ディルドリン	検出せず	0.01 ppm	ECD－ガスクロマトグラフ法	
アルドリン	検出せず	0.01 ppm	ECD－ガスクロマトグラフ法	
N－ニトロソジエチルアミン	検出せず	10 ppb	TEA－ガスクロマトグラフ法	
N－ニトロソジメチルアミン	検出せず	10 ppb	TEA－ガスクロマトグラフ法	

NOSAN

報告書No. 06－11413
2006年6月19日

バイオ部 バイオ第1G　御中

日本農産工業株式会社
研究開発[redacted]
安全QCステ[redacted]

検査報告書

受付年月日	2006年6月12日
依頼事業所	バイオ部
担当部署	バイオ第1G
担当者氏名	[redacted]
検査名	サルモネラ分離検査、細菌検査、真菌数
検体内容	製品 ラボMRストック(Lot. 060659)

以上の検体の検査結果をご報告します。

検体名	一般生菌数 (CFU/g)	大腸菌群	サルモネラ	真菌数 (CFU/g)
ラボMRストック	1.4×10^{4}	－	－	＜20

＋:陽性　－:陰性　NT:検査せず

以上

Appendix 6　飲料水の水質検査

No. D－060529

水質試験検査成績書

平成１８年　８月２２日

財団法人　畜産生物科学安全研究所　殿

東京テクニ[redacted]ス株式会社
東京都江戸川[redacted]２０－２０
ＴＥＬ　[redacted]）３２８４

水道法第20条[redacted]検査機関
登録番号 [redacted]

登録建築物飲料水水質検査業
東京都５６水第３２７号

検査責任者 [redacted]

採水担当者 [redacted]

検　体	飲料水
採水場所	クリーンルーム
採取日時	平成18年 7月31日　10：30
試験目的	水道法水質基準値適否 （ 15項目＋消毒副生物11項目 ）

No.	分析項目	単位	分析結果	基準値
1	一般細菌	個/1mℓ	0	100 以下/1mℓ
2	大腸菌	－	陰性（不検出）	検出されないこと
3	硝酸態窒素及び亜硝酸態窒素	mg/ℓ	1.2	10 以下
4	塩化物イオン	mg/ℓ	7.8	200 以下
5	有機物（全有機炭素（TOC）の量）	mg/ℓ	0.5	5 以下
6	ｐＨ値	－	7.6	5.8～8.6
7	味	－	異常なし	異常でないこと
8	臭気	－	異常なし	異常でないこと
9	色度	度	1　未満	5 以下
10	濁度	度	1　未満	2 以下
11	鉛及びその化合物	mg/ℓ	0.001 未満	0.01 以下
12	亜鉛及びその化合物	mg/ℓ	0.1　未満	1.0 以下
13	鉄及びその化合物	mg/ℓ	0.03　未満	0.3 以下
14	銅及びその化合物	mg/ℓ	0.1　未満	1.0 以下
15	蒸発残留物	mg/ℓ	130	500 以下
16	クロロホルム	mg/ℓ	0.0096	0.06 以下
17	ブロモジクロロメタン	mg/ℓ	0.0039	0.03 以下
18	ジブロモクロロメタン	mg/ℓ	0.003	0.1 以下
19	ブロモホルム	mg/ℓ	0.011	0.09 以下
20	総トリハロメタン	mg/ℓ	0.027	0.1 以下
21	シアン化合物及び塩化シアン	mg/ℓ	0.001 未満	0.01 以下
22	臭素酸	mg/ℓ	0.001 未満	0.01 以下
23	クロロ酢酸	mg/ℓ	0.002 未満	0.02 以下
24	ジクロロ酢酸	mg/ℓ	0.004	0.04 以下
25	トリクロロ酢酸	mg/ℓ	0.02　未満	0.2 以下
26	ホルムアルデヒド	mg/ℓ	0.008 未満	0.08 以下
			以下余白	

分析方法：水道水質基準に関する省令（平成15年厚生労働省令第101号）に基づく検査法

判定：上記の試験項目について水道法水質基準に適合しています。

Appendix 7 Scoring lists for clinical signs in datailed observation in the FOB (Functional Observtion Batteries) of rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

Reactivity on removal from the cage	1: Normal (easy); 2: Slightly difficult; 3: Difficult; 4: Almost impossible; 5: Impossible for aggression
Reactivity on handling	1: Normal(easy for handling); 2: Slightly hard as resistance; 3: Hard as resistance; 4: Fairly hard as escape; 5: Impossible for handling
Muscle tone	1: Atonic; 2: Slightly atonic; 3: Normal; 4: Slightly rigid; 5: Rigid
Skin	1: Normal; 2: Slightly flush; 3: Flush; 4: Discoloration; 5: Pale
Fur	1: Normal; 2: Slightly poor; 3: moderately poor; 4: severely poor
Piloerection	1: Not detected; 2: Around head; 3: Around head and back; 4: Almost whole body; 5: Whole body
Eye discharge	1: Not detected; 2: Slight; 3: Moderate; 4: Severe; 5: Almost closing eye
Palpebral closure	1: Not detected; 2: 1/4; 3: 1/2; 4: 3/4; 4: Closure
Exophthalmos	1: Not detected; 2: Very slight; 3: Slight; 4: Moderate; 5: Severe
Lacrimation	1: Not detected; 2: Slightly moisture around eye; 3: Moisture; 4: Fairly moisture; 5: Lacrimation
Smudge around mouth-nose	1: Not detected; 2: Slight; 3: Moderate; 4: Severe
Salivation	1: Not detected; 2: Slightly moisture around mouth; 3: Moisture; 4: Fairly moisture; 5: Salivation
Blotted fur in the lower abdomen with urine	1: Not detected; 2: Slight; 3: Moderate; 4: Severe
Blotted fur around anus with feces	1: Not detected; 2: Slight; 3: Moderate; 4: Severe
Vocalization	1: Not detected; 2: Temporal in handling; 3: Slightly continuous; 4: Almost continuous; 5: Absolutely continuous
Breathing	1: Normal; 2: Slight panting; 3: Moderate panting; 4: Severe panting with opened mouth; 5: Endeavor breathing
Body position	1: Normal; 2: Reluctance; 3: Lateral position; 4: Prone position; 5: Supine position
Convulsion	1: Not detected; 2: Intermittent; 3: Slightly continuous; 4: Almost continuous; 5: Absolutely continuous
Tremor	1: Not detected; 2: Intermittent; 3: Slightly continuous; 4: Almost continuous; 5: Absolutely continuous
Exploration	1: Not detected; 2: Slight; 3: Normal; 4: Moderate; 5: Frequent
Alertness	1: No alertness to falling from edge; 2: Slight alertness as nearly as falling; 3: Normal; 4: Slightly hypersensitive; 5: Hypersensitive on the edge
Locomotor activity	1: Decreased; 2: Slightly decreased; 3: Normal; 4: Slightly increased; 5:Increased
Walk	1: Normal; 2: Slightly reeling gait; 3: Reeling gait
Abnormal behavior	1: Not detected; 2: Slightly repeated; 3: Repeated; 4: Fairly repeated; 5: Frequently repeated
Stereotypy	1: Not detected; 2: Rarely; 3: Sometimes; 4: Frequently
Failure of consciousness	1: Not detected; 2: Stupor; 3: Catalepsy; 4: Coma
Limb tone	1: Normal tone; 2: Weak tone; 3: Lacking tone; 4: No response for slackness
Urination	Frequency, color
Defecation	Frequency, appearance

Appendix 8 Scoring lists for sensory/reflex function tests of rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

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 diphenylene oxide 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
10	011	KA	29	NAD
	012	KA	29	NAD
	013	KA	29	NAD
	014	KA	29	NAD
	015	KA	29	NAD
40	016	KA	29	NAD
	017	KA	29	NAD
	018	KA	29	NAD
	019	KA	29	NAD
	020	KA	29	NAD
150	021	KA	29	Decrease in locomotor activity : + (1)[b] Salivation : + (11-28)[b]
	022	KA	29	Salivation : + (24)[b]
	023	KA	29	Salivation : + (16,23,27-28)[b]
	024	KA	29	Salivation : + (7-8,11-28)[b]
	025	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.
b : Experimental day when the sign was observed.
NAD : No abnormalities were detected.

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

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
600	026	KA	29	Decrease in locomotor activity : + (1-2)[b] Salivation : + (7-28)[b]
	027	KA	29	Decrease in locomotor activity : + (1-2)[b] Salivation : + (3-5,7-28)[b]
	028	KA	29	Decrease in locomotor activity : + (1-2)[b] Salivation : + (2,4-28)[b]
	029	KA	29	Decrease in locomotor activity : + (1)[b] Salivation : + (1-2,6-28)[b]
	030	KA	29	Decrease in locomotor activity : + (1-2)[b] Salivation : + (4-5,7-19,21-28)[b]
	031	KR	43	Decrease in locomotor activity : + (1)[b] Salivation : + (1-2,4-28)[b]
	032	KR	43	Decrease in locomotor activity : + (1-2)[b] Salivation : + (1-2,4-5,7,9-28)[b]
	033	KR	43	Decrease in locomotor activity : + (1-2)[b] Salivation : + (2,4-28)[b]
	034	KR	43	Decrease in locomotor activity : + (1)[b] Salivation : + (1-2,4-23,25-28)[b]
	035	KR	43	Decrease in locomotor activity : + (1)[b] Salivation : + (1-2,4-28)[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 10-1 Individual general conditions of female rats treated with diphenylene oxide 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
10	511	KA	29	NAD
	512	KA	29	NAD
	513	KA	29	NAD
	514	KA	29	NAD
	515	KA	29	NAD
40	516	KA	29	NAD
	517	KA	29	NAD
	518	KA	29	NAD
	519	KA	29	NAD
	520	KA	29	NAD
150	521	KA	29	Salivation : + (6-27)[b]
	522	KA	29	Salivation : + (10,14,17-18,25-26)[b]
	523	KA	29	Salivation : + (11-16,18-21,23-27)[b]
	524	KA	29	Salivation : + (19)[b]
	525	KA	29	Salivation : + (6,10-15,18,20-21,23-24,26-28)[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.
NAD : No abnormalities were detected.
+ : Slight.

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

Dose (mg/kg/day)	Animal number	Fate	Day of death [a]	General conditions (clinical signs)
600	526	KA	29	Decrease in locomotor activity : + (1-2)[b]
				Salivation : + (3-21,23-28)[b]
	527	KA	29	Decrease in locomotor activity : + (1)[b]
				Salivation : + (3-28)[b]
				Soiled perineal region with urine : + (10-28)[b]
	528	KA	29	Decrease in locomotor activity : + (1)[b]
				Salivation : + (3-28)[b]
	529	KA	29	Decrease in locomotor activity : + (1)[b]
				Salivation : + (3-4,6-28)[b]
	530	KA	29	Salivation : + (6-28)[b]
				Soiled perineal region with urine : + (9-16)[b]
	531	KR	43	Salivation : + (10,12-15,18,20-28)[b]
	532	KR	43	Decrease in locomotor activity : + (1)[b]
				Salivation : + (4-28)[b]
	533	KR	43	Decrease in locomotor activity : + (1)[b]
				Salivation : + (1-4,6-28)[b]
	534	KR	43	Salivation : + (5-28)[b]
				Soiled perineal region with urine : + (9-23)[b]
	535	KR	43	Salivation : + (6-28)[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.
NAD : No abnormalities were detected.
+ : Slight.

Appendix 11-1 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 Before the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		1	1	1	1	1	1	1	1	1	1
Salivetion		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	1	0	0	0	1	1	0	0
	: tone of color	-	-	PY	-	-	-	PY	PY	-	-
Defecation	: count	0	0	1	0	0	1	1	0	0	0
	: appearance	-	-	N	-	-	N	N	-	-	-

PY : Pale yellow; N : Negative

Criterions for scoring are shown in appendix 7.

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

〈 Before the the administration period 〉

Items	Dose(mg/kg/day) / Animal number	10					40					150				
		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 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
Exphthalmos		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
Smudge around mouth-nose		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivetion		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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	1	0	1	0	1	0	1	0	1	0	0	0	1	0	1
	: tone of color	PY	-	PY	-	PY	-	PY	-	PY	-	-	-	PY	-	PY
Defecation	: count	1	0	1	0	0	0	0	0	1	1	0	0	0	0	1
	: appearance	N	-	N	-	-	-	-	-	N	N	-	-	-	-	N

PY : Pale yellow; N : Negative

Criterions for scoring are shown in appendix 7.

Appendix 11-3 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 Before the the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		1	1	1	1	1	1	1	1	1	1
Salivetion		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	2	0	1	2	0	1	1	0	0	0
	: tone of color	PY	-	PY	PY	-	PY	PY	-	-	-
Defecation	: count	3	2	1	1	0	0	2	2	0	0
	: appearance	N	N	N	N	-	-	N	N	-	-

PY : Pale yellow; N : Negative

Criterions for scoring are shown in appendix 7.

Appendix 11-4 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 1 of the the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	1	0	0	0	0
	: tone of color	-	-	-	-	-	PY	-	-	-	-
Defecation	: count	0	0	1	0	0	3	0	0	0	0
	: appearance	-	-	N	-	-	N	-	-	-	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 11-5 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 1 of the the administration period 〉

Items	Dose(mg/kg/day)	10					40					150				
	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 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
Exphthalmos		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
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	1	1	1	0	1	0	0	0	0	1	0	0	0	0	1
	: tone of color	PY	PY	PY	-	PY	-	-	-	-	PY	-	-	-	-	PY
Defecation	: count	0	0	0	0	1	0	0	0	0	0	0	0	0	0	2
	: appearance	-	-	-	-	N	-	-	-	-	-	-	-	-	-	N

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 11-6 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 1 of the the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	1	1	0	1	0	0	0	0	1	0
	: tone of color	PY	PY	-	PY	-	-	-	-	PY	-
Defecation	: count	0	2	0	0	0	0	0	0	0	0
	: appearance	-	N	-	-	-	-	-	-	-	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 11-7 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	1	0	0	0	0
	: tone of color	-	-	-	-	-	PY	-	-	-	-
Defecation	: count	0	0	1	0	0	2	0	0	0	0
	: appearance	-	-	N	-	-	N	-	-	-	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 11-8 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the administration period 〉

Items	Dose(mg/kg/day)	10					40					150				
	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 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
Exphthalmos		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
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0
	: tone of color	PY	-	-	-	PY	-	-	PY	-	-	-	-	-	-	-
Defecation	: count	2	0	0	0	3	0	0	0	2	0	0	0	0	0	1
	: appearance	N	-	-	-	N	-	-	-	N	-	-	-	-	-	N

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 11-9 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	1	0	0	0	0	0	0	1	0
	: tone of color	-	PY	-	-	-	-	-	-	PY	-
Defecation	: count	2	2	0	0	0	0	0	0	0	0
	: appearance	N	N	-	-	-	-	-	-	-	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 11-10 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 3 of the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	0	0	0	0	0
	: tone of color	-	-	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	1	0	0	0	0
	: appearance	-	-	-	-	-	N	-	-	-	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 11-11 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 3 of the administration period 〉

Items	Dose(mg/kg/day)	10					40					150				
	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 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
Exphthalmos		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
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	1	0	0	0	0	0	0	0	1	0	1	0	0	1	1
	: tone of color	PY	-	-	-	-	-	-	-	PY	-	PY	-	-	PY	PY
Defecation	: count	0	0	0	0	2	0	0	0	0	0	0	0	0	0	1
	: appearance	-	-	-	-	N	-	-	-	-	-	-	-	-	-	N

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 11-12 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 3 of the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	2	1	0	0	0	0	0
	: tone of color	-	-	-	PY	PY	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 11-13 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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	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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	1	0	0	0	0	0	0	0	0
	: tone of color	-	PY	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 11-14 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the administration period 〉

Items	Dose(mg/kg/day)	10					40					150				
	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 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
Exphthalmos		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
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	0	1	0	0	0	0	2	0	0	0	0	0	0	0	0
	: tone of color	-	PY	-	-	-	-	PY	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 11-15 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	1	0	0	0	0	0	0
	: tone of color	-	-	-	PY	-	-	-	-	-	-
Defecation	: count	1	0	0	0	0	0	0	0	0	0
	: appearance	N	-	-	-	-	-	-	-	-	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 11-16 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 1 of the recovery period 〉

Items	Dose(mg/kg/day) / Animal number	0					600				
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	0	0	0	0	0
	: tone of color	-	-	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 11-17 Individual clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the recovery period 〉

Items	Dose(mg/kg/day) / Animal number	0					600				
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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	2	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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	1	1	0	0	0	0	1	0	0
	: tone of color	-	PY	PY	-	-	-	-	PY	-	-
Defecation	: count	1	0	0	0	0	0	0	0	0	0
	: appearance	N	-	-	-	-	-	-	-	-	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 12-1 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 Before the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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	2	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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	1	0	0	0	0	0	0	0	0
	: tone of color	-	PY	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	1
	: appearance	-	-	-	-	-	-	-	-	-	N

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

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

〈 Before the administration period 〉

Items	Dose(mg/kg/day) / Animal number	10					40					150				
		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 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
Exphthalmos		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
Smudge around mouth-nose		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		2	1	1	1	1	2	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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	1	0	0	0	1	0	0	0	0	0	1	0	1
	: tone of color	-	-	PY	-	-	-	PY	-	-	-	-	-	PY	-	PY
Defecation	: count	0	0	2	0	0	0	1	0	0	0	0	0	0	0	0
	: appearance	-	-	N	-	-	-	N	-	-	-	-	-	-	-	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 12-3 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 Before the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	1	0	1	0	0
	: tone of color	-	-	-	-	-	PY	-	PY	-	-
Defecation	: count	0	0	0	0	3	1	0	2	1	0
	: appearance	-	-	-	-	N	N	-	N	N	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 12-4 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

(On week 1 of the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	1	0	0	0	0
	: tone of color	-	-	-	-	-	PY	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 12-5 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 1 of the administration period 〉

Items	Dose(mg/kg/day)	10					40					150				
	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 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
Exphthalmos		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
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0
	: tone of color	-	-	PY	-	-	-	-	-	-	-	PY	-	-	-	-
Defecation	: count	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	N	-	-	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow; N : Normal.

Criterions for scoring are shown in appendix 7.

Appendix 12-6 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 1 of the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		1	1	1	1	1	1	1	1	1	1
Salivation		1	1	2	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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	2	1	0	0	1	0	0	0	0
	: tone of color	-	PY	PY	-	-	PY	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 12-7 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	0	0	0	0	0
	: tone of color	-	-	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

Criterions for scoring are shown in appendix 7.

Appendix 12-8 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the administration period 〉

Items	Dose(mg/kg/day) / Animal number	10					40					150				
		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 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
Exphthalmos		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
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: tone of color	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Criterions for scoring are shown in appendix 7.

Appendix 12-9 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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	2	1	1	2	1	1	1	2	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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	1	0	0	1	0
	: tone of color	-	-	-	-	-	PY	-	-	PY	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 12-10 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 3 of the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	0	0	0	0	0
	: tone of color	-	-	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

Criterions for scoring are shown in appendix 7.

Appendix 12-11 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 3 of the administration period 〉

Items	Dose(mg/kg/day)	10					40					150				
	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 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
Exphthalmos		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
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: tone of color	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Criterions for scoring are shown in appendix 7.

Appendix 12-12 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 3 of the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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	2	1	1	1	1	1	1	2	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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	0	0	0	0	0
	: tone of color	-	-	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

Criterions for scoring are shown in appendix 7.

Appendix 12-13 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the 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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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	2	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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	1	0	0	0	0	0	0	0	0
	: tone of color	-	PY	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 12-14 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the administration period 〉

Items	Dose(mg/kg/day)	10					40					150				
	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 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
Exphthalmos		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
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	: tone of color	-	-	PY	-	-	-	-	-	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 12-15 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the administration period 〉

Items	Dose(mg/kg/day) / Animal number	600									
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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	2	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	2	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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	1	1	0	0	0	0	0	0	0
	: tone of color	-	PY	PY	-	-	-	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 12-16 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 1 of the recovery period 〉

Items	Dose(mg/kg/day) / Animal number	0					600				
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	0	0	0	1	0	0	0	0
	: tone of color	-	-	-	-	-	PY	-	-	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

Appendix 12-17 Individual clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the recovery period 〉

Items	Dose(mg/kg/day) / Animal number	0					600				
		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 discharge		1	1	1	1	1	1	1	1	1	1
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Exphthalmos		1	1	1	1	1	1	1	1	1	1
Lacrimation		1	1	1	1	1	1	1	1	1	1
Smudge around mouth-nose		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
Alertness		3	3	3	3	3	3	3	3	3	3
Locomotor activity		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
Failure of consciousness		1	1	1	1	1	1	1	1	1	1
Limb tone		1	1	1	1	1	1	1	1	1	1
Urination	: count	0	0	1	0	0	1	0	1	0	0
	: tone of color	-	-	PY	-	-	PY	-	PY	-	-
Defecation	: count	0	0	0	0	0	0	0	0	0	0
	: appearance	-	-	-	-	-	-	-	-	-	-

PY : Pale yellow.

Criterions for scoring are shown in appendix 7.

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

〈 On week 4 of the 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
10	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
40	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
150	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
600	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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the recovery 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
600	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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the 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
10	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
40	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
150	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
600	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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the recovery 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
600	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 diphenylene oxide 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) $0\sim60_{min.}$
0	001	772	513	7655
	002	585	553	11818
	003	514	280	11920
	004	627	212	8296
	005	581	385	13090
	Mean	616	389	10556
10	011	521	236	17220
	012	376	194	11607
	013	312	311	16801
	014	611	321	15823
	015	803	361	11460
	Mean	525	285	14582
40	016	718	393	11958
	017	597	427	7492
	018	445	304	12826
	019	608	314	15395
	020	637	479	15898
	Mean	601	383	12714
150	021	585	297	10207
	022	581	319	16171
	023	491	331	12745
	024	467	379	10069
	025	724	463	11728
	Mean	570	358	12184
600	026	394	233	11460
	027	602	276	6752
	028	366	314	12404
	029	514	299	10984
	030	625	352	7657
	Mean	500	295	9851

Appendix 15-2 Individual grip strength and motor activity data of male rats treated with diphenylene oxide 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	738	316	15361
	007	611	279	16640
	008	714	402	9519
	009	696	421	13676
	010	585	466	9259
	Mean	669	377	12891
600	031	630	369	6288
	032	749	495	6933
	033	684	508	10842
	034	569	393	6628
	035	712	572	10566
	Mean	669	467	8251

Appendix 16-1 Individual grip strength and motor activity data of female rats treated with diphenylene oxide 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	556	295	17171
	502	680	307	20280
	503	429	249	13246
	504	689	257	14787
	505	479	328	13380
	Mean	567	287	15773
10	511	444	326	10637
	512	397	331	14624
	513	350	243	11720
	514	316	254	11577
	515	281	222	12899
	Mean	358	275	12291
40	516	527	347	9998
	517	347	261	17920
	518	579	402	18178
	519	371	287	8878
	520	495	300	15983
	Mean	464	319	14191
150	521	362	216	9836
	522	509	223	10587
	523	453	234	16563
	524	539	334	12893
	525	537	318	11120
	Mean	480	265	12200
600	526	461	278	16442
	527	526	218	13535
	528	566	373	5044
	529	382	233	9909
	530	500	292	9080
	Mean	487	279	10802

Appendix 16-2 Individual grip strength and motor activity data of female rats treated with diphenylene oxide 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	506	672	305	17526
	507	654	377	13071
	508	678	396	16743
	509	663	421	16475
	510	704	373	8033
	Mean	674	374	14370
600	531	475	357	11961
	532	606	327	12315
	533	628	299	16966
	534	786	339	15119
	535	667	314	16602
	Mean	632	327	14593

Appendix 17 Individual body weight of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

(g)

Dose (mg/kg/day)	Animal number	Day	Day of the administration period 1	7	14	21	28	Gain 1~28	Day of the recovery period 0	7	14	Gain 0~14
0	001		153	195	248	303	345	192	--	--	--	--
	002		158	203	257	310	340	182	--	--	--	--
	003		161	215	258	301	329	168	--	--	--	--
	004		167	217	267	311	339	172	--	--	--	--
	005		170	236	304	374	422	252	--	--	--	--
	006		156	210	271	311	347	191	347	367	380	33
	007		161	218	288	364	413	252	413	460	473	60
	008		163	215	265	304	334	171	334	371	376	42
	009		163	215	271	320	365	202	365	394	411	46
	010		171	236	314	385	447	276	447	493	520	73
	Mean		162	216	274	328	368	206	381	417	432	51
10	011		156	202	247	292	331	175	--	--	--	--
	012		159	217	289	354	398	239	--	--	--	--
	013		164	221	284	348	391	227	--	--	--	--
	014		164	213	266	315	343	179	--	--	--	--
	015		172	220	263	306	354	182	--	--	--	--
	Mean		163	215	270	323	363	200	--	--	--	--
40	016		154	215	280	345	386	232	--	--	--	--
	017		160	200	257	320	367	207	--	--	--	--
	018		165	219	293	366	406	241	--	--	--	--
	019		162	214	268	326	359	197	--	--	--	--
	020		168	227	288	339	376	208	--	--	--	--
	Mean		162	215	277	339	379	217	--	--	--	--
150	021		161	226	300	363	414	253	--	--	--	--
	022		160	216	276	325	363	203	--	--	--	--
	023		163	209	261	315	350	187	--	--	--	--
	024		162	209	260	302	327	165	--	--	--	--
	025		165	211	251	293	319	154	--	--	--	--
	Mean		162	214	270	320	355	192	--	--	--	--
600	026		153	201	262	322	359	206	--	--	--	--
	027		158	188	239	275	294	136	--	--	--	--
	028		162	200	261	313	338	176	--	--	--	--
	029		167	202	256	315	346	179	--	--	--	--
	030		169	202	255	312	338	169	--	--	--	--
	031		161	200	266	334	396	235	396	452	468	72
	032		156	188	236	279	329	173	329	386	411	82
	033		166	205	251	293	326	160	326	360	393	67
	034		166	202	254	290	319	153	319	365	397	78
	035		169	220	290	352	399	230	399	425	450	51
	Mean		163	201	257	309	344	182	354	398	424	70

Appendix 18 Individual body weight of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

(g)

Dose (mg/kg/day)	Animal number	Day	Day of the administration period 1	7	14	21	28	Gain 1~28	Day of the recovery period 0	7	14	Gain 0~14
0	501		128	147	162	174	197	69	--	--	--	--
	502		132	158	169	195	212	80	--	--	--	--
	503		138	165	191	210	223	85	--	--	--	--
	504		140	150	167	191	204	64	--	--	--	--
	505		146	168	182	218	241	95	--	--	--	--
	506		128	148	164	180	191	63	191	206	215	24
	507		129	151	164	179	189	60	189	215	231	42
	508		138	159	180	208	230	92	230	247	254	24
	509		141	162	179	210	217	76	217	238	247	30
	510		146	170	193	212	237	91	237	259	265	28
	Mean		137	158	175	198	214	78	213	233	242	30
10	511		132	154	176	187	205	73	--	--	--	--
	512		134	162	184	196	222	88	--	--	--	--
	513		134	166	187	204	232	98	--	--	--	--
	514		139	165	182	209	227	88	--	--	--	--
	515		148	171	185	217	236	88	--	--	--	--
	Mean		137	164	183	203	224	87	--	--	--	--
40	516		131	150	174	190	198	67	--	--	--	--
	517		138	167	182	202	217	79	--	--	--	--
	518		138	164	185	220	245	107	--	--	--	--
	519		140	166	185	200	219	79	--	--	--	--
	520		147	168	189	214	230	83	--	--	--	--
	Mean		139	163	183	205	222	83	--	--	--	--
150	521		134	153	177	198	205	71	--	--	--	--
	522		137	158	175	199	208	71	--	--	--	--
	523		136	160	182	209	216	80	--	--	--	--
	524		141	166	192	216	229	88	--	--	--	--
	525		145	169	185	214	234	89	--	--	--	--
	Mean		139	161	182	207	218	80	--	--	--	--
600	526		128	153	173	199	212	84	--	--	--	--
	527		134	150	174	199	214	80	--	--	--	--
	528		136	158	191	219	227	91	--	--	--	--
	529		135	163	181	198	220	85	--	--	--	--
	530		141	160	194	219	232	91	--	--	--	--
	531		123	146	168	181	206	83	206	218	223	17
	532		134	147	162	175	185	51	185	200	210	25
	533		138	153	185	203	212	74	212	222	239	27
	534		140	156	178	198	205	65	205	224	237	32
	535		139	159	195	209	236	97	236	257	268	32
	Mean		135	155	180	200	215	80	209	224	235	27

Appendix 19 Individual food consumption of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

(g/rat/day)

Dose (mg/kg/day)	Animal number	Week of the administration period 1	2	3	4	Week of the recovery period 1	2
0	001	24	26	26	28	--	--
	002	27	31	33	30	--	--
	003	28	29	30	29	--	--
	004	30	29	28	25	--	--
	005	35	35	36	42	--	--
	006	28	29	32	26	32	37
	007	29	33	35	33	34	41
	008	28	31	30	28	34	43
	009	28	29	31	31	34	34
	010	36	38	41	39	43	46
	Mean	29	31	32	31	35	40
10	011	26	24	25	21	--	--
	012	30	31	36	34	--	--
	013	29	32	34	34	--	--
	014	24	26	29	24	--	--
	015	32	28	31	29	--	--
	Mean	28	28	31	28	--	--
40	016	30	32	34	33	--	--
	017	26	28	29	30	--	--
	018	32	37	40	32	--	--
	019	28	29	32	28	--	--
	020	31	32	33	32	--	--
	Mean	29	32	34	31	--	--
150	021	30	31	38	37	--	--
	022	29	29	32	37	--	--
	023	28	30	33	32	--	--
	024	29	28	26	25	--	--
	025	31	29	30	30	--	--
	Mean	29	29	32	32	--	--
600	026	26	32	33	35	--	--
	027	23	35	31	33	--	--
	028	27	37	33	31	--	--
	029	30	31	32	31	--	--
	030	28	29	35	35	--	--
	031	30	32	37	37	43	41
	032	22	24	29	27	36	40
	033	29	28	27	26	27	29
	034	28	29	32	34	38	39
	035	33	38	43	40	38	44
	Mean	28	32	33	33	36	39

Appendix 20 Individual food consumption of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

(g/rat/day)

Dose (mg/kg/day)	Animal number	Week of the administration period 1	2	3	4	Week of the recovery period 1	2
0	501	14	18	21	24	--	--
	502	19	21	20	16	--	--
	503	20	20	21	21	--	--
	504	29	24	22	24	--	--
	505	19	20	23	17	--	--
	506	15	17	18	19	22	19
	507	19	21	16	21	21	27
	508	19	21	21	19	22	25
	509	20	21	19	18	25	24
	510	19	20	21	24	24	27
	Mean	19	20	20	20	23	24
10	511	19	18	18	21	--	--
	512	16	20	22	17	--	--
	513	20	23	22	22	--	--
	514	22	20	22	24	--	--
	515	22	21	25	17	--	--
	Mean	20	20	22	20	--	--
40	516	21	14	16	23	--	--
	517	22	21	20	19	--	--
	518	25	21	25	20	--	--
	519	21	21	21	20	--	--
	520	22	22	21	17	--	--
	Mean	22	20	21	20	--	--
150	521	21	20	17	20	--	--
	522	22	21	21	16	--	--
	523	19	18	21	22	--	--
	524	24	25	23	25	--	--
	525	23	24	25	17	--	--
	Mean	22	22	21	20	--	--
600	526	19	17	20	22	--	--
	527	18	21	25	25	--	--
	528	19	22	25	24	--	--
	529	21	23	24	25	--	--
	530	21	19	20	26	--	--
	531	15	18	19	23	17	25
	532	18	16	19	18	25	19
	533	22	21	21	23	28	28
	534	23	23	24	21	27	17
	535	27	22	25	22	30	33
	Mean	20	20	22	23	25	24

Appendix 21-1 Individual urinary findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 4 of the administration period >

Dose (mg/kg/day)	Animal number	Color	Cloudy	Volume (mL/18hr)	Specific gravity	pH	Protein	Glucose	Ketone body	Occult blood	Urobilinogen	Bilirubin
0	001	PY	−	10.0	1.046	8.5	±	−	−	−	0.1	−
	002	PY	−	3.0	1.080	8.5	1+	−	−	−	0.1	−
	003	PY	−	6.1	1.060	8.5	1+	−	−	−	0.1	−
	004	PY	−	9.8	1.054	8.5	1+	−	−	−	0.1	−
	005	PY	−	4.8	1.076	8.5	1+	−	−	−	0.1	−
10	011	PY	−	8.1	1.062	8.0	±	−	−	−	0.1	−
	012	PY	−	4.4	1.060	8.0	1+	−	−	−	0.1	−
	013	PY	−	10.4	1.054	8.0	1+	−	−	−	0.1	−
	014	PY	−	7.3	1.060	8.5	1+	−	−	−	0.1	−
	015	PY	−	10.3	1.046	8.0	±	−	−	−	0.1	−
40	016	PY	−	6.0	1.064	8.5	1+	−	−	−	0.1	−
	017	PY	−	9.4	1.054	8.0	1+	−	−	−	0.1	−
	018	PY	−	8.6	1.060	8.0	1+	−	−	−	0.1	−
	019	PY	−	9.4	1.054	8.5	1+	−	−	−	0.1	−
	020	PY	−	13.0	1.042	8.0	1+	−	−	−	0.1	−
150	021	PY	−	11.6	1.058	8.5	1+	−	−	−	0.1	−
	022	PY	−	14.0	1.038	8.5	±	−	−	−	0.1	−
	023	PY	−	11.2	1.054	8.0	1+	−	−	−	0.1	−
	024	PY	−	10.0	1.052	8.5	±	−	−	−	0.1	−
	025	PY	−	8.7	1.052	8.0	1+	−	−	−	0.1	−
600	021	PY	−	12.0	1.054	8.5	±	−	−	−	0.1	−
	022	PY	−	6.2	1.060	8.5	±	−	−	−	0.1	−
	023	PY	−	9.9	1.058	8.0	1+	−	−	−	0.1	−
	024	PY	−	13.6	1.050	8.0	1+	−	−	−	0.1	−
	025	PY	−	9.0	1.064	8.0	±	−	−	−	0.1	−

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

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

< On week 2 of the recovery period >

Dose (mg/kg/day)	Animal number	Color	Cloudy	Volume (mL/18hr)	Specific gravity	pH	Protein	Glucose	Ketone body	Occult blood	Urobilinogen	Bilirubin
0	006	PY	−	8.6	1.044	8.0	1+	−	−	−	0.1	−
	007	PY	−	15.2	1.032	8.5	1+	−	−	−	0.1	−
	008	PY	−	15.1	1.026	8.0	1+	−	−	−	0.1	−
	009	PY	−	13.6	1.032	8.0	1+	−	−	−	0.1	−
	010	PY	−	10.1	1.062	8.0	1+	−	−	−	0.1	−
600	031	PY	−	22.1	1.022	8.0	±	−	−	−	0.1	−
	032	PY	−	10.4	1.046	8.0	1+	−	−	−	0.1	−
	033	PY	−	13.0	1.038	8.0	−	−	−	−	0.1	−
	034	PY	−	12.5	1.048	8.0	±	−	−	−	0.1	−
	035	PY	−	13.6	1.042	8.0	1+	−	−	−	0.1	−

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

Appendix 21-3 Individual urinary findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 4 of the 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	–	–	–	–	–	1+	–	–	–	–	–	–
	002	–	–	–	–	–	–	–	–	–	–	–	–
	003	–	–	–	–	–	1+	–	–	–	–	–	–
	004	–	–	1+	–	–	–	–	–	–	–	–	–
	005	–	–	–	–	–	–	–	–	–	–	–	–
10	011	–	–	–	–	–	1+	–	–	–	–	–	–
	012	–	–	–	–	–	1+	–	–	–	–	–	–
	013	–	–	–	–	–	–	–	–	–	–	–	–
	014	–	–	–	–	–	–	–	–	–	–	–	–
	015	–	–	–	–	–	–	–	–	–	–	–	–
40	016	–	–	–	–	–	–	–	–	–	–	–	–
	017	–	–	–	–	–	–	–	–	–	–	–	–
	018	–	–	1+	–	–	1+	–	–	–	–	–	–
	019	–	–	–	–	–	–	–	–	–	–	–	–
	020	–	–	–	–	–	–	–	–	–	–	–	–
150	021	–	–	–	–	–	1+	–	–	–	–	–	–
	022	–	–	–	–	–	1+	–	–	–	–	–	–
	023	–	–	1+	–	–	–	–	–	–	–	–	–
	024	–	–	–	–	–	1+	–	–	–	–	–	–
	025	–	–	1+	–	–	1+	–	–	–	–	–	–
600	026	–	–	–	–	–	–	–	–	–	–	–	–
	027	–	–	–	–	–	1+	–	–	–	–	–	–
	028	–	–	–	–	–	1+	–	–	–	–	–	–
	029	–	–	–	–	–	–	–	–	–	–	–	–
	030	–	–	–	–	–	–	–	–	–	–	–	–

– : Not observed, 1+ : A few in some 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 21-4 Individual urinary findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 2 of the 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	–	–	–	–	–	–	–	–	–	–	–	–
	007	–	–	1+	–	–	1+	–	–	–	–	–	–
	008	–	–	–	–	–	–	–	–	–	–	–	–
	009	–	–	1+	–	–	1+	–	–	–	–	–	–
	010	–	–	1+	–	–	1+	–	–	–	–	–	–
600	031	–	–	–	–	–	1+	–	–	–	–	–	–
	032	–	–	–	–	–	–	–	–	–	–	–	–
	033	–	–	–	–	–	–	–	–	–	–	–	–
	034	–	–	1+	–	–	1+	–	–	–	–	–	–
	035	–	–	2+	–	–	1+	–	–	–	–	–	–

– : Not observed, 1+ : A few in some fields, 2+ : A few 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 diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 4 of the administration period >

Dose (mg/kg/day)	Animal number	Color	Cloudy	Volume (mL/18hr)	Specific gravity	pH	Protein	Glucose	Ketone body	Occult blood	Urobilinogen	Bilirubin
0	501	PY	−	2.9	1.074	8.0	1+	−	−	−	0.1	−
	502	PY	−	5.7	1.062	6.5	1+	−	−	−	0.1	−
	503	PY	−	8.6	1.048	8.0	±	−	−	−	0.1	−
	504	PY	−	3.3	1.068	8.5	−	−	−	−	0.1	−
	505	PY	−	9.8	1.046	8.0	1+	−	−	−	0.1	−
10	511	PY	−	8.4	1.048	8.0	1+	−	−	−	0.1	−
	512	PY	−	11.7	1.040	8.5	−	−	−	−	0.1	−
	513	PY	−	6.8	1.058	8.5	±	−	−	−	0.1	−
	514	PY	−	7.4	1.050	7.5	1+	−	−	−	0.1	−
	515	PY	−	11.8	1.040	8.0	−	−	−	−	0.1	−
40	516	PY	−	6.2	1.054	8.5	±	−	−	−	0.1	−
	517	PY	−	5.6	1.060	8.5	±	−	−	−	0.1	−
	518	PY	−	3.8	1.072	7.0	1+	−	±	−	0.1	−
	519	PY	−	10.6	1.044	8.0	1+	−	−	−	0.1	−
	520	PY	−	9.8	1.046	8.5	±	−	−	−	0.1	−
150	521	PY	−	3.9	1.058	8.0	±	−	−	−	0.1	−
	522	PY	−	8.2	1.048	7.5	±	−	−	−	0.1	−
	523	PY	−	7.6	1.052	8.0	±	−	−	−	0.1	−
	524	PY	−	4.8	1.060	8.0	−	−	−	−	0.1	−
	525	PY	−	7.7	1.058	7.0	±	−	−	−	0.1	−
600	526	PY	−	9.8	1.044	8.5	−	−	−	−	0.1	−
	527	PY	−	12.6	1.040	8.0	−	−	−	−	0.1	−
	528	PY	−	14.5	1.040	8.0	−	−	−	−	0.1	−
	529	PY	−	12.4	1.044	8.5	−	−	−	−	0.1	−
	530	PY	−	17.0	1.040	8.5	−	−	−	−	0.1	−

Color : PY(pale yellow).
Cloudy : −(negligible).
Protein : −(negligible), ±(15~30mg/dL), 1+(30mg/dL).
Glucose : −(negligible).
Ketone body : −(negligible), ±(5mg/dL).
Occult blood : −(negligible).
Urobilinogen : Ehrlich unit/dL.
Bilirubin : −(negligible).

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

< On week 2 of the recovery period >

Dose (mg/kg/day)	Animal number	Color	Cloudy	Volume (mL/18hr)	Specific gravity	pH	Protein	Glucose	Ketone body	Occult blood	Urobilinogen	Bilirubin
0	506	PY	−	6.4	1.052	7.0	1+	−	−	−	0.1	−
	507	PY	−	5.8	1.054	8.0	−	−	−	−	0.1	−
	508	PY	−	6.2	1.064	8.5	1+	−	−	−	0.1	−
	509	PY	−	6.4	1.046	7.5	±	−	−	−	0.1	−
	510	PY	−	12.3	1.038	8.0	−	−	−	−	0.1	−
600	531	PY	−	4.0	1.032	8.0	±	−	−	−	0.1	−
	532	PY	−	7.9	1.052	8.5	±	−	−	−	0.1	−
	533	PY	−	7.6	1.032	8.5	−	−	−	−	0.1	−
	534	PY	−	6.7	1.054	7.5	1+	−	−	−	0.1	−
	535	PY	−	6.8	1.056	8.5	±	−	−	−	0.1	−

Color : PY(pale yellow).
Cloudy : −(negligible).
Protein : −(negligible), ±(15～30mg/dL), 1+(30mg/dL).
Glucose : −(negligible).
Ketone body : −(negligible), ±(5mg/dL).
Occult blood : −(negligible).
Urobilinogen : Ehrlich unit/dL.
Bilirubin : −(negligible).

Appendix 22-3 Individual urinary findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 4 of the 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+	–	–	–	–	–	–
	502	–	–	2+	–	–	1+	–	–	–	–	–	–
	503	–	–	–	–	–	–	–	–	–	–	–	–
	504	–	–	–	–	–	–	–	–	–	–	–	–
	505	–	–	–	–	–	1+	–	–	–	–	–	–
10	511	–	–	1+	–	–	1+	–	–	–	–	–	–
	512	–	–	–	–	–	–	–	–	–	–	–	–
	513	–	–	1+	–	–	1+	–	–	–	–	–	–
	514	–	–	–	–	–	–	–	–	–	–	–	–
	515	–	–	–	–	–	–	–	–	–	–	–	–
40	516	–	–	–	–	–	1+	–	–	–	–	–	–
	517	–	–	1+	–	–	1+	–	–	–	–	–	–
	518	–	–	–	–	–	1+	–	–	–	–	–	–
	519	–	–	–	–	–	1+	–	–	–	–	–	–
	520	–	–	–	–	–	–	–	–	–	–	–	–
150	521	–	–	–	–	–	–	–	–	–	–	–	–
	522	–	–	1+	–	–	1+	–	–	–	–	–	–
	523	–	–	–	–	–	–	–	–	–	–	–	–
	524	–	–	–	–	–	–	–	–	–	–	–	–
	525	–	–	–	–	–	–	–	–	–	–	–	–
600	526	–	–	–	–	–	1+	–	–	–	–	–	–
	527	–	–	–	–	–	1+	–	–	–	–	–	–
	528	–	–	–	–	–	–	–	–	–	–	–	–
	529	–	–	1+	–	–	1+	–	–	–	–	–	–
	530	–	–	–	–	–	1+	–	–	–	–	–	–

– : Not observed, 1+ : A few in some fields, 2+ : A few 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 22-4 Individual urinary findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 2 of the 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	−	−	1+	−	−	1+	−	−	−	−	−	−
	507	−	−	3+	−	−	1+	−	−	−	−	−	−
	508	−	−	−	−	−	−	−	−	−	−	−	−
	509	−	−	−	−	−	1+	−	−	−	−	−	−
	510	−	−	−	−	−	1+	−	−	−	−	−	−
600	531	−	−	−	−	−	1+	−	−	−	−	−	−
	532	−	−	1+	−	−	1+	−	−	−	−	−	−
	533	−	−	−	−	−	1+	−	−	−	−	−	−
	534	−	−	1+	−	−	1+	−	−	−	−	−	−
	535	−	−	−	−	−	1+	−	−	−	−	−	−

− : Not observed, 1+ : A few in some 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 diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration 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	001	798	15.2	46.6	58	19.0	32.6	37.1	12.5
	002	756	14.8	46.1	61	19.6	32.1	36.2	12.6
	003	767	15.5	47.5	62	20.2	32.6	26.0	12.4
	004	781	15.6	47.6	61	20.0	32.8	27.8	12.6
	005	767	15.5	47.5	62	20.2	32.6	37.9	11.4
	Mean	774	15.3	47.1	61	19.8	32.5	33.0	12.3
10	011	785	14.6	45.7	58	18.6	31.9	37.1	13.1
	012	729	14.4	44.5	61	19.8	32.4	31.9	12.5
	013	753	14.6	45.5	60	19.4	32.1	26.0	12.4
	014	769	15.1	47.3	62	19.6	31.9	31.3	12.1
	015	738	14.6	45.4	62	19.8	32.2	41.2	12.8
	Mean	755	14.7	45.7	61	19.4	32.1	33.5	12.6
40	016	710	14.0	43.7	62	19.7	32.0	32.0	13.0
	017	746	14.1	43.4	58	18.9	32.5	44.9	12.5
	018	689	14.5	45.0	65	21.0	32.2	36.3	11.9
	019	752	14.6	44.7	59	19.4	32.7	34.8	12.6
	020	733	14.0	43.2	59	19.1	32.4	31.6	13.0
	Mean	726	14.2	44.0	61	19.6	32.4	35.9	12.6
150	021	711	13.9	43.6	61	19.5	31.9	38.3	13.2
	022	722	14.2	44.1	61	19.7	32.2	36.6	12.9
	023	722	14.2	45.0	62	19.7	31.6	35.3	14.2
	024	734	14.7	45.7	62	20.0	32.2	23.9	13.5
	025	789	15.1	45.4	58	19.1	33.3	27.4	13.7
	Mean	736	14.4	44.8	61	19.6	32.2	32.3	13.5
600	026	704	13.9	43.4	62	19.7	32.0	36.0	13.8
	027	755	14.9	45.3	60	19.7	32.9	30.9	13.5
	028	713	14.0	43.5	61	19.6	32.2	35.4	12.7
	029	714	13.2	41.4	58	18.5	31.9	45.4	12.6
	030	731	14.3	44.9	61	19.6	31.8	31.4	14.1
	Mean	723	14.1	43.7	60	19.4	32.2	35.8	13.3

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

< At the end of administration period >

Dose (mg/kg/day)	Animal number	APTT (sec)	Plat. ($10^4/\mu L$)	WBC ($10^2/\mu L$)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	001	20.6	135	76	0.0	1.0	10.7	85.9	2.4
	002	19.9	118	55	0.0	0.4	13.9	83.8	1.9
	003	19.0	119	51	0.0	0.6	11.5	85.9	2.0
	004	17.4	121	47	0.0	0.8	20.4	77.0	1.8
	005	21.0	119	69	0.0	0.3	15.1	83.0	1.6
	Mean	19.6	122	60	0.0	0.6	14.3	83.1	1.9
10	011	19.8	130	67	0.0	0.7	10.5	86.3	2.5
	012	19.0	127	73	0.0	0.7	17.6	79.7	2.0
	013	19.7	98	42	0.0	1.4	18.6	77.8	2.2
	014	19.1	137	65	0.0	0.6	16.5	81.1	1.8
	015	19.2	111	43	0.0	2.1	15.5	80.7	1.7
	Mean	19.4	121	58	0.0	1.1	15.7	81.1	2.0
40	016	20.2	128	56	0.0	1.3	11.7	84.6	2.4
	017	18.7	141	59	0.0	0.9	16.0	81.1	2.0
	018	18.6	141	87	0.0	1.5	11.5	84.6	2.4
	019	19.3	149	70	0.0	0.9	15.3	81.8	2.0
	020	19.0	130	48	0.0	1.2	19.3	77.5	2.0
	Mean	19.2	138	64	0.0	1.2	14.8	81.9	2.2
150	021	19.1	138	77	0.0	0.6	12.3	84.5	2.6
	022	19.2	120	76	0.0	0.4	10.2	87.5	1.9
	023	22.3	130	83	0.0	1.3	15.0	81.0	2.7
	024	17.9	107	57	0.0	0.7	20.9	76.9	1.5
	025	22.7	141	46	0.0	0.4	16.5	81.4	1.7
	Mean	20.2	127	68	0.0	0.7	15.0	82.3	2.1
600	026	22.5	127	89	0.0	0.5	8.0	89.3	2.2
	027	23.0	136	87	0.0	1.0	21.7	74.5	2.8
	028	21.4	123	58	0.0	0.9	10.4	86.7	2.0
	029	18.3	114	53	0.0	0.9	17.4	79.2	2.5
	030	24.9	128	72	0.0	0.6	13.9	83.8	1.7
	Mean	22.0	126	72	0.0	0.8	14.3	82.7	2.2

Appendix 23-3 Individual hematological findings of male rats treated with diphenylene oxide 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	006	956	17.3	51.7	54	18.1	33.5	18.8	12.4
	007	827	15.0	45.0	54	18.1	33.3	21.4	13.3
	008	883	16.1	48.4	55	18.2	33.3	18.1	12.1
	009	793	15.7	47.0	59	19.8	33.4	30.7	12.8
	010	821	15.5	46.6	57	18.9	33.3	27.6	13.0
	Mean	856	15.9	47.7	56	18.6	33.4	23.3	12.7
600	031	861	16.0	49.4	57	18.6	32.4	19.1	13.1
	032	872	16.0	47.7	55	18.3	33.5	22.7	13.7
	033	846	15.0	46.1	55	17.7	32.5	27.9	12.5
	034	856	15.9	47.8	56	18.6	33.3	25.4	13.2
	035	842	15.5	46.5	55	18.4	33.3	35.3	13.3
	Mean	855	15.7	47.5	56	18.3	33.0	26.1	13.2

Appendix 23-4 Individual hematological findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	APTT (sec)	Plat. ($10^4/\mu L$)	WBC ($10^2/\mu L$)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	006	21.3	135	87	0.0	0.6	15.0	82.6	1.8
	007	20.0	132	67	0.0	1.8	10.8	83.4	4.0
	008	21.4	152	64	0.0	0.9	7.4	89.8	1.9
	009	20.2	121	74	0.0	0.7	12.4	83.9	3.0
	010	20.8	144	107	0.0	0.9	9.3	86.7	3.1
	Mean	20.7	137	80	0.0	1.0	11.0	85.3	2.8
600	031	21.7	159	74	0.0	1.0	12.0	84.4	2.6
	032	20.5	148	115	0.0	1.0	13.6	81.8	3.6
	033	21.2	150	98	0.0	1.0	9.5	85.9	3.6
	034	21.3	154	67	0.0	1.5	12.4	82.4	3.7
	035	21.6	178	105	0.0	0.8	9.9	91.9	2.4
	Mean	21.3	158	92	0.0	1.1	11.5	85.3	3.2

Appendix 24-1 Individual hematological findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration 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	501	720	14.3	43.4	60	19.9	32.9	29.6	12.9
	502	766	14.7	43.4	57	19.2	33.9	23.4	13.3
	503	794	15.4	46.1	58	19.4	33.4	21.9	13.2
	504	756	14.1	42.8	57	18.7	32.9	17.5	12.0
	505	757	14.7	44.1	58	19.4	33.3	29.7	13.3
	Mean	759	14.6	44.0	58	19.3	33.3	24.4	12.9
10	511	739	14.8	45.1	61	20.0	32.8	26.8	13.3
	512	682	13.8	41.8	61	20.2	33.0	19.8	12.9
	513	782	14.9	44.9	57	19.1	33.2	21.3	12.2
	514	735	15.0	44.9	61	20.4	33.4	22.7	12.5
	515	772	15.2	46.2	60	19.7	32.9	30.0	12.5
	Mean	742	14.7	44.6	60	19.9	33.1	24.1	12.7
40	516	724	14.3	42.6	59	19.8	33.6	23.2	13.4
	517	745	14.1	42.0	56	18.9	33.6	20.4	13.2
	518	715	13.6	42.3	59	19.0	32.2	21.7	13.0
	519	738	14.6	44.0	60	19.8	33.2	19.4	12.4
	520	760	14.4	42.8	56	18.9	33.6	19.0	13.0
	Mean	736	14.2	42.7	58	19.3	33.2	20.7	13.0
150	521	780	14.8	43.6	56	19.0	33.9	20.6	13.2
	522	755	14.2	43.3	57	18.8	32.8	21.6	12.9
	523	729	13.8	42.7	59	18.9	32.3	23.8	13.1
	524	726	14.4	43.5	60	19.8	33.1	22.2	12.3
	525	749	13.8	42.0	56	18.4	32.9	22.5	12.7
	Mean	748	14.2	43.0	58	19.0	33.0	22.1	12.8
600	526	737	14.3	43.0	58	19.4	33.3	19.7	12.7
	527	712	14.1	42.6	60	19.8	33.1	24.1	12.4
	528	716	13.5	41.4	58	18.9	32.6	16.4	11.4
	529	715	14.0	43.8	61	19.6	32.0	17.9	11.7
	530	682	13.0	40.3	59	19.1	32.3	24.3	11.9
	Mean	712	13.8	42.2	59	19.4	32.7	20.5	12.0

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

< At the end of administration period >

Dose (mg/kg/day)	Animal number	APTT (sec)	Plat. ($10^4/\mu L$)	WBC ($10^2/\mu L$)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	501	20.6	118	58	0.0	1.0	11.2	85.4	2.4
	502	18.7	113	39	0.0	0.5	10.5	86.5	2.5
	503	20.2	124	86	0.0	0.8	12.7	84.6	1.9
	504	18.7	141	40	0.0	0.8	10.6	86.1	2.5
	505	17.7	119	48	0.0	1.0	10.8	86.5	1.7
	Mean	19.2	123	54	0.0	0.8	11.2	85.8	2.2
10	511	19.9	125	78	0.0	1.0	13.9	83.2	1.9
	512	18.4	117	90	0.0	0.3	7.8	90.9	1.0
	513	20.1	116	67	0.0	0.9	14.1	82.8	2.2
	514	18.6	123	42	0.0	1.4	11.5	85.4	1.7
	515	16.3	129	60	0.0	1.2	16.7	80.4	1.7
	Mean	18.7	122	67	0.0	1.0	12.8	84.5	1.7
40	516	18.2	110	74	0.0	1.4	8.6	86.2	3.8
	517	17.2	132	32	0.0	2.5	12.4	83.5	1.6
	518	19.7	141	36	0.0	1.1	11.8	84.9	2.2
	519	17.9	121	54	0.0	1.7	14.7	81.2	2.4
	520	17.9	145	72	0.0	0.4	10.7	87.2	1.7
	Mean	18.2	130	54	0.0	1.4	11.6	84.6	2.3
150	521	17.2	142	44	0.0	2.5	10.7	83.8	3.0
	522	17.6	128	38	0.0	1.1	11.7	84.8	2.4
	523	18.8	132	69	0.0	0.9	8.8	86.5	3.8
	524	17.8	133	62	0.0	1.9	10.5	84.1	3.5
	525	18.5	136	69	0.0	1.0	15.0	80.5	3.5
	Mean	18.0	134	56	0.0	1.5	11.3	83.9	3.2
600	526	16.7	123	74	0.0	0.8	11.8	85.1	2.3
	527	18.1	142	85	0.0	1.1	8.8	88.1	2.0
	528	21.1	148	57	0.0	1.4	15.1	81.2	2.3
	529	18.4	105	50	0.0	0.8	16.4	80.2	2.6
	530	16.3	116	59	0.0	1.3	15.6	80.6	2.5
	Mean	18.1	127	65	0.0	1.1	13.5	83.0	2.3

Appendix 24-3 Individual hematological findings of female rats treated with diphenylene oxide 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	752	14.3	41.2	55	19.0	34.7	22.0	12.1
	507	812	15.3	45.3	56	18.8	33.8	23.6	12.7
	508	820	15.5	45.4	55	18.9	34.1	18.1	12.5
	509	778	14.5	42.4	55	18.6	34.2	23.2	12.1
	510	838	16.3	46.8	56	19.5	34.8	17.6	13.3
	Mean	800	15.2	44.2	55	19.0	34.3	20.9	12.5
600	531	860	15.8	45.4	53	18.4	34.8	20.4	12.0
	532	824	15.8	46.8	57	19.2	33.8	21.7	12.6
	533	744	14.6	43.3	58	19.6	33.7	22.5	11.8
	534	819	15.4	45.3	55	18.8	34.0	26.4	12.6
	535	818	15.1	44.3	54	18.5	34.1	16.9	11.9
	Mean	813	15.3	45.0	55	18.9	34.1	21.6	12.2

Appendix 24-4 Individual hematological findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	APTT (sec)	Plat. ($10^4/\mu L$)	WBC ($10^2/\mu L$)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	506	16.9	151	59	0.0	0.7	11.2	85.4	2.7
	507	18.9	155	66	0.0	1.2	12.6	83.8	2.4
	508	16.6	124	93	0.0	1.2	8.5	87.4	2.9
	509	16.5	141	57	0.0	1.9	7.3	88.0	2.8
	510	18.4	120	43	0.0	2.3	10.6	83.6	3.5
	Mean	17.5	138	64	0.0	1.5	10.0	85.6	2.9
600	531	20.0	138	38	0.0	1.3	13.1	83.3	2.3
	532	20.0	143	64	0.0	2.0	9.1	85.2	3.7
	533	17.4	119	60	0.0	1.0	11.8	85.7	1.5
	534	18.7	125	63	0.0	2.1	12.6	82.8	2.5
	535	16.8	141	42	0.0	2.6	16.8	76.8	3.8
	Mean	18.6	133	54	0.0	1.8	12.7	82.8	2.8

Appendix 25-1 Individual blood biochemical findings of male rats treated with diphenylene oxide 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	254	62	37	584	0.52	5.84	2.84	0.95	67	70
	002	400	73	35	931	0.57	5.50	2.73	0.99	63	41
	003	322	68	38	790	0.57	5.53	2.56	0.86	81	104
	004	217	85	38	834	0.37	5.61	2.84	1.03	59	52
	005	313	59	27	778	0.75	5.53	2.85	1.06	58	89
	Mean	301	69	35	783	0.56	5.60	2.76	0.98	66	71
10	011	313	66	24	888	0.60	5.68	2.87	1.02	53	39
	012	258	54	31	850	0.48	5.80	2.82	0.95	56	41
	013	221	61	30	810	0.41	5.86	2.81	0.92	74	51
	014	193	55	28	783	0.40	5.54	2.89	1.09	73	39
	015	710	78	30	938	0.65	5.64	2.97	1.11	53	32
	Mean	339	63	29	854	0.51	5.70	2.87	1.02	62	40
40	016	297	62	26	668	0.99	5.94	2.91	0.96	68	66
	017	344	62	34	797	0.80	5.78	2.93	1.03	72	55
	018	675	60	29	810	0.38	5.46	2.74	1.01	90	93
	019	227	63	26	811	0.69	5.49	2.64	0.93	49	51
	020	203	66	29	872	0.49	5.62	2.68	0.91	66	33
	Mean	349	63	29	792	0.67	5.66	2.78	0.97	69	60
150	021	224	61	31	637	0.63	5.66	2.85	1.01	82	115
	022	546	72	34	737	0.71	5.38	2.72	1.02	71	80
	023	268	71	37	836	0.86	5.66	2.99	1.12	76	75
	024	206	86	44	761	0.45	6.18	3.25	1.11	83	76
	025	365	71	30	674	0.48	5.89	3.16	1.16	69	54
	Mean	322	72	35	729	0.63	5.75	2.99	1.08	76	80
600	026	559	87	45	651	1.24	5.30	2.73	1.06	70	33
	027	472	70	43	947	1.00	5.98	3.10	1.08	115	56
	028	216	73	47	716	2.10	5.75	2.98	1.08	112	64
	029	415	66	42	707	1.49	5.84	2.99	1.05	121	63
	030	304	66	38	621	1.15	5.87	2.83	0.93	89	47
	Mean	393	72	43	728	1.40	5.75	2.93	1.04	101	53

Appendix 25-2 Individual blood biochemical findings of male rats treated with diphenylene oxide 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	148	12.0	0.43	0.38	10.0	8.1	146	4.23	105
	002	168	14.0	0.45	0.43	9.8	9.5	145	4.90	104
	003	154	13.0	0.38	0.23	10.0	8.5	145	4.89	105
	004	128	10.4	0.33	0.45	9.7	9.3	147	4.46	106
	005	164	13.8	0.29	0.35	9.7	9.3	145	5.72	105
	Mean	152	12.6	0.38	0.37	9.8	8.9	146	4.84	105
10	011	158	16.7	0.33	0.39	9.8	9.2	146	5.71	106
	012	140	11.7	0.34	0.37	10.0	8.2	147	4.95	106
	013	140	13.0	0.40	0.35	10.4	10.2	151	6.26	103
	014	145	10.8	0.30	0.36	9.8	9.0	146	5.41	105
	015	135	12.3	0.29	0.40	9.8	9.3	146	5.60	106
	Mean	144	12.9	0.33	0.37	10.0	9.2	147	5.59	105
40	016	139	9.9	0.40	0.36	9.6	9.1	148	4.69	105
	017	159	14.2	0.39	0.35	9.6	9.0	146	5.12	104
	018	140	14.9	0.36	0.36	9.6	9.1	145	6.02	106
	019	154	13.4	0.36	0.39	9.3	9.4	147	5.08	105
	020	120	11.5	0.33	0.41	9.6	8.9	148	4.87	105
	Mean	142	12.8	0.37	0.37	9.5	9.1	147	5.16	105
150	021	148	13.1	0.36	0.41	9.9	8.9	148	4.60	105
	022	125	11.5	0.37	0.38	9.1	8.4	147	5.10	107
	023	139	9.5	0.33	0.35	9.4	8.5	147	5.37	107
	024	166	12.0	0.39	0.33	10.2	9.7	151	6.35	103
	025	138	9.9	0.36	0.34	9.7	8.3	147	4.73	107
	Mean	143	11.2	0.36	0.36	9.7	8.8	148	5.23	106
600	026	140	10.3	0.40	0.38	9.1	10.1	145	5.14	106
	027	134	12.6	0.44	0.37	9.7	8.3	147	4.89	108
	028	135	13.3	0.36	0.37	9.1	9.4	145	4.92	105
	029	125	11.1	0.37	0.39	9.7	9.7	147	5.66	107
	030	127	11.0	0.36	0.41	9.6	9.5	147	5.15	107
	Mean	132	11.7	0.39	0.38	9.4	9.4	146	5.15	107

Appendix 25-3 Individual blood biochemical findings of male rats treated with diphenylene oxide 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	587	77	36	737	0.58	6.52	3.10	0.91	58	54
	007	345	63	28	735	0.54	6.23	2.80	0.82	74	32
	008	174	71	34	615	0.65	5.91	2.85	0.93	57	74
	009	184	63	31	426	0.56	6.10	2.76	0.83	71	36
	010	245	68	24	566	0.69	5.96	2.69	0.82	66	98
	Mean	307	68	31	616	0.60	6.14	2.84	0.86	65	59
600	031	458	67	30	429	0.37	6.13	2.75	0.81	70	78
	032	457	72	37	605	0.69	5.97	2.94	0.97	78	49
	033	236	74	34	533	0.64	5.93	2.79	0.89	63	46
	034	341	74	35	607	0.85	5.86	2.78	0.90	86	52
	035	278	70	29	365	0.69	6.22	3.01	0.94	88	70
	Mean	354	71	33	508	0.65	6.02	2.85	0.90	77	59

Appendix 25-4 Individual blood biochemical findings of male rats treated with diphenylene oxide 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	142	13.4	0.35	0.35	9.7	8.1	147	4.83	107
	007	169	16.3	0.39	0.35	10.1	8.5	145	5.09	106
	008	164	16.8	0.37	0.39	9.5	8.2	146	5.30	105
	009	151	14.1	0.36	0.35	10.1	8.2	146	4.29	107
	010	157	17.7	0.38	0.31	10.0	8.5	145	4.97	106
	Mean	157	15.7	0.37	0.35	9.9	8.3	146	4.90	106
600	031	146	15.6	0.43	0.32	9.9	8.2	146	4.86	106
	032	172	20.6	0.64	0.33	9.6	8.4	143	5.50	106
	033	152	16.6	0.38	0.35	9.6	7.8	144	5.09	108
	034	158	16.8	0.38	0.31	9.6	7.9	144	5.54	108
	035	174	18.3	0.39	0.32	9.7	8.6	147	5.09	105
	Mean	160	17.6	0.44	0.33	9.7	8.2	145	5.22	107

Appendix 26-1 Individual blood biochemical findings of female rats treated with diphenylene oxide 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	319	67	29	621	0.54	6.02	3.02	1.01	78	39
	502	499	95	32	631	0.89	5.59	3.00	1.16	62	18
	503	404	69	24	517	1.80	5.81	2.93	1.02	75	36
	504	481	67	30	456	0.74	5.62	3.03	1.17	96	23
	505	375	67	30	461	1.95	5.65	3.03	1.16	62	21
	Mean	416	73	29	537	1.18	5.74	3.00	1.10	75	27
10	511	468	80	26	647	2.87	5.56	2.76	0.99	73	15
	512	461	74	34	555	0.81	5.70	2.92	1.05	69	14
	513	297	68	28	422	1.32	6.24	3.35	1.16	72	33
	514	505	69	24	673	1.37	5.63	2.93	1.09	68	26
	515	284	68	29	762	0.63	5.82	3.07	1.12	79	18
	Mean	403	72	28	612	1.40	5.79	3.01	1.08	72	21
40	516	434	67	26	346	0.66	5.83	3.08	1.12	79	28
	517	467	67	29	339	1.56	5.61	2.85	1.03	74	31
	518	463	69	34	540	0.97	5.21	2.77	1.14	76	25
	519	339	70	28	683	1.61	5.68	2.91	1.05	87	21
	520	616	69	28	582	1.10	5.77	3.12	1.18	60	23
	Mean	464	68	29	498	1.18	5.62	2.95	1.10	75	26
150	521	449	69	28	402	1.02	5.96	3.27	1.22	82	47
	522	389	61	28	506	1.72	5.83	3.22	1.23	93	30
	523	591	71	29	508	1.95	5.37	2.71	1.02	70	31
	524	427	63	26	381	0.80	5.69	3.04	1.15	110	36
	525	629	75	31	528	1.07	5.78	3.22	1.26	106	74
	Mean	497	68	28	465	1.31	5.73	3.09	1.18	92	44
600	526	474	65	40	653	1.10	6.10	3.28	1.16	135	87
	527	618	65	36	407	1.64	5.97	3.14	1.11	141	101
	528	548	67	32	608	1.38	6.03	3.44	1.33	101	40
	529	556	67	37	460	2.21	5.93	3.39	1.33	115	45
	530	375	66	32	544	1.09	6.16	3.28	1.14	92	78
	Mean	514	66	35	534	1.48	6.04	3.31	1.21	117	70

Appendix 26-2 Individual blood biochemical findings of female rats treated with diphenylene oxide 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	138	18.1	0.47	0.21	9.7	7.3	146	4.57	108
	502	135	13.7	0.45	0.25	9.3	7.5	145	4.71	106
	503	151	14.1	0.48	0.23	9.1	7.0	144	4.98	107
	504	115	12.7	0.34	0.23	9.2	8.3	146	5.01	107
	505	128	14.1	0.38	0.27	9.6	8.1	146	4.87	105
	Mean	133	14.5	0.42	0.24	9.4	7.6	145	4.83	107
10	511	120	18.8	0.46	0.25	8.7	8.9	146	5.02	107
	512	119	12.8	0.30	0.25	9.3	7.1	146	4.73	107
	513	144	15.8	0.41	0.21	9.8	7.7	146	4.63	106
	514	126	13.1	0.38	0.28	9.2	7.4	147	4.51	108
	515	137	17.5	0.42	0.25	9.5	7.4	148	4.40	108
	Mean	129	15.6	0.39	0.25	9.3	7.7	147	4.66	107
40	516	106	16.3	0.33	0.27	9.8	7.9	146	5.20	105
	517	125	14.5	0.35	0.27	9.4	7.0	147	4.58	106
	518	128	12.1	0.40	0.26	9.5	7.8	146	5.03	106
	519	138	13.8	0.43	0.20	9.5	8.0	146	4.89	109
	520	139	15.5	0.34	0.24	10.0	7.8	145	5.40	107
	Mean	127	14.4	0.37	0.25	9.6	7.7	146	5.02	107
150	521	117	17.2	0.38	0.28	10.0	7.5	145	5.16	108
	522	129	10.0	0.35	0.28	9.4	6.0	147	4.77	110
	523	122	17.8	0.36	0.23	9.2	7.7	144	5.79	110
	524	113	16.4	0.37	0.27	9.8	7.4	144	5.13	106
	525	130	11.9	0.35	0.25	10.3	8.5	147	4.84	106
	Mean	122	14.7	0.36	0.26	9.7	7.4	145	5.14	108
600	526	122	11.6	0.39	0.32	9.8	7.7	148	4.91	108
	527	135	11.8	0.36	0.29	10.0	7.9	145	4.49	106
	528	118	11.5	0.42	0.30	9.6	6.8	147	4.73	108
	529	127	14.8	0.36	0.34	10.1	7.8	148	4.53	108
	530	116	13.1	0.35	0.33	10.2	8.9	147	4.82	105
	Mean	124	12.6	0.38	0.32	9.9	7.8	147	4.70	107

Appendix 26-3 Individual blood biochemical findings of female rats treated with diphenylene oxide 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	295	69	24	297	1.58	6.16	3.10	1.01	69	16
	507	931	85	24	458	1.72	5.98	2.98	0.99	54	19
	508	331	64	20	403	1.67	6.02	2.92	0.94	60	24
	509	291	62	20	295	0.96	5.91	3.02	1.04	69	22
	510	309	73	30	465	0.90	6.10	2.92	0.92	58	20
	Mean	431	71	24	384	1.37	6.03	2.99	0.98	62	20
600	531	482	75	32	345	1.02	6.31	3.22	1.04	80	13
	532	514	71	26	356	1.05	5.84	2.94	1.01	84	24
	533	395	57	20	452	0.29	6.02	3.23	1.16	59	20
	534	400	62	22	421	1.70	5.82	3.12	1.16	97	41
	535	492	103	29	245	0.69	6.15	3.30	1.16	107	27
	Mean	457	74	26	364	0.95	6.03	3.16	1.11	85	25

Appendix 26-4 Individual blood biochemical findings of female rats treated with diphenylene oxide 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	121	19.1	0.45	0.27	9.5	7.7	145	5.17	110
	507	118	17.5	0.40	0.28	9.5	8.1	143	5.34	108
	508	121	16.5	0.40	0.25	9.8	8.9	143	5.09	106
	509	126	14.7	0.45	0.30	9.6	7.2	144	4.80	108
	510	130	17.8	0.43	0.22	9.6	7.5	143	4.45	107
	Mean	123	17.1	0.43	0.26	9.6	7.9	144	4.97	108
600	531	130	15.7	0.40	0.23	9.6	8.2	142	5.40	107
	532	127	14.7	0.37	0.24	9.4	7.0	144	5.07	111
	533	143	12.5	0.42	0.22	9.7	7.7	144	4.44	105
	534	126	16.9	0.44	0.27	9.5	7.9	146	4.70	109
	535	122	15.6	0.39	0.25	10.2	7.3	145	4.32	110
	Mean	130	15.1	0.40	0.24	9.7	7.6	144	4.79	108

Appendix 27-1 Individual pathological findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy			Histopathology
0	001	NAD	a	Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	002	NAD	a	Lung	: Accumulation, foam cell +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
					Cast, hyaline, unilateral +
				Parathyroid	: Not in section
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	003	NAD	a	Liver	: Microgramuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule +
					Cast, hyaline, unilateral +
				Parathyroid	: Not in section
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	004	NAD	a	Liver	: Necrosis, focal +
				Kidney	: Hyaline droplet, proximal tubular epithelium ++
					Basophilic tubule +
					Cellular infiltration, lymphocyte, cortex, unilateral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	005	NAD	a	Kidney	: Hyaline droplet, proximal tubular epithelium ++
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +

NAD : No abnormalities 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 27-2 Individual pathological findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy	Histopathology
10	011	NAD	c Kidney : Hyaline droplet, proximal tubular epithelium + Cellular infiltration, lymphocyte, cortex, unilateral +
	012	NAD	c Liver : Microgramuloma + Kidney : Hyaline droplet, proximal tubular epithelium +
	013	NAD	c Kidney : Hyaline droplet, proximal tubular epithelium + Basophilic tubule +
	014	NAD	c Liver : Necrosis, focal + Kidney : Basophilic tubule +
	015	NAD	c Kidney : Hyaline droplet, proximal tubular epithelium + Cellular infiltration, lymphocyte, cortex, unilateral +
40	016	NAD	c Kidney : Hyaline droplet, proximal tubular epithelium +
	017	NAD	c Liver : Microgramuloma + Kidney : Hyaline droplet, proximal tubular epithelium + Basophilic tubule +
	018	NAD	c Kidney : Basophilic tubule + Cellular infiltration, lymphocyte, cortex, unilateral +
	019	NAD	c Liver : Microgramuloma + Kidney : Basophilic tubule + Cellular infiltration, lymphocyte, cortex, unilateral +
	020	NAD	c Kidney : Hyaline droplet, proximal tubular epithelium + Basophilic tubule + Cellular infiltration, lymphocyte, cortex, unilateral +

NAD : No abnormalities detected; + : Slight.
c : Organs of the liver and kidney were examined.

Appendix 27-3 Individual pathological findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy		Histopathology
150	021	NAD	c	Liver : Hypertrophy, hepatocyte, centrilobular +
				Kidney : Hyaline droplet, proximal tubular epithelium +
	022	NAD	c	Kidney : Hyaline droplet, proximal tubular epithelium ++
				Basophilic tubule +
				Cellular infiltration, lymphocyte, cortex, unilateral +
	023	NAD	c	Liver : Hypertrophy, hepatocyte, centrilobular +
				Kidney : Hyaline droplet, proximal tubular epithelium +
				Basophilic tubule +
				Fibrosis, cortex, unilateral +
	024	NAD	c	Kidney : Basophilic tubule +
				Cyst, solitary, unilateral +
	025	NAD	c	Kidney : Hyaline droplet, proximal tubular epithelium +
600	026	NAD	a	Liver : Hypertrophy, hepatocyte, centrilobular ++
				Necrosis, focal +
				Kidney : Hyaline droplet, proximal tubular epithelium +
				Spleen : Hematopoiesis, extramedullary +
				Deposit, pigment, brown +
	027	NAD	a	Liver : Hypertrophy, hepatocyte, centrilobular +
				Kidney : Hyaline droplet, proximal tubular epithelium ++
				Basophilic tubule +
				Spleen : Hematopoiesis, extramedullary +
				Deposit, pigment, brown +

NAD : No abnormalities 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.

c : Organs of the liver and kidney were examined.

Appendix 27-4 Individual pathological findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy		Histopathology	
600 (Continued)	028	NAD	a	Heart	: Myocardial degeneration/fibrosis +
				Liver	: Hypertrophy, hepatocyte, centrilobular ++
					Necrosis, focal +
				Kidney	: Hyaline droplet, proximal tubular epithelium +
					Basophilic tubule ++
					Cast, hyaline, unilateral +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	029	NAD	a	Liver	: Hypertrophy, hepatocyte, centrilobular +
					Microgramuloma +
				Kidney	: Hyaline droplet, proximal tubular epithelium ++
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +
	030	NAD	a	Liver	: Hypertrophy, hepatocyte, centrilobular ++
				Kidney	: Hyaline droplet, proximal tubular epithelium +
				Spleen	: Hematopoiesis, extramedullary +
					Deposit, pigment, brown +

NAD : No abnormalities 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 27-5 Individual pathological findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	Necropsy	Histopathology
0	006	NAD	c NAD
	007	NAD	c Liver : Microgranuloma + Kidney : Hyaline droplet, proximal tubular epithelium + Cast, hyaline, unilateral +
	008	NAD	c Kidney : Hyaline droplet, proximal tubular epithelium + Cellular infiltration, lymphocyte, cortex, unilateral +
	009	NAD	c Kidney : Hyaline droplet, proximal tubular epithelium + Basophilic tubule +
	010	NAD	c Liver : Necrosis, focal + Kidney : Hyaline droplet, proximal tubular epithelium + Basophilic tubule +
600	031	NAD	c Kidney : Cellular infiltration, lymphocyte, cortex, unilateral +
	032	NAD	c Kidney : Hyaline droplet, proximal tubular epithelium + Basophilic tubule + Cellular infiltration, lymphocyte, cortex, unilateral +
	033	NAD	c Liver : Necrosis, focal + Kidney : Hyaline droplet, proximal tubular epithelium + Basophilic tubule +
	034	NAD	c Liver : Microgranuloma +
	035	NAD	c Liver : Necrosis, focal + Kidney : Hyaline droplet, proximal tubular epithelium +

NAD : No abnormalities detected; + : Slight.
c : Organs of the liver and kidney were examined.

Appendix 28-1 Individual pathological findings of female rats treated with diphenylene oxide 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	Liver : Degeneration, fatty change, hepatocyte, periportal + Kidney : Basophilic tubule + Mineralization, cortico-medullary junction + Spleen : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	502	NAD	b	Kidney : Basophilic tubule + Spleen : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	503	NAD	b	Lung : Mineralization, artery + Thymus : Hemorrhage + Spleen : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	504	NAD	b	Liver : Microgranuloma + Spleen : Hematopoiesis, extramedullary + Deposit, pigment, brown +
	505	NAD	b	Spleen : Hematopoiesis, extramedullary + Deposit, pigment, brown +
10	511	NAD	c	NAD
	512	NAD	c	Kidney : Cellular infiltration, lymphocyte, cortex, unilateral + Fibrosis, cortex, unilateral +
	513	NAD	c	Kidney : Basophilic tubule +
	514	NAD	c	NAD
	515	NAD	c	NAD

NAD : No abnormalities 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.

c : Organs of the liver and kidney were examined.

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

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy	Histology
40	516	NAD	c Liver : Microgramuloma +
	517	NAD	c NAD
	518	NAD	c NAD
	519	NAD	c Liver : Necrosis, focal +
	520	NAD	c Kidney : Basophilic tubule +
150	521	NAD	c NAD
	522	NAD	c NAD
	523	NAD	c Kidney : Basophilic tubule + Cellular infiltration, lymphocyte, cortex, unilateral +
	524	NAD	c Liver : Microgramuloma +
	525	NAD	c Kidney : Basophilic tubule + Mineralization, cortico-medullary junction +

NAD : No abnormalities detected; + : Slight.
c : Organs of the liver and kidney were examined.

Appendix 28-3 Individual pathological findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	Necropsy		Histology
600	526	NAD	b	Liver : Hypertrophy, hepatocyte, centrilobular ++
				Kidney : Dilatation, tubular, cortex +
				Degenertion, vacuolar, tubular epithelium, cortex +
				Basophilic tubule +
				Spleen : Hematopoiesis, extramedullary +
				Deposit, pigment, brown +
	527	NAD	b	Lung : Mineralization, artery +
				Liver : Hypertrophy, hepatocyte, centrilobular ++
				Kidney : Dilatation, tubular, cortex ++
				Degenertion, vacuolar, tubular epithelium, cortex +
				Spleen : Hematopoiesis, extramedullary +
				Deposit, pigment, brown +
	528	NAD	b	Liver : Hypertrophy, hepatocyte, centrilobular ++
				Kidney : Dilatation, tubular, cortex +
				Degenertion, vacuolar, tubular epithelium, cortex +
				Spleen : Hematopoiesis, extramedullary +
				Deposit, pigment, brown +
	529	NAD	b	Liver : Hypertrophy, hepatocyte, centrilobular ++
				Kidney : Dilatation, tubular, cortex ++
				Degenertion, vacuolar, tubular epithelium, cortex +
				Spleen : Hematopoiesis, extramedullary +
				Deposit, pigment, brown +
	530	NAD	b	Lung : Accumulation, foam cell +
				Liver : Hypertrophy, hepatocyte, centrilobular ++
				Microgramuloma +
				Spleen : Hematopoiesis, extramedullary +
				Deposit, pigment, brown +

NAD : No abnormalities detected; + : Slight; ++ : Moderate.

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 28-4 Individual pathological findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	Necropsy			Histopathology
0	506	NAD	c	Kidney	: Cast, hyaline +
	507	NAD	c		NAD
	508	NAD	c		NAD
	509	NAD	c	Liver	: Microgramuloma +
				Kidney	: Basophilic tubule +
	510	NAD	c	Liver	: Microgramuloma +
				Kidney	: Cellular infiltration, lymphocyte, cortex, unilateral +
600	531	NAD	c		NAD
	532	NAD	c	Liver	: Microgramuloma +
				Kidney	: Cellular infiltration, lymphocyte, cortex, unilateral +
	533	NAD	c	Kidney	: Basophilic tubule +
	534	NAD	c	Liver	: Microgramuloma +
	535	NAD	c	Kidney	: Cellular infiltration, lymphocyte, cortex, unilateral +

NAD : No abnormalities detected; + : Slight.
c : Organs of the liver and kidney were examined.

Appendix 29-1 Individual absolute organ weights of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	B.W. (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland(mg)	Spleen (g)	Testis (g)	Epididymis (g)
0	001	312	1.83	0.46	0.99	9.27	2.28	44.5	0.65	3.02	0.84
	002	319	1.88	0.49	1.07	9.71	2.16	55.0	0.70	3.27	0.80
	003	304	1.79	0.37	1.04	10.08	2.21	50.6	0.58	2.83	0.73
	004	308	1.95	0.45	0.97	9.02	2.31	56.9	0.57	3.30	0.81
	005	389	2.08	0.56	1.22	13.59	3.05	65.8	0.92	3.43	0.79
	Mean	326	1.91	0.47	1.06	10.33	2.40	54.6	0.68	3.17	0.79
10	011	304	1.90	0.60	1.03	8.93	2.31	65.4	0.67	3.33	0.86
	012	372	1.94	0.54	1.23	11.72	2.84	62.4	0.72	3.17	0.76
	013	358	1.94	0.66	1.26	11.99	2.96	49.2	0.85	3.16	0.82
	014	318	2.05	0.52	1.16	9.84	2.59	55.4	0.69	3.13	0.82
	015	319	1.85	0.42	1.24	9.41	2.60	59.2	0.68	3.30	0.82
	Mean	334	1.94	0.55	1.18	10.38	2.66	58.3	0.72	3.22	0.82
40	016	354	2.00	0.47	1.17	12.19	2.90	68.5	0.71	3.29	0.79
	017	335	1.87	0.57	1.05	11.84	2.76	57.2	0.84	3.26	0.87
	018	377	1.89	0.47	1.23	12.79	2.84	53.8	0.64	3.20	0.75
	019	333	2.02	0.49	1.22	10.70	2.59	55.9	0.71	3.03	0.80
	020	355	2.06	0.49	1.26	11.97	2.98	45.4	0.80	3.35	0.81
	Mean	351	1.97	0.50	1.19	11.90	2.81	56.2	0.74	3.23	0.80
150	021	381	1.95	0.61	1.20	14.85	3.18	70.4	0.79	3.54	0.81
	022	338	1.95	0.52	1.18	12.02	2.68	70.7	0.75	3.11	0.78
	023	319	1.78	0.60	1.15	11.95	2.83	45.3	0.74	3.20	0.80
	024	297	1.79	0.41	0.97	11.21	2.21	49.5	0.48	3.28	0.72
	025	292	1.82	0.61	0.98	10.37	2.52	51.4	0.53	3.54	0.80
	Mean	325	1.86	0.55	1.10	12.08	2.68	57.5	0.66	3.33	0.78
600	026	319	1.91	0.51	1.10	13.33	2.81	51.2	0.72	3.06	0.82
	027	270	1.79	0.33	0.98	10.19	2.09	44.1	0.44	2.85	0.73
	028	301	1.90	0.36	1.05	12.83	2.74	45.1	0.48	3.11	0.78
	029	314	1.80	0.38	1.01	12.59	2.57	48.5	0.70	3.08	0.81
	030	303	1.90	0.50	1.01	12.41	2.50	52.5	0.59	3.54	0.78
	Mean	301	1.86	0.42	1.03	12.27	2.54	48.3	0.59	3.13	0.78

Appendix 29-2 Individual relative organ weights of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	B.W. (g)	Brain (%)	Thymus (%)	Heart (%)	Liver (%)	Kidney (%)	Adrenal gland(mg%)	Spleen (%)	Testis (%)	Epididymis (%)
0	001	312	0.59	0.15	0.32	2.97	0.73	14.3	0.21	0.97	0.27
	002	319	0.59	0.15	0.34	3.04	0.68	17.2	0.22	1.03	0.25
	003	304	0.59	0.12	0.34	3.32	0.73	16.6	0.19	0.93	0.24
	004	308	0.63	0.15	0.31	2.93	0.75	18.5	0.19	1.07	0.26
	005	389	0.53	0.14	0.31	3.49	0.78	16.9	0.24	0.88	0.20
	Mean	326	0.59	0.14	0.32	3.15	0.73	16.7	0.21	0.98	0.24
10	011	304	0.63	0.20	0.34	2.94	0.76	21.5	0.22	1.10	0.28
	012	372	0.52	0.15	0.33	3.15	0.76	16.8	0.19	0.85	0.20
	013	358	0.54	0.18	0.35	3.35	0.83	13.7	0.24	0.88	0.23
	014	318	0.64	0.16	0.36	3.09	0.81	17.4	0.22	0.98	0.26
	015	319	0.58	0.13	0.39	2.95	0.82	18.6	0.21	1.03	0.26
	Mean	334	0.58	0.16	0.35	3.10	0.80	17.6	0.22	0.97	0.25
40	016	354	0.56	0.13	0.33	3.44	0.82	19.4	0.20	0.93	0.22
	017	335	0.56	0.17	0.31	3.53	0.82	17.1	0.25	0.97	0.26
	018	377	0.50	0.12	0.33	3.39	0.75	14.3	0.17	0.85	0.20
	019	333	0.61	0.15	0.37	3.21	0.78	16.8	0.21	0.91	0.24
	020	355	0.58	0.14	0.35	3.37	0.84	12.8	0.23	0.94	0.23
	Mean	351	0.56	0.14	0.34	3.39	0.80	16.1	0.21	0.92	0.23
150	021	381	0.51	0.16	0.31	3.90	0.83	18.5	0.21	0.93	0.21
	022	338	0.58	0.15	0.35	3.56	0.79	20.9	0.22	0.92	0.23
	023	319	0.56	0.19	0.36	3.75	0.89	14.2	0.23	1.00	0.25
	024	297	0.60	0.14	0.33	3.77	0.74	16.7	0.16	1.10	0.24
	025	292	0.62	0.21	0.34	3.55	0.86	17.6	0.18	1.21	0.27
	Mean	325	0.57	0.17	0.34	3.71	0.82	17.6	0.20	1.03	0.24
600	026	319	0.60	0.16	0.34	4.18	0.88	16.1	0.23	0.96	0.26
	027	270	0.66	0.12	0.36	3.77	0.77	16.3	0.16	1.06	0.27
	028	301	0.63	0.12	0.35	4.26	0.91	15.0	0.16	1.03	0.26
	029	314	0.57	0.12	0.32	4.01	0.82	15.4	0.22	0.98	0.26
	030	303	0.63	0.17	0.33	4.10	0.83	17.3	0.19	1.17	0.26
	Mean	301	0.62	0.14	0.34	4.06	0.84	16.0	0.19	1.04	0.26

Appendix 30-1 Individual absolute organ weights of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	B.W. (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland(mg)	Spleen (g)	Testis (g)	Epididymis (g)
0	006	356	2.03	0.46	1.08	9.47	2.77	46.5	0.71	3.22	1.20
	007	436	1.95	0.56	1.37	12.42	3.56	82.4	0.68	3.61	1.05
	008	342	1.93	0.28	1.19	9.35	2.72	66.8	0.53	3.39	1.10
	009	376	1.97	0.47	1.15	10.89	2.82	75.0	0.81	3.83	1.18
	010	486	1.98	0.72	1.60	15.66	3.69	77.1	0.93	3.85	1.24
	Mean	399	1.97	0.50	1.28	11.56	3.11	69.6	0.73	3.58	1.15
600	031	435	1.98	0.48	1.28	13.63	3.11	71.7	0.79	3.58	1.22
	032	364	1.92	0.33	1.03	9.62	2.71	72.5	0.69	3.82	1.20
	033	349	1.85	0.34	1.20	9.64	2.59	65.2	0.61	3.64	1.17
	034	351	1.95	0.32	1.33	10.37	2.61	75.7	0.62	3.82	1.17
	035	408	2.13	0.45	1.33	12.36	3.14	67.7	0.71	3.20	1.26
	Mean	381	1.97	0.38	1.23	11.12	2.83	70.6	0.68	3.61	1.20

Appendix 30-2 Individual relative organ weights of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	B.W. (g)	Brain (%)	Thymus (%)	Heart (%)	Liver (%)	Kidney (%)	Adrenal gland(mg%)	Spleen (%)	Testis (%)	Epididymis (%)
0	006	356	0.57	0.13	0.30	2.66	0.78	13.1	0.20	0.90	0.34
	007	436	0.45	0.13	0.31	2.85	0.82	18.9	0.16	0.83	0.24
	008	342	0.56	0.08	0.35	2.73	0.80	19.5	0.15	0.99	0.32
	009	376	0.52	0.13	0.31	2.90	0.75	19.9	0.22	1.02	0.31
	010	486	0.41	0.15	0.33	3.22	0.76	15.9	0.19	0.79	0.26
	Mean	399	0.50	0.12	0.32	2.87	0.78	17.5	0.18	0.91	0.29
600	031	435	0.46	0.11	0.29	3.13	0.71	16.5	0.18	0.82	0.28
	032	364	0.53	0.09	0.28	2.64	0.74	19.9	0.19	1.05	0.33
	033	349	0.53	0.10	0.34	2.76	0.74	18.7	0.17	1.04	0.34
	034	351	0.56	0.09	0.38	2.95	0.74	21.6	0.18	1.09	0.33
	035	408	0.52	0.11	0.33	3.03	0.77	16.6	0.17	0.78	0.31
	Mean	381	0.52	0.10	0.32	2.90	0.74	18.7	0.18	0.96	0.32

Appendix 31-1 Individual absolute organ weights of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	B.W. (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland(mg)	Spleen (g)	Ovary (mg)
0	501	179	1.63	0.41	0.77	5.89	1.42	57.4	0.48	97.3
	502	195	1.77	0.39	0.71	5.65	1.43	74.8	0.52	86.2
	503	205	1.90	0.44	0.76	6.53	1.41	70.2	0.46	98.1
	504	186	1.70	0.36	0.71	6.00	1.51	57.5	0.35	71.0
	505	219	1.80	0.35	0.78	5.86	1.59	73.6	0.54	82.0
	Mean	197	1.76	0.39	0.75	5.99	1.47	66.7	0.47	86.9
10	511	186	1.87	0.39	0.71	5.31	1.46	71.5	0.49	94.1
	512	204	1.66	0.56	0.72	5.96	1.73	55.3	0.54	109.4
	513	212	1.80	0.50	0.81	6.83	1.60	75.6	0.52	75.6
	514	205	1.85	0.41	1.06	5.92	1.73	66.2	0.44	83.4
	515	214	1.71	0.47	0.87	6.63	1.51	74.5	0.43	106.4
	Mean	204	1.78	0.47	0.83	6.13	1.61	68.6	0.48	93.8
40	516	187	1.68	0.45	0.65	5.40	1.49	73.7	0.43	93.6
	517	200	1.78	0.52	0.69	5.71	1.70	61.5	0.34	75.4
	518	226	1.90	0.48	0.86	6.90	1.73	71.8	0.51	99.2
	519	204	1.71	0.41	0.77	6.73	1.48	63.3	0.42	95.5
	520	210	1.81	0.70	0.86	6.57	1.91	67.4	0.54	77.6
	Mean	205	1.78	0.51	0.77	6.26	1.66	67.5	0.45	88.3
150	521	187	1.80	0.41	0.70	5.93	1.53	62.8	0.36	76.7
	522	190	1.79	0.51	0.74	6.21	1.69	59.1	0.41	93.6
	523	200	1.69	0.33	0.79	6.94	1.64	73.7	0.50	113.5
	524	210	1.71	0.39	0.84	7.16	1.87	67.4	0.49	78.7
	525	210	1.81	0.48	0.85	7.06	1.66	69.8	0.47	81.5
	Mean	199	1.76	0.42	0.78	6.66	1.68	66.6	0.45	88.8
600	526	190	1.68	0.33	0.68	7.95	1.52	61.1	0.48	82.3
	527	191	1.60	0.39	0.76	8.13	1.73	50.8	0.44	64.6
	528	202	1.85	0.42	0.79	8.63	1.74	67.9	0.36	100.9
	529	193	1.79	0.35	0.70	8.38	1.83	65.9	0.38	84.9
	530	208	1.71	0.46	0.80	9.46	1.75	52.2	0.59	65.2
	Mean	197	1.73	0.39	0.75	8.51	1.71	59.6	0.45	79.6

Appendix 31-2 Individual relative organ weights of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	Animal number	B.W. (g)	Brain (%)	Thymus (%)	Heart (%)	Liver (%)	Kidney (%)	Adrenal gland(mg%)	Spleen (%)	Ovary (mg%)
0	501	179	0.91	0.23	0.43	3.29	0.79	32.1	0.27	54.4
	502	195	0.91	0.20	0.36	2.90	0.73	38.4	0.27	44.2
	503	205	0.93	0.21	0.37	3.19	0.69	34.2	0.22	47.9
	504	186	0.91	0.19	0.38	3.23	0.81	30.9	0.19	38.2
	505	219	0.82	0.16	0.36	2.68	0.73	33.6	0.25	37.4
	Mean	197	0.90	0.20	0.38	3.06	0.75	33.8	0.24	44.4
10	511	186	1.01	0.21	0.38	2.85	0.78	38.4	0.26	50.6
	512	204	0.81	0.27	0.35	2.92	0.85	27.1	0.26	53.6
	513	212	0.85	0.24	0.38	3.22	0.75	35.7	0.25	35.7
	514	205	0.90	0.20	0.52	2.89	0.84	32.3	0.21	40.7
	515	214	0.80	0.22	0.41	3.10	0.71	34.8	0.20	49.7
	Mean	204	0.87	0.23	0.41	3.00	0.79	33.7	0.24	46.1
40	516	187	0.90	0.24	0.35	2.89	0.80	39.4	0.23	50.1
	517	200	0.89	0.26	0.35	2.86	0.85	30.8	0.17	37.7
	518	226	0.84	0.21	0.38	3.05	0.77	31.8	0.23	43.9
	519	204	0.84	0.20	0.38	3.30	0.73	31.0	0.21	46.8
	520	210	0.86	0.33	0.41	3.13	0.91	32.1	0.26	37.0
	Mean	205	0.87	0.25	0.37	3.05	0.81	33.0	0.22	43.1
150	521	187	0.96	0.22	0.37	3.17	0.82	33.6	0.19	41.0
	522	190	0.94	0.27	0.39	3.27	0.89	31.1	0.22	49.3
	523	200	0.85	0.17	0.40	3.47	0.82	36.9	0.25	56.8
	524	210	0.81	0.19	0.40	3.41	0.89	32.1	0.23	37.5
	525	210	0.86	0.23	0.40	3.36	0.79	33.2	0.22	38.8
	Mean	199	0.88	0.22	0.39	3.34	0.84	33.4	0.22	44.7
600	526	190	0.88	0.17	0.36	4.18	0.80	32.2	0.25	43.3
	527	191	0.84	0.20	0.40	4.26	0.91	26.6	0.23	33.8
	528	202	0.92	0.21	0.39	4.27	0.86	33.6	0.18	50.0
	529	193	0.93	0.18	0.36	4.34	0.95	34.1	0.20	44.0
	530	208	0.82	0.22	0.38	4.55	0.84	25.1	0.28	31.3
	Mean	197	0.88	0.20	0.38	4.32	0.87	30.3	0.23	40.5

Appendix 32-1 Individual absolute organ weights of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	B.W. (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland(mg)	Spleen (g)	Ovary (mg)
0	506	196	1.72	0.35	0.73	5.30	1.55	73.3	0.42	75.3
	507	210	1.74	0.43	0.72	5.34	1.77	80.6	0.45	107.1
	508	236	1.91	0.54	0.82	5.98	1.88	65.6	0.57	73.3
	509	226	1.77	0.44	0.85	6.22	1.78	72.8	0.50	78.1
	510	242	1.82	0.44	0.80	6.04	1.78	67.8	0.57	75.8
	Mean	222	1.79	0.44	0.78	5.78	1.75	72.0	0.50	81.9
600	531	194	1.87	0.26	0.72	5.54	1.52	62.3	0.41	76.7
	532	188	1.65	0.40	0.69	5.47	1.51	57.0	0.37	66.2
	533	213	1.71	0.32	0.73	6.49	1.57	72.7	0.38	91.5
	534	215	1.76	0.33	0.77	6.03	1.53	60.2	0.43	72.4
	535	243	1.78	0.39	0.89	7.48	1.90	81.6	0.44	77.6
	Mean	211	1.75	0.34	0.76	6.20	1.61	66.8	0.41	76.9

Appendix 32-2 Individual relative organ weights of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	Animal number	B.W. (g)	Brain (%)	Thymus (%)	Heart (%)	Liver (%)	Kidney (%)	Adrenal gland(mg%)	Spleen (%)	Ovary (mg%)
0	506	196	0.88	0.18	0.37	2.70	0.79	37.4	0.21	38.4
	507	210	0.83	0.20	0.34	2.54	0.84	38.4	0.21	51.0
	508	236	0.81	0.23	0.35	2.53	0.80	27.8	0.24	31.1
	509	226	0.78	0.19	0.38	2.75	0.79	32.2	0.22	34.6
	510	242	0.75	0.18	0.33	2.50	0.74	28.0	0.24	31.3
	Mean	222	0.81	0.20	0.35	2.60	0.79	32.8	0.22	37.3
600	531	194	0.96	0.13	0.37	2.86	0.78	32.1	0.21	39.5
	532	188	0.88	0.21	0.37	2.91	0.80	30.3	0.20	35.2
	533	213	0.80	0.15	0.34	3.05	0.74	34.1	0.18	43.0
	534	215	0.82	0.15	0.36	2.80	0.71	28.0	0.20	33.7
	535	243	0.73	0.16	0.37	3.08	0.78	33.6	0.18	31.9
	Mean	211	0.84	0.16	0.36	2.94	0.76	31.6	0.19	36.7

Appendix 33 Historical baseline data of the Crl:CD(SD) strain male rats on the hematological and biochemical parameters

Parameters	Mean	Normal range[a)]
Hematological parameters		
① Erythrocyte count (10^4/μL)	698 (46)	637 ~ 759
② Hemoglobin concentration (g/dL)	14.5 (46)	13.4 ~ 15.5
③ Hematocrit value (%)	45.1 (46)	41.8 ~ 48.3
④ Mean corpuscular volume (fL)	65 (46)	60 ~ 69
⑤ Mean corpuscular hemoglobin (pg)	20.7 (46)	19.4 ~ 22.0
⑥ Mean corpuscular hemoglobin concentration (%)	31.9 (42)	31.2 ~ 32.6
⑦ Reticulocyte count (‰)	60.9 (46)	29.2 ~ 92.6
⑧ Prothrombin time (sec)	12.9 (126)	12.0 ~ 13.7
⑨ Activated partialthromboplastin time (sec)	19.4* (131)	16.2 ~ 23.2
⑩ Total leukocyte count (10^2/μL)	56* (46)	31 ~ 101
⑪ Platelet count (10^4/μL)	145 (46)	114 ~ 176
Biochemical parameters		
① Lactate dehydrogenase (IU/L)	323* (119)	154 ~ 681
② Aspartate aminotransferase (IU/L)	76* (117)	60 ~ 95
③ Alanine aminotransferase (IU/L)	32* (116)	24 ~ 44
④ Alkaline phosphatase (IU/L)	1077 (118)	626 ~ 1527
⑤ γ-Glutamyl transpeptidase (IU/L)	0.55* (107)	0.22 ~ 1.39
⑥ Cholinesterase (IU/L)	57 (33)	26 ~ 88
⑦ Total protein (g/dL)	5.52 (115)	5.13 ~ 5.91
⑧ Albumin (g/dL)	2.78 (118)	2.41 ~ 3.14
⑨ A/G ratio	1.00 (114)	0.86 ~ 1.14
⑩ Total cholesterol (mg/dL)	76* (117)	51 ~ 114
⑪ Triglyceride (mg/dL)	44* (119)	20 ~ 97
⑫ Glucose (mg/dL)	131 (119)	94 ~ 167
⑬ Urea nitrogen (mg/dL)	12.6 (118)	7.7 ~ 17.4
⑭ Creatinine (mg/dL)	0.37 (119)	0.26 ~ 0.48
⑮ Total bilirubin (mg/dL)	0.37* (118)	0.29 ~ 0.46
⑯ Calcium (mg/dL)	9.8 (113)	9.2 ~ 10.4
⑰ Inorganic phosphorus (mg/dL)	8.9* (115)	7.9 ~ 10.1
⑱ Sodium (mEq/L)	146 (117)	143 ~ 148
⑲ Potassium (mEq/L)	4.93 (118)	4.20 ~ 5.65
⑳ Chloride (mEq/L)	106 (116)	103 ~ 108

a) : (mean−2S.D.) ~ (mean+2S.D.) .

( ) : Number of animals.

* : Calculated from log-transformed data.

Appendix 34 Historical baseline data of the Crl:CD(SD) strain female rats on the hematological and biochemical parameters

Parameters	Mean	Normal range[a)]
Hematological parameters		
① Erythrocyte count (10^4/μL)	736 (47)	671 ~ 800
② Hemoglobin concentration (g/dL)	14.7 (47)	13.5 ~ 15.9
③ Hematocrit value (%)	44.6 (47)	41.2 ~ 47.9
④ Mean corpuscular volume (fL)	61 (46)	57 ~ 64
⑤ Mean corpuscular hemoglobin (pg)	19.9 (45)	19.0 ~ 20.8
⑥ Mean corpuscular hemoglobin concentration (%)	33.0 (45)	32.0 ~ 33.9
⑦ Reticulocyte count (‰)	33.0 (45)	22.9 ~ 43.1
⑧ Prothrombin time (sec)	13.2 (133)	12.2 ~ 14.2
⑨ Activated partialthromboplastin time (sec)	17.6* (134)	14.3 ~ 20.9
⑩ Total leukocyte count (10^2/μL)	46* (46)	25 ~ 85
⑪ Platelet count (10^4/μL)	143 (47)	113 ~ 173
Biochemical parameters		
① Lactate dehydrogenase (IU/L)	439* (119)	191 ~ 1008
② Aspartate aminotransferase (IU/L)	76* (117)	59 ~ 98
③ Alanine aminotransferase (IU/L)	26* (118)	18 ~ 38
④ Alkaline phosphatase (IU/L)	697 (118)	356 ~ 1037
⑤ γ-Glutamyl transpeptidase (IU/L)	0.79* (111)	0.31 ~ 2.06
⑥ Cholinesterase (IU/L)	297* (34)	114 ~ 775
⑦ Total protein (g/dL)	5.73 (114)	5.26 ~ 6.20
⑧ Albumin (g/dL)	2.97 (113)	2.54 ~ 3.39
⑨ A/G ratio	1.09 (116)	0.87 ~ 1.30
⑩ Total cholesterol (mg/dL)	74* (116)	43 ~ 126
⑪ Triglyceride (mg/dL)	22* (117)	9 ~ 81
⑫ Glucose (mg/dL)	122 (117)	96 ~ 148
⑬ Urea nitrogen (mg/dL)	13.8 (119)	8.9 ~ 18.6
⑭ Creatinine (mg/dL)	0.40 (115)	0.28 ~ 0.51
⑮ Total bilirubin (mg/dL)	0.25 (118)	0.17 ~ 0.33
⑯ Calcium (mg/dL)	9.9 (116)	9.2 ~ 10.5
⑰ Inorganic phosphorus (mg/dL)	8.3* (116)	7.0 ~ 9.9
⑱ Sodium (mEq/L)	146 (117)	143 ~ 149
⑲ Potassium (mEq/L)	4.72 (117)	3.86 ~ 5.58
⑳ Chloride (mEq/L)	107 (118)	103 ~ 110

a) : (mean−2S.D.) ~ (mean+2S.D.) .

( ) : Number of animals.

* : Calculated from log-transformed data.

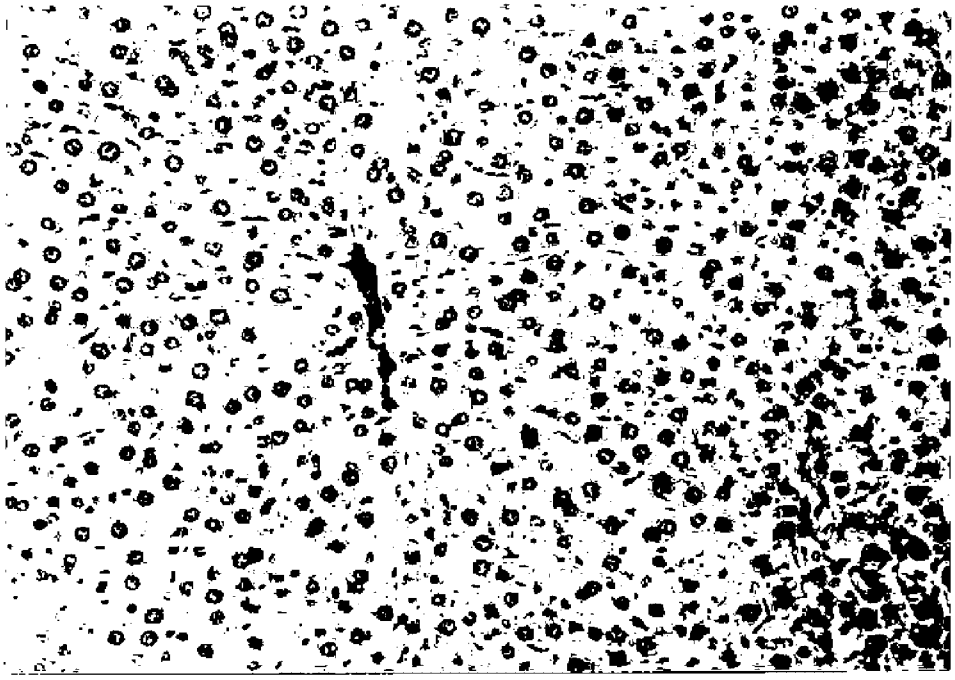


Photo 1. Liver (0 mg/kg group, female, No. 504, at the end of administration period, H-E stain, ×264)

No abnormalities.

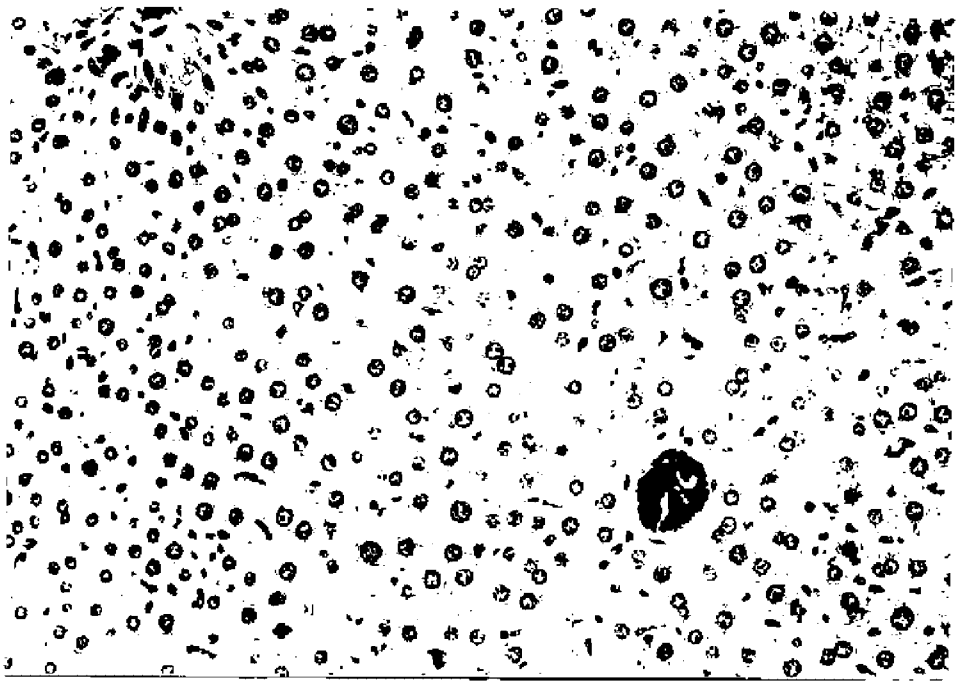


Photo 2. Liver (600 mg/kg group, female, No. 530, at the end of administration period, H-E stain, ×264)

Hypertrophy, hepatocyte, centrilobular.

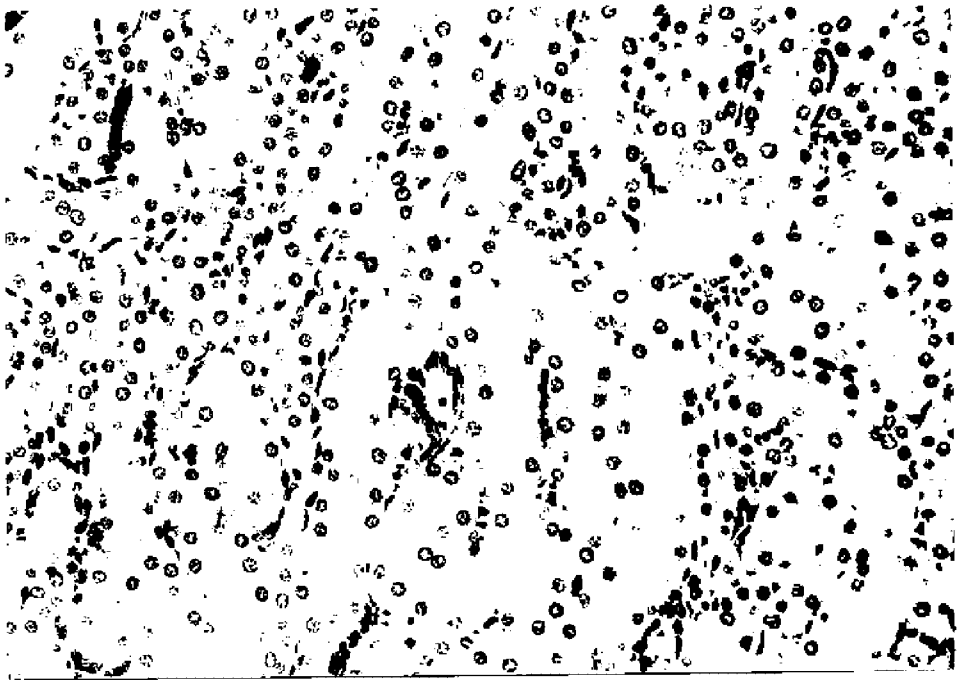


Photo 3. Kidney (0 mg/kg group, female, No. 503, at the end of administration period, H-E stain, ×264)

No abnormalities.

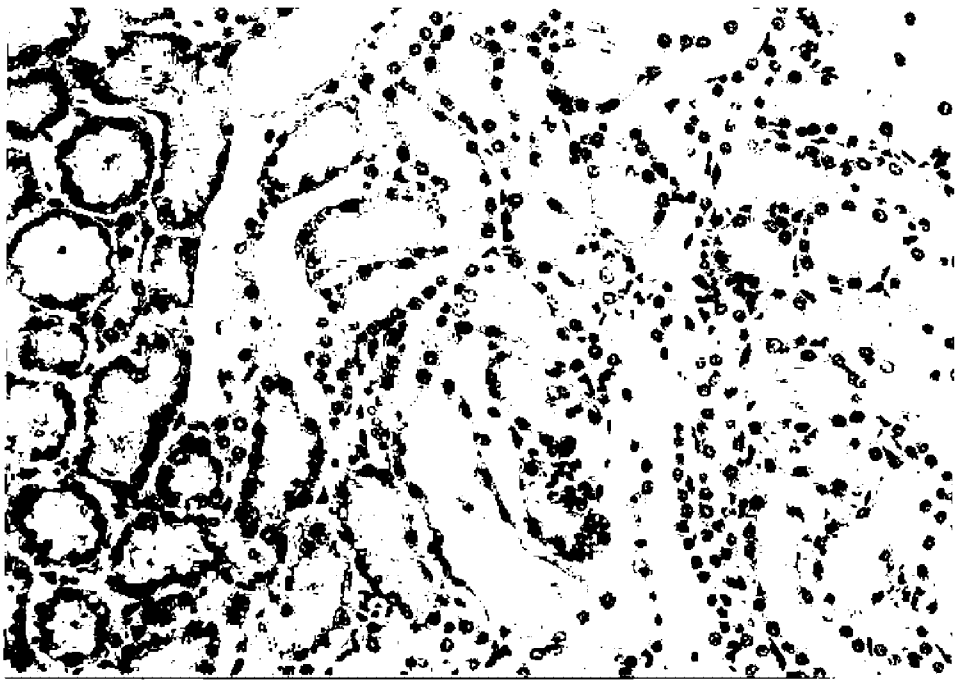


Photo 4. Kidney (600 mg/kg group, female, No. 529, at the end of administration period, H-E stain, ×264)

Dilatation, tubular, cortex.

ジフェニレンオキシドのラットを用いる28日間反復経口投与毒性試験

(試験番号：05-232)

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

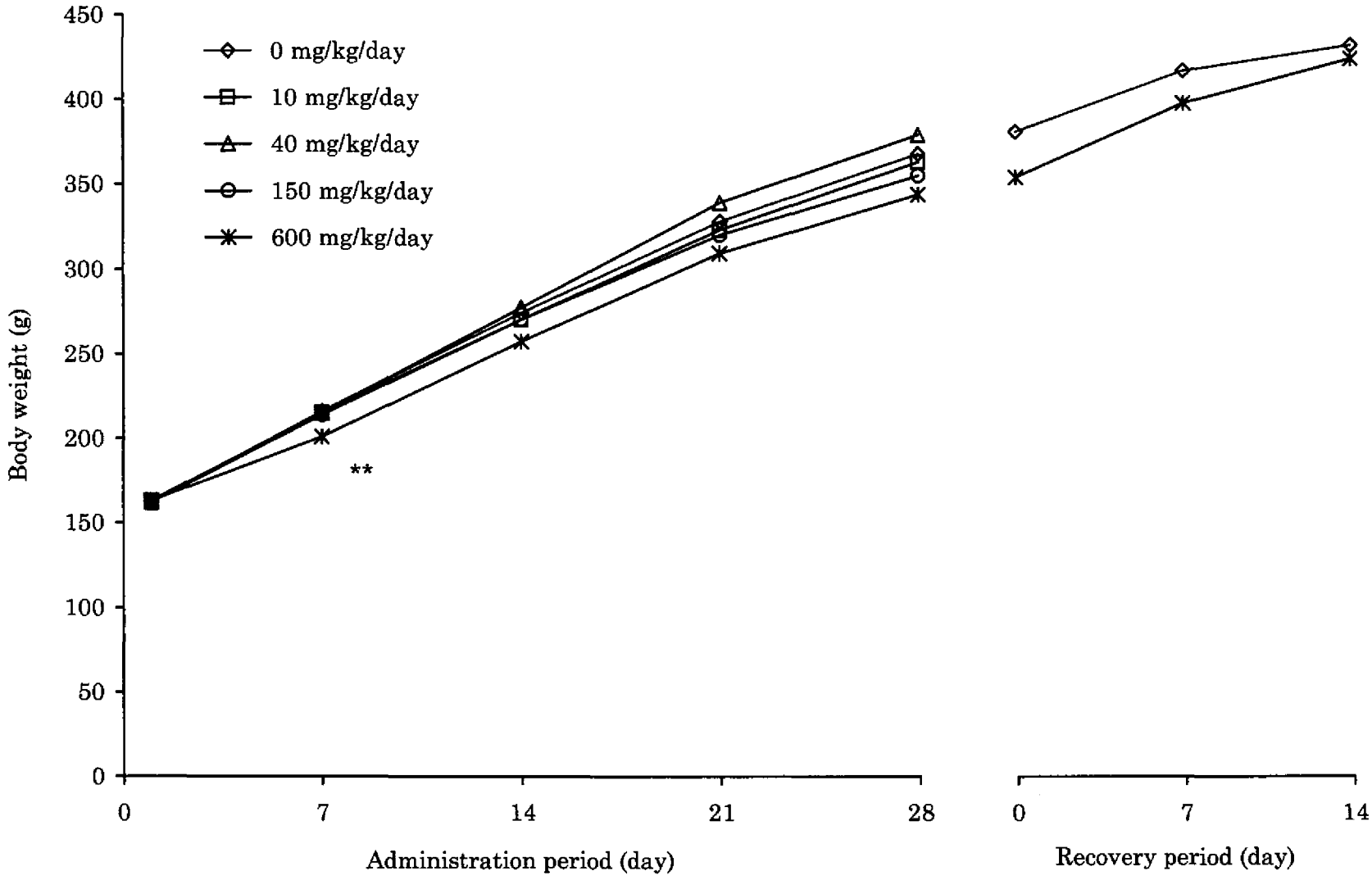


Fig.1 Body weight change of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

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

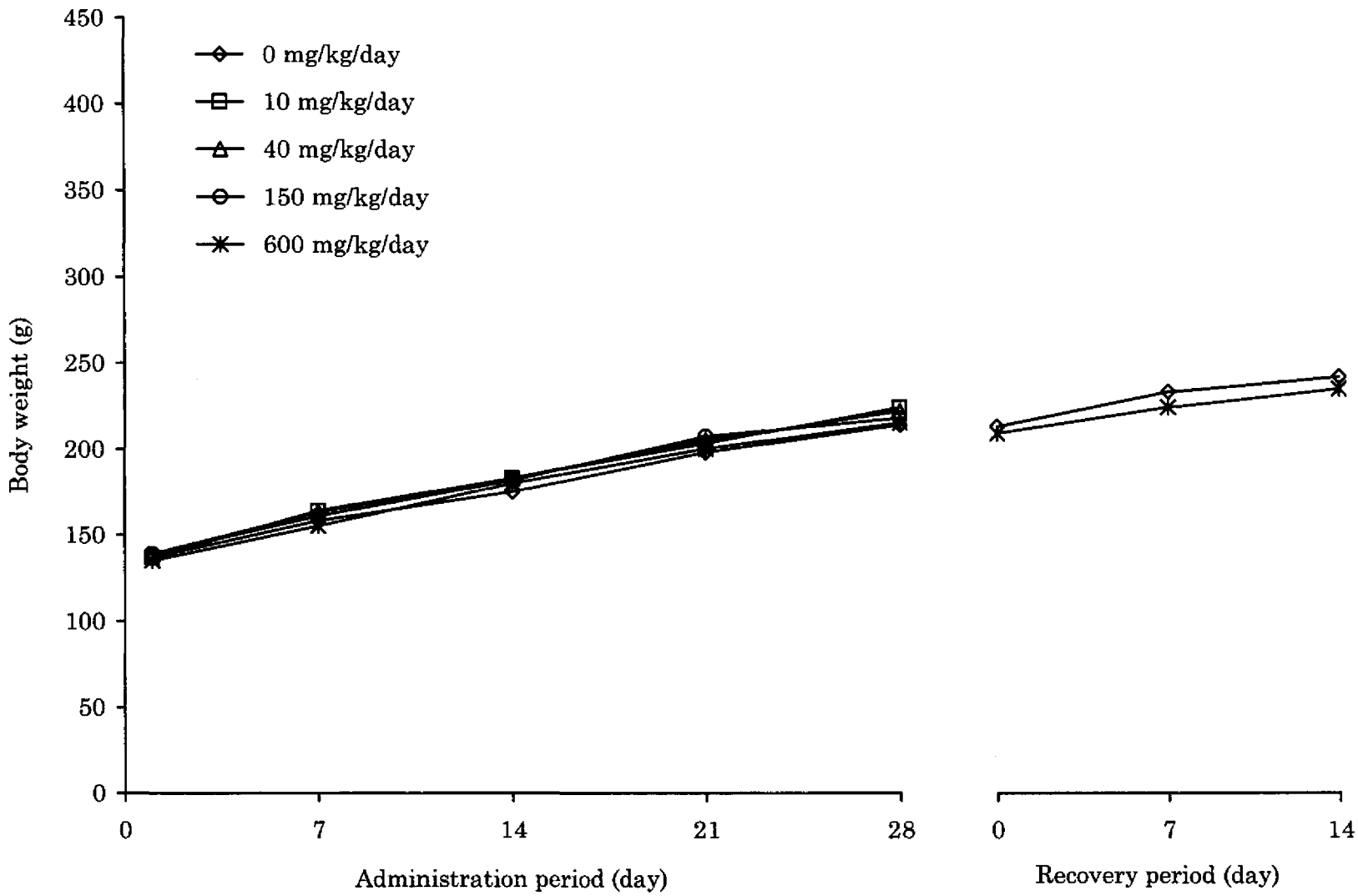


Fig.2 Body weight change of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

Table 1 General conditions and mortality of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

General conditions			Administration period									Recovery period	
		Dose (mg/kg/day)	0			10	40	150	600			0	600
		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
Decrease in locomotor activity	−		5	5	10	5	5	4	0	0	0	5	5
	+		0	0	0	0	0	1	5	5	10 **	0	0
Salivation	−		5	5	10	5	5	1	0	0	0	5	5
	+		0	0	0	0	0	4*	5	5	10 **	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 5% level of probability.
** : Significantly different from control at 1% level of probability.

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

General conditions			Administration period									Recovery period	
		Dose (mg/kg/day)	0			10	40	150	600			0	600
		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
Decrease in locomotor activity	−		5	5	10	5	5	5	1	3	4	5	5
	+		0	0	0	0	0	0	4	2	6 **	0	0
Salivation	−		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 with urine	−		5	5	10	5	5	5	3	4	7	5	5
	+		0	0	0	0	0	0	2	1	3	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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 Before the administration period 〉

Items	Score	Dose(mg/kg/day) / No. of animals	0 / 10	10 / 5	40 / 5	150 / 5	600 / 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 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
Smudge around mouth-nose	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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		10	5	5	5	10
Urination	Not detected or 1		10	5	5	5	8
	2 or more		0	0	0	0	2
	Color: Pale yellow		3/3	3/3	2/2	2/2	5/5
Defecation	Not detected or 1		10	5	5	5	6
	2 or more		0	0	0	0	4 *
	Appearance: Normal		3/3	2/2	2/2	1/1	6/6

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

〈 On week 1 of the administration period 〉

Items	Score	Dose(mg/kg/day)	0	10	40	150	600
		No. of animals	10	5	5	5	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 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
Smudge around mouth-nose	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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		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		1/1	4/4	1/1	1/1	4/4
Defecation	Not detected or 1		9	5	5	4	9
	2 or more		1	0	0	1	1
	Appearance: Normal		2/2	1/1	-	1/1	1/1

Table 3-3 Incidence of clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the administration period 〉

Items	Score	Dose(mg/kg/day) / No. of animals	0 / 10	10 / 5	40 / 5	150 / 5	600 / 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 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
Smudge around mouth-nose	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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		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		1/1	2/2	1/1	-	2/2
Defecation	Not detected or 1		9	3	4	4	8
	2 or more		1	2	1	1	2
	Appearance: Normal		2/2	2/2	1/1	1/1	2/2

Table 3-4 Incidence of clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 3 of the administration period 〉

Items	Score	Dose(mg/kg/day)	0	10	40	150	600
		No. of animals	10	5	5	5	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 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
Smudge around mouth-nose	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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		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		-	1/1	1/1	3/3	2/2
Defecation	Not detected or 1		10	4	5	5	10
	2 or more		0	1	0	0	0
	Appearance: Normal		1/1	1/1	-	1/1	-

Table 3-5 Incidence of clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the administration period 〉

Items	Score	Dose(mg/kg/day) / No. of animals	0 / 10	10 / 5	40 / 5	40 / 5	600 / 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 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
Smudge around mouth-nose	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	4	4	10
	Temporally in handling		0	0	1	1	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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		10	5	5	5	10
Urination	Not detected or 1		10	5	4	5	10
	2 or more		0	0	1	0	0
	Color: Pale yellow		1/1	1/1	1/1	-	1/1
Defecation	Not detected or 1		10	5	5	5	10
	2 or more		0	0	0	0	0
	Appearance: Normal		-	-	-	-	1/1

Table 3-6 Incidence of clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 1 of the recovery period 〉

Items	Score	Dose(mg/kg/day)	0	600
		No. of animals	5	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 discharge	Not detected		5	5
Palpebral closure	Not detected		5	5
Exophthalmos	Not detected		5	5
Lacrimation	Not detected		5	5
Smudge around mouth-nose	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
Alertness	Normal		5	5
Locomotor activity	Normal		5	5
Walk	Normal		5	5
Abnormal behavior	Not detected		5	5
Stereotypy	Not detected		5	5
Failure of consciousness	Not detected		5	5
Limb tone	Normal		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 3-7 Incidence of clinical signs in detailed observation of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the recovery period 〉

Items	Score	Dose(mg/kg/day) No. of animals	0 5	600 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 discharge	Not detected		5	5
Palpebral closure	Not detected		5	5
Exophthalmos	Not detected		5	5
Lacrimation	Not detected		5	5
Smudge around mouth-nose	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
Alertness	Normal		5	5
Locomotor activity	Normal		5	5
Walk	Normal		5	5
Abnormal behavior	Not detected		5	5
Stereotypy	Not detected		5	5
Failure of consciousness	Not detected		5	5
Limb tone	Normal		5	5
Urination	Not detected or 1		5	5
	2 or more		0	0
	Color: Pale yellow		2/2	1/1
Defecation	Not detected or 1		5	5
	2 or more		0	0
	Appearance: Normal		1/1	-

Table 4-1 Incidence of clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 Before the administration period 〉

Items	Score	Dose(mg/kg/day)	0	10	40	150	600
		No. of animals	10	5	5	5	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 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
Smudge around mouth-nose	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	4	4	5	10
	Temporally in handling		1	1	1	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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		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		1/1	1/1	1/1	2/2	2/2
Defecation	Not detected or 1		10	4	5	5	8
	2 or more		0	1	0	0	2
	Appearance:Normal		1/1	1/1	1/1	-	4/4

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

〈 On week 1 of the administration period 〉

Items	Score	Dose(mg/kg/day) / No. of animals	0 / 10	10 / 5	40 / 5	150 / 5	600 / 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 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
Smudge around mouth-nose	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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		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		1/1	1/1	-	1/1	3/3
Defecation	Not detected or 1		10	4	5	5	10
	2 or more		0	1	0	0	0
	Appearance:Normal		-	1/1	-	-	-

Table 4-3 Incidence of clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the administration period 〉

Items	Score	Dose(mg/kg/day)	0	10	40	150	600
		No. of animals	10	5	5	5	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 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
Smudge around mouth-nose	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	7
	Slight		0	0	0	0	3
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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		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
Defecation	Not detected or 1		10	5	5	5	10
	2 or more		0	0	0	0	0
	Appearance:Normal		-	-	-	-	-

Table 4-4 Incidence of clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 3 of the administration period 〉

Items	Score	Dose(mg/kg/day)	0	10	40	150	600
		No. of animals	10	5	5	5	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 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
Smudge around mouth-nose	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	8
	Slight		0	0	0	0	2
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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		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		-	-	-	-	-
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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the administration period 〉

Items	Score	Dose(mg/kg/day)	0	10	40	40	600
		No. of animals	10	5	5	5	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 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
Smudge around mouth-nose	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		9	4	4	5	9
	Temporally in handling		1	1	1	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
Alertness	Normal		10	5	5	5	10
Locomotor activity	Normal		10	5	5	5	10
Walk	Normal		10	5	5	5	10
Abnormal behavior	Not detected		10	5	5	5	10
Stereotypy	Not detected		10	5	5	5	10
Failure of consciousness	Not detected		10	5	5	5	10
Limb tone	Normal		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		1/1	1/1	-	-	2/2
Defecation	Not detected or 1		10	5	5	5	10
	2 or more		0	0	0	0	0
	Appearance:Normal		-	-	-	-	-

Table 4-6 Incidence of clinical signs in detailed observation of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 1 of the recovery period 〉

Items	Score	Dose(mg/kg/day) No. of animals	0 5	600 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 discharge	Not detected		5	5
Palpebral closure	Not detected		5	5
Exophthalmos	Not detected		5	5
Lacrimation	Not detected		5	5
Smudge around mouth-nose	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
Alertness	Normal		5	5
Locomotor activity	Normal		5	5
Walk	Normal		5	5
Abnormal behavior	Not detected		5	5
Stereotypy	Not detected		5	5
Failure of consciousness	Not detected		5	5
Limb tone	Normal		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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the recovery period 〉

Items	Score	Dose(mg/kg/day)	0	600
		No. of animals	5	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 discharge	Not detected		5	5
Palpebral closure	Not detected		5	5
Exophthalmos	Not detected		5	5
Lacrimation	Not detected		5	5
Smudge around mouth-nose	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
Alertness	Normal		5	5
Locomotor activity	Normal		5	5
Walk	Normal		5	5
Abnormal behavior	Not detected		5	5
Stereotypy	Not detected		5	5
Failure of consciousness	Not detected		5	5
Limb tone	Normal		5	5
Urination	Not detected or 1		5	5
	2 or more		0	0
	Color: Pale yellow		1/1	2/2
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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the administration period 〉

Items	Score	Dose(mg/kg/day)	0	10	40	150	600
		No. of animals	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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the recovery period 〉

Items	Score	Dose(mg/kg/day)	0	600
		No. of animals	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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 4 of the administration period 〉

Items	Score	Dose(mg/kg/day)	0	10	40	150	600
		No. of animals	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 diphenylene oxide in the repeated dose 28-day oral toxicity study

〈 On week 2 of the recovery period 〉

Items	Score	Dose(mg/kg/day)	0	600
		No. of animals	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 Grip strength and motor activity of male rats treated with diphenylene oxide 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	20	616 ± 96	389 ± 146	10556 ± 2419
10	10	525 ± 195	285 ± 68	14582 ± 2829
40	10	601 ± 99	383 ± 75	12714 ± 3361
150	10	570 ± 101	358 ± 66	12184 ± 2490
600	20	500 ± 118	295 ± 44	9851 ± 2490

Each value is exprssed as mean±S.D.

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

Table 7-2 Grip strength and motor activity of male rats treated with diphenylene oxide 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) Forelimb	Grip strength (g) Hindlimb	Motor activity (counts) 0~60min.
0	10	669 ± 67	377 ± 77	12891 ± 3367
600	10	669 ± 71	467 ± 85	8251 * ± 2253

Each value is exprssed as mean±S.D.

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

Table 8-1 Grip strength and motor activity of female rats treated with diphenylene oxide 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	20	567 ± 117	287 ± 33	15773 ± 2973
10	10	358 ** ± 65	275 ± 50	12291 ± 1532
40	10	464 ± 101	319 ± 56	14191 ± 4439
150	10	480 ± 75	265 ± 56	12200 ± 2687
600	20	487 ± 70	279 ± 61	10802 ± 4365

Each value is exprssed as mean±S.D.

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

Table 8-2 Grip strength and motor activity of female rats treated with diphenylene oxide 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	10	674 ± 19	374 ± 43	14370 ± 3933
600	10	632 ± 112	327 ± 22	14593 ± 2348

Each value is exprssed as mean±S.D.

Table 9 Body weight of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

(g)

Dose (mg/kg/day)	Day of the administration period						Day of the recovery period			
Day	1	7	14	21	28	Gain 1~28	0	7	14	Gain 0~14
0	162 ± 6 (10)	216 ± 13 (10)	274 ± 21 (10)	328 ± 33 (10)	368 ± 43 (10)	206 ± 40 (10)	381 ± 47 (5)	417 ± 57 (5)	432 ± 63 (5)	51 ± 16 (5)
10	163 ± 6 (5)	215 ± 8 (5)	270 ± 17 (5)	323 ± 27 (5)	363 ± 30 (5)	200 ± 30 (5)				
40	162 ± 5 (5)	215 ± 10 (5)	277 ± 15 (5)	339 ± 18 (5)	379 ± 18 (5)	217 ± 19 (5)				
150	162 ± 2 (5)	214 ± 7 (5)	270 ± 19 (5)	320 ± 27 (5)	355 ± 38 (5)	192 ± 39 (5)				
600	163 ± 6 (10)	201 ** ± 9 (10)	257 ± 15 (10)	309 ± 24 (10)	344 ± 33 (10)	182 ± 32 (10)	354 ± 40 (5)	398 ± 40 (5)	424 ± 33 (5)	70 ± 12 (5)

Each value is expressed as mean±S.D.

(n) : No. of animals.

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

Table 10 Body weight of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

(g)

Dose (mg/kg/day)	Day of the administration period						Day of the recovery period			
Day	1	7	14	21	28	Gain 1～28	0	7	14	Gain 0～14
0	137 ± 7 (10)	158 ± 8 (10)	175 ± 11 (10)	198 ± 16 (10)	214 ± 19 (10)	78 ± 13 (10)	213 ± 22 (5)	233 ± 22 (5)	242 ± 20 (5)	30 ± 7 (5)
10	137 ± 6 (5)	164 ± 6 (5)	183 ± 4 (5)	203 ± 12 (5)	224 ± 12 (5)	87 ± 9 (5)				
40	139 ± 6 (5)	163 ± 7 (5)	183 ± 6 (5)	205 ± 12 (5)	222 ± 17 (5)	83 ± 15 (5)				
150	139 ± 4 (5)	161 ± 6 (5)	182 ± 7 (5)	207 ± 8 (5)	218 ± 13 (5)	80 ± 9 (5)				
600	135 ± 6 (10)	155 ± 6 (10)	180 ± 11 (10)	200 ± 14 (10)	215 ± 15 (10)	80 ± 14 (10)	209 ± 18 (5)	224 ± 21 (5)	235 ± 22 (5)	27 ± 6 (5)

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

Table 11 Food consumption of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

(g/rat/day)

Dose (mg/kg/day)	Week	Week of the administration period 1	2	3	4	Week of the recovery period 1	2
0		29 ± 4 (10)	31 ± 3 (10)	32 ± 4 (10)	31 ± 6 (10)	35 ± 4 (5)	40 ± 5 (5)
10		28 ± 3 (5)	28 ± 3 (5)	31 ± 4 (5)	28 ± 6 (5)		
40		29 ± 2 (5)	32 ± 4 (5)	34 ± 4 (5)	31 ± 2 (5)		
150		29 ± 1 (5)	29 ± 1 (5)	32 ± 4 (5)	32 ± 5 (5)		
600		28 ± 3 (10)	32 ± 4 (10)	33 ± 4 (10)	33 ± 4 (10)	36 ± 6 (5)	39 ± 6 (5)

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

Table 12 Food consumption of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

(g/rat/day)

Dose (mg/kg/day)	Week	Week of the administration period 1	2	3	4	Week of the recovery period 1	2
0		19 ± 4 (10)	20 ± 2 (10)	20 ± 2 (10)	20 ± 3 (10)	23 ± 2 (5)	24 ± 3 (5)
10		20 ± 2 (5)	20 ± 2 (5)	22 ± 2 (5)	20 ± 3 (5)		
40		22 ± 2 (5)	20 ± 3 (5)	21 ± 3 (5)	20 ± 2 (5)		
150		22 ± 2 (5)	22 ± 3 (5)	21 ± 3 (5)	20 ± 4 (5)		
600		20 ± 3 (10)	20 ± 3 (10)	22 ± 3 (10)	23 ± 2 (10)	25 ± 5 (5)	24 ± 7 (5)

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

Table 13-1 Urinary findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 4 of the administration period >

Dose (mg/kg/day)	No. of animals	Color	Cloudy		Volume[a] (mL/18hr)	Specific gravity[a]	pH						Protein				
		PY	−	+			6.0	6.5	7.0	7.5	8.0	8.5	−	±	1+	2+	3+
0	5	5	5		6.7 ± 3.1	1.063 ± 0.014						5		1	4		
10	5	5	5		8.1 ± 2.5	1.056 ± 0.007					4	1		2	3		
40	5	5	5		9.3 ± 2.5	1.055 ± 0.008					3	2			5		
150	5	5	5		11.1 ± 2.0	1.051 ± 0.008					2	3		2	3		
600	5	5	5		10.1 ± 2.8	1.057 ± 0.005					3	2		3	2		

Dose (mg/kg/day)	No. of animals	Glucose				Ketone body				Occult blood					Urobilinogen				Bilirubin			
		−	±	1+	2+	−	±	1+	2+	−	±	1+	2+	3+	0.1	1	2	4	−	1+	2+	3+
0	5	5				5				5					5				5			
10	5	5				5				5					5				5			
40	5	5				5				5					5				5			
150	5	5				5				5					5				5			
600	5	5				5				5					5				5			

a) : Mean±S.D.
Color : PY(pale yellow).
Cloudy : −(negligible), +(cloudy).
Protein : −(negligible), ±(15~30mg/dL), 1+(30mg/dL), 2+(100mg/dL), 3+(300mg/dL).
Glucose : −(negligible), ±(0.1g/dL), 1+(0.25g/dL), 2+(0.5g/dL).
Ketone body : −(negligible), ±(5mg/dL), 1+(15mg/dL), 2+(40mg/dL).
Occult blood : −(negligible), ±(trace), 1+(slight), 2+(moderate), 2+(marked).
Urobilinogen : Ehrlich unit/dL.
Bilirubin : −(negligible), 1+(slight), 2+(moderate), 3+(marked).

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

< On week 2 of the recovery period >

Dose (mg/kg/day)	No. of animals	Color	Cloudy		Volume[a] (mL/18hr)	Specific gravity[a]	pH						Protein				
		PY	−	+			6.0	6.5	7.0	7.5	8.0	8.5	−	±	1+	2+	3+
0	5	5	5		12.5 ± 3.0	1.039 ± 0.014					4	1			5		
600	5	5	5		14.3 ± 4.5	1.039 ± 0.010					5		1	2	2		

Dose (mg/kg/day)	No. of animals	Glucose				Ketone body				Occult blood					Urobilinogen				Bilirubin			
		−	±	1+	2+	−	±	1+	2+	−	±	1+	2+	3+	0.1	1	2	4	−	1+	2+	3+
0	5	5				5				5					5				5			
600	5	5				5				5					5				5			

a) : Mean±S.D.
Color : PY(pale yellow).
Cloudy : −(negligible), +(cloudy).
Protein : −(negligible), ±(15~30mg/dL), 1+(30mg/dL), 2+(100mg/dL), 3+(300mg/dL).
Glucose : −(negligible), ±(0.1g/dL), 1+(0.25g/dL), 2+(0.5g/dL).
Ketone body : −(negligible), ±(5mg/dL), 1+(15mg/dL), 2+(40mg/dL).
Occult blood : −(negligible), ±(trace), 1+(slight), 2+(moderate), 2+(marked).
Urobilinogen : Ehrlich unit/dL.
Bilirubin : −(negligible), 1+(slight), 2+(moderate), 3+(marked).

Table 13-3 Urinary findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 4 of the 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				4	1			5			5		
10	5	5				5				5				5			5		
40	5	5				5				4	1			5			5		
150	5	5				5				3	2			5			5		
600	5	5				5				5				5			5		

Dose (mg/kg/day)	No. of animals	Epithelial cells																					
		Sq				R			S			Casts								Fat globules		
												G		H		W						
		−	1+	2+	3+	−	1+	2+	−	1+	2+	−	1+	−	1+	−	1+	−	1+	2+
0	5	3	2			5			5			5		5		5		5		
10	5	3	2			5			5			5		5		5		5		
40	5	4	1			5			5			5		5		5		5		
150	5	1	4			5			5			5		5		5		5		
600	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 13-4 Urinary findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 2 of the 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	3			5			5		
600	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	2	3			5			5			5		5		5		5				
600	5	2	3			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 diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 4 of the administration period >

Dose (mg/kg/day)	No. of animals	Color PY	Cloudy −	Cloudy +	Volume[a] (mL/18hr)	Specific gravity[a]	pH 6.0	pH 6.5	pH 7.0	pH 7.5	pH 8.0	pH 8.5	Protein −	Protein ±	Protein 1+	Protein 2+	Protein 3+
0	5	5	5		6.1 ± 3.1	1.060 ± 0.012		1			3	1	1	1	3		
10	5	5	5		9.2 ± 2.4	1.047 ± 0.008				1	2	2	2	1	2		
40	5	5	5		7.2 ± 2.9	1.055 ± 0.011			1		1	3		3	2		
150	5	5	5		6.4 ± 1.9	1.055 ± 0.005			1	1	3		1	4			
600	5	5	5		13.3 ** ± 2.7	1.042 * ± 0.002					2	3	5 *				

Dose (mg/kg/day)	No. of animals	Glucose −	Glucose ±	Glucose 1+	Glucose 2+	Ketone body −	Ketone body ±	Ketone body 1+	Ketone body 2+	Occult blood −	Occult blood ±	Occult blood 1+	Occult blood 2+	Occult blood 3+	Urobilinogen 0.1	Urobilinogen 1	Urobilinogen 2	Urobilinogen 4	Bilirubin −	Bilirubin 1+	Bilirubin 2+	Bilirubin 3+
0	5	5				5				5					5				5			
10	5	5				5				5					5				5			
40	5	5				4	1			5					5				5			
150	5	5				5				5					5				5			
600	5	5				5				5					5				5			

a) : Mean±S.D.
Color : PY(pale yellow).
Cloudy : −(negligible), +(cloudy).
Protein : −(negligible), ±(15～30mg/dL), 1+(30mg/dL), 2+(100mg/dL), 3+(300mg/dL).
Glucose : −(negligible), ±(0.1g/dL), 1+(0.25g/dL), 2+(0.5g/dL).
Ketone body : −(negligible), ±(5mg/dL), 1+(15mg/dL), 2+(40mg/dL).
Occult blood : −(negligible), ±(trace), 1+(slight), 2+(moderate), 2+(marked).
Urobilinogen : Ehrlich unit/dL.
Bilirubin : −(negligible), 1+(slight), 2+(moderate), 3+(marked).
* : 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 diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 2 of the recovery period >

Dose (mg/kg/day)	No. of animals	Color		Cloudy		Volume[a] (mL/18hr)	Specific[a] gravity	pH						Protein				
		PY		−	+			6.0	6.5	7.0	7.5	8.0	8.5	−	±	1+	2+	3+
0	5	5		5		7.4 ± 2.7	1.051 ± 0.010			1	1	2	1	2	1	2		
600	5	5		5		6.6 ± 1.5	1.045 ± 0.012				1	1	3	1	3	1		

Dose (mg/kg/day)	No. of animals	Glucose				Ketone body				Occult blood					Urobilinogen				Bilirubin			
		−	±	1+	2+	−	±	1+	2+	−	±	1+	2+	3+	0.1	1	2	4	−	1+	2+	3+
0	5	5				5				5					5				5			
600	5	5				5				5					5				5			

a) : Mean±S.D.
Color : PY(pale yellow).
Cloudy : −(negligible), +(cloudy).
Protein : −(negligible), ±(15~30mg/dL), 1+(30mg/dL), 2+(100mg/dL), 3+(300mg/dL).
Glucose : −(negligible), ±(0.1g/dL), 1+(0.25g/dL), 2+(0.5g/dL).
Ketone body : −(negligible), ±(5mg/dL), 1+(15mg/dL), 2+(40mg/dL).
Occult blood : −(negligible), ±(trace), 1+(slight), 2+(moderate), 2+(marked).
Urobilinogen : Ehrlich unit/dL.
Bilirubin : −(negligible), 1+(slight), 2+(moderate), 3+(marked).

Table 14-3 Urinary findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 4 of the 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				4		1		5			5		
10	5	5				5				3	2			5			5		
40	5	5				5				4	1			5			5		
150	5	5				5				4	1			5			5		
600	5	5				5				4	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		
10	5	3	2			5			5			5		5		5		5		
40	5	1	4			5			5			5		5		5		5		
150	5	4	1			5			5			5		5		5		5		
600	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 14-4 Urinary findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< On week 2 of the 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				3	1		1	5			5		
600	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	1	4			5			5			5		5		5		5		
600	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 15-1 Hematological findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	No. of animals	RBC ($10^4/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	5	774 ± 16	15.3 ± 0.3	47.1 ± 0.7	61 ± 2	19.8 ± 0.5	32.5 ± 0.3	33.0 ± 5.6	12.3 ± 0.5
10	5	755 ± 23	14.7 ± 0.3	45.7 ± 1.0	61 ± 2	19.4 ± 0.5	32.1 ± 0.2	33.5 ± 5.8	12.6 ± 0.4
40	5	726 * ± 26	14.2 ** ± 0.3	44.0 ** ± 0.8	61 ± 3	19.6 ± 0.8	32.4 ± 0.3	35.9 ± 5.4	12.6 ± 0.5
150	5	736 ± 31	14.4 ** ± 0.5	44.8 ** ± 0.9	61 ± 2	19.6 ± 0.3	32.2 ± 0.6	32.3 ± 6.3	13.5 ** ± 0.5
600	5	723 * ± 20	14.1 ** ± 0.6	43.7 ** ± 1.5	60 ± 2	19.4 ± 0.5	32.2 ± 0.4	35.8 ± 5.8	13.3 * ± 0.7

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. ($10^4/\mu L$)	WBC ($10^2/\mu L$)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	19.6 ± 1.4	122 ± 7	60 ± 12	0.0 ± 0.0	0.6 ± 0.3	14.3 ± 3.8	83.1 ± 3.7	1.9 ± 0.3
10	5	19.4 ± 0.4	121 ± 16	58 ± 14	0.0 ± 0.0	1.1 ± 0.6	15.7 ± 3.2	81.1 ± 3.2	2.0 ± 0.3
40	5	19.2 ± 0.6	138 ± 9	64 ± 15	0.0 ± 0.0	1.2 ± 0.3	14.8 ± 3.3	81.9 ± 2.9	2.2 ± 0.2
150	5	20.2 ± 2.1	127 ± 14	68 ± 16	0.0 ± 0.0	0.7 ± 0.4	15.0 ± 4.1	82.3 ± 4.0	2.1 ± 0.5
600	5	22.0 ± 2.4	126 ± 8	72 ± 16	0.0 ± 0.0	0.8 ± 0.2	14.3 ± 5.5	82.7 ± 5.9	2.2 ± 0.4

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 diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

Dose (mg/kg/day)	No. of animals	RBC ($10^4/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	5	856 ± 65	15.9 ± 0.9	47.7 ± 2.5	56 ± 2	18.6 ± 0.7	33.4 ± 0.1	23.3 ± 5.6	12.7 ± 0.5
600	4	855 ± 12	15.7 ± 0.4	47.5 ± 1.3	56 ± 1	18.3 ± 0.4	33.0 ± 0.5	26.1 ± 6.1	13.2 ± 0.4

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. ($10^4/\mu L$)	WBC ($10^2/\mu L$)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	20.7 ± 0.6	137 ± 12	80 ± 18	0.0 ± 0.0	1.0 ± 0.5	11.0 ± 2.9	85.3 ± 3.0	2.8 ± 0.9
600	4	21.3 ± 0.5	158 * ± 12	92 ± 21	0.0 ± 0.0	1.1 ± 0.3	11.5 ± 1.7	85.3 ± 4.0	3.2 ± 0.6

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 diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

Dose (mg/kg/day)	No. of animals	RBC ($10^4/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	5	759 ± 26	14.6 ± 0.5	44.0 ± 1.3	58 ± 1	19.3 ± 0.4	33.3 ± 0.4	24.4 ± 5.2	12.9 ± 0.6
10	5	742 ± 39	14.7 ± 0.5	44.6 ± 1.6	60 ± 2	19.9 ± 0.5	33.1 ± 0.2	24.1 ± 4.2	12.7 ± 0.4
40	5	736 ± 18	14.2 ± 0.4	42.7 ± 0.8	58 ± 2	19.3 ± 0.5	33.2 ± 0.6	20.7 ± 1.7	13.0 ± 0.4
150	5	748 ± 22	14.2 ± 0.4	43.0 ± 0.7	58 ± 2	19.0 ± 0.5	33.0 ± 0.6	22.1 ± 1.2	12.8 ± 0.4
600	5	712 ± 20	13.8 * ± 0.5	42.2 ± 1.4	59 ± 1	19.4 ± 0.4	32.7 ± 0.5	20.5 ± 3.6	12.0 * ± 0.5

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. ($10^4/\mu L$)	WBC ($10^2/\mu L$)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	19.2 ± 1.2	123 ± 11	54 ± 19	0.0 ± 0.0	0.8 ± 0.2	11.2 ± 0.9	85.8 ± 0.8	2.2 ± 0.4
10	5	18.7 ± 1.5	122 ± 5	67 ± 18	0.0 ± 0.0	1.0 ± 0.4	12.8 ± 3.3	84.5 ± 4.0	1.7 ± 0.4
40	5	18.2 ± 0.9	130 ± 14	54 ± 20	0.0 ± 0.0	1.4 ± 0.8	11.6 ± 2.2	84.6 ± 2.4	2.3 ± 0.9
150	5	18.0 ± 0.7	134 ± 5	56 ± 15	0.0 ± 0.0	1.5 ± 0.7	11.3 ± 2.3	83.9 ± 2.2	3.2 ± 0.6
600	5	18.1 ± 1.9	127 ± 18	65 ± 14	0.0 ± 0.0	1.1 ± 0.3	13.5 ± 3.2	83.0 ± 3.4	2.3 ± 0.2

Each value is expressed as mean±S.D.
* : Significantly different from control at 5% level of probability

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

< At the end of recovery period >

Dose (mg/kg/day)	No. of animals	RBC ($10^4/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (‰)	PT (sec)
0	5	800 ± 35	15.2 ± 0.8	44.2 ± 2.3	55 ± 1	19.0 ± 0.3	34.3 ± 0.4	20.9 ± 2.9	12.5 ± 0.5
600	5	813 ± 42	15.3 ± 0.5	45.0 ± 1.3	55 ± 2	18.9 ± 0.5	34.1 ± 0.4	21.6 ± 3.4	12.2 ± 0.4

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. ($10^4/\mu L$)	WBC ($10^2/\mu L$)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	17.5 ± 1.1	138 ± 16	64 ± 18	0.0 ± 0.0	1.5 ± 0.6	10.0 ± 2.1	85.6 ± 2.0	2.9 ± 0.4
600	5	18.6 ± 1.5	133 ± 11	54 ± 12	0.0 ± 0.0	1.8 ± 0.6	12.7 ± 2.8	82.8 ± 3.6	2.8 ± 1.0

Each value is expressed as mean±S.D.

Table 17-1 Blood biochemical findings of male rats treated with diphenylene oxide 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	301 ± 70	69 ± 10	35 ± 5	783 ± 127	0.56 ± 0.14	5.60 ± 0.14	2.76 ± 0.12	0.98 ± 0.08	66 ± 9	71 ± 26
10	5	339 ± 212	63 ± 10	29 ± 3	854 ± 62	0.51 ± 0.11	5.70 ± 0.13	2.87 ± 0.06	1.02 ± 0.08	62 ± 11	40 ± 7
40	5	349 ± 191	63 ± 2	29 ± 3	792 ± 75	0.67 ± 0.24	5.66 ± 0.20	2.78 ± 0.13	0.97 ± 0.05	69 ± 15	60 ± 22
150	5	322 ± 140	72 ± 9	35 ± 6	729 ± 78	0.63 ± 0.17	5.75 ± 0.30	2.99 ± 0.22	1.08 ± 0.07	76 ± 6	80 ± 22
600	5	393 ± 136	72 ± 9	43 * ± 3	728 ± 128	1.40 ** ± 0.43	5.75 ± 0.26	2.93 ± 0.15	1.04 ± 0.06	101 ** ± 21	53 ± 13

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 ± 16	12.6 ± 1.5	0.38 ± 0.07	0.37 ± 0.09	9.8 ± 0.2	8.9 ± 0.6	146 ± 1	4.84 ± 0.57	105 ± 1
10	5	144 ± 9	12.9 ± 2.3	0.33 ± 0.04	0.37 ± 0.02	10.0 ± 0.3	9.2 ± 0.7	147 ± 2	5.59 ± 0.48	105 ± 1
40	5	142 ± 15	12.8 ± 2.1	0.37 ± 0.03	0.37 ± 0.03	9.5 ± 0.1	9.1 ± 0.2	147 ± 1	5.16 ± 0.51	105 ± 1
150	5	143 ± 15	11.2 ± 1.5	0.36 ± 0.02	0.36 ± 0.03	9.7 ± 0.4	8.8 ± 0.6	148 ± 2	5.23 ± 0.70	106 ± 2
600	5	132 ± 6	11.7 ± 1.2	0.39 ± 0.03	0.38 ± 0.02	9.4 ± 0.3	9.4 ± 0.7	146 ± 1	5.15 ± 0.31	107 ± 1

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 17-2 Blood biochemical findings of male rats treated with diphenylene oxide 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	307 ± 171	68 ± 6	31 ± 5	616 ± 130	0.60 ± 0.06	6.14 ± 0.24	2.84 ± 0.16	0.86 ± 0.05	65 ± 8	59 ± 28
600	5	354 ± 102	71 ± 3	33 ± 3	508 ± 108	0.65 ± 0.17	6.02 ± 0.15	2.85 ± 0.11	0.90 ± 0.06	77 ± 11	59 ± 14

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	157 ± 11	15.7 ± 1.8	0.37 ± 0.02	0.35 ± 0.03	9.9 ± 0.3	8.3 ± 0.2	146 ± 1	4.90 ± 0.38	106 ± 1
600	5	160 ± 12	17.6 ± 1.9	0.44 ± 0.11	0.33 ± 0.02	9.7 ± 0.1	8.2 ± 0.3	145 ± 2	5.22 ± 0.29	107 ± 1

Each value is expressed as mean±S.D.

Table 18-1 Blood biochemical findings of female rats treated with diphenylene oxide 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	416 ± 75	73 ± 12	29 ± 3	537 ± 85	1.18 ± 0.65	5.74 ± 0.18	3.00 ± 0.04	1.10 ± 0.08	75 ± 14	27 ± 9
10	5	403 ± 104	72 ± 5	28 ± 4	612 ± 129	1.40 ± 0.88	5.79 ± 0.27	3.01 ± 0.22	1.08 ± 0.07	72 ± 4	21 ± 8
40	5	464 ± 100	68 ± 1	29 ± 3	498 ± 151	1.18 ± 0.40	5.62 ± 0.24	2.95 ± 0.15	1.10 ± 0.06	75 ± 10	26 ± 4
150	5	497 ± 106	68 ± 6	28 ± 2	465 ± 68	1.31 ± 0.49	5.73 ± 0.22	3.09 ± 0.23	1.18 ± 0.10	92 ± 17	44 ± 18
600	5	514 ± 93	66 ± 1	35 * ± 3	534 ± 102	1.48 ± 0.47	6.04 ± 0.09	3.31 * ± 0.12	1.21 ± 0.11	117 ** ± 21	70 * ± 27

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	133 ± 13	14.5 ± 2.1	0.42 ± 0.06	0.24 ± 0.02	9.4 ± 0.3	7.6 ± 0.5	145 ± 1	4.83 ± 0.19	107 ± 1
10	5	129 ± 11	15.6 ± 2.6	0.39 ± 0.06	0.25 ± 0.02	9.3 ± 0.4	7.7 ± 0.7	147 ± 1	4.66 ± 0.24	107 ± 1
40	5	127 ± 13	14.4 ± 1.6	0.37 ± 0.04	0.25 ± 0.03	9.6 ± 0.3	7.7 ± 0.4	146 ± 1	5.02 ± 0.31	107 ± 2
150	5	122 ± 7	14.7 ± 3.5	0.36 ± 0.01	0.26 ± 0.02	9.7 ± 0.4	7.4 ± 0.9	145 ± 2	5.14 ± 0.40	108 ± 2
600	5	124 ± 8	12.6 ± 1.4	0.38 ± 0.03	0.32 ** ± 0.02	9.9 * ± 0.2	7.8 ± 0.7	147 ± 1	4.70 ± 0.18	107 ± 1

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 diphenylene oxide 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	431 ± 280	71 ± 9	24 ± 4	384 ± 83	1.37 ± 0.40	6.03 ± 0.10	2.99 ± 0.08	0.98 ± 0.05	62 ± 7	20 ± 3
600	5	457 ± 55	74 ± 18	26 ± 5	364 ± 80	0.95 ± 0.52	6.03 ± 0.21	3.16 * ± 0.14	1.11 * ± 0.07	85 * ± 18	25 ± 10

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	123 ± 5	17.1 ± 1.6	0.43 ± 0.03	0.26 ± 0.03	9.6 ± 0.1	7.9 ± 0.7	144 ± 1	4.97 ± 0.35	108 ± 1
600	5	130 ± 8	15.1 ± 1.6	0.40 ± 0.03	0.24 ± 0.02	9.7 ± 0.3	7.6 ± 0.5	144 ± 1	4.79 ± 0.45	108 ± 2

Each value is expressed as mean±S.D.
* : Significantly different from control at 5% level of probability.

Table 19 Incidence of necropsy findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

Organ	: Findings		At the end of administration period					At the end of recovery period	
		Dose(mg/kg/day)	0	10	40	150	600	0	600
		Fate	KA	KA	KA	KA	KA	KR	KR
		No.of animals	5	5	5	5	5	5	5
	Abnormality		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.

Table 20 Incidence of necropsy findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

Organ	: Findings		At the end of administration period					At the end of recovery period	
		Dose(mg/kg/day)	0	10	40	150	600	0	600
		Fate	KA	KA	KA	KA	KA	KR	KR
		No.of animals	5	5	5	5	5	5	5
	Abnormality		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.

Table 21-1 Absolute and relative organ weights of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

	Dose (mg/kg/day)	No.of Animals	B.W. (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland(mg)	Spleen (g)	Testis (g)	Epididymis (g)
Absolute	0	5	326 ± 35	1.91 ± 0.11	0.47 ± 0.07	1.06 ± 0.10	10.33 ± 1.87	2.40 ± 0.37	54.6 ± 7.9	0.68 ± 0.14	3.17 ± 0.24	0.79 ± 0.04
	10	5	334 ± 29	1.94 ± 0.07	0.55 ± 0.09	1.18 ± 0.09	10.38 ± 1.39	2.66 ± 0.25	58.3 ± 6.3	0.72 ± 0.07	3.22 ± 0.09	0.82 ± 0.04
	40	5	351 ± 18	1.97 ± 0.08	0.50 ± 0.04	1.19 ± 0.08	11.90 ± 0.76	2.81 ± 0.15	56.2 ± 8.3	0.74 ± 0.08	3.23 ± 0.12	0.80 ± 0.04
	150	5	325 ± 36	1.86 ± 0.09	0.55 ± 0.09	1.10 ± 0.11	12.08 ± 1.69	2.68 ± 0.36	57.5 ± 12.2	0.66 ± 0.14	3.33 ± 0.20	0.78 ± 0.04
	600	5	301 ± 19	1.86 ± 0.06	0.42 ± 0.08	1.03 ± 0.05	12.27 ± 1.21	2.54 ± 0.28	48.3 ± 3.7	0.59 ± 0.13	3.13 ± 0.25	0.78 ± 0.04
Relative @	0	5	326 ± 35	0.59 ± 0.04	0.14 ± 0.01	0.32 ± 0.02	3.15 ± 0.24	0.73 ± 0.04	16.7 ± 1.5	0.21 ± 0.02	0.98 ± 0.08	0.24 ± 0.03
	10	5	334 ± 29	0.58 ± 0.05	0.16 ± 0.03	0.35 ± 0.02	3.10 ± 0.17	0.80 ± 0.03	17.6 ± 2.8	0.22 ± 0.02	0.97 ± 0.10	0.25 ± 0.03
	40	5	351 ± 18	0.56 ± 0.04	0.14 ± 0.02	0.34 ± 0.02	3.39 ± 0.12	0.80 ± 0.04	16.1 ± 2.6	0.21 ± 0.03	0.92 ± 0.04	0.23 ± 0.02
	150	5	325 ± 36	0.57 ± 0.04	0.17 ± 0.03	0.34 ± 0.02	3.71 ** ± 0.15	0.82 * ± 0.06	17.6 ± 2.5	0.20 ± 0.03	1.03 ± 0.12	0.24 ± 0.02
	600	5	301 ± 19	0.62 ± 0.03	0.14 ± 0.02	0.34 ± 0.02	4.06 ** ± 0.19	0.84 ** ± 0.05	16.0 ± 0.9	0.19 ± 0.03	1.04 ± 0.08	0.26 ± 0.004

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 diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

	Dose (mg/kg/day)	No.of Animals	B.W. (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland(mg)	Spleen (g)	Testis (g)	Epididymis (g)
Absolute	0	5	399 ±60	1.97 ±0.04	0.50 ±0.16	1.28 ±0.21	11.56 ±2.61	3.11 ±0.47	69.6 ±14.1	0.73 ±0.15	3.58 ±0.27	1.15 ±0.08
	600	5	381 ±38	1.97 ±0.10	0.38 ±0.08	1.23 ±0.13	11.12 ±1.79	2.83 ±0.27	70.6 ±4.1	0.68 ±0.07	3.61 ±0.25	1.20 ±0.04
Relative @	0	5	399 ±60	0.50 ±0.07	0.12 ±0.03	0.32 ±0.02	2.87 ±0.22	0.78 ±0.03	17.5 ±2.9	0.18 ±0.03	0.91 ±0.10	0.29 ±0.04
	600	5	381 ±38	0.52 ±0.04	0.10 ±0.01	0.32 ±0.04	2.90 ±0.20	0.74 * ±0.02	18.7 ±2.2	0.18 ±0.01	0.96 ±0.14	0.32 ±0.02

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 diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of administration period >

	Dose (mg/kg/day)	No.of Animals	B.W. (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland(mg)	Spleen (g)	Ovary (mg)
Absolute	0	5	197 ± 16	1.76 ± 0.10	0.39 ± 0.04	0.75 ± 0.03	5.99 ± 0.33	1.47 ± 0.08	66.7 ± 8.6	0.47 ± 0.07	86.9 ± 11.3
	10	5	204 ± 11	1.78 ± 0.09	0.47 ± 0.07	0.83 ± 0.14	6.13 ± 0.61	1.61 ± 0.12	68.6 ± 8.3	0.48 ± 0.05	93.8 ± 14.5
	40	5	205 ± 14	1.78 ± 0.09	0.51 ± 0.11	0.77 ± 0.10	6.26 ± 0.66	1.66 ± 0.18	67.5 ± 5.3	0.45 ± 0.08	88.3 ± 11.0
	150	5	199 ± 11	1.76 ± 0.06	0.42 ± 0.07	0.78 ± 0.06	6.66 ± 0.55	1.68 ± 0.12	66.6 ± 5.7	0.45 ± 0.06	88.8 ± 15.3
	600	5	197 ± 8	1.73 ± 0.10	0.39 ± 0.05	0.75 ± 0.05	8.51 ** ± 0.59	1.71 ± 0.12	59.6 ± 7.8	0.45 ± 0.09	79.6 ± 15.2
Relative @	0	5	197 ± 16	0.90 ± 0.04	0.20 ± 0.03	0.38 ± 0.03	3.06 ± 0.26	0.75 ± 0.05	33.8 ± 2.9	0.24 ± 0.03	44.4 ± 7.1
	10	5	204 ± 11	0.87 ± 0.09	0.23 ± 0.03	0.41 ± 0.07	3.00 ± 0.16	0.79 ± 0.06	33.7 ± 4.3	0.24 ± 0.03	46.1 ± 7.5
	40	5	205 ± 14	0.87 ± 0.03	0.25 ± 0.05	0.37 ± 0.03	3.05 ± 0.18	0.81 ± 0.07	33.0 ± 3.6	0.22 ± 0.03	43.1 ± 5.7
	150	5	199 ± 11	0.88 ± 0.06	0.22 ± 0.04	0.39 ± 0.01	3.34 ± 0.12	0.84 ± 0.05	33.4 ± 2.2	0.22 ± 0.02	44.7 ± 8.2
	600	5	197 ± 8	0.88 ± 0.05	0.20 ± 0.02	0.38 ± 0.02	4.32 ** ± 0.14	0.87 * ± 0.06	30.3 ± 4.2	0.23 ± 0.04	40.5 ± 7.7

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 diphenylene oxide in the repeated dose 28-day oral toxicity study

< At the end of recovery period >

	Dose (mg/kg/day)	No.of Animals	B.W. (g)	Brain (g)	Thymus (g)	Heart (g)	Liver (g)	Kidney (g)	Adrenal gland(mg)	Spleen (g)	Ovary (mg)
Absolute	0	5	222 ± 19	1.79 ± 0.08	0.44 ± 0.07	0.78 ± 0.06	5.78 ± 0.43	1.75 ± 0.12	72.0 ± 5.8	0.50 ± 0.07	81.9 ± 14.2
	600	5	211 ± 22	1.75 ± 0.08	0.34 * ± 0.06	0.76 ± 0.08	6.20 ± 0.82	1.61 ± 0.17	66.8 ± 10.2	0.41 * ± 0.03	76.9 ± 9.3
Relative @	0	5	222 ± 19	0.81 ± 0.05	0.20 ± 0.02	0.35 ± 0.02	2.60 ± 0.11	0.79 ± 0.04	32.8 ± 5.0	0.22 ± 0.02	37.3 ± 8.2
	600	5	211 ± 22	0.84 ± 0.09	0.16 ± 0.03	0.36 ± 0.01	2.94 ** ± 0.12	0.76 ± 0.04	31.6 ± 2.5	0.19 * ± 0.01	36.7 ± 4.5

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 23 Incidence of histopathological findings of male rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

Organ	: Findings	Grade	At the end of administration period					At the end of recovery period	
		Dose(mg/kg/day)	0	10	40	150	600	0	600
		Fate	KA	KA	KA	KA	KA	KR	KR
		No.of animals	5	5	5	5	5	5	5
Lung	: Accumulation, foam cell, focal	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
Heart	: Myocardial degeneration/fibrosis	-	5	#	#	#	4	#	#
		+	0	#	#	#	1	#	#
Liver	: Hypertrophy, hepatocyte, centrilobular	-	5	5	5	3	0	5	5
		+	0	0	0	2	2 **	0	0
		++	0	0	0	0	3	0	0
	Necrosis, focal	-	4	4	5	5	3	4	3
		+	1	1	0	0	2	1	2
	Microgramuloma	-	4	4	3	5	4	4	4
		+	1	1	2	0	1	1	1
Kidney	: Hyaline droplet, proximal tubular epithelium	-	0	1	2	1	0	1	2
		+	3	4	3	3	3	4	3
		++	2	0	0	1	2	0	0
	Basophilic tubule	-	2	3	1	2	3	3	3
		+	3	2	4	3	1	2	2
		++	0	0	0	0	1	0	0
	Cellular infiltration, lymphocyte, cortex	-	4	3	2	4	5	4	3
		+	1	2	3	1	0	1	2
	Cast,hyaline	-	3	5	5	5	4	4	5
		+	2	0	0	0	1	1	0
	Cyst, solitary	-	5	5	5	4	5	5	5
		+	0	0	0	1	0	0	0
	Fibrosis, cortex	-	5	5	5	4	5	5	5
		+	0	0	0	1	0	0	0
Spleen	: Hematopoiesis, extramedullary	-	0	#	#	#	0	#	#
		+	5	#	#	#	5	#	#
	Deposit, pigment, brown	-	0	#	#	#	0	#	#
		+	5	#	#	#	5	#	#

KA : Killed by design at the end of administration period; KR : Killed by design at the end of recovery period; #:Not examined.
Grade, - : Negative; + : Slight; ++ : Moderate.
No abnormalities were detected in the brain, pituitary, thyroid, parathyroid, thymus, trachea, stomach, small intestine, large intestine, adrenal, urinary bladder, testis, epididymis, prostate, seminal vesicle, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball from animals of control and 600 mg/kg group.
** : Significantly different from control at 1% level of probability.

Table 24-1 Incidence of histopathological findings of female rats treated with diphenylene oxide in the repeated dose 28-day oral toxicity study

Organ	: Findings	Grade	At the end of administration period					At the end of recovery period	
		Dose(mg/kg/day)	0	10	40	150	600	0	600
		Fate	KA	KA	KA	KA	KA	KR	KR
		No.of animals	5	5	5	5	5	5	5
Lung	: Accumulation, foam cell	-	5	#	#	#	4	#	#
		+	0	#	#	#	1	#	#
	Mineralization, artery	-	4	#	#	#	4	#	#
		+	1	#	#	#	1	#	#
Liver	: Hypertrophy, hepatocyte, centrilobular	-	5	5	5	5	0	5	5
		++	0	0	0	0	5 **	0	0
	Degeneration, fatty change, hepatocyte, periportal	-	4	5	5	5	5	5	5
		+	1	0	0	0	0	0	0
	Necrosis, focal	-	5	5	4	5	5	5	5
		+	0	0	1	0	0	0	0
	Microgramuloma	-	4	5	4	4	4	3	3
		+	1	0	1	1	1	2	2
Kidney	: Dilatation, tubular, cortex	-	5	5	5	5	1	5	5
		+	0	0	0	0	2] *	0	0
		++	0	0	0	0	2]	0	0
	Degenertion, vacuolar, tubular epithelium, cortex	-	5	5	5	5	1	5	5
		+	0	0	0	0	4 *	0	0
	Basophilic tubule	-	3	4	4	3	4	4	4
		+	2	1	1	2	1	1	1
	Cellular infiltration, lymphocyte, cortex	-	5	4	5	4	5	4	3
		+	0	1	0	1	0	1	2
	Cast,hyaline	-	5	5	5	5	5	4	5
		+	0	0	0	0	0	1	0
	Fibrosis, cortex	-	5	4	5	5	5	5	5
		+	0	1	0	0	0	0	0
	Mineralization, cortico-medullary junction	-	4	5	5	4	5	5	5
		+	1	0	0	1	0	0	0

KA : Killed by design at the end of administration period; KR : Killed by design at the end of recovery period; #:Not examined.

Grade, - : Negative; + : Slight; ++ : Moderate.

No abnormalities were brain, pituitary, thyroid, parathyroid, trachea, heart, stomach, small intestine, large intestine, adrenal, urinary bladder, ovary, uterus, vagina, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball from animals of control and 600 mg/kg group.

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

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

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

Organ	: Findings	Grade	At the end of administration period					At the end of recovery period	
		Dose(mg/kg/day)	0	10	40	150	600	0	600
		Fate	KA	KA	KA	KA	KA	KR	KR
		No.of animals	5	5	5	5	5	5	5
Thymus	: Hemorrhage	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
Spleen	: Hematopoiesis, extramedullary	-	0	#	#	#	0	#	#
		+	5	#	#	#	5	#	#
	Deposit, pigment, brown	-	0	#	#	#	0	#	#
		+	5	#	#	#	5	#	#

KA : Killed by design at the end of administration period; KR : Killed by design at the end of recovery period; #:Not examined.

Grade, - : Negative; + : Slight.

No abnormalities were brain, pituitary, thyroid, parathyroid, trachea, heart, stomach, small intestine, large intestine, adrenal, urinary bladder, ovary, uterus, vagina, spinal cord, sciatic nerve, bone marrow, lymph nodes and eye ball from animals of control and 600 mg/kg group.