

最 終 報 告 書

テトラフェニルスズのラットを用いる
反復経口投与毒性・生殖発生毒性併合試験
(試験番号：07-110)

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要 約

テトラフェニルスズの 0 (被験物質の媒体である局方オリーブ油のみ投与)、4、20、100 および 500 mg/kg/day を、1 群雌雄各 12 匹の SD 系ラットに、交配開始 2 週間前から、雄は 42 日間、雌は分娩後哺育 4 日まで経口投与し、その反復投与毒性および生殖発生毒性を調べた。また、雄については対照群および 500 mg/kg 群の各 12 匹からそれぞれ 5 匹を選別し、雌についてはサテライト群として別に 1 群 5 匹の対照群および 500 mg/kg 群を設け、投与終了後 14 日間観察を継続し、毒性の回復性についても検討した。

1. 反復投与毒性

動物の一般状態および詳細な臨床観察、感覚反射機能検査、握力、自発運動量、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、器官重量の測定並びに病理組織学検査において、被験物質の投与による影響は認められなかった。また、回復群において、遅発的な毒性影響は認められなかった。

2. 生殖発生毒性

親動物の性周期 (雌)、交尾成立期間、交尾率、受胎率、妊娠期間、黄体数、着床数、着床率、出産率、分娩率、分娩および哺育状態に変化は認められなかった。児動物に対しても、総出産児数、新生児数、性比、出生率、体重、形態および哺育 4 日生存率に、被験物質の投与に起因する変化は認められなかった。

以上の結果から、本試験条件下におけるテトラフェニルスズの親動物への反復投与毒性並びに生殖発生毒性に関する無影響量 (NOEL) および無毒性量 (NOAEL) は、雌雄とも 500 mg/kg/day と推定した。

目 的

テトラフェニルスズをラットに反復経口投与し、本物質の反復投与毒性および生殖発生毒性を検討した。

材料および方法

1. 被験物質

被験物質であるテトラフェニルスズ(CAS No. 595-90-4)は、水に不溶で、食物油にも難溶であるが懸濁は可能な白色～微黄色粉末である。試験には、

試薬 (純度 97.9% : 2008

年 2 月 7 日分析) を購入し、冷暗所 (2～6℃)、密栓下で保管して使用した。用いた被験物質は投与終了後に分析し、使用期間中安定であったことを確認した (Appendix 1)。本物質の特性は、Appendix 1 に示す。

投与液はオリーブ油 (局方、ロット番号 NA-15、小堺製薬株式会社) を媒体とし、所定の投与用量となる濃度の懸濁液に調製した。調製した投与液は、1 日の使用量ごとに小分けし、使用時まで冷所 (2～6℃) 遮光下で密栓して保管した。投与液中の被験物質は、冷所遮光下で少なくとも 7 日間は安定であることが確認された (Appendix 2) ので、調製後 7 日以内に使用した。初回に調製された投与液について分析し、所定の濃度で調製されていることを確認した (Appendix 3)。

2. 動物および飼育条件

動物は、SD 系 [CrI : 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 8 週齢のものを搬入 (雄 68 匹、雌 80 匹) し、14 日間試験環境に馴化させた。馴化期間中に検疫および雌については 10 日間の性周期観察も併せて行い、発育および一般健康状態が良好で、雌では性周期に異常の認められなかったものについて、投与開始前日に体重を測定し、無作為抽出法により雄は 60 匹、雌は 70 匹を選び、10 週齢で試験に用いた。1 群の動物数は雌雄各 12 匹とし、雌についてはさらに対照群と最高用量群の回復群として各 5 匹からなる 2 群のサテライト群を設け、無作為抽出法により群分けを行った。なお、雌の回復群については交配を行わなかった。雄の回復群については、投与 42 日に対照群と最高

用量群の中から体重による無作為抽出法によりそれぞれ 5 匹を選別し、回復群とした。投与開始時の平均体重(体重範囲)は、雄 388(357~421)g、雌 243(213~278)g であった。ラットは、温度 $22 \pm 3^{\circ}\text{C}$ 、湿度 $55 \pm 10\%$ 、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 1 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。ただし、交尾の成立した雌は、妊娠 0 日に巣作り材料(ホワイトフレック、日本チャールス・リバー株式会社)を入れたポリカーボネート製ケージ [265W×426D×200H(mm)] に収容し、分娩後は児動物と同居させた。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 20080371、20070459、20080855) および飲料水(孔径 $1\mu\text{m}$ のカートリッジフィルターで濾過後紫外線照射した殺菌水道水)は、それぞれ給餌器および自動給水装置または給水瓶(ポリカーボネートケージの場合)により、自由に摂取させた。

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

飼育期間中、動物室の温度は $20.7 \sim 24.9^{\circ}\text{C}$ 、湿度は $45 \sim 63\%$ の範囲で推移(Appendix 4)した。また、飼料および巣作り材料の汚染物質の分析結果(Appendices 5、6)は、「米国環境保護庁毒性物質規制法の飼料および媒体の汚染物質限度(1979)」等を参考にして当研究所が設定した許容範囲内にあり、飲料水は水道法に基づく水質基準に適合する(Appendix 7)ことが確認された。したがって、動物の飼育期間を通じて、試験成績の信頼性に影響を及ぼすと思われる環境要因の変化は、なかったものと判断した。

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

3. 投与量の設定、試験群の構成および投与方法

本物質の 500、1000 および 2000 mg/kg/day を雌雄各 1 匹のラットに 3 日間反復経口投与した結果、いずれの用量にも変化は認められなかった。

そこで、50、100、200、500 および 1000 mg/kg/day (試験 I) で 14 日間反復経口投与した結果、50 mg/kg でも投与の影響が認められたため、さらに 1.5、3、6、12.5、

25 および 50 mg/kg/day での追加試験（試験Ⅱ）を行った。両試験とも、一般状態の観察、体重および摂餌量の測定、血液学および血液生化学検査、剖検並びに器官重量の測定を行った。その結果、雄は 3 mg/kg 以上の用量群、雌は 6 mg/kg 群および 25 mg/kg 以上の用量群で肝臓相対重量の有意な高値が認められた。さらに、1000 mg/kg 群では雄に血清 ALT 活性の有意な高値が認められた。一般状態、体重、摂餌量、尿検査、血液学検査および剖検においては、被験物質の投与に起因する変化は認められなかった。

以上の結果から、本試験における設定用量としては、明確な毒性が見られている 500 mg/kg/day を最高用量とし、公比 5 で、以下 100、20 および 4 mg/kg/day の計 4 用量を設定した。

試験群の構成は、①媒体投与群（以下、対照群）、②被験物質の 4 mg/kg/day 投与群（4 mg/kg 群）、③同 20 mg/kg/day 投与群（20 mg/kg 群）、④同 100 mg/kg/day 投与群（100 mg/kg 群）および⑤同 500 mg/kg/day 投与群（500 mg/kg 群）の 5 群とした。

投与方法は、投与液量を体重 1kg 当たり 5 mL とし、テフロン製胃ゾンデを装着した注射筒を用いて、投与液を胃内に投与した。対照群には、媒体として用いた局方オリーブ油を同様に投与した。各個体の投与液量は、至近日の測定体重を基に算出した。投与期間は、雌雄とも交配開始 14 日前から、雄は 42 日間、雌は交配および妊娠期間を経て分娩後の哺育 4 日まで、最短 42 日～最長 54 日間、1 日 1 回、午前中（8：50～12：00）に投与した。ただし、雌の回復群は、雄と同様に 42 日間投与した。

4. 観察および検査

1) 親動物に関する項目

親動物について、次の項目を観察あるいは検査した。なお、感覚反射機能検査、握力、自発運動量、尿検査、血液学検査、血液生化学検査、器官重量および病理組織学検査については、雄は投与 35 日に、雌は交配終了時に各群から無作為抽出法により雌雄各 5 匹を選び、検査の対象とした。

(1) 一般状態観察

投与期間中毎日、投与直後から投与後 1 時間に、動物の生死、外観、行動等について観察した。さらに、朝夕 2 回は、動物の生死や瀕死状態の有無について確認した。また、妊娠、出産、哺育の状態については、注意深く観察した。

(2) 詳細な臨床観察

投与開始前日およびその後は週 1 回、ケージサイドでの観察に加えて、動物をケージから取り出す時およびケージ外のアルミ製オープンフィールド（370W×560D×40Hmm）で、ケージからの出し易さ、ケージから出す時の扱い易さ、体躯緊張（弛緩～強直）、皮膚（色）、毛並み、立毛、眼分泌物、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、後ろ向き歩行等）、常同行動（過度の毛繕い、反復旋回運動等）、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観察し、認められた変化を評点（Appendix 8）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) 感覚反射機能検査

雄は投与 42 日、雌は哺育 3 日、また回復群の雌雄は投与 42 日および回復 14 日に、聴覚反応（ピンセットで軽くケージを叩く音に対する驚愕反応）、視覚反応（顔面に棒を近づけた場合の接近反応）、触覚反応（腰部に触れた場合の反応）、痛覚反応（尾根部をピンセットで摘んだ場合の逃避、発声等の反応）、瞳孔反射（暗所から急に明るい場所に移した時の瞳孔の反射）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射）を調べ、認められた反応を評点（Appendix 9）で記録した。

(4) 握力および自発運動量

雄は投与 41 日、雌は哺育 3 日、また回復群の雌雄は投与 42 日（最終投与日）および回復 13 日に、雄は 30 および 60 分間、雌は 30 分間の自発運動量（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間における移動回数を測定）並び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）を測定した。回復群の雌の自発運動量は、30 および 60 分間測定した。

(5) 体重および摂餌量

体重は、雄については投与 1（投与開始日、投与直前）、7、14、21、28、35 および

42 日並びに回復 7（投与 49 日）および 14 日（投与 56 日）、雌は投与 1、7 および 14 日、妊娠 0、7、14 および 20 日並びに哺育 0 および 4 日に、また、サテライト群として設けた雌の回復群については交配を行わないため、雄と同じ日に測定した。さらに、雌雄とも屠殺日に測定した。摂餌量は、体重測定日に合わせて、ケージごとに翌日までの 24 時間飼料消費量を測定した。ただし、摂餌量の最終測定日は、雄では投与 41 日、雌では哺育 3 日、回復群では回復 13 日とした。交配期間中の投与 21 および 28 日には、交尾の成立していない雌雄の摂餌量は測定しなかった。

(6) 雌の性周期検査

雌について、馴化・検疫期間に引き続き、交配前の 2 週間を経て交配期間の交尾が確認されるまで、Giemsa 染色による膣垢塗抹標本を作製し、鏡検により性周期段階の判定を行った。また、投与開始日から交配開始日までの性周期段階の判定から性周期を算出した。1 性周期は、発情期（Ⅲ）像が認められた日から次のⅢ期像が認められた前日までとし、Ⅲ期像が連続した場合は、最初のⅢ期像が認められた日から起算した。

(7) 交配および分娩状態観察

交配前 2 週間の投与を終了（投与 15 日の午後）した雌雄を同一群内で 1 対 1 の組み合わせを作り、2 週間を限度として交尾が確認されるまで連続同居させた。交配期間中は毎朝一定時刻（9：30 頃）に交尾の確認を行い、交尾率（％） $[(\text{交尾動物数} / \text{同居動物数}) \times 100]$ を算出した。交尾は、膣栓形成あるいは膣垢中の精子の有無により確認し、確認された日を妊娠 0 日とした。分娩状態の観察も同じ時刻に行い、分娩の完了が確認された日を哺育 0 日とした。交配および分娩の観察結果から、各群について、受胎率（％） $[(\text{受胎雌数} / \text{交尾成立雌数}) \times 100]$ 、妊娠期間（妊娠 0 日から分娩の完了が確認された日までの日数）および出産率（％） $[(\text{生児出産雌数} / \text{妊娠雌数}) \times 100]$ を算出した。

(8) 雄の尿検査

雄について、投与 39 日および回復群については回復 8 日に、動物を約 3 時間代謝ケージに収容し、得られた尿について、外観の観察、試験紙法（マルティスティックス、バイエルメディカル株式会社）による pH、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並びに沈渣の検査（URI-CELL 液、ケンブリッジケミカルプロダクト社、で染色して鏡検）を行った。さらに、18 時間収容して得られた尿について、尿量、比重（屈折計、エルマ光学株式会社）並びにナトリウムお

よびカリウム（電解質自動分析装置、NAKL-132、東亜ディーケーケー株式会社）を測定した。

(9) 血液学検査

最終投与の翌日あるいは回復期間終了の翌日の解剖直前に、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（赤血球パルス波高値検出法）、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）、白血球数、網状赤血球数、白血球百分率（以上、フローサイトメトリー法）および血小板数（電気抵抗検出法）を測定した。また、血液の一部を3.8%クエン酸ナトリウム液で凝固阻止処理して血漿を得、血液凝固自動測定装置（STart-4、ロシュダイアグノスティックス株式会社）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（エラヂン酸活性化法）を測定した。なお、必要に応じて検査できるように、血液塗抹標本を作製した。

(10) 血液生化学検査

採取した血液の一部から血清を分離し、生化学自動分析装置（JCA-BM8型クリナライザー、日本電子株式会社）により、総タンパク（ビューレット法）、アルブミン（BCG¹⁾法）、A/G比（計算値）、血糖（GluK²⁾-G-6-PDH³⁾法）、総コレステロール（酵素法、CES⁴⁾-COD⁵⁾-POD⁶⁾系）、トリグリセライド（酵素法、LPL⁷⁾-GK⁸⁾-GPO⁹⁾-POD⁶⁾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、 γ -GTP、ALP（以上、JSCC¹⁰⁾法）、LDH（SFBC法¹¹⁾）、ChE（BTC¹²⁾-DTNB¹³⁾法）、無機リン（酵素法、PNP¹⁴⁾-XOD¹⁵⁾-POD⁶⁾系）およびカルシウム（OCPC¹⁶⁾法）を、また電解質自動分析装置（NAKL-132、東亜ディーケーケー株式会社）により、ナトリウム、カリウムおよび塩素（以上、イオン電極法）を測定した。

1) : プロムクレゾールグリーン、2) グルコキナーゼ、3) グルコース-6-リン酸脱水素酵素、4) コレステロールエステラーゼ、5) コレステロールオキシダーゼ、6) ペルオキシダーゼ、7) リボプロテインリパーゼ、8) グリセロールキナーゼ、9) L- α -グリセリン酸オキシダーゼ、10) 日本臨床化学会、11) フランス臨床生物学会、12) プチリルチオコリン、13) 5、5'

・ジチオビス-2-ニトロ安息香酸、14) プリンヌクレオシドホスホリラーゼ、15) キサンチンオキシダーゼ、16) α-クレゾールフタレンコンプレクソン

(11) 剖検および器官重量

雄の計画屠殺動物は投与 42 日の翌日、雌は哺育 5 日、また、回復群については回復 14 日の翌日に、それぞれエーテル麻酔下で放血屠殺し、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、各群雌雄各 5 匹の肝臓、腎臓、副腎、胸腺、脾臓、脳、心臓、下垂体、甲状腺および精嚢並びに全ての雄の精巣および精巣上体を秤量（絶対重量）し、屠殺日の体重に基づいて対体重比（相対重量）を算出した。なお、対器官は左右を一括して、下垂体および甲状腺は固定後に秤量した。雌については、卵巣の黄体数および子宮の着床数を調べ、着床率（%） $[(\text{着床数}/\text{黄体数}) \times 100]$ を算出した。

(12) 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、下垂体、甲状腺、胸腺、気管・肺（固定液を注入後浸漬）、胃、腸、心臓、肝臓、脾臓、腎臓、副腎、膀胱、精巣、精巣上体、前立腺、精嚢、卵巣、子宮、脊髄（頸部、胸部、腰部）、坐骨神経、骨髓（大腿骨）、リンパ節（頸部リンパ節、腸間膜リンパ節）、乳腺）

病理組織学検査は、対照群および 500 mg/kg 群の雌雄各 5 匹について、上記保存器官について実施した。精巣については、精子形成サイクル検査（ステージⅡ・Ⅲ、Ⅴ、ⅦおよびⅩⅡ）も行った。その結果、被験物質の投与による影響は認められなかったため、回復群を含むその他の群については検査しなかった。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。また、精子形成サイクル検査のために精巣の PAS 染色標本も作製した。

2) 新生児に関する項目

(1) 産児数、性比および外表検査

分娩完了の確認後、各腹の産児数（生産児と死亡児の合計）を調べ、分娩率（%） $[(\text{総出産児数}/\text{着床数}) \times 100]$ を、また肛門と生殖突起間の長短により性別を判定し、群ごとの性比を算出した。さらに、新生児について、口腔内を含む外表の異常を観察した。

(2) 一般状態観察

毎日、一般状態および生死を確認し、出生率 (%) [(出産確認時生児数 / 総出産児数) × 100] および哺育 4 日生存率 (%) [(哺育 4 日の生児数 / 出産確認時生児数) × 100] を算出した。

(3) 体重

新生児について、哺育 0 および 4 日に、雌雄別に腹ごとの体重を測定し、1 匹当たりの平均体重を算出した。

(4) 病理学検査

死亡例はその都度、生存例は哺育 4 日にエーテル麻酔下で放血死させ、胸部および腹部における主要器官について、肉眼的に観察した。

5. 統計解析

得られた平均値あるいは頻度について、対照群との有意差(危険率 5%以下)を、次の方法で検定した。なお、出産児に関するデータは、1 腹の平均を 1 標本とした。

(1) パラメトリックデータ

多群間の比較については、Bartlett の分散検定を行った。分散が一樣な場合は一元配置の分散分析を行い、その結果有意差を認めた場合、Dunnett 法により対照群に対する各群の比較検定を行った。分散が一樣でない場合は、ノンパラメトリックデータに用いる検定法に従った(体重、体重増加量、摂餌量、握力、自発運動量、尿検査における定量的データ、血液学検査データ、血液生化学検査データ、器官重量、黄体数、着床数、交尾成立期間、妊娠期間、産児数、生児数、死亡児数)。2 群間の比較については、F 検定を行い、その結果分散が一樣な場合は Student の t 検定を、分散が一樣でない場合は Aspin-Welch の t 検定を行った。

(2) ノンパラメトリックデータ

多群間の比較については、Kruskal-Wallis の順位検定を行い、その結果有意差を認めた場合、Dunnett 型の検定法により対照群と各群を比較した(白血球百分率、尿検査における定性的データ、精子形成サイクル検査、着床率、出生率、分娩率、性周期、新生児生存率)。2 群間の比較については、Mann-Whitney の U 検定を行った。

(3) カテゴリカルデータ

Fisher の直接確率法を用いた(詳細な臨床観察、感覚反射機能検査、一般状態の観察および病理学検査における異常例の発現率、交尾率、受胎率、出産率)。なお、病理組織学検査所見のうち、グレード分けしたデータについては Mann-Whitney の U 検定、児動物の性比については、 χ^2 検定を用いた。

結 果

1. 反復投与毒性

1) 一般状態および死亡 (Tables 1～4、Appendices 10～13)

投与期間および回復期間を通じて、一般状態の変化および死亡は認められなかった。

2) 詳細な臨床観察 (Tables 5, 6、Appendices 14, 15)

投与期間および回復期間とも、各観察項目に有意な変化は認められなかった。

3) 感覚反射機能検査 (Tables 7, 8、Appendices 16, 17)

投与期間中および回復期間中の検査において、各検査項目に変化は認められなかった。

4) 握力および自発運動量 (Tables 9, 10、Appendices 18, 19)

投与期間中の検査において、回復群の雄に後肢握力の有意な低値が認められた。投与期間終了時屠殺動物には有意な変化は認められなかった。回復期間中の検査において、雄で自発運動量の有意な高値が認められた。

5) 体重 (Figures 1, 2、Tables 11, 12、Appendices 20, 21)

投与期間において、20 mg/kg 群で雌に哺育期間中体重増加量の有意な低値が認められた。各測定時点の体重には、有意な変化は認められなかった。回復期間においては、各測定時点の体重および回復期間中体重増加量に、有意な変化は認められなかった。

6) 摂餌量 (Figures 3, 4、Tables 13, 14、Appendices 22, 23)

投与期間において、500 mg/kg 群で雌の投与 14 日の摂餌量に有意な高値が認められた。回復期間においては、有意な変化は認められなかった。

7) 雄の尿検査 (Table 15、Appendix 24)

投与期間中および回復期間中の検査において、各検査項目に有意な変化は認められなかった。

8) 血液学検査 (Tables 16, 17, Appendices 25, 26、背景データ： Appendices 42, 43)

投与期間終了時の検査において、4、100 および 500 mg/kg 群の雌の血小板数は有意な高値を示した。さらに、500 mg/kg 群で雄に網状赤血球数の有意な低値が認められた。回復期間終了時の検査においては、雄に血色素量およびヘマトクリット値の有意な低値、雌に活性化部分トロンボプラスチン時間および白血球百分率における単球比の有意な高値が認められた。

9) 血液生化学検査 (Tables 18, 19, Appendices 27, 28、背景データ： Appendices 42, 43)

投与期間終了時の検査において、20 mg/kg 群で雄に AST の有意な低値、雌に無機リンの有意な高値が認められた。回復期間終了時屠殺動物においては、雄でコリンエステラーゼ、尿素窒素および無機リンの有意な低値、雌に ALP およびカルシウムの有意な低値並びにカリウムの有意な高値が認められた。

10) 剖検 (Tables 20, 21, Appendices 29～30)

投与期間終了時屠殺動物および回復期間終了時屠殺動物とも、変化は認められなかった。

11) 器官重量 (Tables 22, 23, Appendices 32～35)

投与期間終了時屠殺動物において、4 mg/kg 群で雌に下垂体絶対重量の有意な高値および心臓相対重量の有意な低値が、また、20 mg/kg 群で雌に甲状腺絶対重量の有意な高値が認められた。回復期間終了時屠殺動物においては、変化は認められなかった。

12) 病理組織学検査 (Tables 24～26, Appendices 29～31)

投与期間終了時屠殺動物において、被験物質の投与に起因する変化は認められなかった。なお、対照群にのみ、肝臓の微小肉芽腫 (雄) および巣状壊死 (雌)、腺胃の胃底腺拡張 (雌)、腎臓の好塩基性尿細管 (雄)、皮質リンパ球浸潤 (雌)、腎盂上皮過形成性 (雄) および孤立性嚢胞 (雌) 並びに胸腺の出血 (雌雄) が認められた。また、

対照群および 500 mg/kg 群に、肺の泡沫細胞集簇（雌雄）、腺胃の胃底腺拡張（雄）、腎臓の近位尿細管上皮硝子滴（雄）並びに脾臓の髄外造血（雌雄）および褐色色素沈着（雌雄）が認められたが、発現率および変化の程度において、両群間に差は認められなかった。さらに、500 mg/kg 群にのみ、心臓の心筋変性・繊維化（雄）および腎臓の好塩基性尿細管（雌）が認められたが、これらは各 1 匹の発現で、しかもラットにおける自然発生病変として知られている変化¹⁾である。したがって、これらはいずれも被験物質の投与とは無関係な偶発的变化と判断された。また、精子形成サイクル検査においても、変化は認められなかった。

対照群並びに 100 および 500 mg/kg 群で認められた妊娠不成立の各ペア並びに対照群で分娩が認められなかった雌について、雄では、下垂体、精巣、精巣上体、前立腺および精囊等に変化はなく、また、雌にも下垂体、卵巣および子宮等に変化は認められず、その原因となるような所見は認められなかった。

2. 生殖発生毒性

1) 親動物に及ぼす影響

(1) 性周期検査 (Table 27、Appendices 37, 38)

被験物質投与各群とも、対照群と比べて性周期に有意な変化は認められなかった。

(2) 交尾率および受胎率 (Table 27、Appendix 38)

交尾成立までに要する日数、交尾率および受胎率に有意な変化は認められなかった。いずれの投与群とも交尾不成立は認められず、対照群並びに 100 および 500 mg/kg 群でそれぞれ 1、1 および 2 例の妊娠不成立例が認められた。また、対照群で交尾成立までに 12 日および 13 日を要した例 (No. 003 と 503 および No. 004 と 504 のペア) の雌は、いずれも交配前は順調な性周期を示していたが、交配開始後 2 日から発情休止期 (V) 像が続き、交配開始後 11 日および 12 日に発情前期 (I) 像が認められ、それぞれ翌日、発情期 (III) 像と共に精子および膣栓が認められ、交尾が確認されたことから、偽妊娠を起こしていたものと判断された。

(3) 黄体数、着床数および着床率 (Table 27、Appendix 38)

黄体数、着床数および着床率に有意な変化は認められなかった。

(4) 出産率および妊娠期間 (Table 27、Appendix 38)

出産率および妊娠期間に有意な変化は認められなかった。

(5) 分娩および哺育状態 (Table 27、Appendix 38)

妊娠不成立例とは別に、対照群の 1 匹 (No. 512) で分娩が認められなかった。この例の子宮内にはミイラ化変性した胎児が 1 匹のみ認められ、他に着床痕跡は認められなかった。その他の投与群の雌に分娩および哺育状態の異常は認められなかった。

2) 新生児に及ぼす影響

(1) 生存性および体重 (Table 28、Appendix 39)

一腹当たりの総出産児数、分娩率、哺育 0 日および 4 日の新生児数、出生率、性比、哺育 4 日の生存率並びに新生児体重に有意な変化は認められず、新生児の一般状態にも異常は認められなかった。

(2) 形態 (Table 29、30、Appendices 40、41)

外表検査では、いずれの投与群においても外表異常を有する児動物は認められなかった。内臓検査では、いずれの投与群においても内臓異常は認められず、内臓変異として、左臍動脈遺残を呈する児動物が対照群で 1 匹 (0.6%) および 500 mg/kg 群で 1 匹 (0.7%)、胸腺の頸部残留を呈する児動物が 4 mg/kg 群で 1 匹 (0.6%) 認められたが、これらは、いずれも 1 例ずつの低い発現率であり、自然発生的範疇のものと判断した。

考 察

1. 反復投与毒性について

投与期間中あるいは投与期間終了時の観察および検査において、動物の一般状態、詳細な臨床観察、感覚反射機能検査および自発運動量に変化は認められなかった。

投与期間中の検査で、回復群の雄に認められた後肢握力の低値については、各個体値が当研究所の背景データにおける基準値（平均 421, 199～644 g）内の値であり、投与期間終了時屠殺動物では握力に変化は認められていないこと、および関連する変化も認められなかったことから、投与とは無関係な偶発的变化と判断された。

体重および摂餌量に、被験物質の投与による変化は認められなかった。

20 mg/kg 群の雌で認められた哺育期間中体重増加量の低値について、用量相関性のない変化であり、哺育 0 日の体重が若干高値であったことによる偶発的な変化と判断された。また、500 mg/kg 群の雌で認められた摂餌量の高値は、投与 14 日のみの変化であり、妊娠および哺育期間を通じて対照群と同様の摂餌量を示しており、当該日の対照群の摂餌量がやや低値であったための偶発的变化と判断された。

尿検査では、変化は認められなかった。

血液学検査では、4, 100 および 500 mg/kg 群の雌の血小板数に高値が認められたが、これらの各個体値はいずれも背景データにおける基準値 (Appendix 43 参照) 内の値で、むしろ対照群が低値傾向にあり、偶発的变化と判断された。

さらに、500 mg/kg 群の雄に認められた網状赤血球数の低値についても、ほかに貧血所見や造血器系組織の変化は認められず、各個体値は概ね背景データにおける基準値 (Appendix 42 参照) 内の値であり、被験物質の投与と関連付けるのは妥当でないと考えられる。

血液生化学検査で認められた 20 mg/kg 群の雄の AST の低値および雌の無機リンの高値並びに器官重量で認められた 4 および 20 mg/kg 群の雌の下垂体および甲状腺の絶対重量の高値、4 mg/kg 群の雌の心臓相対重量の低値についても、用量相関性は認められず、器官重量に変化の認められた器官に被験物質の投与による病理組織学的変化も認められなかった。したがって、これら血液生化学検査および器官重量で認められた変化についても、被験物質の投与とは無関係な偶発的变化と判断された。

回復群の回復期間終了時の検査で認められた雄の自発運動量の高値については、各個

体値が背景データにおける基準値（平均 10869, 4311～17427 Count/60 min）を 1 例（18115 Count/60 min）が僅かに上回った以外は、いずれも基準値内の値で、ほかに関連する変化も認められなかった。さらに、血液学検査および血液生化学検査で認められた雄の血色素量、ヘマトクリット値、コリンエステラーゼ活性、尿素窒素濃度および無機リン濃度の低値並びに雌の活性化部分トロンボプラスチン時間、白血球百分率における単球比およびカリウム濃度の高値、カルシウム濃度の低値についても、2 匹のカリウム濃度が上限を僅かに上回ったほかは、いずれもその個体値は基準値（雌の単球比：平均 2.1, 0.5～3.7%、その他の項目：Appendix 42、43 参照）内の値であり、遅発的な毒性影響を示す変化とは考え難く、投与とは無関係な偶発的变化と判断された。

一般的に、有機スズ化合物は無機スズ化合物と比べて腸から吸収されやすく、主に肝臓で脱アルキル化および脱アリル化され、その一部が組織、特に肝臓に残留し、毒性影響を示すことが知られている²⁾。

テトラフェニルスズは、主に有機スズ化合物の合成中間体として用いられており、難分解性、高濃縮性であるため、第一種監視化学物質に指定されている物質である。

本試験では、このテトラフェニルスズについて、反復投与毒性を検討したが、有害影響は認められなかった。

投与用量設定試験（予備試験）において、雄は 3～1000 mg/kg の用量群、雌は 6、25、50、500 および 1000 mg/kg の用量群で肝臓相対重量の有意な高値が認められたが、これらの増加は、いずれも平均値において対照群の値の一割程度のものであった。本試験においても被験物質投与群で対照群の値の一割程度の肝臓相対重量の増加が認められたが、統計学的有意差は認められなかった。この原因の一つとして、予備試験に比べて本試験では対照群も含めて標準偏差が大きい傾向にあり、個体値のバラツキの程度が統計学的有意差に反映された可能性が考えられる。この個体値のバラツキに関しては、肝臓重量の測定時の剖検が予備試験では 12 週齢、本試験では 16 週齢ないしそれ以降で行われていることが関連しているものと思われる。また、この肝臓重量の変化は、薬物代謝酵素誘導との関連性も考えられ、14 日間投与の予備試験と 42 日以上投与の本試験では、少なからず薬物代謝の程度に違いが生じるものと考えられ、これも本試験で肝臓重量に有意差が生じなかった一因と推察される。ただし、予備試験と本試験での肝臓重量における統計学的有意差の有無について、明らかな原因は不明であった。

2. 生殖発生毒性について

雌雄親動物の生殖能に対する影響について、観察した各指標とも対照群と比べて有意な変化は認められなかった。また、児動物に対しても、発生に関する各指標において被験物質の投与による影響は認められなかった。

以上の結果から、500mg/kg/day を最高用量として実施した本試験条件下において、いずれの被験物質投与群においても影響が認められなかったことから、テトラフェニルスズの親動物への反復投与毒性並びに生殖発生毒性に関する無影響量 (NOEL) および無毒性量 (NOAEL) は、雌雄とも 500 mg/kg/day と推定した。

文 献

- 1) 日本毒性病理学会編, 毒性病理組織学, 2000.
- 2) Environmental Health Criteria 15: Tin and organotin compounds, International Programme on chemical Safety (1980),
<http://www.inchem.org/documents/ehc/ehc/ehc015.htm>

テトラフェニルスズのラットを用いる反復経口投与毒性・生殖発生毒性併合試験

(試験番号：07-110)

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

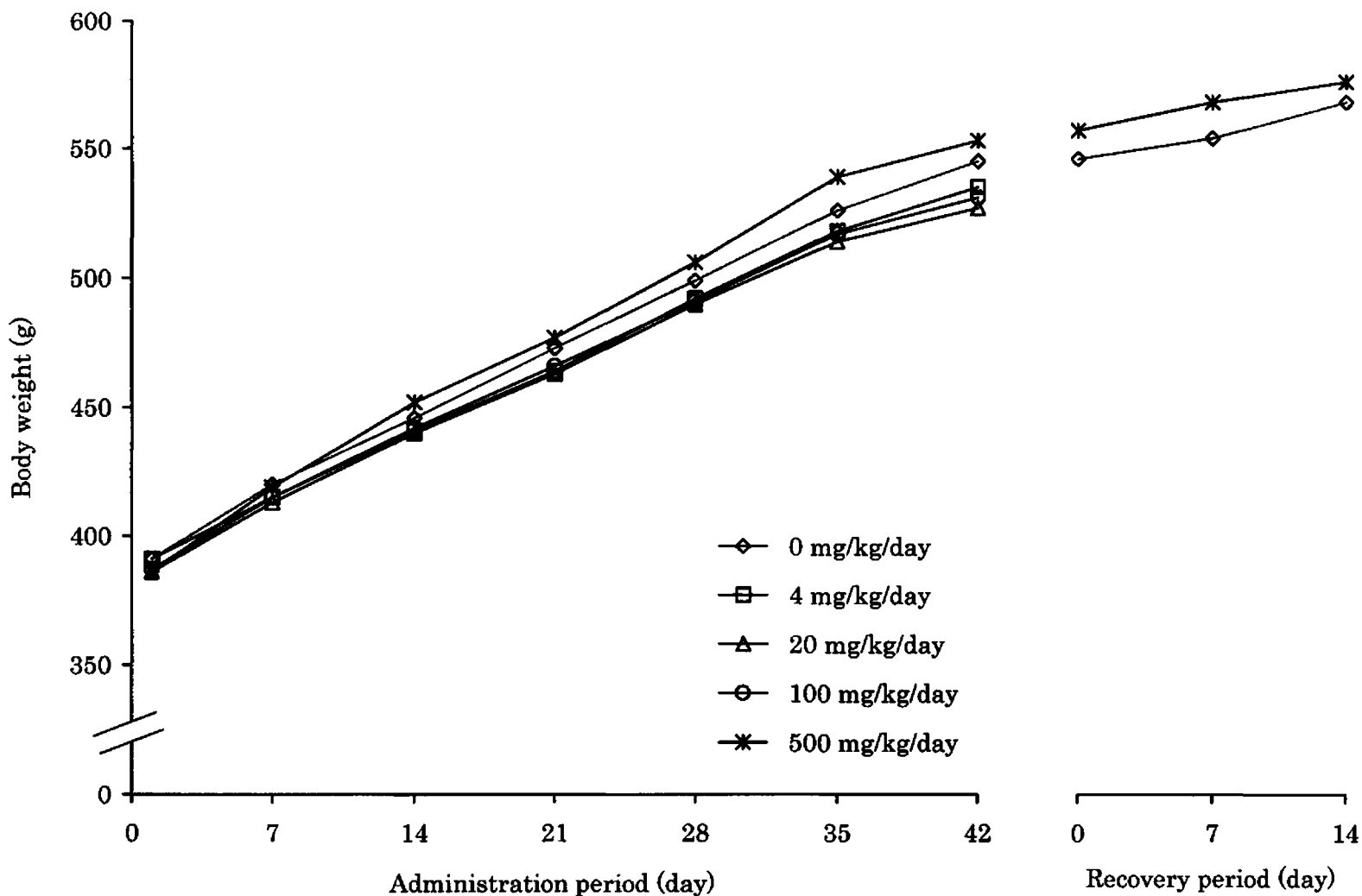


Fig.1 Body weight changes of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

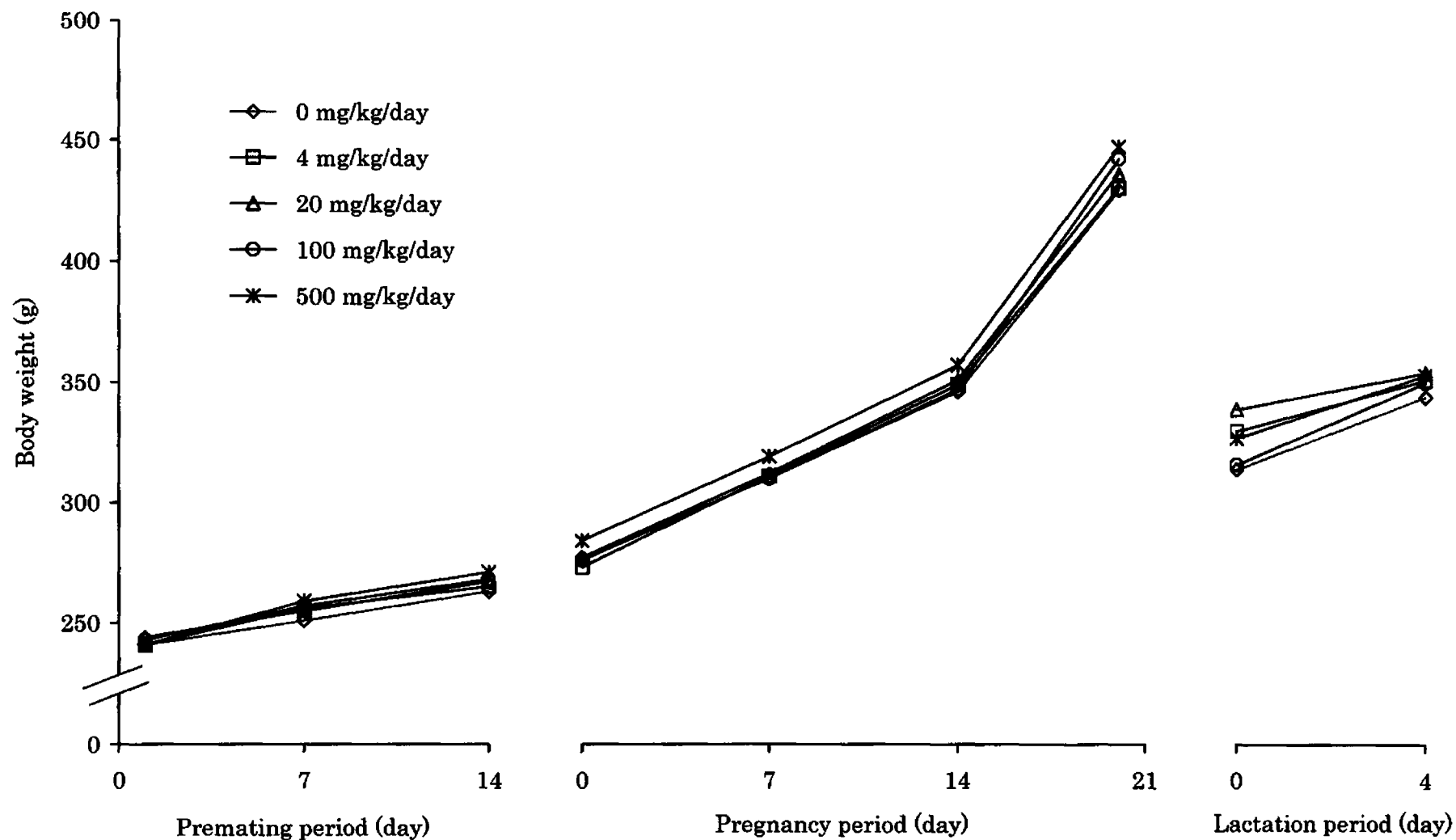


Fig.2-1 Body weight changes of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

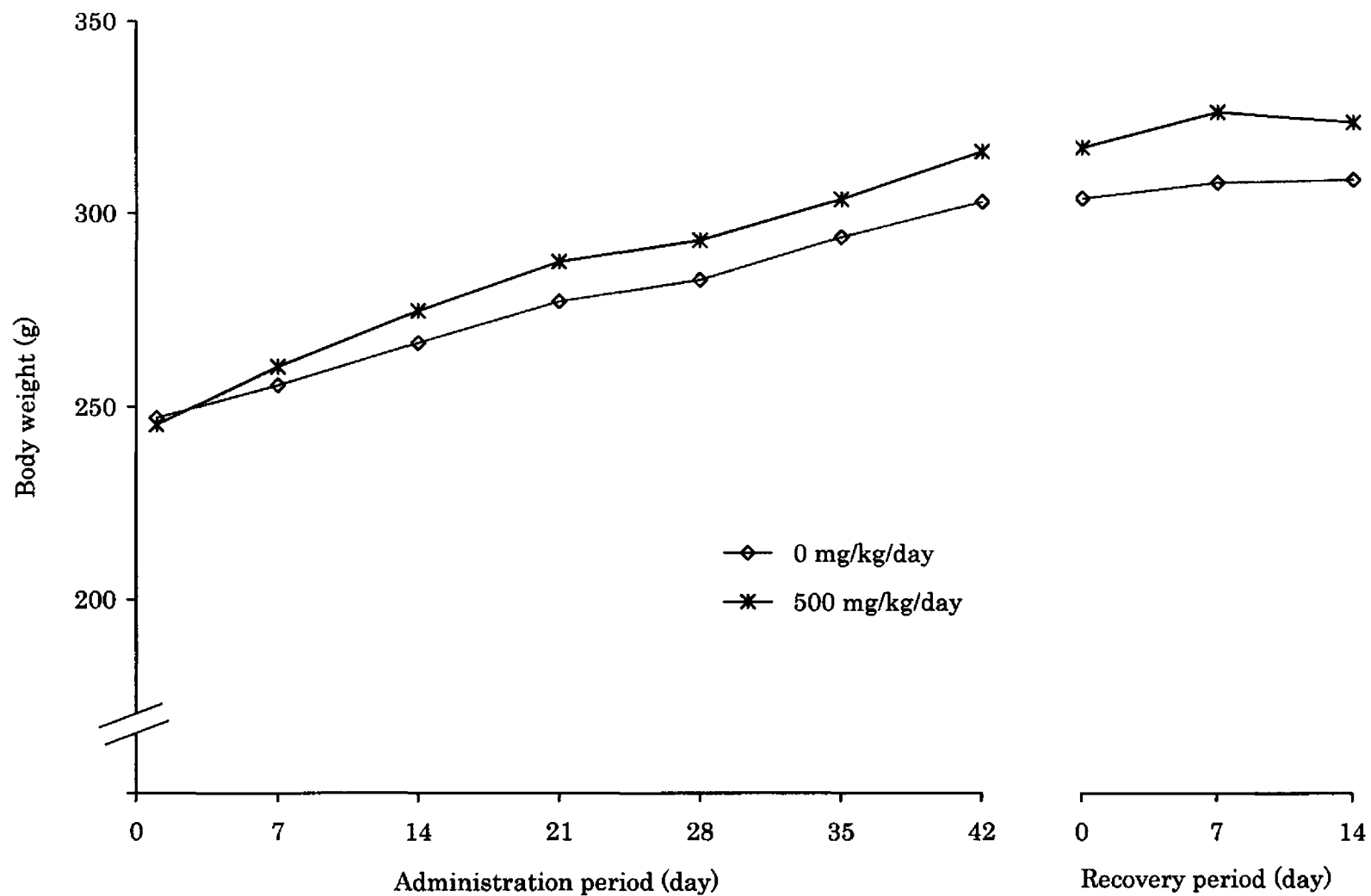


Fig.2-2 Body weight changes of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

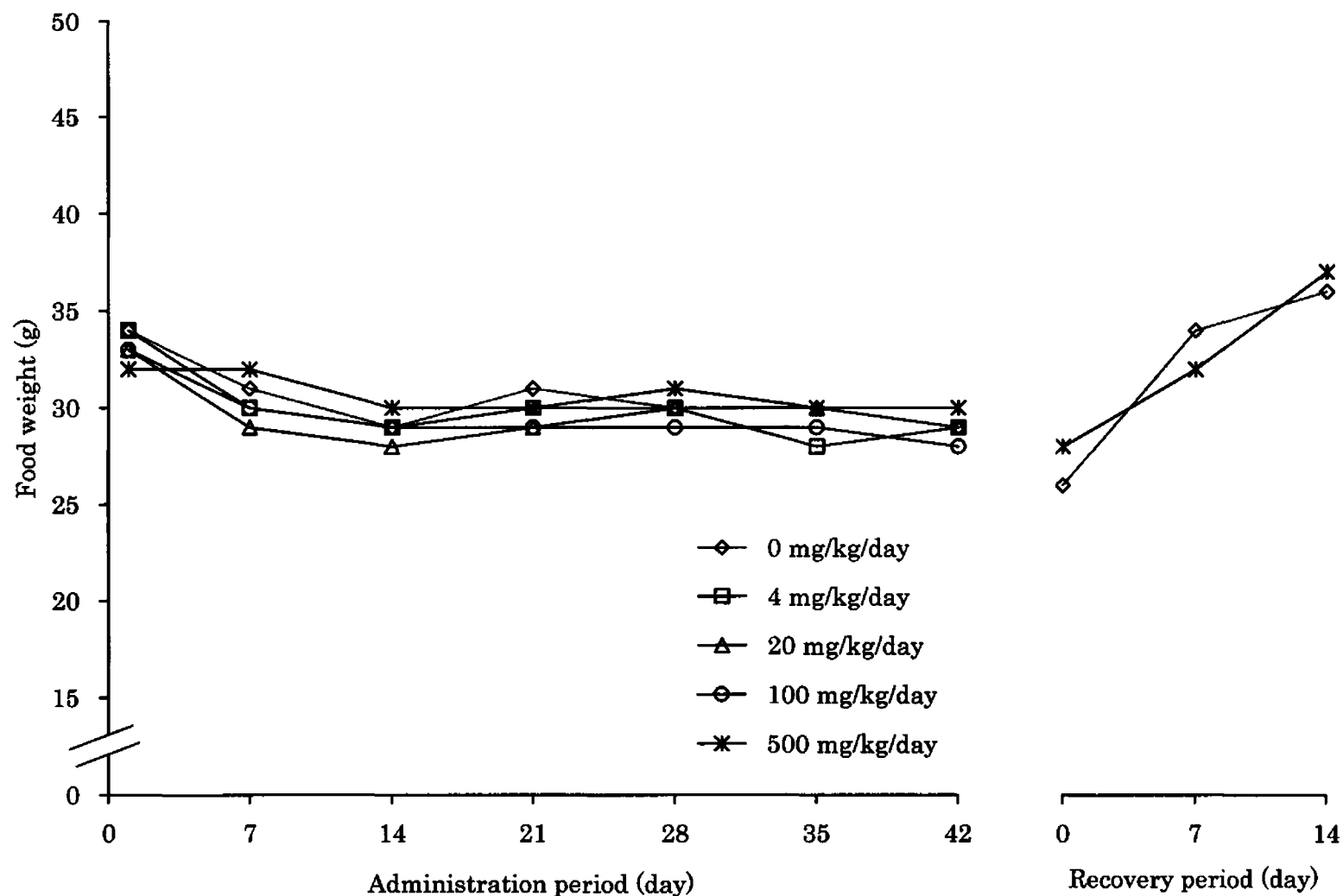


Fig.3 Food consumption of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

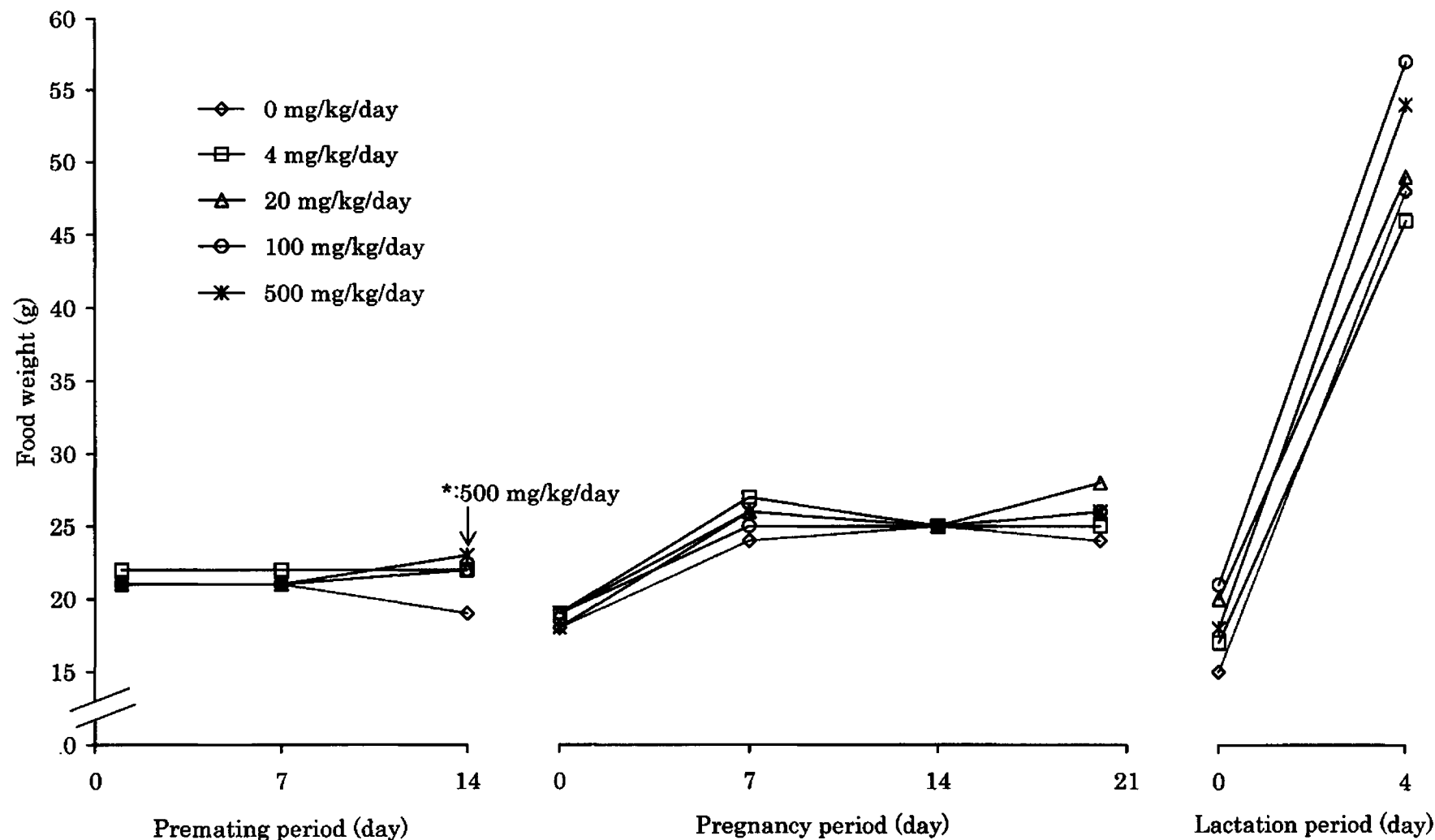


Fig.4-1 Food consumption of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

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

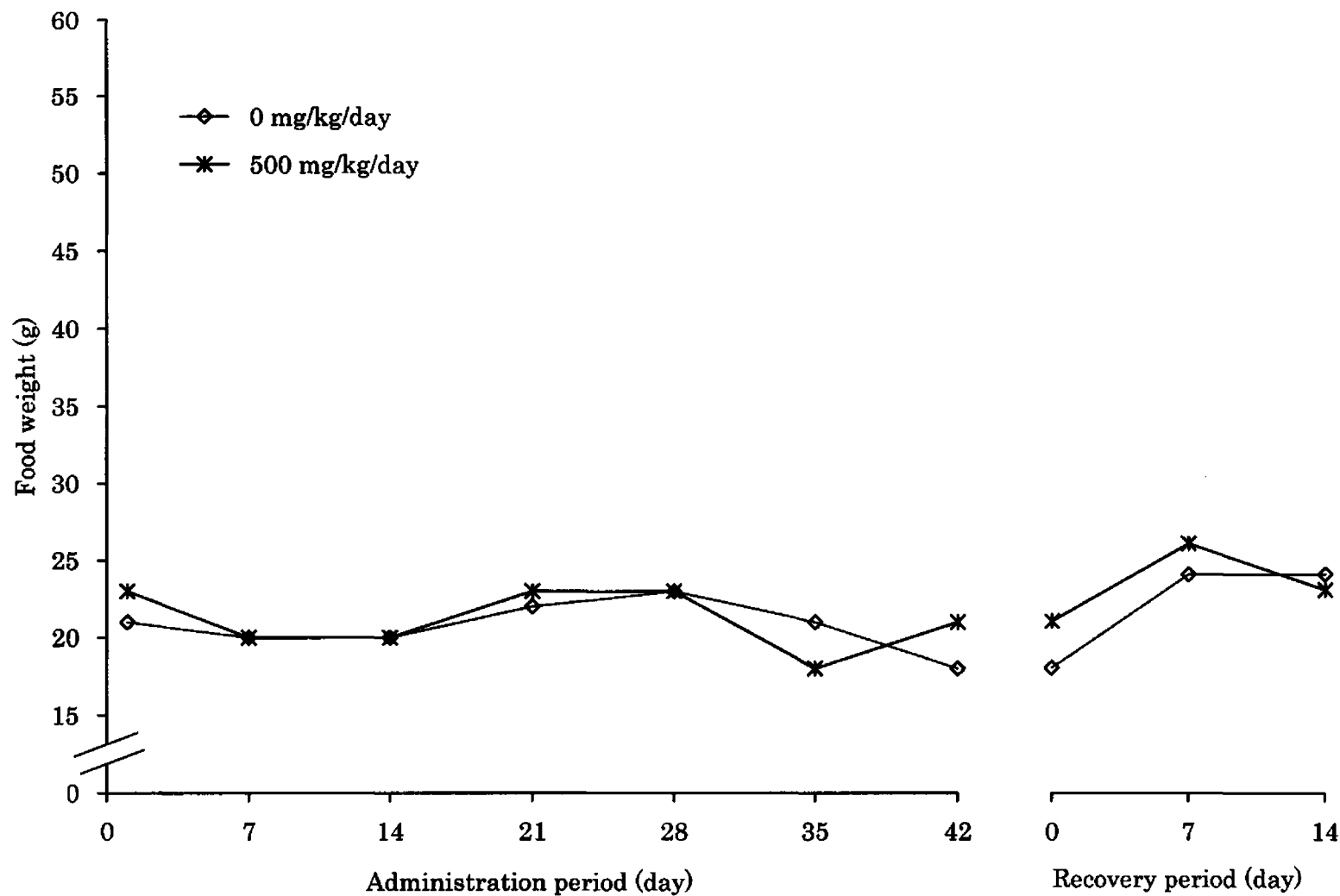


Fig.4-2 Food consumption of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Table 1 Mortality rate of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Dose (mg/kg/day)	0	4	20	100	500
No. of animals examined	12	12	12	12	12
No. of animals that died	0	0	0	0	0
Mortality (%)	0	0	0	0	0

Table 2 Mortality rate of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Dose (mg/kg/day)	0	4	20	100	500	<u>Satellite group</u>	
						0	500
No. of animals examined	12	12	12	12	12	5	5
No. of animals that died	0	0	0	0	0	0	0
Mortality (%)	0	0	0	0	0	0	0

Table 3 **Clinical signs of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test**

General conditions	Dose (mg/kg/day) No. of animals	Administration period					Recovery period	
		0	4	20	100	500	0	500
		12	12	12	12	12	5	5
Abnormality		0	0	0	0	0	0	0

Table 4-1 Clinical signs of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

General conditions	Dose (mg/kg/day) No. of animals	Administration period				
		0	4	20	100	500
		12	12	12	12	12
Abnormality		0	0	0	0	0

Table 4-2 Clinical signs of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

General conditions	Dose (mg/kg/day) No. of animals	Administration period		Recovery period	
		0 5	500 5	0 5	500 5
Abnormality		0	0	0	0

Table 5-1 Incidence of clinical signs in detailed observation of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 Before administration period 〉

Items	Dose(mg/kg/day) No. of animals	0	4	20	100	500
		12	12	12	12	12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	11	11	8	11	12
	2 or more	1	1	4	1	0
	Color : Pale yellow	3/3	2/2	4/4	1/1	-
Defecation	Not detected or 1	12	12	10	11	12
	2 or more	0	0	2	1	0
	Appearance : Normal	3/3	-	2/2	1/1	1/1

Table 5-2 Incidence of clinical signs in detailed observation of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 1 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0	4	20	100	500
		12	12	12	12	12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	11	12	12	9	12
	2 or more	1	0	0	3	0
	Color : Pale yellow	4/4	3/3	1/1	5/5	1/1
Defecation	Not detected or 1	11	12	11	12	12
	2 or more	1	0	1	0	0
	Appearance : Normal	3/3	3/3	2/2	-	-

Table 5-3 Incidence of clinical signs in detailed observation of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 2 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0 12	4 12	20 12	100 12	500 12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	9	12	12	12	12
	2 or more	3	0	0	0	0
	Color : Pale yellow	5/5	2/2	4/4	2/2	1/1
Defecation	Not detected or 1	11	12	12	12	12
	2 or more	1	0	0	0	0
	Appearance : Normal	2/2	-	1/1	1/1	-

Table 5-4 Incidence of clinical signs in detailed observation of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 3 of the administration period 〉

Items	Dose(mg/kg/day) No. of animals	0	4	20	100	500
		12	12	12	12	12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
	Temporally in handling	0	0	0	0	1
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	12	12	12	11	12
	2 or more	0	0	0	1	0
	Color : Pale yellow	3/3	2/2	2/2	1/1	1/1
Defecation	Not detected or 1	11	12	11	12	12
	2 or more	1	0	1	0	0
	Appearance : Normal	1/1	-	1/1	-	-

Table 5-5 Incidence of clinical signs in detailed observation of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 4 of the administration period 〉

Items	Dose(mg/kg/day) No. of animals	0	4	20	100	500
		12	12	12	12	12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	12	12	11	12	12
	2 or more	0	0	1	0	0
	Color : Pale yellow	3/3	3/3	4/4	3/3	1/1
Defecation	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Appearance : Normal	-	-	-	-	-

Table 5-6 Incidence of clinical signs in detailed observation of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 5 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0 12	4 12	20 12	100 12	500 12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	10	12	10	11	12
	2 or more	2	0	2	1	0
	Color : Pale yellow	5/5	3/3	4/4	4/4	2/2
Defecation	Not detected or 1	12	12	12	11	12
	2 or more	0	0	0	1	0
	Appearance : Normal	-	-	1/1	1/1	-

Table 5-7 Incidence of clinical signs in detailed observation of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 6 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0 12	4 12	20 12	100 12	500 12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	11	12	11
	Temporarily in handling	0	0	1	0	1
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	10	11	9	12	12
	2 or more	2	1	3	0	0
	Color : Pale yellow	2/2	1/1	4/4	1/1	1/1
Defecation	Not detected or 1	11	11	12	12	12
	2 or more	1	1	0	0	0
	Appearance : Normal	1/1	1/1	-	-	-

Table 5-8 Incidence of clinical signs in detailed observation of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 1 of the recovery period)

Items	Dose(mg/kg/day)	0	500
	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	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	2	5
	2 or more	3	0
	Color: Pale yellow	3/3	-
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance: Normal	1/1	-

Table 5-9 Incidence of clinical signs in detailed observation of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 2 of the recovery period)

Items	Dose(mg/kg/day) No. of animals	0	500
		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	Not detected	5	5
Blotted fur around anus with feces	Not detected	5	5
Vocalization	Not detected	5	5
	Temporally in handling	0	0
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	2	5
	2 or more	3	0
	Color: Pale yellow	3/3	-
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance: Normal	-	-

Table 6-1-1 Incidence of clinical signs in detailed observation of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(Before administration period)

Items	Dose(mg/kg/day) No. of animals	0	4	20	100	500
		12	12	12	12	12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	11	12	12
	Temporally in handling	0	0	1	0	0
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Color : Pale yellow	-	-	-	2/2	1/1
Defecation	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Appearance : Normal	-	-	-	-	-

Table 6-1-2 Incidence of clinical signs in detailed observation of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 1 of the administration period 〉

Items	Dose(mg/kg/day) No. of animals	0 12	4 12	20 12	100 12	500 12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	11	12
	Temporarily in handling	0	0	0	1	0
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	12	11	12	12	11
	2 or more	0	1	0	0	1
	Color : Pale yellow	1/1	4/4	1/1	-	1/1
Defecation	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Appearance : Normal	-	1/1	-	-	-

Table 6-1-3 Incidence of clinical signs in detailed observation of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 2 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0 12	4 12	20 12	100 12	500 12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	12	12	12	12	11
	2 or more	0	0	0	0	1
	Color : Pale yellow	-	3/3	-	-	1/1
Defecation	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Appearance : Normal	-	-	-	-	-

Table 6-1-4 Incidence of clinical signs in detailed observation of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 3 of the administration period 〉

Items	Dose(mg/kg/day) No. of animals	0	4	20	100	500
		12	12	12	12	12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	11	12	12	12	12
	2 or more	1	0	0	0	0
	Color : Pale yellow	1/1	1/1	-	2/2	2/2
Defecation	Not detected or 1	12	11	12	12	12
	2 or more	0	1	0	0	0
	Appearance : Normal	-	1/1	-	-	-

Table 6-1-5 Incidence of clinical signs in detailed observation of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 4 of the administration period 〉

Items	Dose(mg/kg/day) No. of animals	0	4	20	100	500
		12	12	12	12	12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Color : Pale yellow	1/1	1/1	1/1	-	1/1
Defecation	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Appearance : Normal	-	-	-	-	-

Table 6-1-6 Incidence of clinical signs in detailed observation of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 5 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0	4	20	100	500
		12	12	12	12	12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Color : Pale yellow	2/2	-	1/1	1/1	2/2
Defecation	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Appearance : Normal	-	1/1	-	-	-

Table 6-1-7 Incidence of clinical signs in detailed observation of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 6 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0	4	20	100	500
		12	12	12	12	12
Reactivity on removal from the cage	Normal	12	12	12	12	12
Reactivity on handling	Normal	12	12	12	12	12
Muscle tone	Normal	12	12	12	12	12
Skin	Normal	12	12	12	12	12
Fur	Normal	12	12	12	12	12
Piloerection	Not detected	12	12	12	12	12
Eye discharge	Not detected	12	12	12	12	12
Palpebral closure	Not detected	12	12	12	12	12
Exophthalmos	Not detected	12	12	12	12	12
Lacrimation	Not detected	12	12	12	12	12
Smudge around mouth-nose	Not detected	12	12	12	12	12
Salivation	Not detected	12	12	12	12	12
Blotted fur in the lower abdomen with urine	Not detected	12	12	12	12	12
Blotted fur around anus with feces	Not detected	12	12	12	12	12
Vocalization	Not detected	12	12	12	12	12
Breathing	Normal	12	12	12	12	12
Body position	Normal	12	12	12	12	12
Convulsion	Not detected	12	12	12	12	12
Tremor	Not detected	12	12	12	12	12
Exploration	Normal	12	12	12	12	12
Alertness	Normal	12	12	12	12	12
Locomotor activity	Normal	12	12	12	12	12
Walk	Normal	12	12	12	12	12
Abnormal behavior	Not detected	12	12	12	12	12
Stereotypy	Not detected	12	12	12	12	12
Failure of consciousness	Not detected	12	12	12	12	12
Limb tone	Normal	12	12	12	12	12
Urination	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Color : Pale yellow	-	1/1	-	-	1/1
Defecation	Not detected or 1	12	12	12	12	12
	2 or more	0	0	0	0	0
	Appearance : Normal	-	-	-	-	-

Table 6-2-1 Incidence of clinical signs in detailed observation of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(Before administration period)

Items	Dose(mg/kg/day) No. of animals	0	500
		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
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance : Normal	-	-

Table 6-2-2 Incidence of clinical signs in detailed observation of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 1 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0	500
		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 6-2-3 Incidence of clinical signs in detailed observation of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 2 of the administration period)

Items	Dose(mg/kg/day)	0	500
	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 6-2-4 Incidence of clinical signs in detailed observation of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 3 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0	500
		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 6-2-5 Incidence of clinical signs in detailed observation of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 4 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0	500
		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 6-2-6 Incidence of clinical signs in detailed observation of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 5 of the administration period 〉

Items	Dose(mg/kg/day) No. of animals	0	500
		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	-
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance : Normal	-	-

Table 6-2-7 Incidence of clinical signs in detailed observation of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 6 of the administration period)

Items	Dose(mg/kg/day) No. of animals	0	500
		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	1/1
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance : Normal	-	-

Table 6-2-8 Incidence of clinical signs in detailed observation of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 1 of the recovery period 〉

Items	Dose(mg/kg/day)	0	500
	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	1/1
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance: Normal	-	-

Table 6-2-9 Incidence of clinical signs in detailed observation of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 2 of the recovery period)

Items	Dose(mg/kg/day) No. of animals	0	500
		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	3	5
	2 or more	2	0
	Color: Pale yellow	2/2	1/1
Defecation	Not detected or 1	5	5
	2 or more	0	0
	Appearance: Normal	-	-

Table 7-1 Incidence of responses in the sensory/reflex function test of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

<On week 6 of the administration period >

		Dose(mg/kg/day)	0	4	20	100	500
Items	No. of animals examined		5	5	5	5	5
Hearing reaction	Normal		5	5	5	5	5
Eye sight 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 7-2 Incidence of responses in the sensory/reflex function test of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

<On week 6 of the administration period >

Items	Dose(mg/kg/day)	0	500
	No. of animals examined	5	5
Hearing reaction	Normal	5	5
Eye sight reaction	Normal	5	5
Sense of touch reaction	Normal	5	5
Pain reaction	Normal	5	5
Pupil reflex	Normal	5	5
Righting reflex	Normal	5	5

Table 7-3 Incidence of responses in the sensory/reflex function test of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈On week 2 of the recovery period〉

Items	Dose(mg/kg/day)	0	500
	No. of animals examined	5	5
Hearing reaction	Normal	5	5
Eye sight reaction	Normal	5	5
Sense of touch reaction	Normal	5	5
Pain reaction	Normal	5	5
Pupil reflex	Normal	5	5
Righting reflex	Normal	5	5

Table 8-1 Incidence of responses in the sensory/reflex function test of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

<On week 6 of the administration period >

		Dose(mg/kg/day)	0	4	20	100	500
Items	No. of animals examined		5	5	5	5	5
Hearing reaction	Normal		5	5	5	5	5
Eye sight 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 8-2 Incidence of responses in the sensory/reflex function test of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test
 <On week 6 of the administration period >

Items	Dose(mg/kg/day) No. of animals examined	0	500
		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 8-3 Incidence of responses in the sensory/reflex function test of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

<On week 2 of the recovery period >

Items	Dose(mg/kg/day)	0	500
	No. of animals examined	5	5
Hearing reaction	Normal	5	5
Eye sight reaction	Normal	5	5
Sense of touch reaction	Normal	5	5
Pain reaction	Normal	5	5
Pupil reflex	Normal	5	5
Righting reflex	Normal	5	5

Table 9-1 Mean value of grip strength and motor activity of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(On week 6 of the administration period)

Dose (mg/kg/day)	No. of animals	Grip strength (g)		Motor activity (counts)	
		Forelimb	Hindlimb	0~30 _{min.}	0~60 _{min.}
0	5	1107	519	7591	11171
		± 71	± 108	± 988	± 3006
4	5	954	491	8069	12141
		± 134	± 111	± 657	± 3514
20	5	910	446	8557	11364
		± 141	± 98	± 883	± 2032
100	5	936	566	6863	9071
		± 140	± 51	± 1711	± 3503
500	5	969	590	8666	14000
		± 142	± 74	± 440	± 2760

Each value is expressed as mean±S.D.

Table 9-2 Mean value of grip strength and motor activity of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 6 of the administration period 〉

Dose (mg/kg/day)	No. of animals	Grip strength (g)		Motor activity (counts)	
		Forelimb	Hindlimb	0~30 _{min.}	0~60 _{min.}
0	5	955	438	7283	10841
		± 124	± 43	± 1787	± 2890
500	5	790	346 *	7882	12102
		± 272	± 62	± 2163	± 4151

Each value is expressed as mean±S.D.

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

Table 9-3 Mean value of grip strength and motor activity of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 2 of the recovery period 〉

Dose (mg/kg/day)	No. of animals	Grip strength (g)		Motor activity (counts)	
		Forelimb	Hindlimb	0~30 _{min.}	0~60 _{min.}
0	5	868	536	7907	10641
		± 193	± 135	± 995	± 2747
500	5	782	467	8910	16275 **
		± 95	± 102	± 441	± 1177

Each value is expressed as mean±S.D.

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

Table 10-1 Mean value of grip strength and motor activity of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 6 of the administration period 〉

Dose (mg/kg/day)	No. of animals	Grip strength (g)		Motor activity (counts)
		Forelimb	Hindlimb	0~30 _{min.}
0	5	473	427	6012
		± 100	± 106	± 1185
4	5	606	403	6687
		± 135	± 42	± 1618
20	5	635	457	6350
		± 130	± 78	± 1662
100	5	505	425	5738
		± 77	± 73	± 1874
500	5	487	421	5724
		± 88	± 78	± 536

Each value is expressed as mean±S.D.

Table 10-2 Mean value of grip strength and motor activity of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 6 of the administration period 〉

Dose (mg/kg/day)	No. of animals	Grip strength (g)		Motor activity (counts)	
		Forelimb	Hindlimb	0~30 _{min.}	0~60 _{min.}
0	5	636	256	6864	9062
		± 98	± 54	± 1885	± 1573
500	5	528	267	6607	10389
		± 95	± 93	± 2132	± 4314

Each value is expressed as mean±S.D.

Table 10-3 Mean value of grip strength and motor activity of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

〈 On week 2 of the recovery period 〉

Dose (mg/kg/day)	No. of animals	Grip strength (g)		Motor activity (counts)	
		Forelimb	Hindlimb	0~30 _{min.}	0~60 _{min.}
0	5	669	414	9239	16005
		± 150	± 53	± 471	± 1031
500	5	539	370	8797	14784
		± 69	± 63	± 609	± 1404

Each value is expressed as mean±S.D.

Table 11 Body weights of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(g)													
Dose (mg/kg/day)	Day	Administration period							Gain 1~42	Recovery period			
		1	7	14	21	28	35	42		42(0)	49(7)	56(14)	Gain 42~56
0		391	420	446	473	499	526	545	154	546	554	568	22
		± 18	± 23	± 27	± 32	± 34	± 35	± 38	± 27	± 53	± 45	± 45	± 19
		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(5)	(5)
4		391	415	441	464	492	518	535	144				
		± 15	± 19	± 24	± 27	± 32	± 37	± 40	± 27				
		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)				
20		386	413	440	463	490	514	527	141				
		± 17	± 22	± 26	± 27	± 32	± 35	± 41	± 32				
		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)				
100		387	415	442	466	491	517	531	144				
		± 14	± 19	± 20	± 19	± 18	± 22	± 24	± 17				
		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)				
500		386	419	452	477	506	539	553	167	562	568	576	14
		± 11	± 17	± 21	± 23	± 29	± 34	± 40	± 33	± 47	± 46	± 50	± 6
		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(5)	(5)

Each value is expressed as mean±S.D.

(n) : No. of animals

Table 12-1 Body weights of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

													(g)
Dose (mg/kg/day)	Day	Premating period				Premating period				Lactation period			
		1	7	14	Gain 1~14	0	7	14	20	Gain 0~20	0	4	Gain 0~4
0		241	251	263	22	277	310	346	429	152	314	344	30
		± 12 (12)	± 17 (12)	± 18 (12)	± 7 (12)	± 16 (11)	± 15 (11)	± 17 (11)	± 28 (11)	± 28 (11)	± 25 (10)	± 22 (10)	± 17 (10)
4		241	256	265	24	273	311	349	430	157	330	351	21
		± 11 (12)	± 12 (12)	± 12 (12)	± 7 (12)	± 11 (12)	± 12 (12)	± 14 (12)	± 22 (12)	± 20 (12)	± 26 (12)	± 18 (12)	± 12 (12)
20		244	255	267	23	277	312	351	436	159	339	354	15 *
		± 10 (12)	± 17 (12)	± 19 (12)	± 9 (12)	± 17 (12)	± 20 (12)	± 24 (12)	± 38 (12)	± 27 (12)	± 26 (12)	± 22 (12)	± 15 (12)
100		243	257	268	25	276	310	347	442	166	316	350	34
		± 9 (12)	± 13 (12)	± 15 (12)	± 9 (12)	± 16 (11)	± 17 (11)	± 17 (11)	± 22 (11)	± 13 (11)	± 22 (11)	± 15 (11)	± 13 (11)
500		241	259	271	30	284	319	357	447	163	327	353	26
		± 12 (12)	± 12 (12)	± 14 (12)	± 8 (12)	± 13 (10)	± 23 (10)	± 21 (10)	± 26 (10)	± 15 (10)	± 24 (10)	± 21 (10)	± 7 (10)

Each value is expressed as mean±S.D.

(n) : No. of animals

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

Table 12-2 Body weights of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(g)

Dose (mg/kg/day)	Day	Administration period							Gain 1~42	Recovery period			
		1	7	14	21	28	35	42		42(0)	49(7)	56(14)	Gain 42~56
0		247	256	267	277	283	294	303	56	303	307	308	5
		± 18	± 24	± 26	± 25	± 26	± 30	± 29	± 14	± 29	± 27	± 29	± 4
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
500		245	260	275	287	293	304	316	70	316	325	322	7
		± 16	± 22	± 28	± 28	± 30	± 39	± 40	± 26	± 40	± 44	± 41	± 5
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Each value is expressed as mean±S.D.

(n) : No. of animals

Table 13 Food consumption of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

(g/rat/day)											
Dose		Administration period							Recovery period		
(mg/kg/day)	Day	1	7	14	21	28	35	41	42(0)	49(7)	55(13)
0		34	31	29	31	30	30	29	26	34	36
		± 3	± 4	± 4	± 3	± 3	± 3	± 4	± 3	± 3	± 4
		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(5)
4		34	30	29	30	30	28	29			
		± 3	± 3	± 4	± 3	± 3	± 4	± 3			
		(12)	(12)	(12)	(10)	(10)	(12)	(12)			
20		33	29	28	29	30	30	29			
		± 4	± 3	± 4	± 2	± 3	± 3	± 4			
		(12)	(12)	(12)	(11)	(11)	(12)	(12)			
100		33	30	29	29	29	29	28			
		± 4	± 2	± 3	± 3	± 2	± 3	± 3			
		(12)	(12)	(12)	(11)	(11)	(12)	(12)			
500		32	32	30	30	31	30	30	28	32	37
		± 3	± 3	± 3	± 3	± 3	± 3	± 5	± 4	± 2	± 2
		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(5)

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

Table 14-1 Food consumption of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Dose (mg/kg/day)	Day	Premating period			Pregnancy period				Lactation period	
		1	7	14	0	7	14	20	0	3
0		21	21	19	18	24	25	24	15	48
		± 4	± 4	± 4	± 4	± 5	± 2	± 3	± 7	± 9
		(12)	(12)	(12)	(11)	(11)	(11)	(11)	(10)	(10)
4		22	22	22	19	27	25	25	17	46
		± 3	± 4	± 4	± 3	± 4	± 3	± 5	± 6	± 9
		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
20		21	21	22	19	26	25	28	20	49
		± 4	± 4	± 3	± 3	± 6	± 3	± 4	± 6	± 13
		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
100		21	21	22	19	25	25	26	21	57
		± 3	± 3	± 4	± 3	± 4	± 1	± 5	± 6	± 5
		(12)	(12)	(12)	(11)	(11)	(11)	(11)	(11)	(11)
500		21	21	23 *	18	26	25	26	18	54
		± 3	± 4	± 2	± 2	± 3	± 2	± 7	± 10	± 5
		(12)	(12)	(12)	(10)	(10)	(10)	(10)	(10)	(10)

Each value is expressed as mean±S.D.

(n) : No. of animals

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

Table 14·2 Food consumption of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Dose (mg/kg/day)	Day	Administration period							(g/rat/day) Recovery period		
		1	7	14	21	28	35	42	42(0)	49(7)	55(13)
0		21	20	20	22	23	21	18	18	24	24
		± 2	± 4	± 4	± 2	± 2	± 3	± 3	± 3	± 3	± 4
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
500		23	20	20	23	23	18	21	21	26	23
		± 3	± 2	± 3	± 2	± 5	± 4	± 3	± 3	± 2	± 3
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Each value is expressed as mean±S.D.

(n) : No. of animals

Table 15 - 1 Urinary findings of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity with the reproduction/developmental toxicity screening test

< On week 6 of the administration period >

Dose (mg/kg/day)	No. of animals	Color		Cloudy		Volume ^{a)} (mL/18hr)	Specific ^{a)} gravity	Na ^{a)} (mEq/18hr)	K ^{a)} (mEq/18hr)	pH						Protein			
		PY	C	—	1+					6.0	6.5	7.0	7.5	8.0	8.5	—	±	1+	2+
0	5	5		5		9.8 ± 2.8	1.064 ± 0.006	2.00 ± 0.82	4.08 ± 1.53				1	2	2		2	3	
4	5	5		5		8.8 ± 2.4	1.071 ± 0.008	1.58 ± 0.26	3.38 ± 0.46				1	1	3		1	4	
20	5	5		5		7.7 ± 3.6	1.070 ± 0.008	1.43 ± 0.27	2.88 ± 0.80				1	1	3		1	4	
100	5	5		5		8.8 ± 2.5	1.072 ± 0.012	1.63 ± 0.27	3.34 ± 0.59					2	3		3	2	
500	5	5		5		6.8 ± 1.5	1.074 ± 0.006	1.48 ± 0.26	2.88 ± 0.43					3	2			5	

Dose (mg/kg/day)	No. of animals	Glucose				Ketone body					Occult blood					Urobilinogen			Bilirubin			
		—	±	1+	2+	—	±	1+	2+	3+	—	±	1+	2+	3+	0.1	1	2	—	1+	2+	3+
0	5	5				5					5					5			5			
4	5	5				5					5					5			5			
20	5	5				5					5					5			5			
100	5	5				4	1				5					5			5			
500	5	5				3	2				5					5			5			

a) : Mean±S.D.

Color :PY(pale yellow), C(colorless).

Cloudy : —(negligible), 1+(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), 3+(80mg/dL).

Occult blood : —(negligible), ±(trace), 1+(slight), 2+(moderate), 3+(marked).

Urobilinogen : Ehrlich unit/dL.

Bilirubin : —(negligible), 1+(slight), 2+(moderate), 3+(marked).

Table 15 · 2 Urinary findings of male rats treated with tetraphenyltin in the combined repeated dose toxicity with the reproduction/developmental toxicity screening test

< On week 6 of the administration period >

Dose (mg/kg/day)	No. of animals	Crystals																	
		Erythrocytes				Leukocytes				Mg				Ca			Ams		
		—	1+	2+	3+	—	1+	2+	3+	—	1+	2+	3+	—	1+	2+	—	1+	2+
0	5	5				5				3	2			5			5		
4	5	5				5				3	2			5			5		
20	5	5				5				3	2			5			5		
100	5	5				5				2	3			5			5		
500	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+	2+		
0	5	4	1			5			5			5		5		5				
4	5	5				5			5			5		5		5				
20	5	3	2			5			5			5		5		5				
100	5	4	1			5			5			5		5		5				
500	5	4	1			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 - 3 Urinary findings of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity with the reproduction/developmental toxicity screening test

< On week 2 of the recovery period >

Dose (mg/kg/day)	No. of animals	Color		Cloudy		Volume ^{a)} (mL/18hr)	Specific ^{a)} gravity	Na ^{a)} (mEq/18hr)	K ^{a)} (mEq/18hr)	pH						Protein			
		PY	C	-	1+					6.0	6.5	7.0	7.5	8.0	8.5	-	±	1+	2+
0	5	5		5		11.1 ± 1.5	1.068 ± 0.005	2.16 ± 0.50	4.26 ± 0.36					3	2		1	4	
500	5	5		5		10.5 ± 2.1	1.070 ± 0.015	1.91 ± 0.78	4.20 ± 1.26				2	1	2			5	

Dose (mg/kg/day)	No. of animals	Glucose				Ketone body					Occult blood					Urobilinogen			Bilirubin			
		-	±	1+	2+	-	±	1+	2+	3+	-	±	1+	2+	3+	0.1	1	2	-	1+	2+	3+
0	5	5				5					5								5			
500	5	5				3	2				5								5			

a) : Mean±S.D.

Color :PY(pale yellow), C(colorless).

Cloudy : -(negligible), 1+(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), 3+(80mg/dL).

Occult blood : -(negligible), ±(trace), 1+(slight), 2+(moderate), 3+(marked).

Urobilinogen : Ehrlich unit/dL.

Bilirubin : -(negligible), 1+(slight), 2+(moderate), 3+(marked).

Table 15 · 4 Urinary findings of male rats treated with tetraphenyltin in the combined repeated dose toxicity with the reproduction/developmental toxicity screening test

< On week 2 of the recovery period >

Dose (mg/kg/day)	No. of animals	Crystals																	
		Erythrocytes				Leukocytes				Mg				Ca			Ams		
		—	1+	2+	3+	—	1+	2+	3+	—	1+	2+	3+	—	1+	2+	—	1+	2+
0	5	5				5				3	2			5			5		
500	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	4	1			5			5			5		5		5		5		
500	5	4	1			5			5			5		5		5		5		

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

Table 16-1 Hematological findings of male rats treated orally with tetraphenyltin in the combined repeat dose and reproductive/developmental toxicity screening test

< At the end of administration period >

Dose (mg/kg/day)	No. of animals	RBC (10 ⁴ /μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (%)	PT (sec)
0	5	875 ± 45	15.4 ± 1.0	44.5 ± 2.5	51 ± 2	17.6 ± 0.6	34.6 ± 0.5	24.4 ± 3.7	14.4 ± 0.7
4	5	873 ± 40	15.8 ± 0.7	46.5 ± 2.1	53 ± 2	18.2 ± 0.6	34.0 ± 0.5	20.6 ± 5.9	14.5 ± 0.6
20	5	861 ± 57	15.6 ± 0.8	45.7 ± 2.0	53 ± 3	18.2 ± 1.0	34.2 ± 0.3	19.5 ± 4.2	14.7 ± 0.5
100	5	858 ± 40	15.6 ± 0.8	45.3 ± 1.8	53 ± 1	18.2 ± 0.5	34.4 ± 0.4	21.2 ± 3.9	15.1 ± 0.6
500	5	899 ± 25	15.8 ± 0.3	45.5 ± 1.1	51 ± 2	17.6 ± 0.5	34.7 ± 0.5	15.0 * ± 4.2	15.3 ± 0.7

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. (10 ⁴ /μL)	WBC (10 ² /μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	19.0 ± 0.9	120 ± 16	93 ± 22	0.0 ± 0.0	1.2 ± 0.3	15.8 ± 4.6	81.2 ± 4.4	1.8 ± 0.2
4	5	17.3 ± 1.4	120 ± 12	96 ± 25	0.0 ± 0.0	0.7 ± 0.3	19.2 ± 6.0	77.8 ± 6.6	2.3 ± 0.9
20	5	18.1 ± 0.9	134 ± 17	81 ± 22	0.0 ± 0.0	1.3 ± 0.6	13.9 ± 3.2	82.8 ± 3.2	2.0 ± 0.5
100	5	20.3 ± 0.8	130 ± 11	89 ± 21	0.0 ± 0.0	1.1 ± 0.5	25.8 ± 5.1	70.9 ± 4.7	2.3 ± 0.6
500	5	19.3 ± 1.1	134 ± 9	83 ± 26	0.0 ± 0.0	1.1 ± 0.5	18.6 ± 4.5	77.9 ± 5.2	2.4 ± 0.8

Each value is expressed as mean±S.D.

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

Table 16-2 Hematological findings of male rats treated orally with tetraphenyltin in the combined repeat dose and reproductive/developmental toxicity screening test

< At the end of recovery period >

Dose (mg/kg/day)	No. of animals	RBC (10 ⁴ /μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (%)	PT (sec)
0	5	886 ± 10	15.8 ± 0.5	45.4 ± 1.0	51 ± 1	17.8 ± 0.6	34.7 ± 0.6	29.1 ± 8.9	15.8 ± 0.7
500	5	858 ± 47	15.0 * ± 0.5	42.7 ** ± 0.8	50 ± 2	17.5 ± 0.7	35.1 ± 0.6	24.1 ± 3.5	15.6 ± 1.0
Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. (10 ⁴ /μL)	WBC (10 ² /μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	16.7 ± 3.1	115 ± 25	80 ± 15	0.0 ± 0.0	2.0 ± 2.1	22.5 ± 7.2	72.6 ± 6.1	3.0 ± 0.8
500	5	18.4 ± 0.8	138 ± 16	94 ± 16	0.0 ± 0.0	1.5 ± 0.7	23.2 ± 5.8	72.8 ± 5.9	2.5 ± 1.1

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 17.1 Hematological findings of female rats treated orally with tetraphenyltin in the combined repeat dose and reproductive/developmental toxicity screening test

< At the end of administration period >

Dose (mg/kg/day)	No. of animals	RBC (10 ⁴ /μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (%)	PT (sec)
0	5	673 ± 35	13.0 ± 1.0	39.0 ± 3.1	58 ± 2	19.3 ± 0.6	33.3 ± 0.5	79.5 ± 15.2	18.0 ± 0.7
4	5	689 ± 20	13.5 ± 0.3	40.7 ± 0.9	59 ± 2	19.6 ± 0.8	33.1 ± 0.2	84.9 ± 22.4	17.1 ± 1.4
20	5	684 ± 35	12.9 ± 0.5	39.1 ± 1.9	57 ± 2	18.9 ± 0.5	33.1 ± 0.4	76.2 ± 23.5	16.8 ± 1.1
100	5	667 ± 32	12.6 ± 0.4	37.6 ± 1.6	57 ± 3	18.9 ± 1.0	33.5 ± 0.4	70.8 ± 22.8	17.6 ± 0.5
500	5	670 ± 57	12.8 ± 1.1	38.9 ± 3.9	58 ± 2	19.1 ± 0.6	32.9 ± 0.5	95.4 ± 17.0	17.3 ± 1.1
Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. (10 ⁴ /μL)	WBC (10 ² /μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	14.9 ± 1.6	113 ± 11	95 ± 29	0.0 ± 0.0	0.6 ± 0.4	32.0 ± 5.0	64.8 ± 5.0	2.6 ± 0.9
4	5	15.6 ± 1.0	140 * ± 11	76 ± 14	0.0 ± 0.0	0.6 ± 0.4	29.1 ± 10.9	67.3 ± 10.8	3.0 ± 0.9
20	5	14.7 ± 1.2	133 ± 11	83 ± 18	0.0 ± 0.0	0.7 ± 0.3	31.7 ± 7.3	65.3 ± 7.0	2.4 ± 1.0
100	5	16.4 ± 0.8	142 * ± 17	79 ± 8	0.0 ± 0.0	0.8 ± 0.2	36.1 ± 7.6	61.0 ± 7.4	2.1 ± 0.4
500	5	15.2 ± 0.9	140 * ± 22	65 ± 18	0.0 ± 0.0	0.5 ± 0.4	37.7 ± 8.9	59.9 ± 8.6	1.9 ± 0.9

Each value is expressed as mean±S.D.

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

Table 17-2 Hematological findings of female rats of the satellite group treated orally with tetraphenyltin in the combined repeat dose and reproductive/developmental toxicity screening test

< At the end of recovery period >

Dose (mg/kg/day)	No. of animals	RBC (10 ⁴ /μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (%)	Ret. (%)	PT (sec)
0	5	819 ± 31	15.0 ± 0.4	42.7 ± 1.2	52 ± 2	18.4 ± 0.7	35.2 ± 0.3	17.9 ± 4.7	16.4 ± 0.5
500	5	818 ± 39	14.7 ± 0.4	41.7 ± 0.9	51 ± 2	18.0 ± 0.5	35.3 ± 0.5	14.4 ± 4.1	16.4 ± 0.4

Dose (mg/kg/day)	No. of animals	APTT (sec)	Plat. (10 ⁴ /μL)	WBC (10 ³ /μL)	Differential leukocyte counts (%)				
					Baso.	Eosin.	Neutro.	Lymph.	Mono.
0	5	15.8 ± 0.6	119 ± 18	52 ± 18	0.0 ± 0.0	1.3 ± 0.4	14.5 ± 3.4	82.7 ± 3.6	1.6 ± 0.3
500	5	16.7 * ± 0.5	130 ± 17	59 ± 17	0.0 ± 0.0	1.6 ± 0.5	15.4 ± 6.5	80.5 ± 6.7	2.5 ** ± 0.3

Each value is expressed as mean±S.D.

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

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

Table 18-1

Blood biochemical findings of male rats treated orally with tetraphenyltin
in the combined repeat dose and reproductive/developmental toxicity screening test

< 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)	ChE (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Chol. (mg/dL)
0	5	523 ± 49	78 ± 11	38 ± 3	378 ± 65	0.83 ± 0.13	44 ± 21	5.78 ± 0.21	2.88 ± 0.20	0.99 ± 0.07	73 ± 7
4	5	462 ± 75	66 ± 5	32 ± 6	518 ± 197	0.68 ± 0.19	46 ± 22	5.64 ± 0.23	2.78 ± 0.14	0.97 ± 0.09	70 ± 10
20	5	448 ± 30	60 * ± 8	31 ± 8	432 ± 83	0.71 ± 0.15	50 ± 14	5.66 ± 0.13	2.74 ± 0.10	0.95 ± 0.09	75 ± 17
100	5	503 ± 72	76 ± 8	39 ± 8	411 ± 66	1.01 ± 0.37	51 ± 7	5.84 ± 0.11	2.85 ± 0.23	0.96 ± 0.11	78 ± 8
500	5	505 ± 90	84 ± 13	48 ± 10	480 ± 53	1.05 ± 0.25	47 ± 7	5.70 ± 0.14	2.80 ± 0.20	0.96 ± 0.09	69 ± 12
Dose (mg/kg/day)	No. of animals	T.G. (mg/dL)	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	41 ± 14	166 ± 10	13.4 ± 2.1	0.43 ± 0.03	0.28 ± 0.02	10.1 ± 0.2	7.3 ± 0.3	147 ± 1	4.46 ± 0.08	106 ± 1
4	5	61 ± 24	158 ± 14	13.1 ± 1.3	0.43 ± 0.02	0.24 ± 0.02	10.5 ± 0.5	8.1 ± 0.8	147 ± 2	5.00 ± 0.43	105 ± 2
20	5	36 ± 18	149 ± 13	14.7 ± 1.9	0.45 ± 0.04	0.26 ± 0.03	10.5 ± 0.2	7.3 ± 0.4	148 ± 1	4.75 ± 0.42	106 ± 1
100	5	51 ± 24	153 ± 22	12.1 ± 2.0	0.44 ± 0.03	0.25 ± 0.03	10.1 ± 0.2	7.4 ± 0.8	148 ± 1	4.56 ± 0.30	107 ± 2
500	5	39 ± 17	163 ± 10	12.5 ± 1.0	0.42 ± 0.03	0.26 ± 0.02	10.2 ± 0.2	7.4 ± 0.7	149 ± 1	4.88 ± 0.55	108 ± 1

Each value is expressed as mean±S.D.

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

Table 18-2 Blood biochemical findings of male rats treated orally with tetraphenyltin in the combined repeat dose and reproductive/developmental toxicity screening test

< 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)	ChE (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Cho. (mg/dL)
0	5	554 ± 97	92 ± 25	50 ± 14	365 ± 54	0.97 ± 0.13	51 ± 8	5.64 ± 0.19	2.66 ± 0.17	0.90 ± 0.10	78 ± 7
500	5	541 ± 161	76 ± 7	39 ± 9	382 ± 168	0.91 ± 0.15	37 * ± 9	5.72 ± 0.34	2.65 ± 0.26	0.87 ± 0.10	80 ± 19
Dose (mg/kg/day)	No. of animals	T.G. (mg/dL)	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	44 ± 19	154 ± 14	21.0 ± 2.7	0.51 ± 0.07	0.26 ± 0.02	10.5 ± 0.3	7.3 ± 0.5	146 ± 1	5.00 ± 0.43	107 ± 1
500	5	60 ± 7	163 ± 10	17.2 * ± 2.4	0.43 ± 0.05	0.26 ± 0.03	10.6 ± 0.4	6.6 * ± 0.4	147 ± 1	4.87 ± 0.43	108 ± 1

Each value is expressed as mean±S.D.

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

Table 19-1 Blood biochemical findings of female rats treated orally with tetraphenyltin in the combined repeat dose and reproductive/developmental toxicity screening test

< 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)	ChE (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Chol. (mg/dL)
0	5	486 ± 34	81 ± 7	74 ± 18	428 ± 186	1.02 ± 0.35	192 ± 65	5.48 ± 0.33	2.78 ± 0.22	1.03 ± 0.08	73 ± 12
4	5	491 ± 132	75 ± 8	61 ± 9	475 ± 318	1.21 ± 0.59	253 ± 58	5.91 ± 0.46	2.97 ± 0.45	1.01 ± 0.17	68 ± 5
20	5	550 ± 172	92 ± 10	68 ± 6	460 ± 217	0.83 ± 0.13	214 ± 42	5.64 ± 0.35	3.03 ± 0.19	1.17 ± 0.08	78 ± 11
100	5	544 ± 107	90 ± 15	75 ± 12	338 ± 100	1.03 ± 0.19	238 ± 65	5.63 ± 0.32	2.90 ± 0.30	1.07 ± 0.14	87 ± 10
500	5	494 ± 52	86 ± 10	73 ± 15	402 ± 184	1.08 ± 0.17	281 ± 90	5.97 ± 0.40	3.16 ± 0.32	1.13 ± 0.11	90 ± 12
Dose (mg/kg/day)	No. of animals	T.G. (mg/dL)	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	105 ± 38	149 ± 10	23.3 ± 3.2	0.59 ± 0.04	0.24 ± 0.02	10.8 ± 0.2	8.3 ± 1.0	145 ± 2	4.86 ± 0.21	104 ± 2
4	5	101 ± 22	156 ± 12	20.5 ± 3.7	0.57 ± 0.06	0.25 ± 0.01	10.8 ± 0.5	9.3 ± 1.2	147 ± 2	4.94 ± 0.29	105 ± 2
20	5	83 ± 24	141 ± 19	24.4 ± 3.1	0.56 ± 0.07	0.26 ± 0.02	11.3 ± 0.7	10.5 * ± 0.9	148 ± 3	5.11 ± 0.16	103 ± 2
100	5	130 ± 53	145 ± 11	24.2 ± 5.9	0.56 ± 0.02	0.26 ± 0.03	10.3 ± 0.2	8.1 ± 1.5	143 ± 1	4.79 ± 0.29	102 ± 2
500	5	107 ± 23	138 ± 15	24.8 ± 4.6	0.57 ± 0.03	0.26 ± 0.03	10.6 ± 0.3	8.8 ± 0.8	147 ± 3	4.90 ± 0.16	102 ± 2

Each value is expressed as mean±S.D.

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

Table 19-2 Blood biochemical findings of female rats of the satellite group treated orally with tetraphenyltin in the combined repeat dose and reproductive/developmental toxicity screening test

< 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)	ChE (IU/L)	T.P. (g/dL)	Alb. (g/dL)	A/G	T-Chol. (mg/dL)
0	5	481 ± 100	74 ± 19	33 ± 15	191 ± 42	1.33 ± 0.31	449 ± 96	6.11 ± 0.24	3.25 ± 0.21	1.14 ± 0.14	85 ± 20
500	5	541 ± 118	72 ± 12	36 ± 11	142 * ± 22	0.95 ± 0.32	568 ± 119	6.39 ± 0.45	3.60 ± 0.42	1.29 ± 0.15	93 ± 12
Dose (mg/kg/day)	No. of animals	T.G. (mg/dL)	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	21 ± 10	131 ± 7	19.3 ± 1.9	0.50 ± 0.04	0.27 ± 0.02	10.7 ± 0.1	6.6 ± 0.2	146 ± 2	4.34 ± 0.24	110 ± 2
500	5	26 ± 13	132 ± 14	18.9 ± 2.4	0.49 ± 0.05	0.25 ± 0.02	10.3 ** ± 0.2	6.4 ± 0.8	146 ± 2	5.04 * ± 0.44	110 ± 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 20 Incidence of necropsy findings of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with reproduction/developmental toxicity screening test

Organ	: Findings	Grade	Dose(mg/kg/day) No. of animals	At the end of administration period					At the end of recovery period	
				0	4	20	100	500	0	500
				7	12	12	12	7	5	5
	Abnormality			0	0	0	0	0	0	0

Table 21 Incidence of necropsy findings of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with reproduction/developmental toxicity screening test

Organ	: Findings	Grade	Dose(mg/kg/day) No. of animals	At the end of administration period					At the end of recovery period ^a	
				0	4	20	100	500	0	500
				12	12	12	12	12	5	5
Abnormality				0	0	0	0	0	0	0

a : Satellite group.

Table 22-1 Absolute and relative organ weights of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

< At the end of administration period >

	Dose	B.W.	Brain	Thymus	Heart	Liver	Kidney	Adrenal gland	Spleen	Seminal vesicle	Testis	Epididymis	Pituitary	Thyroid
	(mg/kg/day)	(g)	(g)	(g)	(g)	(g)	(g)	(mg)	(g)	(g)	(g)	(g)	(mg)	(mg)
Absolute	0	515	2.01	0.37	1.43	13.35	3.12	63.7	0.71	1.69	3.31	1.68	14.8	34.7
		±25	±0.04	±0.05	±0.12	±1.49	±0.29	±9.5	±0.07	±0.56	±0.27	±0.33	±0.5	±3.5
		(7)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(7)	(7)	(5)	(5)
	4	504	2.03	0.36	1.39	14.54	3.20	72.7	0.81	1.83	3.34	1.41	13.4	35.7
		±35	±0.05	±0.05	±0.15	±1.54	±0.33	±4.5	±0.14	±0.48	±0.39	±0.25	±1.2	±2.5
		(12)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(12)	(12)	(5)	(5)
	20	500	2.00	0.32	1.35	14.84	3.02	69.6	0.73	1.85	3.49	1.55	14.2	36.3
		±37	±0.03	±0.03	±0.12	±1.25	±0.31	±7.7	±0.12	±0.56	±0.21	±0.39	±1.1	±3.1
		(12)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(12)	(12)	(5)	(5)
	100	506	2.03	0.29	1.33	14.95	3.05	74.0	0.71	2.09	3.25	1.44	15.2	37.9
		±22	±0.10	±0.04	±0.12	±1.12	±0.16	±15.5	±0.08	±0.61	±0.60	±0.49	±1.3	±9.6
		(12)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(12)	(12)	(5)	(5)
	500	520	2.07	0.31	1.42	14.91	3.17	77.3	0.79	2.15	3.14	1.63	14.9	37.1
		±36	±0.04	±0.07	±0.10	±2.06	±0.17	±10.0	±0.08	±0.78	±0.77	±0.67	±1.6	±7.2
		(7)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(7)	(7)	(5)	(5)
Relative @	0	515	0.39	0.07	0.28	2.57	0.60	12.3	0.14	0.33	0.64	0.33	2.8	6.7
		±25	±0.02	±0.01	±0.03	±0.22	±0.04	±1.6	±0.01	±0.10	±0.07	±0.07	±0.2	±0.6
		(7)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(7)	(7)	(5)	(5)
	4	504	0.40	0.07	0.28	2.89	0.63	14.4	0.16	0.36	0.66	0.28	2.7	7.1
		±35	±0.02	±0.01	±0.02	±0.40	±0.07	±0.8	±0.02	±0.08	±0.09	±0.06	±0.3	±0.5
		(12)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(12)	(12)	(5)	(5)
	20	500	0.41	0.06	0.27	3.00	0.61	14.1	0.15	0.37	0.70	0.31	2.9	7.4
		±37	±0.03	±0.01	±0.02	±0.12	±0.03	±1.5	±0.02	±0.10	±0.05	±0.09	±0.1	±1.0
		(12)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(12)	(12)	(5)	(5)
	100	506	0.41	0.06	0.27	3.01	0.62	14.9	0.14	0.42	0.64	0.29	3.0	7.6
		±22	±0.02	±0.01	±0.02	±0.30	±0.03	±3.3	±0.01	±0.12	±0.11	±0.10	±0.2	±2.1
		(12)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(12)	(12)	(5)	(5)
	500	520	0.41	0.06	0.28	2.90	0.62	15.1	0.16	0.41	0.60	0.32	2.9	7.2
		±36	±0.03	±0.01	±0.02	±0.30	±0.04	±2.0	±0.01	±0.13	±0.15	±0.15	±0.5	±1.1
		(7)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(7)	(7)	(5)	(5)

Each value is expressed as mean ± S.D.

@ : Relative organ weight per 100g body weight.

(n) : Number of animals.

Table 22-2 Absolute and relative organ weights of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

< At the end of recovery period >

	Dose	B.W.	Brain	Thymus	Heart	Liver	Kidney	Adrenal gland	Spleen	Seminal vesicle	Testis	Epididymis	Pituitary	Thyroid
	(mg/kg/day)	(g)	(g)	(g)	(g)	(g)	(g)	(mg)	(g)	(g)	(g)	(g)	(mg)	(mg)
Absolute	0	527	2.08	0.29	1.43	12.37	3.10	70.4	0.72	2.53	3.40	1.49	15.3	33.6
		±42	±0.12	±0.09	±0.16	±1.81	±0.41	±7.6	±0.07	±0.34	±0.39	±0.16	±1.2	±4.5
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
	500	540	2.10	0.34	1.44	13.79	3.32	69.4	0.80	2.75	3.42	1.57	15.5	37.6
		±48	±0.13	±0.06	±0.10	±1.59	±0.25	±16.0	±0.17	±0.19	±0.21	±0.10	±1.9	±5.6
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
Relative @	0	527	0.40	0.06	0.27	2.34	0.59	13.4	0.14	0.49	0.65	0.28	2.9	6.4
		±42	±0.03	±0.01	±0.01	±0.18	±0.06	±1.3	±0.02	±0.09	±0.08	±0.03	±0.2	±0.4
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
	500	540	0.39	0.06	0.27	2.55	0.62	12.9	0.15	0.51	0.63	0.29	2.9	7.0
		±48	±0.04	±0.02	±0.03	±0.16	±0.04	±2.9	±0.04	±0.05	±0.04	±0.03	±0.2	±1.1
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Each value is expressed as mean ± S.D.

@ : Relative organ weight per 100g body weight.

(n) : Number of animals.

Table 23-1 Absolute and relative organ weights of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

< At the end of administration period >

	Dose	B.W.	Brain	Thymus	Heart	Liver	Kidney	Adrenal gland	Spleen	Pituitary	Thyroid
	(mg/kg/day)	(g)	(g)	(g)	(g)	(g)	(g)	(mg)	(g)	(mg)	(mg)
Absolute	0	315 ±21 (5)	1.90 ±0.05 (5)	0.21 ±0.11 (5)	1.00 ±0.10 (5)	10.68 ±1.12 (5)	1.86 ±0.20 (5)	75.4 ±8.5 (5)	0.63 ±0.14 (5)	16.3 ±2.0 (5)	23.6 ±2.8 (5)
	4	332 ±19 (5)	1.89 ±0.11 (5)	0.27 ±0.08 (5)	0.94 ±0.06 (5)	11.87 ±0.49 (5)	1.96 ±0.06 (5)	74.8 ±9.3 (5)	0.67 ±0.10 (5)	20.1 * ±1.1 (5)	26.7 ±2.0 (5)
	20	333 ±24 (5)	1.91 ±0.05 (5)	0.24 ±0.01 (5)	0.97 ±0.05 (5)	11.87 ±1.35 (5)	1.94 ±0.20 (5)	74.1 ±16.4 (5)	0.72 ±0.15 (5)	18.4 ±2.3 (5)	30.7 ** ±3.3 (5)
	100	331 ±15 (5)	1.90 ±0.05 (5)	0.22 ±0.04 (5)	1.05 ±0.07 (5)	12.16 ±1.26 (5)	2.00 ±0.15 (5)	74.5 ±14.3 (5)	0.63 ±0.07 (5)	17.4 ±1.5 (5)	26.8 ±4.0 (5)
	500	319 ±10 (5)	1.88 ±0.05 (5)	0.26 ±0.08 (5)	0.96 ±0.06 (5)	12.29 ±0.52 (5)	1.90 ±0.15 (5)	73.7 ±12.1 (5)	0.65 ±0.10 (5)	16.9 ±1.9 (5)	24.1 ±2.2 (5)
Relative @	0	315 ±21 (5)	0.61 ±0.04 (5)	0.07 ±0.03 (5)	0.32 ±0.02 (5)	3.40 ±0.36 (5)	0.59 ±0.05 (5)	24.0 ±2.8 (5)	0.20 ±0.05 (5)	5.2 ±0.6 (5)	7.5 ±0.8 (5)
	4	332 ±19 (5)	0.57 ±0.03 (5)	0.08 ±0.02 (5)	0.28 * ±0.02 (5)	3.58 ±0.24 (5)	0.59 ±0.04 (5)	22.6 ±2.7 (5)	0.20 ±0.02 (5)	6.1 ±0.4 (5)	8.1 ±0.2 (5)
	20	333 ±24 (5)	0.58 ±0.03 (5)	0.08 ±0.01 (5)	0.29 ±0.01 (5)	3.56 ±0.20 (5)	0.58 ±0.05 (5)	22.3 ±5.2 (5)	0.21 ±0.03 (5)	5.5 ±0.8 (5)	9.3 ±1.6 (5)
	100	331 ±15 (5)	0.58 ±0.03 (5)	0.07 ±0.01 (5)	0.32 ±0.02 (5)	3.67 ±0.23 (5)	0.60 ±0.04 (5)	22.5 ±3.8 (5)	0.19 ±0.02 (5)	5.2 ±0.3 (5)	8.1 ±1.1 (5)
	500	319 ±10 (5)	0.59 ±0.02 (5)	0.08 ±0.02 (5)	0.30 ±0.02 (5)	3.85 ±0.06 (5)	0.60 ±0.05 (5)	23.1 ±3.7 (5)	0.20 ±0.03 (5)	5.3 ±0.5 (5)	7.6 ±0.7 (5)

Each value is expressed as mean ± S.D.

@ : Relative organ weight per 100g body weight.

(n) : Number of animals.

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

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

Table 23-2 Absolute and relative organ weights of female rats of the satellite group treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

< At the end of recovery period >

	Dose	B.W.	Brain	Thymus	Heart	Liver	Kidney	Adrenal gland	Spleen	Pituitary	Thyroid
	(mg/kg/day)	(g)	(g)	(g)	(g)	(g)	(g)	(mg)	(g)	(mg)	(mg)
Absolute	0	288	1.90	0.28	0.85	6.91	1.86	73.5	0.61	17.0	26.0
		±28	±0.06	±0.03	±0.04	±1.05	±0.11	±6.6	±0.16	±1.3	±5.6
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
	500	302	1.87	0.29	0.93	7.71	1.99	73.0	0.61	16.9	27.8
		±42	±0.05	±0.03	±0.14	±1.58	±0.35	±9.4	±0.12	±2.0	±3.4
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
Relative @	0	288	0.67	0.10	0.30	2.39	0.65	25.6	0.21	5.9	8.9
		±28	±0.06	±0.02	±0.02	±0.13	±0.05	±2.1	±0.04	±0.6	±1.2
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
	500	302	0.62	0.10	0.31	2.54	0.66	24.6	0.20	5.6	9.3
		±42	±0.07	±0.01	±0.02	±0.20	±0.05	±4.8	±0.03	±0.6	±1.6
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)

Each value is expressed as mean ± S.D.

@ : Relative organ weight per 100g body weight.

(n) : Number of animals.

Table 24 Incidence of histopathological findings of male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with reproduction/developmental toxicity screening test

Organs	Findings	Grade	At the end of administration period					At the end of recovery period	
			0	4	20	100	500	0	500
		Dose(mg/kg/day) No. of animals	5	5	5	5	5	5	5
Heart	Myocardial degeneration/fibrosis	-	5	#	#	#	4	#	#
		+	0	#	#	#	1	#	#
Lung	Accumulation, foam cell	-	3	#	#	#	4	#	#
		+	2	#	#	#	1	#	#
Liver	Microgranuloma	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
Glandular stomach	Dilatation, fundic gland	-	4	#	#	#	4	#	#
		+	1	#	#	#	1	#	#
Kidney	Hyaline droplet, proximal tubular epithelium	-	0	#	#	#	1	#	#
		+	5	#	#	#	4	#	#
	Basophilic tubule, unilateral	-	3	#	#	#	5	#	#
		+	2	#	#	#	0	#	#
	Cellular infiltration, lymphocyte, cortex, unilateral	-	4	#	#	#	4	#	#
		+	1	#	#	#	1	#	#
	Hyperplasia, pelvic epithelium, unilateral	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
	Thymus	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
	Spleen	-	0	#	#	#	0	#	#
		+	5	#	#	#	5	#	#
	Deposit, pigment, brown	-	0	#	#	#	0	#	#
		+	5	#	#	#	5	#	#

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

No abnormalities were detected in the the brain, thyroid, parathyroid, lung, trachea, stomach, small intestine, large intestine, adrenal, urinary bladder, seminal vesicle, spinal cord, sciatic nerve, bone marrow and lymph nodes from animals of control and 500mg/kg groups.

Table 25 Incidence of histopathological findings of female rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with reproduction/developmental toxicity screening test

Organs	Findings	Grade Dose(mg/kg/day) No. of animals	At the end of administration period					At the end of recovery period ^a	
			0	4	20	100	500	0	500
			5	5	5	5	5	5	5
Lung	Accumulation, foam cell	-	3	#	#	#	3	#	#
		+	2	#	#	#	2	#	#
Liver	Necrosis, focal	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
Glandular stomach	Dilatation, fundic gland	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
Kidney	Basophilic tubule, unilateral	-	5	#	#	#	4	#	#
		+	0	#	#	#	1	#	#
	Cellular infiltration, lymphocyte, cortex, unilateral	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
	Cyst, solitary, unilateral	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
Thymus	Hemorrhage	-	4	#	#	#	5	#	#
		+	1	#	#	#	0	#	#
Spleen	Hematopoiesis, extramedullary	-	0	#	#	#	0	#	#
		+	4	#	#	#	3	#	#
		++	1	#	#	#	2	#	#
	Deposit, pigment, brown	-	0	#	#	#	0	#	#
		+	3	#	#	#	4	#	#
		++	2	#	#	#	1	#	#

a : Satellite group.

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

NP : Non pregnant, killed on 27 days after copulation. ED : Animal with all embryonic death, killed on 27 days after copulation.

No abnormalities were detected in the brain, pituitary, thyroid, parathyroid, thymus, trachea, stomach, small intestine, large intestine, adrenal, urinary bladder, ovary, vagina, spinal cord, sciatic nerve, bone marrow and lymph nodes from animals of control and 500mg/kg groups.

Table 26 The number of cells in seminiferous epithelia assessed by the individual examination in male rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Dose (mg/kg/day)	No. of animals		Stage II-III			Stage V			Stage VII			Stage X II	
			G	P	T	G	P	T	G	R/P	T	G	Z/P
0	5	Mean	0.53	2.02	5.93	0.59	2.09	6.28	0.06	3.26	6.33	0.06	4.76
		S.D.	0.04	0.08	0.49	0.03	0.23	0.28	0.01	0.35	0.38	0	0.44
500	5	Mean	0.52	1.88	6.07	0.56	2.16	6.46	0.06	3.18	6.37	0.06	4.46
		S.D.	0.07	0.17	0.46	0.02	0.22	0.60	0.01	0.19	0.38	0.01	0.16

G : spermatogonia.

P : pachytene spermatocyte.

R : preleptotene spermatocyte.

Z : zygotene spermatocyte.

T : round spermatid.

Table 27 Reproduction results of rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Dose (mg/kg/day)	0	4	20	100	500
Estrous cycle (days, Mean $\pm$ S.D.)	4.0 $\pm$ 0.1	4.3 $\pm$ 0.6	4.0 $\pm$ 0.0	4.0 $\pm$ 0.0	4.0 $\pm$ 0.0
No. of pairs mated	12	12	12	12	12
No. of pairs with successful copulation	12	12	12	12	12
Copulation index (%)	100	100	100	100	100
Pairing days until copulation (days, Mean $\pm$ S.D.)	4.3 $\pm$ 4.0	2.3 $\pm$ 1.2	2.1 $\pm$ 1.1	2.3 $\pm$ 1.2	2.3 $\pm$ 1.1
No. of pregnant females	11	12	12	11	10
Fertility index (%)	91.7	100	100	91.7	83.3
No. of corpora lutea (Mean $\pm$ S.D.)	15.3 $\pm$ 2.4	16.3 $\pm$ 2.0	15.9 $\pm$ 2.1	16.5 $\pm$ 1.1	15.4 $\pm$ 1.6
No. of implantation sites (Mean $\pm$ S.D.)	13.5 $\pm$ 4.9	16.0 $\pm$ 2.3	14.8 $\pm$ 4.4	16.1 $\pm$ 1.2	15.0 $\pm$ 1.6
Implantation index (% , Mean $\pm$ S.D.)	86.0 $\pm$ 27.1	97.8 $\pm$ 5.1	91.0 $\pm$ 23.7	97.8 $\pm$ 3.1	97.5 $\pm$ 4.3
No. of pregnant females with parturition	10	12	12	11	10
Gestation length (days, Mean $\pm$ S.D.)	22.6 $\pm$ 0.5	22.5 $\pm$ 0.5	22.3 $\pm$ 0.5	22.7 $\pm$ 0.5	22.6 $\pm$ 0.5
No. of pregnant females with live pups	10	12	12	11	10
Gestation index (%)	90.9	100	100	100	100
No. of pregnant females with live pups on day 4	10	12	12	11	10
Copulation index = (No. of pairs with successful copulation/No. of pairs mated) $\times$ 100. Fertility index = (No. of pregnant females/No. of pairs with successful copulation) $\times$ 100. Gestation index = (No. of females with live pups/No. of pregnant females) $\times$ 100.					

Table 28 Litter results of rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Dose(mg/kg/day)	0	4	20	100	500
No. of pregnant females with live pups	10	12	12	11	10
No. of pups born	13.1 ± 5.2	14.2 ± 4.1	13.5 ± 4.5	15.5 ± 1.4	14.3 ± 1.9
Delivery index (%)	88.1 ± 29.6	88.5 ± 22.3	92.1 ± 12.3	96.0 ± 4.3	95.2 ± 5.2
No. of pups alive on day 0 of lactation					
Total	14.1 ± 2.7	13.9 ± 3.9	13.5 ± 4.5	15.5 ± 1.4	14.1 ± 1.7
Male	5.8 ± 2.1	7.6 ± 3.2	6.7 ± 2.5	6.4 ± 1.1	6.6 ± 2.7
Female	8.3 ± 2.8	6.3 ± 2.0	6.8 ± 3.1	9.1 ± 1.3	7.5 ± 1.8
Live birth index (%)	98.3 ± 5.3	98.5 ± 3.8	100.0 ± 0.0	100.0 ± 0.0	98.8 ± 2.6
Sex ratio(Male/Female)	0.73	1.21	0.98	0.70	0.88
No. of pups alive on day 4 of lactation					
Total	14.0 ± 2.6	12.7 ± 4.6	13.2 ± 4.5	15.4 ± 1.4	13.9 ± 1.8
Male	5.8 ± 2.1	6.8 ± 3.1	6.6 ± 2.7	6.4 ± 1.1	6.6 ± 2.7
Female	8.2 ± 2.6	5.8 ± 2.4	6.6 ± 2.9	9.0 ± 1.3	7.3 ± 1.8
Viability index (%)	99.4 ± 2.0	92.5 ± 21.9	94.3 ± 14.2	99.4 ± 1.9	98.6 ± 3.0
Body weight of live pups (g)					
on day 0					
Male	7.1 ± 0.6	7.0 ± 0.8	7.2 ± 0.8	7.3 ± 0.5	7.1 ± 0.5
Female	6.7 ± 0.5	6.6 ± 0.8	6.6 ± 0.6	6.8 ± 0.5	6.7 ± 0.6
on day 4					
Male	11.2 ± 1.5	11.0 ± 2.4	11.2 ± 1.6	11.4 ± 1.3	11.1 ± 1.3
Female	10.6 ± 1.0	10.5 ± 2.5	10.5 ± 1.4	10.8 ± 1.1	10.7 ± 1.4

Delivery index = (No. of pups born/No. of implantation sites)×100.

Live birth index = (No. of live pups on day 0/No. of pups born)×100.

Viability index = (No. of live pups on day 4/No. of live pups on day 0)×100.

Sex ratio = Total number of male pups/Total number of female pups.

Each value is expressed as Mean±S.D.,except sex ratio.

Table 29 External findings of pups from pregnant rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Dose(mg/kg/day)	0	4	20	100	500
No. of pups examined	144	170	162	170	143
No. of pups with external malformations [#]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[#] : No. of pups (Mean±S.D. of individual litter percentages).

Table 30 Visceral findings of pups from pregnant rats treated orally with tetraphenyltin in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Dose(mg/kg/day)	0	4	20	100	500
No. of pups examined	144	170	162	170	143
No. of pups with visceral malformations [#]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No. of pups with visceral variations [#]	1 (0.6±1.8)	1 (0.6±1.9)	0 (0)	0 (0)	1 (0.7±2.2)
Visceral variations [#]					
Thymic remnant in neck	0 (0)	1 (0.6±1.9)	0 (0)	0 (0)	0 (0)
Persistent left umbilical artery	1 (0.6±1.8)	0 (0)	0 (0)	0 (0)	1 (0.7±2.2)

: No. of pups (Mean±S.D. of individual litter percentages).