

最終報告書訂正版(第2版)

Phenol, 2,4-bis(1,1-dimethylpropyl)のラットを用いる
反復投与毒性・生殖発生毒性併合試験

厚生労働省医薬食品局審査管理課化学物質安全対策室 委託

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被験物質 Phenol, 2,4-bis(1,1-dimethylpropyl)

試験項目 反復投与毒性ならびに生殖発生毒性試験

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試資料保管場所 秦野研究所資料保存室

被験物質保管場所 秦野研究所被験物質保存庫

保管期間 試験終了後10年間
その後の保管については試験委託者と協議する。

運営管理者 一般財団法人食品薬品安全センター 秦野研究所
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本試験は、「新規化学物質等に係る試験の方法について」(平成23年3月31日付け 薬食発0331第7号厚生労働省医薬食品局長、平成23・03・29製局第5号経済産業省製造産業局長、環保企発第110331009号環境省総合環境政策局長通知)に準拠し、「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成23年3月31日付け 薬食発0331第8号厚生労働省医薬食品局長、平成23・03・29製局第6号経済産業省製造産業局長、環保企発第110331010号環境省総合環境政策局長通知)を遵守して実施した。

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血液学検査

(採血を含む)

血液生化学検査

尿検査

病理解検査

[REDACTED]

被験物質管理

検体調製

化学生分析

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要約

今回、Phenol, 2,4-bis(1,1-dimethylpropyl)の雌雄動物の反復投与毒性および回復性、ならびに生殖能力に対する影響および新生児の発育に及ぼす影響を検討することを目的として、反復投与毒性ならびに生殖発生毒性試験を化審法ガイドラインに従って実施した。雌雄の Crl:CD (SD) ラットに被験物質を 0 (媒体:トウモロコシ油)、10、50 ならびに 100 (投与開始時は 250 mg/kg) の用量で経口投与した。投与開始後、高用量群では死亡あるいは瀕死動物が約半数にみられたことから、投与 12 日以降の投与量を 250 から 100 mg/kg に変更した。また、同群では繁殖能の検査は実施せず、雄は 42 日間投与した後に剖検し、雌は反復毒性およびその回復性を評価した。雄の毒性の回復性は 50 mg/kg 投与群で評価した。

すなわち、雄については、42 日間投与した後に剖検した。なお、0 および 50 mg/kg 投与群の各 5 例は 42 日間投与した後、14 日間回復させて剖検した。雌の 0 および 50 mg/kg 投与群は交配前 2 週間および交配期間、妊娠期間を通して哺育 4 日まで連日投与 (投与日数:41~44 日間) した。交配雌は自然分娩させ、出生児は哺育 4 日、母動物は哺育 5 日に剖検した。また、雌では 0 および 100 mg/kg 投与群に非交配のサテライト群を設け、42 日間投与した後、半数を剖検し、残りの半数は 42 日間投与した後、14 日間回復させて剖検した。

1. 親動物所見

高用量群の雄では投与 6~13 日に 13 例中 9 例が、雌では投与 6~9 日の間に 23 例中 12 例が死亡あるいは瀕死となり切迫屠殺した。これらの動物では、投与 2 日から一般状態に変化がみられ、体重も減少した。病理学検査の結果から、腎臓では皮質および髓質の尿細管に変性あるいは壊死が広範囲に認められ、乳頭部の壊死、腎孟の移行上皮の過形成も観察された。

投与期間中の一般状態の変化として、投与後の一過性の流涎が、雄では 50 mg/kg 以上の投与群に、雌ではサテライト群 (非交配雌) の 100 mg/kg 投与群および繁殖能を評価した分娩雌の 50 mg/kg 投与群に、また、軟便が、雄およびサテライト群 (非交配雌) の 100 mg/kg 投与群に散見された。回復期間中はこれらの変化は消失した。

雄の 50 mg/kg 以上の投与群における体重が、投与期間中を通して、対照群と比較して低値に推移する傾向がみられた。回復期間中も体重は低値に推移した。サテライト群 (非交配雌) および繁殖能を評価した雌の体重には、Phenol, 2,4-bis(1,1-dimethylpropyl) 投与による影響は観察されなかった。

尿検査では、100 mg/kg 投与群において、雄では尿量が増加傾向を示し、雌では有意に増加した。

機能検査では、100 mg/kg 投与群のサテライト群 (非交配雌) において、自発運動量の減少が観察された。

血液学検査では、100 mg/kg 投与群の雄において、血色素量およびヘマトクリット値が減少し、赤血球数も減少傾向を示した。また、プロトロンビン時間の延長および活性化部分トロンボプラスチン時間の延長傾向が観察された。100 mg/kg 投与群のサテライト群 (非交配雌) では、赤血球数、血色素量、ヘマ

トクリット値が減少した。分娩した雌では、50 mg/kg 投与群において、平均赤血球血色素濃度が減少し、網状赤血球比率が増加した。

血液生化学検査では、アルカリファスファターゼ活性の増加傾向が雄の 100 mg/kg 投与群に認められた。

器官重量測定では、投与期間終了時に肝臓重量の増加が、雄では 50 mg/kg 以上の投与群で、雌ではサテライト群(非交配雌)の 100 mg/kg 投与群で、分娩した雌では 50 mg/kg 投与群で認められた。これらの変化は回復後に消失した。また、脾臓重量の増加が、投与期間および回復期間終了時とともに、サテライト群(非交配雌)の 100 mg/kg 投与群で観察された。

病理組織学検査の結果、100 mg/kg 投与群において、雄では腎臓の皮質および髓質に好塩基性尿細管および硝子円柱が、雌(サテライト群; 非交配雌)では皮質に好塩基性尿細管が、それぞれ対照群の変化よりも増強して観察された。しかし、回復期間終了後に実施した 100 mg/kg 投与群(サテライト群; 非交配雌)の病理組織学検査では、腎臓皮質に好塩基性尿細管が観察されたが、投与期間終了時より程度は軽減していた。

その他、詳細な症状観察、機能検査、摂餌量には雌雄のいずれの群においても被験物質投与による影響は認められなかった。また、投与期間終了時にみられた機能検査、血液学検査、血液生化学検査、尿検査の変化は回復期間後には観察されなかった。

2. 生殖発生毒性学的所見および出生児所見

性周期、交配成績、妊娠期間、黄体数、着床数、着床率および出産率には被験物質投与による影響はみられなかった。50 mg/kg 投与群において、母動物の一般状態悪化に起因すると考えられた分娩中死亡および分娩日に瀕死となり切迫屠殺した例が各 1 例認められた。

生児出産率、出生率、新生児出生率、分娩率、体重および性比には被験物質投与による影響は認められなかった。

3. 無毒性量

以上の結果から、本試験条件下における Phenol, 2,4-bis(1,1-dimethylpropyl) の親動物に対する一般毒性学的無毒性量は、一般状態、体重、尿検査、血液学検査、血液生化学検査、器官重量、病理組織学検査の結果から雌雄ともに 10 mg/kg/day、生殖発生毒性学的な無毒性量および次世代児への無毒性量は、いずれの検査項目にも被験物質投与によると考えられる影響はみられなかつたために 50 mg/kg/day と判断された。

試験目的

雌雄ラットの交配前(2 週間)および交配期間中(最長 2 週間)、ならびに雄では交配期間終了後 2 週間(投与日数:42 日間)、交配雌では妊娠期間を通して周産期(哺育 4 日まで、投与日数:41~44 日

間)に、非交配雌(サテライト群)では雄と同様の期間に Phenol, 2,4-bis(1,1-dimethylpropyl)を経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

試験ガイドラインと GLP

本試験は、「新規化学物質等に係る試験の方法について:以下、化審法ガイドライン」(平成 23 年 3 月 31 日付け 薬食発 0331 第 7 号厚生労働省医薬食品局長、平成 23・03・29 製局第 5 号経済産業省製造産業局長、環保企発第 110331009 号環境省総合環境政策局長通知)に準拠し、「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成 23 年 3 月 31 日付け 薬食発 0331 第 8 号厚生労働省医薬食品局長、平成 23・03・29 製局第 6 号経済産業省製造産業局長、環保企発第 110331010 号環境省総合環境政策局長通知)を遵守して実施した。

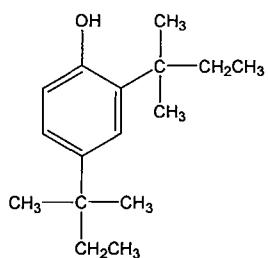
動物愛護

全ての実験操作は、「動物の愛護及び管理に関する法律」(昭和 48 年 10 月 1 日 法律第 105 号、平成 18 年 6 月 2 日 一部改正)、「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」(平成 18 年 4 月 28 日、環境省告示第 88 号)および「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」(平成 18 年 6 月 1 日、科発第 0601001 号)を遵守し、「財団法人食品薬品安全センター秦野研究所動物実験に関する指針」(平成 2 年 10 月 1 日、平成 22 年 10 月 1 日改正)に基づいて実施した。本試験における動物実験計画は、秦野研究所動物実験委員会の審査を受け、承認されている(動物実験承認番号:1110265A)。なお、承認された動物実験計画からの変更はなかった。

材料と方法

1. 被験物質

被験物質である Phenol, 2,4-bis(1,1-dimethylpropyl) (別名:2,4-Di-tert-amylphenol、CAS No.:120-95-6、分子式: C₁₆H₂₆O、分子量:234.38、外観:白色～ほとんど白色の結晶(20°Cで固体)、純度:99.7%、沸点:143°C/0.5kPa、融点(凝固点):26°C、比重:1.0123(20°C)、ロット番号:XPX4F、Annex A、以下、2,4-DTAP)は [REDACTED]より購入し(被験物質入手:2011 年 9 月 27 日)、使用時まで冷蔵・遮光下(実測値 3~6°C)で保管した。2,4-DTAP の構造式を次に示す。



被験物質の安定性は、投与開始前(2011年11月7日)および投与期間終了後(2012年1月30日)に秦野研究所にてフーリエ変換赤外分光光度計(FTIR-8300、島津製作所)を使用し、液膜法にて赤外吸収スペクトル(波数範囲:4000~400 cm⁻¹)を測定して調べた。投与前後の2つのスペクトルに変化がなかったことは同被験物質を用いて実施した他試験(試験番号G-11-031)にて確認されている。

2. 動物および飼育方法

日本チャールス・リバー厚木飼育センターより8週齢のSprague-Dawley(SD)系[Crl:CD(SD)、SPF]ラット雄62匹、雌103匹を購入し、12号室に収容した。入荷日も含めて15日間、検疫と飼育環境への馴化のため飼育した。その間毎日、動物の一般状態を観察し、入荷日(入荷1日)および検疫終了日に体重を測定した。検疫・馴化期間中は動物の尾にフェルトペンで馴化番号を記し、飼育ケージに試験番号、性別および馴化番号を記入した動物カードを掛けて識別した。また、雌動物については、入荷3日から毎日、性周期を観察した。入荷動物の入荷時および検疫終了時の体重は下記の通りであった。

動物入荷日	:2011年11月21日
入荷時体重	:雄 234.0~262.5 g、雌 186.3~219.5 g
検疫終了日	:2011年12月5日
検疫終了時体重	:雄 330.1~413.5 g、雌 228.9~300.4 g

検疫・馴化の結果、雌動物の1例(馴化動物番号31番)で痴皮が見られたが、その他入荷した動物において、検疫期間中の一般状態および体重推移に異常は認められなかった。雌動物では、一般状態に異常がみられた1匹、規則的な4日の性周期の回帰が認められない13匹を除外し、体重別層化無作為抽出法により群分けを行った。群分けした動物には一連の動物番号を割り当て、フェルトペンで尾に動物番号を標識し、色彩の異なる動物カードに試験番号、性別および動物番号を記入して飼育ケージに掛けた。群分けから棄却した雄動物10匹、雌動物17匹、性周期および一般状態の観察結果により除外した14匹は全て余剰動物とし、他目的に使用した。

動物は許容温度21.0~25.0°C、許容湿度40.0~75.0%、換気設定約15回/時間、明暗サイクル12時間(7時~19時)点灯、12時間(19時~7時)消灯に設定された飼育室内で、金属製金網床ケージ(220w×270d×190h mm)に1匹ずつ(交配時は2匹)収容し、固型飼料(CE-2、日本クレア)と水道水(秦野市水道局給水)を自由に摂取させて飼育した(ただし、雄動物、分娩した雌動物ならびにサテライト群の動物は、解剖前に絶食させた)。雌動物は分娩例全例について、妊娠18日から哺育4日までラット用プラスチック製繁殖ケージ(350w×400d×180h mm)に1匹ずつ収容し、床敷として紙パルプ製チップ(ペパークリーン、日本エスエルシー)を適宜供給した。飼育期間中の動物室の温度は23.0~25.5°C、湿度は42.5~70.5%であった。また、供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを確認した。

3. 投与検体

1) 調製

被験物質を秤量し、媒体(トウモロコシ油、製造元:ナカライトスク、製造番号:V9R1728)に溶解させ、5.0 w/v%溶液を調製した。さらに5.0 w/v%溶液を媒体によって希釈し、1.0ならびに0.2 w/v%溶液を段階的に調製した。調製した検体は室温・遮光下(実測値 23.0~25.5°C)で保管し、安定性の保証期間内に使用した。

2) 安定性試験

秦野研究所で、投与に先立ち、0.2 および 5.0 w/v%濃度の投与検体について、室温、遮光条件下(実測値 21.8~23.4°C)における 8 日間の安定性を確認した後、本試験の動物実験を開始した(安定性試験開始日:2011年11月21日、8日目:2011年11月29日、Annex B)。

3) 含量の測定

本試験の初回調製検体(調製日:2011年12月5日)について、0.2、1.0 および 5.0 w/v%濃度の調製検体の含量を測定した。その結果、平均含量は調製指示濃度の 93.8~97.7%であり、各測定値のばらつきは平均値の 98.8~101.5%で規定範囲内にあった(Annex C-1)。

また、高用量群の投与量の変更(250 mg/kg から 100 mg/kg)に先立ち、初回に投与する検体(調製日:2011年12月16日)について、2.0 w/v%濃度の調製検体の含量を測定した。その結果、平均含量は調製指示濃度の 95.9%であり、各測定値のばらつきは平均値の 98.6~101.1%で規定範囲内にあった(Annex C-2)。

調製検体中の被験物質濃度は以下の方法で測定した。投与検体の 1 mL を正確にとり、2-プロパンノールで希釈した後、アセトニトリルで希釈し、試料溶液(約 1 µg/mL)を調製した。別に、約 40°C 以下で加温して溶かした被験物質約 50 mg を精密に量り、アセトニトリルに溶解して適宜希釈し、標準溶液(約 0.5、1 および 4 µg/mL、各濃度 n=1)を調製した。試料溶液および標準溶液を以下に示す高速液体クロマトグラフ(HPLC)法により測定し、標準溶液から作成した検量線を用いて調製検体中の 2,4-DTAP 濃度を算出した。

HPLC 測定条件

検出器	紫外分光光度計(測定波長 225 nm)
分析カラム	XTerra RP18(内径 3.0 mm、長さ 100 mm、粒子径 3.5 µm、Waters)
移動相	蒸留水/アセトニトリル混液(4:6 v/v)
流量	0.8 mL/min
カラム設定温度	40°C
試料設定温度	10°C
試料注入量	20 µL
オートインジェクタ洗浄液	アセトニトリル
システムの適合性	測定開始前および測定終了後に標準溶液(約 1 µg/mL)を 1 回ずつ測

定し、ピーク保持時間および強度(ピーク面積)の変動(測定開始前にに対する測定終了後の偏差%)を確認した。変動の許容基準は、ピーク保持時間が±3.0%以内、ピーク強度が5.0%以内とした。

4. 投与量の設定および投与方法

本試験の投与量は、本被験物質を用いて行った「Phenol, 2,4-bis(1,1-dimethylpropyl)のラットを用いる反復投与毒性・生殖発生毒性併合試験(予備試験)」(試験番号:R-11-002)の結果¹⁾をもとに設定した。なお、この予備試験で用いた被験物質および媒体は本試験と同じロットを用いた。

予備試験では、0(媒体;トウモロコシ油)、250、500 および 1000 mg/kg の 2,4-DTAP を 8 週齢の雌 SD 系ラット(各群 5 匹)に 14 日間、反復経口投与した。その結果、500 mg/kg 以上の投与群の全例において、初回投与日から一般状態に変化がみられ、投与 3 日から 6 日までの間に全例が死亡あるいは瀕死状態となり剖検した。これらの動物の一般状態および剖検結果から、500 mg/kg 以上の 2,4-DTAP の経口投与により、胃、肺、腎臓に変化が認められると判断した。

14 日間投与により死亡が認められなかった 250 mg/kg 投与群では、投与 5 日以降に軟便が 1 例に観察された。また、投与 9 日以降、1~2 例に投与後に流涎が認められたが一過性の変化であった。体重は対照群と同様に推移したが、投与 14 日に 3 例の体重が前回の体重(同群の投与 12 日)と比較してわずかに減少した。しかし、他の 2 例は対照群と同様に増加した。

250 mg/kg 投与群の剖検の結果、胃および肺に肉眼的な異常はなかったが、腎臓では、淡色域が散在する例が観察された。しかし、いずれの変化も 500 mg/kg 投与群と比較して軽度であった。また、肝臓および腎臓重量が対照群と比較して有意に増加した。血液学検査の結果、赤血球数、ヘマトクリット値、血色素量が対照群と比較して低下した。血液生化学検査の結果、総蛋白濃度およびアルブミン濃度に差はなかったが、A/G 比が 250 mg/kg 投与群にて低値を示した。肝臓の逸脱酵素である AST 活性、ALT 活性には対照群と比較して変化はなかった。また、総コレステロール濃度、トリグリセライド濃度、γ-GTP 活性、ALP 活性、BUN 濃度、LDH 活性は対照群と比較して高値を示した。これらは肝臓および腎臓重量の増加に関連している機能障害に伴った変化と考えられた。

本試験の投与期間は予備試験の約 3 倍(42 日間)である。250 mg/kg の 2,4-DTAP は、肝臓および腎臓に影響を及ぼすと考えられるが、急性期に重篤な変化をもたらす濃度ではなく、被験物質の雌雄動物に対する一般毒性学的变化、さらに生殖毒性への影響も評価ができると考えられた。したがって、14 日間の投与により肝臓および腎臓に影響が認められた用量である 250 mg/kg を本試験における高用量群の投与量に設定し、以下、公比が 5 になるように中用量を 50 mg/kg、低用量を 10 mg/kg とした。

本試験では、雄動物は交配前 2 週間、交配期間(14 日間)を通して剖検前日まで(総投与回数 42 回)、雌動物は交配前 2 週間、交配期間、妊娠期間を通して分娩後の哺育 4 日まで、交尾が確認されなかった雌は剖検前日まで(総投与回数 42 回)、交尾は確認されたが分娩しなかった雌は剖検前日(妊娠 25 日相当日)まで、非妊娠雌の反復毒性を評価するために設定したサテライト群では投与 42 日まで、経口的に 1 日 1 回、1 週 7 回、午前中(9 時 11 分~11 時 25 分)に投与した。投与容量は

5 mL/kg とし、雌雄ともに最新の測定日の体重を基準に投与液量を算出した。

なお、対照群には媒体であるトウモロコシ油を同様に投与した。投与経路は化審法ガイドラインに拠り、ラット用胃管による強制経口投与とした。

本試験開始時の群構成および動物番号を以下に示した。

群	投与物質	投与量 (mg/kg)	濃度 (w/v%)	投与容量 (mL/kg)	動物番号	
					雄	雌
1	トウモロコシ油 (媒体)	0	0	5	M01001～M01013*	F01001～F01013
2	2,4-DTAP	10	0.2	5	M02001～M02013	F02001～F02013
3	2,4-DTAP	50	1.0	5	M03001～M03013*	F03001～F03013
4	2,4-DTAP	250 ^{a)}	5.0	5	M04001～M04013	F04001～F04013#
5 (サテライト群)	トウモロコシ油 (媒体)	0	0	5	-	F05001～F05010#
6 (サテライト群)	2,4-DTAP	250 ^{a)}	5.0	5	-	F06001～F06010#

a) 投与12日から100 mg/kgに変更した。

* 雄の対照群と50 mg/kg 投与群の動物番号の大きい各5例は回復観察に供した。

雌の4群および6群の生存例を100 mg/kg投与群のサテライト群とし、約半数例は回復観察に供した。雌の対照群のサテライト群(5群)の動物番号の大きい5例は回復観察に供した。

投与開始後、高用量群において雄の9例、雌の12例(4群;8例、6群;4例)が死亡あるいは瀕死となり切迫屠殺したことから、投与12日から投与量を250から100 mg/kgに変更して試験を継続した。同群では繁殖能の検査は評価せずに、雄では反復投与毒性、雌では反復投与毒性および回復性を評価することとした。したがって、雄の生存例4例は42日間、雌の高用量を投与した4および6群の生存例11例はサテライト群として42日間、投与を続けた。雄に対する毒性の回復性は、50 mg/kg 投与群で評価した。

投与12日以降、100 mg/kg 投与群における生存例を以下に示した。

群	投与物質	投与量 (mg/kg)	濃度 (w/v%)	投与容量 (mL/kg)	動物番号	
					雄	雌
4*	2,4-DTAP	100	2.0	5	4例; M04001 M04004 M04009 M04010	5例; F04001 F04004 F04006 F04012# F04013#
6	2,4-DTAP	100	2.0	5	-	6例; F06001 F06004 F06006 F06007# F06009# F06010#

* 4群は交配を実施せずサテライト群とした。

回復観察に供した。

5. 検査法

1) 親動物(F₀)

①一般状態の観察

全例について、飼育期間中は毎日1回、投与期間中は投与前後の毎日2回以上観察した。さらに、症状が発現した場合には、断続的に観察を継続した。

②回復および遅発毒性の観察

雄動物は対照群および中用量群のうち動物番号の大きい各5例を、雌動物はサテライト群(5群)の動物番号の大きい各5例、および高用量群(4および6群)の5例(動物番号 F04012、F04013、F06007、F06009、F06010)を最終投与翌日(回復1日)から14日間、毎日1回以上、前項に示した方法で、一般状態を観察した。

③詳細な症状観察

雌雄動物は検疫終了日、投与7、14、21、30、36および42日、回復期間中は回復7および14日に、スコアリング法による詳細な症状観察を行った。さらに、分娩例は哺育0日から4日の間に1回観察した。観察は、いずれも13時10分～15時29分の間に行った。

まず、ケージ越しでの観察を行い、ケージから取り出す際に外表を観察し、作業台上での観察を行った。作業台上では、体位、姿勢、探索行動、立毛、眼裂、振戦、痙攣、呼吸数、歩行、常同行動、奇妙な行動、挙尾反応、身づくろい、発声、排尿、排便、接触に対する反応、撤去反射、耳介反射を観察した。

④機能検査

雄では、投与42日の詳細な症状観察に引き続き、各群5例について、刺激に対する感覚運動反応を検査し、握力測定、自発運動測定は、投与39日に検査した。雌では、分娩例は哺育5日に投与期間が近接した各群5例について、刺激に対する感覚運動反応、握力測定、自発運動測定を検査した。サテライト群では、投与42日の詳細な症状観察に引き続き、各群5例について、刺激に対する感覚運動反応を検査し、握力測定、自発運動測定は、投与41日に検査した。さらに、投与最終週に実施した検査で2,4-DTAP投与群で統計学的有意差がみられたため、回復14日の詳細な症状観察後に、回復例全例について機能検査を実施した。

(1) 刺激に対する感覚運動反応

プライエル反応、瞳孔反射、視覚定位、驚愕反応、後肢引込み反射、眼瞼(瞬目)反射、正向反射の有無を検査した。

(2) 握力測定

小動物握力測定システムを用いて握力を測定した。各動物の前肢および後肢の握力をそれぞれ5回測定し、最高値および最低値を除外した3回の握力値の平均値を求めた。

(3) 自発運動測定

自発運動量測定装置(SUPER-MEX、室町機械)を用いて、20分間の自発運動量(区画移動数お

より立ち上がり回数)を計測し、計測値は 5 分毎に集計した。実施場所は 14 号室とし、環境条件は 12 号室に準じた。試験対象動物は、検査直前に 14 号室に運搬し、速やかに自発運動測定を開始した。

⑤体重測定

雄および雌動物のサテライト群は、投与 1、7、10、12、14、17、21、24、28、31、35、38、42 日、回復 1、7、14 日および剖検日に測定した。雌動物は投与 1、7、10、12、14、17 日、妊娠 0、3、7、10、14、17、20 日、哺育 0、4 日および剖検日に、分娩が確認されなかった動物では妊娠 26 日相当日にも測定した。

⑥摂餌量測定

雄および雌動物のサテライト群は、投与 1~2、7~8、14~15、29~30、35~36、41~42 日、回復 6~7、12~13 日に測定し、サテライト群のみ投与 21~22 日にも測定した。雌動物は投与 1~2、7~8、14~15 日および妊娠 0~1、7~8、14~15、20~21 日ならびに哺育 3~4 日に測定した。

⑦尿検査

雄動物および雌動物のサテライト群を検査対象とし、投与 37 日の検査では各群 5 例、また、回復 13 日における検査では回復例全例を検査した。

投与 37 日の検査では当日の投与後に、回復 13 日の検査では一般状態の観察終了後に動物を代謝ケージに収容し、以下の項目について検査した。ただし、色調・濁度、試験紙による検査および尿沈渣は、採尿開始後約 4~8 時間の時点で採取した蓄尿で、その他の項目は約 24 時間の蓄尿を行った。

項目	測定法	使用機器
色調・濁度	視診	
pH・潜血・蛋白・糖・ケトン体	試験紙法	オーションイレブンAE-4020(アークレイ)
ウロビリノーゲン・ビリルビン	同上	同上
沈渣	鏡検	光学顕微鏡
尿量	計量	メスシリンドー
比重	屈折法	デジタル臨床屈折計SU-202(エルマ販売)
ナトリウムイオン濃度	イオン電極法	全自動電解質分析装置EA05(エアントティー)
カリウムイオン濃度	同上	同上
塩素イオン濃度	同上	同上

⑧性周期観察

各群とも全例の雌について、動物入荷 3 日から性周期を観察し、群分け後、投与開始以降も引き続きサテライト群を除く全例の膣スメア標本を作製し、各動物の同居後、交尾が確認されるまで性周期を観察した。また、群ごとの平均発情回帰日数(個体ごとの発情期から発情期までの日数の平均)を算出した。なお、規則的に 4~5 日の間で性周期が回帰している動物は正常と判断した。

⑨交配

投与 15 日の 15 時 39 分より、0、10 および 50 mg/kg 投与群において、同群内の雌雄を 1 対 1 で同居させた。翌朝より毎朝、膣栓を確認し、同居中の雌の膣垢標本を作製して鏡検した。膣内に膣栓

あるいは腔垢標本中に精子が確認された動物を交尾成立動物とし、この日を妊娠 0 日と起算して同居を解消し、個別に飼育した。交配結果および妊娠の成否により、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数、交尾率[(交尾動物数/交配に用いた動物数) × 100, %]、妊娠率[(妊娠動物数/交尾した雌動物数) × 100, %]を算出した。

⑩妊娠・分娩・哺育状態の観察

交尾が確認された全例を自然分娩させた。分娩の確認は、妊娠 21 日相当日から分娩が確認されるまで毎日行い、午前 11 時までに分娩が完了した例について、その日を哺育 0 日(分娩日)とした。分娩状態の直接観察は観察可能な動物について行い、直接観察できなかつた動物についても、分娩後の一般状態および産児の状態から異常の有無を判断した。分娩後は、哺育状態を哺育 1~4 日の間、毎日観察した。分娩した全例の妊娠期間(妊娠 0 日から分娩日までの日数)を求め、各群の出産率[(生児出産雌数/妊娠動物数) × 100, %]を算出した。哺育 5 日の剖検時に卵巣については実体顕微鏡下で妊娠黄体数を、子宮については着床数を数え、着床率[(着床数/妊娠黄体数) × 100, %]を算出した。

⑪採血

いずれも解剖前 18~22 時間絶食させた後、腹部後大静脈から以下の 1)、2)、3)の順に注射筒を換えて採血した。雄の投与終了時剖検では各群 5 例、回復 15 日における剖検では回復例全例で採血を行った。また、雌の投与終了時剖検では、分娩例について哺育 5 日に投与期間が近接した各群 5 例、サテライト群の投与終了時剖検では各群 5 例、回復 15 日における剖検では回復例全例で採血を行った。

- 1) 血液学検査用:抗凝固剤 クエン酸ナトリウム
- 2) 血液学検査用:抗凝固剤 EDTA-2K
- 3) 血液生化学検査用:抗凝固剤 ヘパリン

⑫血液学検査

採血対象動物について以下の項目を検査した。抗凝固剤としてクエン酸ナトリウムを用いて採取した血液から血漿を分離して、プロトロンビン時間および活性化部分トロンボプラスチン時間を測定し、その他の項目は抗凝固剤として EDTA-2K を用いて採取した血液で測定した。

項目	測定法	使用機器
赤血球数 (RBC)	電気抵抗検出法	血液自動分析装置 XT-2000iV (シスメックス)
白血球数 (WBC)	半導体レーザを用いたフローサイトメトリー法	同上
白血球分類	同上	同上
網状赤血球比率 (RET%)	同上	同上
血色素量 (HGB)	SLSヘモグロビン法	同上
平均赤血球容積 (MCV)	計算 (HCT×1000/RBC)	同上
血小板数	電気抵抗検出法	同上
ヘマトクリット値 (HCT)	同上	同上
平均赤血球血色素量 (MCH)	計算 (HGB×1000/RBC)	同上

項目	測定法	使用機器
平均赤血球血色素濃度 (MCHC)	計算(HGB×100/HCT)	血液自動分析装置 XT-2000iV(シスメックス)
活性化部分トロンボプラスチン 時間(APTT)	光散乱検出法	全自動血液凝固測定裝 置 CA-1000(シスメックス)
プロトロンビン時間(PT)	同上	同上

⑬血液生化学検査

採血対象動物について以下の項目を検査した。抗凝固剤としてヘパリンを用いて採取した血液から血漿を分離して測定した。なお、得られた血漿の一部は甲状腺機能に関するホルモン(T3、T4 および TSH)測定用として凍結保存(-70°C以下)したが、甲状腺の病理学検査およびその他全ての検査項目の結果から、本被験物質は甲状腺機能に影響を及ぼさないと判断されたため、甲状腺ホルモン測定は実施しなかった。

項目	測定法	使用機器
総蛋白濃度(TP)	ピュレット法	自動分析装置 JCA-BM6010(日本電子)
アルブミン濃度(rALB)	BCG法	同上
グルコース濃度	ヘキソキナーゼ・G-6-PDH法	同上
総コレステロール濃度	コレステロールオキシダーゼ・HDAOS法	同上
トリグリセライト濃度	GPO・HDAOS(グリセリン消去)法	同上
コレステロール濃度	コレステロールオキシダーゼ・DAOS法	同上
尿素窒素濃度(BUN)	ウレアーゼ・GOD法,ウレアーゼ・律速系	同上
クレアチニン濃度	Jaffé法	同上
γ-グルタミルトランスペプチダーゼ活性(γ-GTP)	IFCC法	同上
アルカリ fosfatas活性(ALP)	GSCC法	同上
アスパラギン酸アミトランスフェラーゼ活性(AST)	IFCC法	同上
アラニンアミトランスフェラーゼ活性(ALT)	IFCC法	同上
乳酸脱水素酵素活性(LDH)	JSCC標準化対応法	同上
カルシウム濃度(Ca)	OCPC法	同上
総ビリルビン濃度	酵素法	同上
無機リン濃度	モリブデン酸直接法	同上
胆汁酸濃度	酵素サイクリング法	同上
A/G比	計算(rALB/(TP-rALB))	同上
ナトリウムイオン濃度(Na)	イオン電極法	全自动電解質分析装置 EA05(エイアンドティー)
カリウムイオン濃度(K)	同上	同上
塩素イオン濃度(Cl)	同上	同上

⑭剖検および器官重量

死亡例は死亡確認日に、瀕死動物は試験責任者が判断した日に、雄動物およびサテライト群の投与終了時剖検例は投与 42 日の翌日に、雌動物の分娩例は哺育 4 日の翌日に、交尾はしたが分娩しなかった雌(10 mg/kg 投与群の 1 例:動物番号 F02012)は妊娠 26 日相当日に、全哺育児が死亡した雌(対照群の 1 例:動物番号 F01005)では全哺育児が死亡した日に、雄動物およびサテライト群の回復観察例は回復 15 日に、それぞれ剖検した。

血液学、血液生化学検査を実施する動物はペントバルビタールナトリウム麻酔下で採血し、これ以外の動物はペントバルビタールナトリウム麻酔下で放血致死させた。

なお、死亡動物以外の全例について、脳、甲状腺および上皮小体、胸腺、心臓、肝臓、腎臓、脾臓、副腎、精巣、精巣上体、前立腺(腹側葉)および精嚢(凝固腺を含む)、卵巣、子宮の重量を測定した。

また、全例の脳、脊髄、下垂体、眼球(ハーダー腺)、顎下腺および舌下腺、気管、甲状腺および上皮小体、胸腺、心臓、肺および気管支、肝臓、腎臓、脾臓、副腎、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、下顎リンパ節、腸間膜リンパ節、精巣、精巣上体、前立腺、精嚢および凝固腺、卵巣、子宮、腔、膀胱、大腿骨および大腿骨骨髄、骨格筋、坐骨神経、乳腺、および病変部を採取し、保存した。死亡動物以外の肺および気管支は 15 cm 水柱以下の圧力で、気管内に 10%中性緩衝ホルマリン溶液 5 mL 以下を注入し固定してから摘出して同固定液に保存した。精巣および精巣上体はブアン液に固定(長期保存は 10%中性緩衝ホルマリン溶液)し、その他は 10%中性緩衝ホルマリン溶液に固定した。

⑯病理組織学検査

投与期間中に死亡あるいは切迫屠殺した母動物を含め、100 mg/kg 投与群の雄、分娩雌およびサテライト群の全例、50 mg/kg 投与群および対照群の選択された雄および分娩雌の各群各 5 例、サテライト群の対照群 5 例を対象として、組織学検査対象器官のヘマトキシリン・エオジン標本(H·E 標本)を作製し、病理組織学検査を行った。

その結果、投与期間終了時のサテライト群(雌)において、100 mg/kg 投与群で観察された腎臓皮質の好塩基性尿細管の変化の程度が対照群と比較して有意に増強したことから、回復期間終了時のサテライト群の対照群の腎臓 5 例についても病理組織学検査を行った。

その他、剖検時に異常所見がみられた雄の低用量群の 1 例(肝臓、胸腺、脾臓)、雌の対照群の 1 例(回腸)、同群の全児死亡例 1 例(胸腺、胃、腎臓)、低用量群の 2 例(胃、胸腺、腎臓、盲腸)、中用量群の 1 例(肺)に関しても、同様に H·E 標本を作製し、病理組織学検査を行った。

2)出生児(F_1)

①出生児の観察

哺育 0 日に生存児数および死亡児数を雌雄別に数えて、性別および外表奇形の有無を観察し、分娩率[(産児数/着床痕数) × 100, %]、生児出産率[(出産生児数/着床痕数) × 100, %]、出産率[(生児出産雌数/妊娠動物数) × 100, %]および出生率[(出産生児数/産児数) × 100, %]を算出した。また、哺育 0~4 日まで、毎日、一般状態を観察し、生存児数と死亡児数を雌雄別に数え、新生児生存率[(哺育 4 日の生児数/哺育 0 日の生児数) × 100, %]を算出した。生存児については、哺育 0 および 4 日に個別の体重を測定し、腹ごとに雌雄別の平均体重を算出するとともに、哺育 0 日および 4 日における性比[(雄生児数/総生児数) × 100, %]を算出した。

②剖検

死亡児は外表奇形の有無を観察して剖検し、10%中性緩衝ホルマリン溶液に固定して保存した。生

存児は哺育 4 日に外表奇形の有無を観察してセボフルラン吸入麻酔下に放血致死させて剖検し、内部器官の異常の有無を観察した。

6. データの解析法

性周期の変化した動物の頻度、交尾率、受胎率については Fisher の直接確率検定を行った(有意水準:5%)。

2,4-DTAP 各投与群の病理組織学検査所見のうち、グレード分けした病理組織所見は、Mann-Whitney の U 検定により、また陽性グレードの合計値は Fisher の直接確率の片側検定により、2,4-DTAP 各投与群と対照群との間の有意差検定を行った(有意水準:5%)。

その他のデータは、個体ごとに得られた値あるいは litter ごとの平均値を 1 標本とし、サテライト群内あるいはその他の群内で比較した。その際、解析の対象が 2 群の場合には、まず F 検定を行い、有意差が認められなければ Student's - t 検定を行った。F 検定において有意差が認められた場合は、Aspin-Welch 検定を行った。解析の対象が 3 群以上の場合は、先ず、Bartlett の方法により各群の分散の一様性について検定(有意水準:5%)を行った。分散が一様である場合には、一元配置型の分散分析(有意水準:5%)を行い、群間に有意性が認められる場合は、Dunnett 法により多重比較を行った(有意水準:5%)。一方、いずれかの群で分散が 0 となる場合および分散が一様でない場合には、Kruskal-Wallis の順位検定(有意水準:5%)を行い、群間に有意性が認められる場合には、Dunnett 型の検定法により多重比較を行った(有意水準:5%)。

予見することができなかつた試験の信頼性に影響を及ぼす疑いのある事態及び試験計画書に従わなかつたこと

2011 年 12 月 14 日、瀕死動物(動物番号 M04006)の途中搬出作業時において、FCuS-plas®システム(以下、システム)から該当動物を選択する際にコンピュータ操作を誤った。しかし、操作の誤りに気付いた後、適切にコンピュータ処理を行い、該当動物の器官重量を測定した。瀕死動物(動物番号 M04006)の一般状態観察、搬出時体重、剖検所見、器官重量測定データは適切に得られ、試験計画書に従って実施されていることから、当該試験への影響はない判断した。

2011 年 12 月 24 日、交配確認を実施した休日出勤者から動物番号 F02012 の性周期が交配適期であったが、交尾が確認されなかつたと報告を受けた。採取した腔スメア標本を確認したところ、標本に精子像が確認されたため、交尾は成立しているものと判断した。しかし、当日実施するすべての作業が終了した後であつたために、投与は交尾が確認された日の体重値を基準とした投与液量(1.60 mL)ではなく 2011 年 12 月 22 日(実施相対日 投与 17 日)の体重値を基準に算出された投与液量(1.56 mL)で投与されていた。システムでは該当ペア(雄動物番号 M02012 と雌動物番号 F02012)は未交尾として処理をされていたため、手動にて該当動物(動物番号 F02012)の妊娠 0 日体重および給餌量を測定した。本来投与しなければいけなかつた液量と実際に投与した液量の差は 0.04 mL と僅かであつたことや、本試

験が反復投与であることから、投与液量の差における当該動物の評価への影響はないと判断した。また、生データは適切に修正されており、試験計画書に基づき妊娠 0 日の体重、妊娠 0 日の給餌量も測定されていることから、試験への影響はないと判断した。

2012 年 1 月 6 日 13 時頃、動物飼育施設用温水ボイラの電源が誤操作によって停止した。温水ボイラの電源を復帰させたところ、オーバーシュートにより、飼育室の温度が許容値を超え、25.5°Cとなつた。オーバーシュートが収束した後、温度が許容範囲内で安定して推移していることを確認した。いずれの動物の一般状態にも上述事象に起因したと考えられる変化は認められず、他の測定項目にも異常は認められていないことから、試験への影響はないと判断した。

2012 年 1 月 17 日、器官重量測定終了後、システムに収集された測定データを確認したところ、雌 1 例(動物番号 F04006)の胸腺と心臓の測定順を誤った可能性があることに気付いた。確認のために 10% 中性緩衝ホルマリン溶液に固定された標本を再測定した。再測定値をシステムに登録されている胸腺重量(0.8681 g)、心臓重量(0.1815 g)と比較した結果、測定順を誤ったと判断した。他の測定器官についても確認を行い、異常は認められていないことから、試験への影響はないと判断した。

2012 年 1 月 17~19 日および 31 日に血液的学検査を実施した。その後 2012 年 2 月 2 日に試験データの点検をした際に 2012 年 1 月 17 日に測定を実施した 3 例(動物番号:M03001、M03002、F04001)の MCH が管理基準値から外れた測定値であったが、再測定が実施されていなかつたことを確認した。血液学検査のサンプルは保存ができないために、報告された時点では再測定はできなかつたが、測定機器である血液自動分析装置 XT-2000iV では MCH は計算(HGB × 1000/RBC)により算出され、計算の元となる HGB および RBC は管理基準値内であり、また、当該試料の前後に測定したコントロール血球により当該試料の精度は保証されていたことから、当該試験への影響はないと判断した。

その他、「予見することができなかつた試験の信頼性に影響を及ぼす疑いのある事態及び試験計画書に従わなかつたこと」はなかつた。

試験成績

1. 親動物

1) 一般状態(Table 1~Table 4, Appendix 1~Appendix 4)

雌雄ともに 100 mg/kg 投与群において、死亡あるいは瀕死動物が観察された。

雄では、投与 6 日に 1 例、投与 7 日に 3 例、投与 11~13 日に各 1 例が死亡し、その他 2 例は投与 7 あるいは 9 日に一般状態の悪化が著しいことから瀕死と判断して切迫屠殺した。これらの 9 例では、投与 2 日に投与前のトレイ上に軟便がみられ、投与 4 日以降に投与後に自発運動の低下、投与 5 日以降に排便量の減少が観察された。投与日数が進むにつれて、下腹部の汚れ、軟便、黒色便、無便、流涙、紅涙、赤色尿、削瘦と一般状態が悪化し、重篤な例は、立毛、体温低下、自発運動消失、緩徐呼吸、側臥位も観察され、投与 6~13 日の間に死あるいは切迫屠殺に至つた。

雌では、投与 6 日に 1 例、投与 7 日に 4 例、投与 8 日に 3 例が死亡し、その他 4 例は投与 7、8 ある

いは 9 日に一般状態の悪化が著しいことから瀕死と判断し、切迫屠殺した。これらの 12 例においても、投与 2 日に投与前のトレイ上に軟便がみられ、投与 3 日以降に排便量減少、下腹部の汚れ、投与後に流涎あるいは自発運動の減少が観察され、さらに、粘液便、無便、立毛、削瘦、体温低下、流涙、紅涙、鼻周囲の汚れ、赤色尿と一般状態が悪化し、投与 6~9 日の間に死あるいは切迫屠殺に至った。

雌雄とも、投与後に観察された自発運動の減少は、投与後約 3~7 時間に回復する動物も認められたが、投与後 5 時間たっても症状が回復しなかった動物の多くが、翌日に死亡あるいは瀕死となり切迫屠殺に至った。

同群の生存例では、投与後に一過性の流涎が、雄では 4 例中 2 例、雌では 11 例中 5 例に、投与期間を通して散見された。その他、軟便が、雄では投与 14 日に 1 例、雌では 2 例に投与 2、6、31、33 あるいは 37 日に観察された。

50 mg/kg 投与群では、投与後に一過性の流涎が、投与 22 日から投与終了日(投与 42 日)まで雄 5 例に散見された。雌では、交配前には一般状態に変化はなかったが、妊娠期間中の妊娠 17 日に投与後に一過性の流涎が 2 例に認められた。

対照群では、雄の 1 例の背側頸部に痂皮が投与 23~31 日まで観察され、雌の 1 例に下腹部の汚れが哺育 4 日に観察された。

50 mg/kg 投与群の 1 例(動物番号 F03002)は妊娠 22 日の分娩中に、10 mg/kg 投与群の 1 例(動物番号 F02001)は妊娠 23 日に死亡したが、死亡前の一般状態に異常は認められなかった。

別の 50 mg/kg 投与群の 1 例(動物番号 F03011)は、分娩後の一般状態の変化として下腹部の汚れ、削瘦、体温低下、立毛、蒼白が観察されたため、瀕死と判断して、分娩日(哺育 0 日)の投与前に切迫屠殺した。

回復期間中の観察では、雌雄とも一般状態に変化は観察されなかった。

2) 詳細な症状観察(Table 5~Table 6, Appendix 5~Appendix 6)

投与 2 日以降、被験物質投与による一般状態の変化が顕著に認められていたため、投与 7 日の観察では、100 mg/kg 投与群の雄において、自発運動の低下が 2 例、被毛の汚れが 1 例に観察され、雌では、うずくまり姿勢、自発運動の低下、除脈、体温下降、被毛の汚れ、蒼白または貧血様、緩除呼吸が各 3 例に、紅涙、爪先歩行が各 2 例に、無抵抗、立毛が各 1 例に、それぞれ観察された。サテライト群の 100 mg/kg 投与群では、自発運動の消失、被毛の汚れが各 3 例に、紅涙、うずくまり姿勢、除脈、体温下降、緩除呼吸が各 2 例に、貧血様、爪先歩行が各 1 例に、それぞれ観察された。

哺育期間中の観察では、対照群で被毛の汚れが 1 例に観察された。

回復 14 日の観察では、雄の対照群でハンドリング時に抵抗する動物が 1 例に観察された。

その他の観察日には、いずれの群にも異常は認められず、また、排尿および排糞数にも対照群と比較して差はなかった。

3) 体重(Table 7~Table 10, Appendix 7~Appendix 10)

雄では、50 mg/kg 以上の投与群で体重が対照群と比較して低値に推移し、100 mg/kg 投与群では、投与 7、10 および 12 日の体重に有意差($P<0.01$)が認められた。

雌では、100 mg/kg 投与群(交配群および非交配群)で、投与 7 日の体重が低値を示し、サテライト群(非交配群)では有意差($P<0.05$)が認められたが、それ以降の体重推移には対照群と差はなかった。

10 および 50 mg/kg 投与群では、交配前、妊娠期間中、哺育期間を通して対照群と同様に推移した。

回復期間中の雄の体重は、対照群と 50 mg/kg 投与群との間には統計学的に有意差は認められなかつたが、対照群と比較してやや低値に推移した。

回復期間中の雌の体重推移には、対照群と 100 mg/kg 投与群との間に差はなかった。

4) 摂餌量 (Table 11～Table 14, Appendix 11～Appendix 14)

雄では、100 mg/kg 投与群において、投与 1～2 日および 7～8 日の摂餌量が対照群と比較して有意に減少($P<0.01$)し、投与 14～15 日では有意に($P<0.01$)増加したが、それ以降、投与終了時まで、対照群と 2,4-DTAP 各投与群の摂餌量に差はなかった。

雌では、100 mg/kg 投与群において、投与開始後の摂餌量が対照群と比較して低値を示し、投与 7～8 日には有意差($P<0.05$)がみられた。さらに、サテライト群(非交配雌)では、投与 1～2 日 ($P<0.01$) の摂餌量に有意な減少が認められ、投与 14～15 日に有意な増加($P<0.01$)が認められた。それ以降、雌の 100 mg/kg 投与群の摂餌量には対照群と差はなかった。

10 および 50 mg/kg 投与群の摂餌量は、投与開始後、交配前、妊娠期間中、哺育期間中を通して、対照群との間に差はなかった。

回復期間の雄の摂餌量は、対照群と 2,4-DTAP (50 mg/kg) 投与群との間に差はなかった。

雌では、回復 12～13 日の 2,4-DTAP (100 mg/kg) 投与群の摂餌量が、対照群と比較して有意($P<0.05$)に増加した。

5) 機能検査 (Table 15～Table 22, Appendix 15～Appendix 22)

投与最終週に実施した機能検査の結果、雄の 2,4-DTAP 各投与群において握力の低下が、雌のサテライト群の 100 mg/kg 投与群において自発運動量が減少したことから、回復期間終了時にも機能検査を実施した。

①刺激に対する感覚運動反応 (Table 15～Table 16, Appendix 15～Appendix 16)

雌雄とも、投与期間終了時および回復期間終了時ともに、いずれの群においても異常は認められなかつた。

②握力測定 (Table 17～Table 19, Appendix 17～Appendix 19)

雄の投与最終週の検査では、2,4-DTAP 各投与群の後肢握力が低下傾向を示し、10 mg/kg ($P<0.05$) および 50 mg/kg 投与群($P<0.01$)では有意差がみられた。

回復期間終了時の検査では、対照群と 50 mg/kg 投与群との間に差は認められなかつた。

雌では、投与期間終了時および回復期間終了時ともに、対照群と 2,4-DTAP 投与群との間に差は認められなかつた。

③自発運動量測定 (Table 20～Table 22, Appendix 20～Appendix 22)

雄では、投与期間終了時および回復期間終了時ともに、対照群と 2,4-DTAP 各投与群の自発運動量には差は認められなかつた。

雌の投与最終週の検査において、分娩した雌では、50 mg/kg 投与群の自発運動量は増加傾向を示した。

サテライト群の 100 mg/kg 投与群では、検査開始 5 分間の区画移動数が有意($P<0.05$)に減少し、20 分間の総区画移動数は有意に($P<0.05$)減少した。また、立ち上がり回数も、検査開始後 5 分～10 分の 5 分間において有意に減少し($P<0.05$)、20 分間の総立ち上がり回数が有意に減少($P<0.05$)した。

雌の回復期間終了時の検査では、対照群と 100 mg/kg 投与群の区画移動数および立ち上がり回数には差は認められなかった。

6) 尿検査 (Table 23～Table 24, Appendix 23～Appendix 24)

①投与期間終了時

雄では、100 mg/kg 投与群において、尿量が増加する傾向が認められた。

雌では、100 mg/kg 投与群において、尿量が有意に($P<0.05$)増加した。

②回復期間終了時

雌雄ともに、対照群と 2,4-DTAP 投与群(雄;50 mg/kg、雌; 100 mg/kg)との間に差は認められなかつた。

7) 血液学検査 (Table 25～Table 26, Appendix 5～Appendix 26)

①投与期間終了時

雄では、100 mg/kg 投与群において、赤血球数の減少傾向がみられ、ヘモグロビン濃度、ヘマトクリット値が有意に($P<0.01$)低下した。プロトロンビン時間が有意に($P<0.01$)延長し、活性化部分トロンボプラスチン時間も延長傾向を示した。

分娩した雌では、50 mg/kg 投与群において、平均赤血球血色素濃度が有意に($P<0.05$)減少し、網状赤血球比率が有意に($P<0.01$)増加した。

サテライト群の 100 mg/kg 投与群では、赤血球数($P<0.05$)、ヘモグロビン濃度およびヘマトクリット値($P<0.01$)が有意に減少し、血小板数が有意に($P<0.05$)増加した。

②回復期間終了時

雄では、50 mg/kg 投与群の雄で好酸球比率が有意に($P<0.05$)低下した。

雌(サテライト群)では、対照群と 100 mg/kg 投与群との間に有意差は認められなかつた。

8) 血液生化学検査 (Table 27～Table 28, Appendix 27～Appendix 28)

①投与期間終了時

雄では、10 mg/kg 以上の投与群において、胆汁酸濃度の減少傾向が、100 mg/kg 投与群においてアルカリファスファターゼ活性の増加傾向が認められた。他の検査項目にも、対照群と 2,4-DTAP 各投与群との間に有意差は認められなかつた。

分娩した雌では、10 および 50 mg/kg 投与群において、グルコース濃度の増加、アスパラギン酸アミノトランスフェラーゼ活性およびアラニンアミノトランスフェラーゼ活性の低下が認められ、10 mg/kg 投与群では有意差($P<0.05$)がみられた。また、50 mg/kg 投与群では胆汁酸が減少傾向を示し、無機リ

ン濃度が有意に低下($P<0.05$)した。

サテライト群では、対照群と 100 mg/kg 投与群との間に有意差は認められなかった。

②回復期間終了時

雄では、 50 mg/kg 投与群において、A/G 比が有意に増加($P<0.05$)し、胆汁酸濃度の増加傾向がみられた。

雌(サテライト群)では、対照群と 100 mg/kg 投与群との間に有意差は認められなかった。

9) 器官重量(Table 29～Table 30, Appendix 29～Appendix 30)

①投与期間終了時

雄では、 50 mg/kg 投与群において、肝臓の相対重量($P<0.01$)が、 100 mg/kg 投与群において、肝臓の実重量および相対重量が有意に($P<0.01$)増加した。

分娩した雌では、 50 mg/kg 投与群において、肝臓の実重量および相対重量が有意に($P<0.01$)増加した。

サテライト群では、 100 mg/kg 投与群の肝臓の実重量($P<0.05$)および相対重量($P<0.01$)が有意に増加し、脾臓の相対重量も有意に($P<0.05$)増加した。

②回復期間終了時

雄では、対照群と 50 mg/kg 投与群との間に差は認められなかった。

雌(サテライト群)では、 100 mg/kg 投与群において、脾臓の実重量および相対重量が有意に($P<0.05$)増加した。

10) 剖検所見(Table 31～Table 32, Appendix 31～Appendix 32)

①雄の死亡例および切迫屠殺例

100 mg/kg 投与群で死亡および切迫屠殺した 9 例全例において、被毛の汚れ(口・鼻周囲や下腹部)が認められた。

腎臓では、4 例に大型化および斑状に散在する白色域が観察され、そのうち 2 例は粗造な表面を呈していた。

脾臓では 7 例に、胸腺では 5 例に小型化が認められ、そのうち各 2 例には淡色化あるいは暗赤色化が観察されたほか、肺では 4 例に赤色化、2 例に暗赤色域がみられた。

胃では、8 例の前胃粘膜に菲薄化、1 例に黒色物の付着が、5 例の腺胃粘膜に暗赤色化あるいは暗色点がみられ、盲腸でも、5 例で粘膜の暗赤色化あるいは黒色の内容物が観察された。

肝臓では 4 例に大型化、3 例に暗赤色化が、副腎では 5 例に大型化、3 例に暗赤色化が認められた。

その他、1 例の左側精巣に大型化および暗赤色化が、3 例の精巣上体の頭部あるいは尾部に暗赤色斑が観察されたほか、1 例の回腸には腸重積がみられ、この例の腹腔には暗赤色調の腹水が貯留していた。

②雌の死亡例あるいは切迫屠殺例

100 mg/kg 投与群で死亡および切迫屠殺した 12 例全例において、被毛の汚れ(口・鼻周囲や下

腹部)が認められた。

腎臓では、6例に斑状に散在する白色域が観察され、そのうち4例は大型化および粗造な表面、1例は暗赤色調を呈していた。

脾臓では10例に、胸腺では5例に小型化が認められ、そのうち1例の胸腺は暗赤色調を呈していたほか、肺では5例に暗赤色化、2例に暗赤色域の散在が認められた。

胃では、11例の前胃粘膜に菲薄化が、2例の腺胃粘膜に暗赤色化がみられ、そのうち1例の小腸および盲腸には、黒色の内容物の貯留が観察された。

肝臓では、5例に暗赤色化がみられ、そのうち4例に大型化、他の1例に斑状に散在する白色域が観察されたほか、副腎では、全例に大型化が認められ、そのうち5例に暗赤色化がみられた。

その他、1例の膀胱に赤色尿の貯留が観察された。

③雄の投与期間終了時屠殺例

肝臓では、100および50mg/kg投与群の各2例に大型化が、10mg/kg投与群の1例に小葉構造の明瞭化が認められた。また、100mg/kg投与群では、腎臓の大型化が2例に、脾臓の大型化および肺に暗赤色域が各1例観察されたほか、50mg/kg投与群の3例、10mg/kg投与群の1例に胸腺の小型化が、10mg/kg投与群の1例に副脾が観察された。

対照群に肉眼的な異常は認められなかつた。

④雌の投与期間終了時屠殺例(哺育5日剖検)

胸腺の小型化が、対照群を含む10および50mg/kg投与群各2例に観察された。胃では、前胃粘膜の肥厚が10および50mg/kg投与群の各1例に、腺胃粘膜に暗色点が対照群の1例ならびに10mg/kg投与群の2例に認められた。腎臓では、対照群および10mg/kg投与群の各1例に淡色化がみられ、このうち対照群の例では肝臓および脾臓に淡色化が、10mg/kg投与群の例では盲腸に黒色の内容物の貯留が認められた。その他、対照群の回腸に憩室が、50mg/kg投与群の肺に暗赤色点の散在が各1例認められた。

⑤周産期雌死亡例(妊娠22日分娩中死亡、妊娠23日死亡、哺育0日切迫屠殺、哺育4日全哺育児死亡)

妊娠22日に分娩中に死亡した50mg/kg投与群の母動物(動物番号F03002)では、脾臓の小型化および淡色化、肺には、退縮不全を伴う暗赤色化が観察された。この動物では、雄生存児4匹が認められた。右子宮角に7匹、左子宮角に3匹(雄6匹、雌4匹)の死亡胎児が観察された。なお、胎児の外表には異常は認められず、産児の外表および内臓にも異常はなかつた。

妊娠23日に死亡した10mg/kg投与群の母動物(動物番号F02001)では、脾臓の小型化および淡色化、肺には、散在する暗赤色点、胃では、腺胃粘膜に陥凹部が認められた。

分娩後、瀕死と判断して切迫屠殺した50mg/kg投与群の母動物(動物番号F03011)では、脾臓の小型化および淡色化、口周囲および外陰部周囲に被毛の汚れがみられたほか、胸腺の小型化、腎臓の淡色化、副腎の大型化に加え、子宮は腔が拡張して大型化し、内膜は暗赤色化し浮腫様を呈していた。

対照群で哺育 4 日に全哺育児が死亡した母動物(動物番号 F01005)では、腎臓に淡色化および大型化が認められたほか、胸腺の小型化ならびに前胃粘膜の肥厚が観察された。

⑥未分姪雌動物

妊娠 26 日相当日に剖検した 10 mg/kg 投与群の 1 例(動物番号 F02011)では、子宮に着床痕は認められず、それ以外の内部器官に肉眼的な異常所見は認められなかった。

⑦サテライト群の投与期間終了時屠殺例

100 mg/kg 投与群の 1 例の肝臓に大型化が認められた。それ以外の例に、肉眼的な異常所見は認められなかった。

⑧雄の回復期間終了時

対照群および 50 mg/kg 投与群に、肉眼的な異常所見は認められなかった。

⑨雌(サテライト群)の回復期間終了時

対照群および 100 mg/kg 投与群に肉眼的な異常所見は認められなかった。

11) 病理組織学的検査(Table 33～Table 34, Appendix 33～Appendix 34)

①雄の死亡例および切迫屠殺例(検査対象動物 9 例; Appendix 33-3-1)

腎臓では、9 例全例の皮質および髓質の尿細管上皮に変性／壊死が認められ、好塩基性尿細管、硝子円柱および管腔内に細胞残屑を伴っていた。さらに、全例の腎孟には移行上皮の過形成がみられ、そのうち 7 例の乳頭部の間質には好中球浸潤も観察された。その他、2 例の皮質および髓質に鉱質沈着がみられた。

胸腺では萎縮が、下顎および腸間膜リンパ節では濾胞の萎縮が全例にみられた。

脾臓では白脾髄ならびに赤脾髄領域の減少が全例にみられ、髓外造血あるいは褐色色素の沈着が観察されない例も認められた。

心臓では、2 例の動脈周囲の心筋に限局性の鉱質沈着が、肝臓では、7 例の小葉中間帯に肝細胞の空胞化が、別の 1 例では門脈周囲性の肝細胞の脂肪化が、胃では、2 例の腺胃粘膜にびらんが、それぞれ観察された。

副腎の皮質索状帯では細胞肥大が、上皮小体では主細胞の過形成が、それぞれ全例に観察された。

その他、精巣および精巣上体では、精細管内の生殖細胞層の減少ならびに管腔内の精子の減少が、肺では肺胞腔に泡沫細胞の集簇、剖検時に重積が認められた回腸では、限局した内腔の狭窄が、それぞれ 1 例に観察された。

他の組織学検査対象器官・組織には、組織学的な異常所見は認められなかった。

②雌の死亡例および切迫屠殺例(検査対象動物 12 例; Appendix 33-3-2)

腎臓では、12 例全例の皮質および髓質の尿細管上皮に変性／壊死が認められ、好塩基性尿細管、硝子円柱および管腔内に細胞残屑を伴っていた。そのうちの 4 例の乳頭部に壊死が認められたほか、9 例の乳頭部の間質に好中球浸潤が、全例の腎孟に移行上皮の過形成が観察された。その他、皮髓境界部に囊胞あるいは鉱質沈着が各 1 例みられた。

胸腺では萎縮が、下顎および腸間膜リンパ節では濾胞の萎縮が全例に認められた。

脾臓では、白脾髄ならびに赤脾髄領域の減少が全例にみられ、髓外造血あるいは褐色色素の沈着が観察されない例も認められた。

心臓では、2例の動脈周囲の心筋に限局性の鉱質沈着が、肝臓では、9例の小葉中間帯に肝細胞の空胞化が、そのうちの1例では小肉芽腫が観察された。

副腎の皮質索状帯では細胞肥大が、上皮小体では主細胞の過形成が、全例に観察された。

肺では、限局性の骨化生が1例に観察された。

他の組織学検査対象器官・組織には、組織学的な異常所見は認められなかった。

なお、1例の上皮小体がスライド標本上になかったため、観察することが出来なかつた。

③雄の投与期間終了時

腎臓では、100 mg/kg 投与群の4例全例の皮質および髓質に好塩基性尿細管が観察され、対照群と比較して変化の程度および頻度は有意に($P<0.01$)増強した。また、同群の3例の皮質および髓質には、硝子円柱が観察され、発現頻度に有意差($P<0.05$)がみられた。腎臓の変化は対照群および50 mg/kg 投与群の各2例の皮質にも観察されたが、髓質まで波及している例はなかつた。その他、対照群および100 mg/kg 投与群の各1例の皮髓境界部には囊胞がみられた。

肝臓では、対照群、50 および 100 mg/kg 投与群の全例に門脈周囲性の肝細胞の脂肪化が、対照群の3例、100 mg/kg 投与群の全例に小肉芽腫が観察されたが、対照群と各投与群との間に程度および頻度の差は認められなかつた。

脾臓では、対照群、50 および 100 mg/kg 投与群の全例に髓外造血および褐色色素の沈着が観察されたが、対照群と各投与群との間に程度の差は認められなかつた。

前立腺では、対照群の3例、50 および 100 mg/kg 投与群の各2例の間質にリンパ球浸潤が観察されたが、対照群と各投与群との間に程度および頻度の差は認められなかつた。

その他、対照群では、心臓に心筋の限局性の変性／線維化が2例に、胰臓に胰管の増生を伴う腺房細胞の限局性の萎縮および血管周囲のリンパ球浸潤が各1例に観察されたほか、50 mg/kg 投与群では、肺の動脈壁に限局性の鉱質沈着が、100 mg/kg 投与群では、肺の肺胞腔に泡沫細胞の集簇がそれぞれ1例観察された。

また、剖検時に肉眼的な異常所見が認められた 10 mg/kg 投与群の1例(胸腺の小型化、肝臓の小葉構造の明瞭化)では、胸腺には組織学的な異常は認められなかつたが、肝臓では軽度な門脈周囲性の肝細胞の脂肪化が観察された。

他の組織学検査対象器官・組織には、組織学的な異常所見は認められなかつた。

なお、対照群の1例の上皮小体がスライド標本上になかったため、観察することが出来なかつたが、他の例では観察可能であったために、評価には問題ないと判断した。

他の組織学検査対象器官・組織には、組織学的な異常所見は認められなかつた。

なお、投与期間終了時の病理組織学検査の結果、対照群と 50 mg/kg 投与群に観察された病理組織学変化に差はなかつたことから、雄では回復期間終了時の病理組織学検査は行なわないこととした。

④雌の投与期間終了時(分娩雌、哺育 5 日剖検)

対照群および 50 mg/kg 投与群で選択された各 5 例の組織学検査対象器官・組織ならびに病変部を鏡検し、検定を行なった。

腎臓では、対照群および 50 mg/kg 投与群の皮質に好塩基性尿細管が観察されたが、両群間に程度および頻度の差は認められなかった。対照群の 3 例の皮質に近位尿細管上皮の変性／壞死が認められ、このうち 1 例の皮質および髓質には硝子円柱が観察された。

肝臓では、50 mg/kg 投与群の 2 例に門脈周囲性の肝細胞の脂肪化が、対照群の 1 例、50 mg/kg 投与群の 3 例に小肉芽腫が観察されたが、いずれの所見も両群間に程度および頻度の差は認められなかった。対照群の 3 例では、小葉中間帯の肝細胞に空胞化が認められた。

脾臓では、対照群および 50 mg/kg 投与群の全例に髓外造血および褐色色素の沈着が観察された。統計学的には両群間に程度の差は認められなかつたが、50 mg/kg 投与群で観察された髓外造血の程度は対照群と比較してやや強かつた。また、対照群の 1 例に赤脾髓領域の減少がみられた。

胸腺では、対照群の 3 例、50 mg/kg 投与群の 2 例に萎縮が認められた。これらの例のうち対照群の 2 例には下顎リンパ節に、1 例には腸間膜リンパ節に濾胞の萎縮が観察された。

胃では、対照群の腺胃粘膜にびらんが、50 mg/kg 投与群の前胃粘膜に粘膜下織の浮腫を伴う扁平上皮細胞の過形成がそれぞれ 1 例観察された。

その他、対照群では、心臓に限局性的心筋の変性／線維化が、病変部として観察した回腸には組織学的に異常のない憩室がそれぞれ 1 例、50 mg/kg 投与群では、病変部として観察した 1 例を含む 2 例の肺の肺胞腔に泡沫細胞の集簇が観察された。

他の組織学検査対象器官・組織には、組織学的な異常所見は認められなかつた。

剖検時に肉眼的な異常所見が認められた 10 mg/kg 投与群の 2 例では、胸腺が萎縮しており、1 例の前胃粘膜には粘膜下織の浮腫を伴う扁平上皮細胞の過形成が、他の 1 例には腺胃粘膜にびらんおよび前胃粘膜に潰瘍が観察された。さらに、このうちの 1 例では腎臓の皮質に近位尿細管上皮の変性／壞死ならびに好塩基性尿細管が認められた。

⑤サテライト群(雌)の投与期間終了時

腎臓では、対照群の 3 例、100 mg/kg 投与群の 6 例全例の皮質に好塩基性尿細管が観察され、100 mg/kg 投与群では、対照群と比較して変化の程度が増強していた($P<0.05$)。その他、対照群の腎孟には、結石を伴った移行上皮の過形成が、100 mg/kg 投与群には、皮質および髓質に鉱質沈着ならびに皮髓境界部に囊胞がそれぞれ 1 例みられた。

肝臓では、対照群および 100 mg/kg 投与群の各 1 例に門脈周囲性の肝細胞の脂肪化が、各 2 例に小肉芽腫が観察されたが、いずれの所見も両群間に程度の差は認められなかつた。

脾臓では、対照群および 100 mg/kg 投与群の全例に髓外造血および褐色色素の沈着が観察されたが、両群間に程度の差は認められなかつた。

その他、対照群の肺では、2 例の肺胞腔に泡沫細胞の集簇、1 例の動脈壁に鉱質沈着が観察されたほか、100 mg/kg 投与群の 1 例では、甲状腺に異所性の胸腺組織が、肺臓に肺管の増生を伴う腺

房細胞の限局性の萎縮が、脳の脳室の脈絡叢にリンパ球浸潤がみられた。

他の組織学検査対象器官・組織には、組織学的な異常所見は認められなかった。

なお、対照群および 100 mg/kg 投与群の各 1 例の上皮小体がスライド標本上になかったため、観察することが出来なかつたが、それ以外の例では鏡検ができたことから、評価に影響はない判断した。

⑥投与期間中の雌死亡例(妊娠 22 日分娩中死亡、妊娠 23 日死亡、哺育 0 日切迫屠殺、哺育 4 日全哺育児死亡)

(i) 周産期死亡および切迫屠殺

50 mg/kg 投与群における分娩中死亡例および哺育 0 日切迫屠殺例、10 mg/kg 投与群における妊娠末期死亡例の病理組織学検査の結果を記載する。

3 例全例に胸腺の萎縮が認められた。

腎臓には、全例に好塩基性尿細管が観察された。このうち、妊娠末期死亡および切迫屠殺例には、皮質の近位尿細管上皮に変性／壞死、皮質および髓質に硝子円柱が観察され、分娩中死亡例では、皮質の糸球体毛細血管に塞栓が観察された。

この 2 例では、下頸リンパ節および腸間膜リンパ節に濾胞の萎縮、脾臓では白脾髄および赤脾髄領域の減少が認められ、妊娠末期死亡例の脾臓では髓外造血も認められなかつた。また、肝臓の小葉中間体の肝細胞に空胞化、上皮小体に主細胞の過形成、副腎の皮質索状帶に細胞肥大が観察され、切迫屠殺例では皮質に壞死巣も認められた。

妊娠末期死亡例では、胃の前胃粘膜に潰瘍が認められた。

その他、全例に、脾臓では褐色色素の沈着がみられた。また、子宮では内膜に出血が観察され、分娩日に解剖した切迫屠殺例には広範囲な壞死を伴っていた。

(ii) 全哺育児死亡母動物(哺育 4 日)

対照群において、哺育 4 日に全哺育児が死亡したため、同日に剖検した。剖検時に肉眼的異常が認められた器官・組織(胸腺、腎臓、胃)を組織学的に検査した。

胸腺は萎縮し、腎臓の皮質に近位尿細管上皮に変性／壞死および好塩基性尿細管が、胃の前胃粘膜に粘膜下織の浮腫を伴う扁平上皮細胞の過形成が観察された。

2 週間の回復期間終了時の病理組織学検査の結果を以下に記載する。

⑦回復期間終了後の雌(サテライト群)の病理組織学検査所見

投与期間終了時の検査において、サテライト群の 100 mg/kg 投与群で観察された腎臓皮質の好塩基性尿細管の変化の程度が対照群と比較して有意に増強したことから、サテライト群の対照群の腎臓についても病理組織学検査を行つた。

腎臓では、対照群の 1 例、100 mg/kg 投与群の 4 例の皮質に好塩基性尿細管が観察された。しかし、統計学的には両群間に程度および頻度の差は認められなかつた。また、投与終了時屠殺例と比較すると、変化の程度は軽減していた。その他、100 mg/kg 投与群の皮質および髓質に硝子円柱、皮髓境界部に鉱質沈着が各 1 例観察された。

また、100 mg/kg 投与群では、脾臓で髓外造血および褐色色素の沈着が全例に、臍臓で臍管の増

生を伴う限局性の萎縮が 2 例に、肺で限局性の骨化生が 1 例にみられたほか、肝臓では、3 例に小肉芽腫、2 例に門脈周囲性の肝細胞の脂肪化、1 例の漿膜下に限局性の壞死巣が観察された。

2. 生殖能力

1) 性周期および交配成績(Table 35～Table 36, Appendix 35～Appendix 36)

性周期には、2,4-DTAP 投与の影響を示唆する変化はみられなかった。

交配の結果、全ての動物において交尾が確認され、交尾までの日数およびその間の発情回数に、対照群と 2,4-DTAP 各投与群との間に有意差は認められなかった。10 mg/kg 投与群の 1 例(動物番号 F02012)では、交尾は確認されたが妊娠していなかった。それ以外の動物は、妊娠が確認され、交尾率および受胎率には 2,4-DTAP 投与の影響は認められなかった。

2) 出産率および妊娠期間(Table 37, Appendix 37)

妊娠期間には対照群と 2,4-DTAP 各投与群との間に有意差は認められなかった。

出産率は対照群と 2,4-DTAP 各投与群との間に有意差は認められなかった。

3) 分娩および哺育状態(Table 37, Appendix 37)

10 mg/kg 投与群の 1 例(動物番号 F02001)が妊娠 23 日に、50 mg/kg 投与群の 1 例(動物番号 F03002)が妊娠 22 日の分娩中に死亡した(前述)。

50 mg/kg 投与群の 1 例(動物番号 F03011)において、分娩終了後に出生児を集めず、児を舐めるとといった哺育行動が観察されなかった。児の腹部にミルクスポット(母乳が貯留している様子)はみられず、授乳している状態ではないと考えられたため分娩状態不良と判断した。この動物は分娩日に下腹部の汚れ、削瘦、体表温低下、立毛、蒼白が観察されたことから瀕死と判断し、切迫屠殺した。

対照群の 1 例(動物番号 F01005)は哺育 4 日に全哺育児が死亡した。この母動物は哺育期間中に餌をほとんど摂取せずに体重が減少した。その他、哺育期間中の摂餌量が他動物よりも少なく、体重が減少した母動物が、対照群に 2 例、10 mg/kg 投与群に 2 例観察された。しかし、これらの動物に哺育状態に異常はなかった。

他の妊娠動物は妊娠 22～23 日に出産し、分娩状態および哺育状態に異常は認められなかった。

4) 黄体数、着床数および着床率(Table 37, Appendix 37)

10 mg/kg 投与群の 1 例(動物番号 F02012)では、妊娠 25 日までに分娩が確認されなかった。剖検の結果、着床痕および妊娠黄体は認められず、不妊例であったと判断した。

黄体数、着床数および着床率には、対照群と 2,4-DTAP 各投与群との間に有意差は認められなかった。

3. 出生児

1) 生存(Table 37, Appendix 37)

分娩率、生児出産率、出生率、新生児生存率および性比には、対照群と 2,4-DTAP 各投与群との間に有意差は認められなかった。

2) 体重(Table 38, Appendix 38)

哺育 0 および 4 日における出生児の体重には、対照群と 2,4-DTAP 各投与群との間に有意差は認められなかった。

母動物の哺育状態に異常はなかったが、哺育期間中に餌を食べず、母動物の体重が増加しなかった対照群の 2 例(動物番号 F01004、F01011)および、10 mg/kg 投与群の 2 例(動物番号 F02002、F02009)の哺育児では、哺育期間中の体重はほとんど増加しなかった。しかし、50 mg/kg 投与群の哺育児体重は対照群と同様に推移した。

3) 出生児観察(Table 39～Table 40, Appendix 39)

死亡児は対照群を含む各投与群に認められた。死亡児には、母動物の食害により存在が不明になつたと推察される児(不明児)、あるいは死後経過が進み自己融解により内臓観察ができなかつた児を含むが、剖検が可能であった死亡児には外表奇形は観察されず、内臓観察が可能であった死亡児についても内臓に異常は認められなかつた。

考察

雌雄ラットの交配前(2 週間)および交配期間中、ならびに雄では交配期間終了後を通して計 42 日間、繁殖能を評価した交配雌では妊娠期間を通して周産期(哺育 4 日まで計 41～44 日間)に、非交配雌のサテライト群では雄と同様の期間に、Phenol, 2,4-bis(1,1-dimethylpropyl)を経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

1. 親動物

100 mg/kg 投与群において、雌雄ともに約半数の動物が投与開始 2 週間までに死亡あるいは瀕死となり切迫屠殺した。一般状態および病理組織学検査の結果から、急激な腎機能障害が発現し、全身状態が悪化したと考えられた。死亡発現頻度および観察された変化には性差は認められなかつた。

生存例では、投与後に一過性の流涎が雌雄とともに 50 mg/kg 以上の投与群で、軟便が雌雄とともに 100 mg/kg 投与群で、それぞれ投与期間を通して観察された。予備試験¹⁾においても同様の変化は認められていることから、本試験で観察された一般状態の変化は被験物質に起因した変化と考えられる。しかし、詳細な症状観察では、神經毒性を示唆する変化は観察されていないことから、流涎は被験物質の刺激性に起因した変化と考えられた。投与期間中に認められた一般状態の変化は、2 週間の回復期間により症状が消失したことから、回復性のある変化と考えられた。

雄の体重が、50 mg/kg 以上の投与群において対照群と比較してやや低値を示し、2 週間の回復期間後も回復しなかつた。雌では、100 mg/kg 投与により投与開始後に一時的に体重が低値を示したが、それ以降、2,4-DTAP 投与による影響は認められなかつた。

摂餌量には、雌雄ともに被験物質投与による影響は認められなかつた。なお、雌では、回復期の摂餌

量に有意な増加が認められたが、僅かな変化であり、一般状態および体重推移にも被験物質投与による影響は認められていないことから、偶発的な変化であると判断した。

投与最終週に実施した機能検査では、雄では 2,4-DTAP 各投与群において後肢の握力が低下したが、その低下は僅かであり、詳細な症状観察では歩行異常もなく、病理組織学検査においても後肢坐骨神経および骨格筋には異常はないことから、2,4-DTAP 投与による影響ではないと判断した。分娩雌では 50 mg/kg 投与群で自発運動量の増加傾向がみられた。しかし、統計学的有意差ではなく個体差が大きいことから、2,4-DTAP 投与による変化ではないと判断した。非交配群であるサテライト群の雌では、100 mg/kg 投与群で自発運動量の減少が観察された。同群では、詳細な症状観察には異常はないが、投与後に一過性の流涎、軟便が観察されていることから、2,4-DTAP 投与に起因した変化と考えられた。回復期間終了時に実施した検査では自発運動量の減少は認められなかったことから、回復性のある変化であると考えられた。

尿検査では、雌雄ともに 100 mg/kg 投与群において尿量の増加がみられた。予備試験での器官重量および本試験の病理組織学検査の結果から、本被験物質の標的器官が腎臓であると考えられたことから、2,4-DTAP 投与による腎障害と関連した尿量の変化と考えられた。

血液学検査の結果から、雌雄の 100 mg/kg 投与群および分娩雌の 50 mg/kg 投与群において、軽度ではあるが貧血状態に陥っていることが示唆された。これらの変化は 250 mg/kg の 2,4-DTAP を 2 週間投与した予備試験においても観察されている。また、非交配雌(サテライト群)の 100 mg/kg 投与群では脾臓重量の増加が、投与終了時および 2 週間の回復期間終了時に観察された。貧血に関連した変化と考えられるが、投与終了時の脾臓の病理組織学検査では対照群と比較して髄外造血が亢進した像は観察されず、回復期間終了時の非交配群(サテライト群)の脾臓の病理組織学検査においても投与終了時と比較して髄外造血亢進像は観察されなかった。さらに、2 週間の回復期間により、貧血を示唆する血液生化学パラメータは消失したことから、貧血は回復性のある変化と考えられた。その他、投与期間終了時の血液学検査では、雄の 100 mg/kg 投与群において凝固時間の延長が認められた。回復期間後にこの変化は消失したことから被験物質の影響と考えられたが、肝障害を示唆する血液生化学パラメータに変動はなく、原因は不明であった。非交配雌(サテライト群)の 100 mg/kg 投与群では血小板数が有意に増加したが、その変化は僅かであること、骨髄の病理学検査においても異常は観察されなかったことから、2,4-DTAP 投与による影響ではないと判断した。回復期間終了時の血液学検査において、雄の好酸球比率の低下が認められたが白血球数に変動がないことから、毒性学的意義はないと判断した。

血液生化学検査では、雄の 100 mg/kg 投与群において、非交配雌(サテライト群)の 100 mg/kg 投与群、および分娩雌の 50 mg/kg 投与群においても僅かであるが ALP 活性の増加が認められた。腎臓の病理組織学検査において、雌雄ともに被験物質投与によると考えられる変化が観察されていることから、ALP 活性の増加は被験物質の影響によると考えられた。

分娩雌の血液生化学検査では、10 mg/kg 以上の投与群において、グルコース濃度、AST 活性および ALT 活性、無機リン濃度に変化が認められた。しかし、変動の程度は僅かであったことから、毒性学的に意義が乏しいと考えられた。また、胆汁酸の減少傾向が、雄では 10 mg/kg 以上の投与群、分娩雌

では 50 mg/kg 投与群に観察された。雄では、対照群において胆汁酸濃度が高い動物が認められたことから、10 mg/kg 投与群で認められた胆汁酸の減少傾向は偶発的な変化であり、被験物質投与による変化ではないと判断した。50 mg/kg 以上の投与群で認められた胆汁酸の減少は被験物質投与の影響と考えられたが、非交配雌(サテライト群)の 100 mg/kg 投与群(サテライト群)では認められていないこと、血液生化学検査では総コレステロール濃度および総ビリルビン濃度に 2,4-DTAP 投与による影響はみられず、肝臓の病理組織学検査においても、胆汁酸の生成あるいは排出異常を示唆する変化は認められないことから原因は不明であった。

回復期間終了時の血液生化学検査では、雄の 50 mg/kg 投与群において、A/G 比の増加が認められたが、総蛋白濃度およびアルブミン濃度には差がないことから偶発的な変化であり、被験物質投与による変化ではないと判断した。また、同群では胆汁酸濃度が増加傾向を示したが、肝臓重量に変動はなく、また、総コレステロール濃度および総ビリルビン濃度も対照群と差はなかったことから、被験物質投与による変化との関連性は低いと考えられた。

器官重量では、肝臓重量の増加が、雄では 50 mg/kg 以上、非交配雌(サテライト群)では 100 mg/kg 投与群、分娩雌では 50 mg/kg 投与群で認められた。回復期間により肝臓重量の増加は消失することから被験物質投与による変化と考えられた。

病理組織学検査では、雌雄ともに 100 mg/kg 投与群において、腎臓に変化がみられ、雄では雌よりも強い変化であった。死亡あるいは切迫屠殺した動物の腎臓所見、血液生化学検査および尿検査の結果から腎臓は本被験物質の標的器官であると考えられた。これらの腎臓の変化は 2 週間の回復期間により軽減し、腎臓の変化に関連すると考えられた血液生化学パラメータの変化および尿量の増加も消失したことから、回復性のある変化と考えられた。また、肝臓では、雄の 100 mg/kg 投与群において、門脈周囲性に肝細胞の脂肪化の程度が対照群と比較して強くなる傾向がみられた。肝細胞内に中性脂肪の蓄積が示唆されたが、脂質異常を示唆する血液生化学パラメータには変動はなく、同群では体重増加抑制も認められていることから総合的に判断し、肝臓で合成された中性脂肪が利用されずに残存している組織像と考えられ、毒性影響ではないと判断した。その他、回復期間終了時の病理組織学検査では、脾臓、肺、肝臓に病理組織学的变化が認められたが、いずれもごく軽度な変化であり、被験物質投与に関連した変化ではないと判断した。

2. 生殖発生毒性および出生児

性周期、交配成績、出産率および妊娠期間、黄体数、着床数および着床率に被験物質投与による影響はみられなかった。

10 および 50 mg/kg 投与群で周産期に死亡(あるいは切迫屠殺)した 3 例の動物の病理学検査の結果、分娩・哺育によるストレスおよび貧血、全身状態の悪化を示唆する所見が、胸腺、リンパ節、脾臓、副腎、前胃粘膜、肝臓に観察された。また、腎臓に急性毒性や分娩過程における血流障害を示唆させる所見、腎機能障害に反応した上皮小体の病変が観察され、分娩中の母動物の状態が悪いことが考えられた。

腎臓の病理組織学的所見は被験物質投与によって認められた変化と類似しているが、50 mg/kg 投与群の分娩雌において実施した病理組織学検査の結果から同様の変化は観察されていないこと、他の雌は正常に分娩し哺育していること、哺育 4 日に全哺育児が死亡した対照群の腎臓所見においても同様の変化が認められていることから、これら 3 例の死亡は、2,4-DTAP 投与に起因した死亡ではないと判断した。出生児の生存性、体重および形態には、被験物質投与の影響はみられなかった。

3. 無毒性量

雌雄ともに 50 mg/kg 以上の投与群において、投与後の一過性の流涎あるいは軟便といった一般状態の変化が観察され、雄では体重増加抑制がみられた。血液学検査の結果から、雌の 50 mg/kg 投与群で貧血傾向がみられ、雄の 50 mg/kg 以上の投与群および分娩雌の 50 mg/kg において肝臓重量が増加したことから 2,4-DTAP の親動物に対する一般毒性学的無毒性量は雌雄ともに 10 mg/kg/day、生殖発生毒性学的な無毒性量および次世代児に対する無毒性量は、50 mg/kg までの 2,4-DTAP 投与による変化は認められなかつたことから 50 mg/kg/day と考えられた。

参考文献

- 1) Phenol, 2,4-bis(1,1-dimethylpropyl)のラットを用いる反復投与毒性・生殖発生毒性併合試験(予備試験)

Annex A



試験成績書

2011年09月27日

東京化成工業株式会社 品質保証部
〒103-0023
東京都中央区日本橋本町4丁目10番地
TEL: 03(5640)8860 FAX: 03(5640)8861

製品名: 2,4-Di-tert-amylphenol		
製品コード: D3294	等級: EP	製品ロット: XPX4F
純度(GC)	結果 99.7 %	規格値 98.0 %以上

Annex B

安定性試験結果

試験番号	R-11-003
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被験(対照)物質: Phenol, 2,4-bis(1,1-dimethylpropyl)

調製年月日

2011年11月21日

ロット番号:XPX4F

測定年月日

A 2011年11月21日(調製直後)

媒体: トウモロコシ油

B 2011年11月29日(調製後8日)

保存条件

室温、遮光

調製濃度 (mg/mL)	A				B			
	試料 番号	測定濃度 (mg/mL)	含量 ^{a)} (%)	ばらつき ^{b)} (%)	試料 番号	測定濃度 (mg/mL)	含量 ^{a)} (%)	ばらつき ^{b)} (%)
2.00	1	1.875	93.8	101.1	7	1.894	94.7	99.6
	2	1.847	92.4	99.6	8	1.922	96.1	101.1
	3	1.843	92.2	99.4	9	1.888	94.4	99.3
	平均	1.855	92.8		平均	1.901	95.1	
50.0	4	48.09	96.2	100.9	10	50.17	100.3	101.3
	5	47.32	94.6	99.3	11	49.89	99.8	100.7
	6	47.53	95.1	99.8	12	48.58	97.2	98.1
	平均	47.64	95.3		平均	49.54	99.1	

a):各測定時の測定濃度/調製濃度×100

b):各測定時の測定濃度/各測定時の平均測定濃度×100

c):各測定時の測定濃度/初回の平均測定濃度×100

安定性の判断基準(溶液検体)

各試料採取時点の平均含量がそれぞれ調製濃度の90.0~110.0%以内であり、また、各測定値のばらつきがそれぞれ平均値の90.0~110.0%以内であり、かつ、調製直後の測定平均値に対する各保管期間後の残存率の平均値が90.0%以上を示す期間とする。

Annex C-1

試験番号	R - 11 - 003
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含 量 試 験 結 果

被験(対照)物質: Phenol, 2,4-bis(1,1-dimethylpropyl)

調製年月日 : 2011年12月5日

ロット番号:XPX4F

測定年月日 : 2011年12月5日

媒体: トウモロコシ油

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
13	2.00	1.905	1.876	95.3	93.8	101.5
14		1.862		93.1		99.3
15		1.862		93.1		99.3
16	10.0	9.552	9.546	95.5	95.5	100.1
17		9.655		96.6		101.1
18		9.433		94.3		98.8
19	50.0	48.74	48.83	97.5	97.7	99.8
20		49.24		98.5		100.8
21		48.51		97.0		99.3

含量の判断基準(溶液検体)

平均含量が調製濃度の90.0~110.0%、また各測定値のばらつきがそれぞれ平均値の90.0~110.0%以内とする。

Annex C-2

試験番号	R - 11 - 003
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含 量 試 験 結 果

被験(対照)物質: Phenol, 2,4-bis(1,1-dimethylpropyl)

調製年月日 : 2011年12月16日

ロット番号:XPX4F

測定年月日 : 2011年12月16日

媒体: トウモロコシ油

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
22	20.0	19.24	19.18	96.2	95.9	100.3
23		19.39		97.0		101.1
24		18.92		94.6		98.6

含量の判断基準(溶液検体)

平均含量が調製濃度の90.0～110.0%、また各測定値のばらつきがそれぞれ平均値の90.0～110.0%以内とする。

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 1-1. General conditions of male rats

Pre: Before administration, Post: after administration

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 1-1 (continued). General conditions of male rats

Group	Number of males and general conditions	Days of administration																																			
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post						
Corn oil (control)	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8						
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8						
	Skin, Crust formation, Posterior neck.	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						
2,4-DTAP 10 mg/kg	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13						
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13						
2,4-DTAP 50 mg/kg	Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8						
	General appearance, No abnormality	13	11	13	11	13	11	13	12	13	11	13	11	13	11	13	11	13	11	13	10	13	11	13	11	13	11	13	11	10	8						
	Mouth, Salivation	0	2	0	2	0	2	0	1	0	2	0	2	0	2	0	2	0	2	0	3	0	2	0	2	0	2	0	3	0							
2,4-DTAP 100 mg/kg	Number of males	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4						
	General appearance, No abnormality	4	3	4	2	4	3	4	2	4	2	4	3	4	3	4	2	4	2	4	3	4	2	4	2	4	3	4	3	4	2	4	3				
	Mouth, Salivation	0	1	0	2	0	1	0	2	0	2	0	1	0	2	0	2	0	1	0	2	0	2	0	1	0	1	0	2	0	1						

Pre: Before administration, Post: after administration.

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 1-2. General conditions of male rats at the recovery period

Group	Number of males and general conditions	Days of recovery													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Corn oil (control)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2,4-DTAP 50 mg/kg	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 2-1. General conditions of female rats

Group	Number of females and general conditions	Days of administration																			
		1		2		3		4		5		6		7		8		9		10	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Corn oil (control)	Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
2,4-DTAP 10 mg/kg	Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
2,4-DTAP 50 mg/kg	Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
2,4-DTAP 250 mg/kg	Number of females	13	13	13	13	13	13	13	13	13	13	13	12	12	9	8	6	6	5	5	
	General appearance, No abnormality	13	13	11	13	12	11	12	11	7	7	6	7	6	6	5	5	5	5	5	
	Anorectal region, Soiled perineal region	0	0	0	0	1	1	1	1	5	5	5	5	3	3	1	1	0	0	0	
	Behavior, Decrease in locomotor activity	0	0	0	0	0	1	0	1	0	6	1	4	1	3	0	1	1	0	0	
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	5	0	5	0	3	0	1	0	1	0	0	
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	1	1	0	3	0	0	1	0	0	
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	1	0	3	0	2	0	0	0	0	
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	1	0	1	0	3	0	0	0	0	0	
	Excretion, Loose stool	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Eye, Eyeball, Bulbi, Globe, Lacrimation	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	
	General appearance, Moribundity	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	
	Excretion, Mucous feces	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	
	General appearance, Emaciation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	
	Nose, Smudge of perinasal area	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	
	Excretion, No-feces	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	
	Mouth, Salivation	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 2-1 (continued). General conditions of female rats

Group	Number of females and general conditions	Days of administration															
		12		13		14		15		16		17		18		19	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Corn oil (control)	Number of females	13	13	13	13	13	13	13	13	10	10	6	6	5	5	1	1
	General appearance, No abnormality	13	13	13	13	13	13	13	13	10	10	6	6	5	5	1	1
2,4-DTAP 10 mg/kg	Number of females	13	13	13	13	13	13	13	13	10	10	6	6	3	3	0	0
	General appearance, No abnormality	13	13	13	13	13	13	13	13	10	10	6	6	3	3	0	0
2,4-DTAP 50 mg/kg	Number of females	13	13	13	13	13	13	13	13	11	11	8	8	4	4	0	0
	General appearance, No abnormality	13	13	13	13	13	13	13	13	11	11	8	8	4	4	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 2-2. General conditions of female rats, satellite group

Group	Number of females and general conditions	Days of administration																							
		1		2		3		4		5		6		7		8		9		10		11			
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Corn oil (control)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
2,4-DTAP 250 mg/kg	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	8	6	6	6	6	6	6	
	General appearance, No abnormality	10	10	9	10	10	10	10	10	10	10	9	8	6	6	6	6	6	6	6	6	6	6	6	
	Anorectal region, Soiled perineal region	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3	2	2	0	0	0	0	0	0
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	2	2	0	0	0	0	0	0	0
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	0	0	0	0	0	0
	General appearance, Moribundity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
	General appearance, Emaciation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
	Excretion, Mucous feces	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0
	Excretion, Loose stool	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	Eye, Eyeball, Bulbi, Globe, Reddish tear	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
	Eye, Eyeball, Bulbi, Globe, Lacrimation	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 2-2 (continued). General conditions of female rats, satellite group

Group	Number of females and general conditions	Days of administration																											
		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Corn oil (control)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
2,4-DTAP 100 mg/kg	Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11		
	General appearance, No abnormality	11	11	11	11	11	11	11	10	11	11	11	10	11	11	11	11	11	11	8	11	9	11	8	11	9	11	10	
	Mouth, Salivation	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	3	0	2	0	3	0	2	0	1		

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 2-2 (continued). General conditions of female rats, satellite group

Group	Number of females and general conditions	Days of administration																																			
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post						
Corn oil (control)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5							
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5							
2,4-DTAP 100 mg/kg	Number of females	11	6	11	6	11	6	11	6	6	6	11	6	6	11	6	11	6	11	6	11	6	11	6	11	6	11	6	11	6	6						
	General appearance, No abnormality	11	5	11	5	11	5	11	5	5	5	11	4	5	5	11	5	11	4	11	5	5	5	11	5	11	4	11	5	11	5	6					
	Mouth, Salivation	0	1	0	1	0	1	0	1	0	1	0	2	0	1	0	1	0	2	0	1	0	1	0	2	0	1	0	1	0	1	0					
	Excretion, Loose stool	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0					

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 2-3. General conditions of female rats at the recovery period

Group	Number of females and general conditions	Days of recovery													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Corn oil (control)	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2,4-DTAP 100 mg/kg	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 3. General conditions in dams during pregnancy

Group	Number of dams and general conditions	Days of pregnancy																											
		0		1		2		3		4		5		6		7		8		9		10		11		12		13	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Corn oil (control)	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
2,4-DTAP 10 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
2,4-DTAP 50 mg/kg	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 3 (continued). General conditions in dams during pregnancy

Group	Number of dams and general conditions	Days of pregnancy																		
		14		15		16		17		18		19		20		21		22		
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Corn oil (control)	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	7	7	0
	General appearance, No abnormality	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	7	7	0
2,4-DTAP 10 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	1
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	6	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
2,4-DTAP 50 mg/kg	Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	5	4	0
	General appearance, No abnormality	13	13	13	13	13	13	13	11	13	13	13	13	13	13	13	13	4	4	0
	Mouth, Salivation	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 4. General conditions in dams during lactation

Group	Number of dams and general conditions	Days of lactation									
		0		1		2		3		4	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Corn oil (control)	Number of dams	13	13	13	13	13	13	13	13	13	12
	General appearance, No abnormality	13	13	13	13	13	13	13	13	12	12
	Anorectal region, Soiled perineal region	0	0	0	0	0	0	0	1	1	0
2,4-DTAP 10 mg/kg	Number of dams	11	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11
2,4-DTAP 50 mg/kg	Number of dams	12	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11
	Anorectal region, Soiled perineal region	1	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation	1	0	0	0	0	0	0	0	0	0
	Body temperature, Hypothermia	1	0	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Piloerection	1	0	0	0	0	0	0	0	0	0
	Skin, Pale skin	1	0	0	0	0	0	0	0	0	0
	General appearance, Moribundity	1	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 5. Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of administration						Days of recovery ^a	
				7	14	21	30	36	42	7	14
[Posture in home-cage]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Crouching position	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0	(8)	0	(4)	0	(4)	0	(4)
[Locomotor in home-cage]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Decrease in locomotor activity	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	, loss of locomotor activity	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	2	(8)	0	(4)	0	(4)	0	(4)
[Handling behavior]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	1
	Resistance	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0	(8)	0	(4)	0	(4)	0	(4)
[Heart beats]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Bradycardia	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0	(8)	0	(4)	0	(4)	0	(4)
[Body temperature]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Decrease of temperature	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0	(8)	0	(4)	0	(4)	0	(4)
[Fur]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Soiled fur	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	1	(8)	0	(4)	0	(4)	0	(4)
[Skin color/Mucous membrane]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Abnormal (a, anemic b, pale skin)	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0	(8)	0	(4)	0	(4)	0	(4)
[Lacrimation]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Slight and severe	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0	(8)	0	(4)	0	(4)	0	(4)
[Piloerection]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Slight	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0	(8)	0	(4)	0	(4)	0	(4)
[Respiratory rate]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Hypopnea	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0	(8)	0	(4)	0	(4)	0	(4)
[Gait]	Corn oil (control)	13	0 ^b	0	0	0	0	0	0	0	0
	Tip toe gait	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0	0
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0	(8)	0	(4)	0	(4)	0	(4)

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

^aThe recovery test was performed in 5 animals of 0 and 50 mg/kg groups.

^bValues represent the number of animals with the findings.

Figures in parenthesis indicate the number of animals examined.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis
(1,1-dimethylpropyl) by oral administration in rats

Table 5 (continued). Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of administration						Days of recovery *	
				7	14	21	30	36	42	7	14
[Urination] (frequency/30sec)	Corn oil (control)	13	4 ^b	2	1	3	1	4	2	0	3
	2,4-DTAP (10 mg/kg)	13	4	1	2	3	3	1	3		
	2,4-DTAP (50 mg/kg)	13	1	3	4	3	3	2	1	1	3
	2,4-DTAP (100 mg/kg)	13	4	2 (8)	0 (4)	1 (4)	1 (4)	1 (4)	1 (4)		
[Defecation] (frequency/30sec)	Corn oil (control)	13	1 ^b	0	1	0	0	0	0	0	0
	2,4-DTAP (10 mg/kg)	13	0	2	0	1	0	0	1		
	2,4-DTAP (50 mg/kg)	13	0	0	2	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	13	0	0 (8)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)		

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

* The recovery test was performed in 5 animals of 0 and 50 mg/kg groups.

^b Values represent total score of each group.

Figures in parenthesis indicate the number of animals examined.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 6-1. Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of administration					The lactation period
				7	14	21	30	36	
[Posture in home-cage]	Corn oil (control)	13	0 *	0	0	0	0	0	0
Crouching position	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	3 (9)					
[Locomotor in home-cage]	Corn oil (control)	13	0 *	0	0	0	0	0	0
Decrease in locomotor activity	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
, loss of locomotor activity	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	3 (9)					
[Handling behavior]	Corn oil (control)	13	0 *	0	0	0	0	0	0
No resistance	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	1 (9)					
[Heart beats]	Corn oil (control)	13	0 *	0	0	0	0	0	0
Bradycardia	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	3 (9)					
[Body temperature]	Corn oil (control)	13	0 *	0	0	0	0	0	0
Decrease of temperature	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	3 (9)					
[Fur]	Corn oil (control)	13	0 *	0	0	0	0	0	1
Soiled fur	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	3 (9)					
[Skin color/Mucous membrane]	Corn oil (control)	13	0 *	0	0	0	0	0	0
Abnormal (a, anemic b, pale skin)	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	3 (9)					0
[Lacrimation]	Corn oil (control)	13	0 *	0	0	0	0	0	0
Slight and severe	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	2 (9)					
[Piloerection]	Corn oil (control)	13	0 *	0	0	0	0	0	0
Slight	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	1 (9)					
[Respiratory rate]	Corn oil (control)	13	0 *	0	0	0	0	0	0
Hypopnea	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	3 (9)					0
[Gait]	Corn oil (control)	13	0 *	0	0	0	0	0	0
Tip toe gait	2,4-DTAP (10 mg/kg)	13	0	0	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	2 (9)					0

* Values represent the number of animals with the findings.

Figures in parenthesis indicate the number of animals examined.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 6-1 (continued). Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of administration				The lactation period
				7	14	21	30	
[Urination] (frequency/30sec)	Corn oil (control)	13	1 *	0	0	0	1	0
	2,4-DTAP (10 mg/kg)	13	2	3	1	0	1	0
	2,4-DTAP (50 mg/kg)	13	0	1	0	0	2	0
	2,4-DTAP (250 mg/kg)	13	2	0	(9)			
[Defecation] (frequency/30sec)	Corn oil (control)	13	0 *	0	0	0	0	0
	2,4-DTAP (10 mg/kg)	13	1	0	0	0	0	0 (11)
	2,4-DTAP (50 mg/kg)	13	0	0	0	0	0	0 (12)
	2,4-DTAP (250 mg/kg)	13	0	0	(9)			

* Values represent total score of each group.

Figures in parenthesis indicate the number of animals examined.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 6-2. Detailed clinical observations of female rats, satellite group

Findings	Group	Initial number of animals	Pre-treatment	Days of administration						Days of recovery *	
				7	14	21	30	36	42	7	14
[Posture in home-cage] Crouching position	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	2 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Locomotor in home-cage] Decrease in locomotor activity , loss of locomotor activity	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	3 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Handling behavior] No resistance	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	0 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Heart beats] Bradycardia	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	2 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Body temperature] Decrease of temperature	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	2 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Fur] Soiled fur	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	3 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Skin color/Mucous membrane] Abnormal (a, anemic b, pale skin)	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	1 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Lacration] Slight and severe	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	2 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Piloerection] Slight	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	0 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Respiratory rate] Hypopnea	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	2 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0
[Gait] Tip toe gait	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	1 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0	0

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

* The recovery test was performed in 5 animals of 0 and 250 mg/kg groups.

^b Values represent the number of animals with the findings.

^c After day 12 of treatment, the number of animals in this group was made up of 11 animals.

Figures in parenthesis indicate the number of animals examined.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 6-2 (continued). Detailed clinical observations of female rats, satellite group

Findings	Group	Initial number of animals	Pre-treatment	Days of administration						Days of recovery *	
				7	14	21	30	36	42	7	14
[Urination] (frequency/30sec)	Corn oil (control)	10	1 ^b	1	0	0	0	1	0	1	1
	2,4-DTAP (100 mg/kg)	10 ^c	1	1 (9)	0 (11)	1 (11)	1 (11)	0 (11)	0 (11)	1 (5)	1 (5)
[Defecation] (frequency/30sec)	Corn oil (control)	10	0 ^b	0	0	0	0	0	0	0	0
	2,4-DTAP (100 mg/kg)	10 ^c	0	0 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0 (5)	0 (5)

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

*The recovery test was performed in 5 animals of 0 and 250 mg/kg groups.

^b Values represent total score of each group.

^c After day 12 of treatment, the number of animals in this group was made up of 11 animals.

Figures in parenthesis indicate the number of animals examined.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 7-1. Body weights of male rats

Group Number of males	Corn oil (control)		2,4-DTAP 10 mg/kg		2,4-DTAP 50 mg/kg		2,4-DTAP 100 mg/kg	
	13		13		13		13	
Days of administration								
1	370.1	± 14.2	373.1	± 15.0	369.0	± 16.2	374.8	± 12.8
7	397.3	± 17.9	398.4	± 21.3	389.8	± 22.8	357.0	± 23.4 ** (9)
10	407.1	± 18.7	408.1	± 23.2	396.5	± 23.2	350.2	± 32.1 ** (7)
12	416.1	± 19.7	416.8	± 24.1	404.3	± 25.0	360.5	± 43.5 ** (5)
14	424.9	± 20.5	422.0	± 25.5	410.2	± 24.9	401.3	± 10.7 (4)
17	426.6	± 21.1	425.1	± 26.2	412.8	± 25.1	410.8	± 12.9 (4)
21	443.5	± 22.0	441.7	± 28.7	429.0	± 26.0	428.3	± 13.5 (4)
24	454.6	± 23.3	450.4	± 30.2	437.6	± 27.0	440.0	± 17.3 (4)
28	468.7	± 23.7	462.7	± 32.2	451.6	± 27.9	456.3	± 19.9 (4)
31	477.9	± 23.0	470.7	± 33.9	460.5	± 27.8	467.8	± 21.6 (4)
35	489.6	± 22.8	479.9	± 35.8	469.7	± 29.2	473.3	± 25.3 (4)
38	496.0	± 24.5	486.9	± 37.2	472.6	± 27.6	476.1	± 26.0 (4)
42	507.0	± 25.1	494.6	± 37.6	482.5	± 28.3	485.1	± 24.1 (4)

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 7-2. Body weights of male rats at the recovery period

Group	Corn oil (control)	2,4-DTAP 50 mg/kg
Number of males	5	5
Days of recovery		
1	513.5 ± 24.6	483.3 ± 36.1
7	528.9 ± 27.4	496.0 ± 37.0
14	541.2 ± 27.7	504.2 ± 38.3

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 8-1. Body weights of female rats

Group Number of females	Corn oil (control)		2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg	2,4-DTAP 250 mg/kg
	13	13	13	13	13
Days of administration					
1	258.0 ± 12.8		260.8 ± 13.1	262.6 ± 10.7	263.3 ± 11.9
7	271.5 ± 13.4		275.0 ± 13.7	274.0 ± 13.0	247.9 ± 30.7 (9)
10	276.2 ± 16.5		280.4 ± 16.1	278.8 ± 15.0	277.7 ± 13.2 (5)
12	281.5 ± 15.0		283.6 ± 15.5	283.4 ± 13.7	
14	283.8 ± 17.7		286.2 ± 16.8	284.2 ± 17.0	
17	296.8 ± 11.7 (6)		293.7 ± 14.0 (6)	288.6 ± 14.1 (8)	

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 8-2. Body weights of female rats, satellite group

Group	Corn oil (control)	2,4-DTAP 250 mg/kg
Number of females	10	10
Days of administration		
1	267.1 ± 13.4	266.2 ± 8.6
7	277.6 ± 13.4	253.2 ± 26.6 * (9)
10	283.3 ± 14.9	284.1 ± 11.6 (6)

Group	Corn oil (control)	2,4-DTAP 100 mg/kg
Number of females	10	11
12	287.1 ± 16.6	283.5 ± 12.8
14	287.4 ± 17.1	291.0 ± 13.1
17	293.1 ± 18.9	291.1 ± 15.8
21	297.8 ± 22.8	297.5 ± 18.0
24	301.1 ± 20.9	303.3 ± 19.3
28	307.2 ± 23.1	307.1 ± 21.5
31	306.3 ± 24.3	306.3 ± 22.4
35	311.5 ± 23.2	311.0 ± 23.2
38	315.8 ± 28.1	312.3 ± 24.1
42	318.2 ± 25.7	317.4 ± 22.2

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 8-3. Body weights of female rats at the recovery period

Group	Corn oil (control)	2,4-DTAP 100 mg/kg
Number of females	5	5
Days of recovery		
1	319.2 ± 25.1	334.5 ± 21.0
7	327.2 ± 24.8	340.1 ± 25.4
14	332.6 ± 27.9	337.1 ± 23.1

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 9. Body weights of dams during pregnancy

Group	Corn oil (control)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg
Number of dams	13	12	13
Days of pregnancy			
0	294.7 ± 14.2	292.3 ± 15.9	294.3 ± 15.6
3	310.9 ± 16.2	310.9 ± 18.2	312.4 ± 17.8
7	327.7 ± 15.7	326.6 ± 18.6	330.7 ± 18.4
10	343.2 ± 16.2	343.2 ± 21.6	345.0 ± 20.9
14	366.2 ± 16.6	367.7 ± 25.6	368.8 ± 24.5
17	398.5 ± 17.6	404.4 ± 27.3	402.9 ± 28.8
20	448.6 ± 20.5	452.5 ± 30.5	446.7 ± 33.9

Each value shows mean ± S.D. (g).

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 10. Body weights of dams during lactation

Group	Corn oil (control)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg
Number of dams	13	11	12
Days of lactation			
0	330.9 ± 20.4	342.9 ± 36.9	329.8 ± 36.3
4	329.4 ± 36.6	343.2 ± 51.4	350.4 ± 23.9 (11)

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 11-1. Food consumption of male rats

Group	Corn oil (control)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg	2,4-DTAP 100 mg/kg
Number of males	13	13	13	13
Days of administration				
1	23.6 ± 3.2	25.3 ± 3.1	22.9 ± 2.6	19.8 ± 2.3 **
7	21.5 ± 2.0	21.7 ± 2.5	20.7 ± 2.8	10.1 ± 6.7 ** (8)
14	20.8 ± 2.2	21.6 ± 2.0	20.5 ± 2.1	25.4 ± 1.7 ** (4)
29	22.5 ± 1.4	21.9 ± 2.2	22.2 ± 2.0	22.7 ± 2.6 (4)
35	20.9 ± 2.1	21.0 ± 2.3	20.1 ± 1.9	22.8 ± 2.2 (4)
41	20.1 ± 2.7	19.9 ± 2.7	20.2 ± 1.8	21.3 ± 2.2 (4)

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 11-2. Food consumption of male rats at the recovery period

Group	Com oil (control)	2,4-DTAP 50 mg/kg
Number of males	5	5
Days of recovery		
6	27.2 ± 3.5	27.6 ± 1.9
12	28.1 ± 2.8	27.8 ± 2.6

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 12-1. Food consumption of female rats

Group	Corn oil (control)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg	2,4-DTAP 250 mg/kg
Number of females	13	13	13	13
Days of administration				
1	17.1 ± 2.8	18.1 ± 3.3	17.6 ± 3.9	15.7 ± 3.7
7	17.4 ± 2.5	17.5 ± 3.1	18.0 ± 1.7	12.0 ± 5.2 * (6)
14	16.0 ± 3.4	17.2 ± 3.3	16.7 ± 2.6	

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 12-2. Food consumption of female rats, satellite group

Group	Corn oil (control)	2,4-DTAP 250 mg/kg
Number of females	10	10
Days of administration		
1	19.0 ± 2.0	16.5 ± 1.6 **
7	18.1 ± 1.9	11.8 ± 7.3 * (8)

Group	Corn oil (control)	2,4-DTAP 100 mg/kg
Number of females	10	11
Days of administration		
14	14.9 ± 3.0	20.5 ± 3.0 **
21	17.7 ± 3.3	17.2 ± 3.3
29	17.7 ± 3.0	17.4 ± 2.7
35	16.8 ± 1.8	17.3 ± 2.9
41	15.3 ± 1.7	16.8 ± 2.4

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.
Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 12-3. Food consumption of female rats at the recovery period

Group	Corn oil (control)	2,4-DTAP 100 mg/kg
Number of females	5	5
Days of recovery		
6	21.3 ± 1.1	21.7 ± 4.6
12	18.5 ± 1.8	23.7 ± 4.0 *

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 13. Food consumption in dams during pregnancy

Group	Corn oil (control)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg
Number of dams	13	12	13
Days of pregnancy			
0	16.8 ± 2.5	17.7 ± 2.2	17.3 ± 2.4
7	22.4 ± 2.6	23.8 ± 3.3	22.8 ± 2.9
14	21.7 ± 1.5	23.1 ± 4.7	22.8 ± 3.6
20	15.7 ± 3.0	15.4 ± 7.6	14.3 ± 5.5

Each value shows mean ± S.D. (g).

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 14. Food consumption in dams during lactation

Group	Corn oil (control)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg
Number of dams	13	11	11
Days of lactation	3 25.9 ± 15.9	29.7 ± 15.2	37.8 ± 5.7

Each value shows mean ± S.D. (g).

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 15. Functional findings of male rats and female rats at the end of the dosing period

Group	Corn oil (control)	2,4-DTAP (10 mg/kg)	2,4-DTAP (50 mg/kg)	2,4-DTAP (100 mg/kg)
Male, Administration period				
Number of animals	5	5	5	4
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Prayer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
Female, dam				
Number of animals	5	5	5	
Righting reflex	100	100	100	
Visual placing	100	100	100	
Pupillary reflex	100	100	100	
Startle reaction	100	100	100	
Prayer's reaction	100	100	100	
Withdrawal reflex	100	100	100	
Eyelid reflex	100	100	100	
Female, Administration period				
Number of animals	5		5	
Righting reflex	100		100	
Visual placing	100		100	
Pupillary reflex	100		100	
Startle reaction	100		100	
Prayer's reaction	100		100	
Withdrawal reflex	100		100	
Eyelid reflex	100		100	

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 16. Functional findings of male rats and female rats at the end of the recovery period

Group	Corn oil (control)	2,4-DTAP (50 mg/kg)	2,4-DTAP (100 mg/kg)
Male, Recovery period			
Number of animals	5	5	
Righting reflex	100	100	
Visual placing	100	100	
Pupillary reflex	100	100	
Startle reaction	100	100	
Prayer's reaction	100	100	
Withdrawal reflex	100	100	
Eyelid reflex	100	100	
Female, Recovery period			
Number of animals	5	5	
Righting reflex	100	100	
Visual placing	100	100	
Pupillary reflex	100	100	
Startle reaction	100	100	
Prayer's reaction	100	100	
Withdrawal reflex	100	100	
Eyelid reflex	100	100	

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 17. Assessment of grip strength of male rats

Group	Corn oil (control)	2,4-DTAP (10 mg/kg)	2,4-DTAP (50 mg/kg)	2,4-DTAP (100 mg/kg)
Number of males	5	5	5	4
<u>Administration period</u>				
Forelimb	1.051 ± 0.144	1.107 ± 0.037	1.108 ± 0.143	1.137 ± 0.029
Hindlimb	0.746 ± 0.139	0.546 ± 0.092 *	0.482 ± 0.082 **	0.543 ± 0.163
<u>Recovery period</u>				
Forelimb	1.128 ± 0.097		1.104 ± 0.039	
Hindlimb	0.580 ± 0.084		0.554 ± 0.108	

Each value shows mean (kg) ±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 18. Assessment of grip strength of female rats

Group	Corn oil (control)	2,4-DTAP (10 mg/kg)	2,4-DTAP (50 mg/kg)
Number of females	5	5	5
<u>Administration period</u>			
Forelimb	1.095 ± 0.063	1.034 ± 0.076	1.089 ± 0.086
Hindlimb	0.452 ± 0.073	0.383 ± 0.073	0.473 ± 0.057

Each value shows mean (kg) ±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 19. Assessment of grip strength of female rats, satellite group

Group	Corn oil (control)	2,4-DTAP (100 mg/kg)
	Number of females	5
<u>Administration period</u>		
Forelimb	1.125 ± 0.120	1.044 ± 0.102
Hindlimb	0.521 ± 0.128	0.457 ± 0.167
<u>Recovery period</u>		
Forelimb	1.078 ± 0.104	1.131 ± 0.061
Hindlimb	0.511 ± 0.112	0.478 ± 0.074

Each value shows mean (kg) ±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 20. Motor activity of male rats

Group Number of males	Corn oil (control)		2,4-DTAP (10 mg/kg)	2,4-DTAP (50 mg/kg)	2,4-DTAP (100 mg/kg)
	5	5	5	4	
<u>Administration period</u>					
Ambulation (counts)					
5min	1174 ± 63		1104 ± 98	1353 ± 301	1068 ± 211
10min	1091 ± 105		1002 ± 148	1220 ± 249	918 ± 203
15min	1025 ± 110		830 ± 170	937 ± 281	832 ± 150
20min	713 ± 219		670 ± 186	868 ± 355	634 ± 142
Total	4003 ± 404		3607 ± 488	4377 ± 1139	3451 ± 604
Rearing (counts)					
5min	39 ± 6		34 ± 5	41 ± 6	34 ± 5
10min	32 ± 10		29 ± 9	35 ± 8	28 ± 2
15min	26 ± 4		16 ± 5	18 ± 13	18 ± 2
20min	12 ± 7		16 ± 9	15 ± 6	15 ± 8
Total	108 ± 21		95 ± 18	109 ± 29	95 ± 9
<u>Recovery period</u>					
Ambulation (counts)					
5min	1018 ± 124			1145 ± 237	
10min	958 ± 112			1046 ± 228	
15min	814 ± 131			948 ± 262	
20min	633 ± 182			850 ± 192	
Total	3422 ± 399			3989 ± 776	
Rearing (counts)					
5min	42 ± 9			39 ± 6	
10min	31 ± 7			31 ± 13	
15min	27 ± 7			25 ± 7	
20min	15 ± 7			25 ± 7	
Total	114 ± 28			120 ± 12	

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 21. Motor activity of female rats

Group Number of females	Corn oil (control)	2,4-DTAP (10 mg/kg)	2,4-DTAP (50 mg/kg)
	5	5	5
<u>Administration period</u>			
Ambulation (counts)			
5min	1129 ± 101	1037 ± 186	1218 ± 326
10min	678 ± 309	898 ± 66	977 ± 329
15min	672 ± 198	771 ± 206	941 ± 220
20min	403 ± 372	518 ± 242	862 ± 299
Total	2882 ± 925	3381 ± 827	3998 ± 1129
Rearing (counts)			
5min	36 ± 16	29 ± 10	36 ± 14
10min	12 ± 9	17 ± 5	17 ± 6
15min	11 ± 5	15 ± 6	12 ± 6
20min	7 ± 6	4 ± 7	8 ± 3
Total	66 ± 29	65 ± 18	74 ± 21

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 22. Motor activity of female rats, satellite group

Group	Corn oil (control)	2,4-DTAP (100 mg/kg)
Number of females	5	5
<u>Administration period</u>		
Ambulation (counts)		
5min	1324 ± 73	1130 ± 173 *
10min	1179 ± 84	1029 ± 167
15min	1075 ± 155	977 ± 147
20min	881 ± 151	844 ± 67
Total	4459 ± 328	3662 ± 455 *
Rearing (counts)		
5min	51 ± 14	39 ± 11
10min	39 ± 9	26 ± 9 *
15min	32 ± 9	27 ± 7
20min	24 ± 9	20 ± 4
Total	146 ± 27	111 ± 20 *
<u>Recovery period</u>		
Ambulation (counts)		
5min	1279 ± 219	1170 ± 232
10min	942 ± 172	1144 ± 307
15min	966 ± 321	985 ± 378
20min	819 ± 111	920 ± 289
Total	4005 ± 703	4219 ± 1149
Rearing (counts)		
5min	43 ± 17	37 ± 8
10min	21 ± 8	31 ± 11
15min	21 ± 10	22 ± 15
20min	12 ± 6	20 ± 16
Total	96 ± 23	110 ± 43

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 23-1. Urinalysis in male rats

Group	Number of males	Quality ^{a)}																	
		Color		Turbidity		pH				Protein			Glucose		Ketone		Bilirubin	Occult blood	Urobilinogen
		Light yellow	Yellow	-	6.5	7.0	7.5	8.0	+	2+	3+	-	±	-	±	+	-	±	+
Com oil (control)	5	4	1	5	2	3	0	0	3	2	0	5	0	1	1	3	5	5	2 2 1
2,4-DTAP (10 mg/kg)	5	2	3	5	1	2	2	0	2	2	1	4	1	0	1	4	5	5	2 2 1
2,4-DTAP (50 mg/kg)	5	4	1	5	5	0	0	0	2	3	0	5	0	0	1	4	5	5	3 2 0
2,4-DTAP (100 mg/kg)	4	4	0	4	1	0	1	2	2	2	0	4	0	1	2	1	4	4	4 0 0

Group	Number of males	Urinary sediments ^{a)}						Urine volume ^{b)} (mL/24hr)	Specific gravity ^{b)}	Electrolyte, density ^{b)} (mEq/L)			Electrolyte, gross volume ^{b)} (mEq/24 hr)			
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	-			Na	K	Cl	Na	K	Cl	
		-	-	-	-	-	±			-	±	-	±	-	±	
Com oil (control)	5	5	5	5	3	2	5	0	10.3 ±4.1	1.066 ±0.019	134.8 ±54.6	186.2 ±21.2	155.5 ±63.0	1.24 ±0.25	1.87 ±0.59	1.44 ±0.36
2,4-DTAP (10 mg/kg)	5	5	5	5	1	4	4	1	12.5 ±7.4	1.065 ±0.023	126.9 ±49.4	185.6 ±39.0	153.8 ±49.2	1.36 ±0.44	2.10 ±0.69	1.67 ±0.48
2,4-DTAP (50 mg/kg)	5	5	5	5	3	2	5	0	15.3 ±9.5	1.053 ±0.019	110.0 ±50.1	173.5 ±47.8	118.7 ±50.9	1.38 ±0.39	2.31 ±0.57	1.48 ±0.36
2,4-DTAP (100 mg/kg)	4	4	4	4	2	2	4	0	22.5 ±7.1	1.035 ±0.010	78.5 ±19.9	142.0 ±41.1	91.3 ±34.1	1.66 ±0.05	3.00 ±0.48	1.87 ±0.34

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL

Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 23-2. Urinalysis in male rats of the recovery period

Group	Number of males	Quality ^{a)}																
		Color	Turbidity	pH				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen					
		Light yellow	-	7.0	7.5	8.0	8.5	+	2+	-	±	+	-	±	+			
Com oil (control)	5	5	5	0	2	2	1	4	1	5	2	1	2	5	0	3	2	
2,4-DTAP (50 mg/kg)	5	5	5	1	2	1	1	5	0	5	0	5	0	5	4	1	3	2

Group	Number of males	Urinary sediments ^{a)}						Urine volume ^{b)} (mL/24hr)	Specific gravity ^{b)}	Electrolyte, density ^{b)} (mEq/L)			Electrolyte, gross volume ^{b)} (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	-			Na	K	Cl	Na	K	Cl
		-	+	-	-	±	-	(mL/24hr)							
Com oil (control)	5	5	0	5	5	5	5	14.2 ±3.3	1.069 ±0.010	133.6 ±15.9	272.0 ±84.6	152.4 ±24.3	1.86 ±0.27	3.74 ±0.95	2.12 ±0.37
2,4-DTAP (50 mg/kg)	5	4	1	5	5	5	5	14.5 ±2.7	1.065 ±0.008	121.9 ±30.4	246.2 ±89.2	135.0 ±29.8	1.75 ±0.46	3.57 ±1.36	1.94 ±0.44

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, +: 30≤and<100 mg/dL; 2+: 100≤and<300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5≤and<10 mg/dL; +: 10≤and<40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative; +: 0.06≤and<0.20 mg/dL

Urobilinogen, ±: normal; +: 2.0≤and<4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed; +: 10-99/3 visual field

Crystals and Epithelial cells, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 24-1. Urinalysis in female rats, satellite group

Group	Number of females	Quality ^{a)}																			
		Color		Turbidity		pH				Protein		Glucose		Ketone		Bilirubin	Occult blood	Urobilinogen			
		Light yellow	Yellow	-	6.0	6.5	7.0	8.0	-	±	+	2+	-	±	-	±	+				
Corn oil (control)	5	4	1	5	1	1	2	1	1	2	1	1	4	1	1	3	1	5	5	4	1
2,4-DTAP (100 mg/kg)	5	5	0	5	0	3	1	1	3	2	0	0	5	0	5	0	0	5	5	5	0

Group	Number of females	Urinary sediments ^{a)}					Urine volume ^{b)} (mL/24hr)	Specific gravity ^{b)}	Electrolyte, density ^{b)} (mEq/L)			Electrolyte, gross volume ^{b)} (mEq/24 hr)			
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells			Na	K	Cl	Na	K	Cl	
		-	-	-	-	±			-	-	-	-	-	-	
Corn oil (control)	5	5	5	5	4	1	5	11.5 ±4.7	1.052 ±0.019	84.5 ±33.9	158.3 ±41.3	112.2 ±52.9	0.92 ±0.39	1.73 ±0.56	1.17 ±0.50
2,4-DTAP (100 mg/kg)	5	5	5	5	4	1	5	18.6* ±2.5	1.028 ±0.005	59.8 ±15.7	113.0 ±22.5	67.1 ±22.8	1.10 ±0.28	2.11 ±0.51	1.24 ±0.45

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, -: negative; ±: 10≤ and < 30 mg/dL; +: 30≤ and < 100 mg/dL; 2+: 100≤ and < 300 mg/dL

Glucose, -: negative; ±: 30≤ and < 70 mg/dL

Ketone, -: negative; ±: 5≤ and < 10 mg/dL; +: 10≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0≤ and < 4.0 mg/dL

Red blood cells, White blood cells, Casts and Epithelial cells -: not observed

Crystals, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 24-2. Urinalysis in female rats of the recovery period

Group	Number of females	Quality ^{a)}													
		Color Light yellow	Turbidity -	pH				Protein -	Glucose -	Ketone -	Bilirubin -	Occult blood -	Urobilinogen ± +		
Com oil (control)	5	5	5	1	1	1	1	0	3	2	5	3	2		
2,4-DTAP (100 mg/kg)	5	5	5	0	1	2	1	1	2	2	5	5	0		
Urinary sediments^{a)}															
Group	Number of females	Red blood cells -	White blood cells -	Casts -	Crystals -	Epithelial cells ±	Urine volume ^{b)} (mL/24hr)	Specific gravity ^{b)}	Electrolyte, density ^{b)} (mEq/L)			Electrolyte, gross volume ^{b)} (mEq/24 hr)			
		-	-	-	-	-	(mL/24hr)		Na	K	Cl	Na	K	Cl	
Com oil (control)	5	5	5	5	1	4	5	11.4 ±4.6	1.068 ±0.014	110.1 ±35.0	210.1 ±32.9	144.6 ±29.1	1.27 ±0.54	2.29 ±0.58	1.63 ±0.56
2,4-DTAP (100 mg/kg)	5	5	5	5	0	5	5	15.1 ±6.9	1.054 ±0.021	102.0 ±41.8	176.1 ±53.4	102.7 ±70.9	1.40 ±0.59	2.48 ±0.84	1.35 ±0.88

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, -: negative; ±: 10≤and<30 mg/dL; +: 30≤and<100 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5≤and<10 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0≤and<4.0 mg/dL

Red blood cells, White blood cells, Casts and Epithelial cells -: not observed

Crystals, -: not observed; ±: a few

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 25-1. Hematological findings of male rats at the end of the dosing period

Group Number of males	Corn oil (control)	2,4-DTAP (10 mg/kg)	2,4-DTAP (50 mg/kg)	2,4-DTAP (100 mg/kg)
	5	5	5	4
RBC ($\times 10^4/\mu\text{L}$)	869 ± 57	886 ± 13	850 ± 18	799 ± 62
Hemoglobin (g/dL)	15.4 ± 0.2	15.1 ± 0.2	14.9 ± 0.2	13.9 ± 0.8 **
Hematocrit (%)	44.9 ± 1.2	43.6 ± 0.7	43.6 ± 0.7	41.0 ± 2.3 **
MCV (fL)	51.9 ± 4.0	49.2 ± 0.4	51.3 ± 1.2	51.4 ± 2.2
MCH (pg)	17.7 ± 1.1	17.1 ± 0.1	17.6 ± 0.3	17.4 ± 0.7
MCHC (g/dL)	34.2 ± 0.7	34.7 ± 0.5	34.2 ± 0.5	33.9 ± 0.4
Platelet ($\times 10^4/\mu\text{L}$)	113.2 ± 8.4	129.7 ± 12.7	114.8 ± 14.7	124.2 ± 9.2
PT (sec)	20.0 ± 4.5	23.6 ± 10.9	26.4 ± 8.2	39.2 ± 5.7 **
APTT (sec)	27.0 ± 2.1	31.5 ± 9.7	32.0 ± 4.1	41.7 ± 4.4
WBC ($\times 10^2/\mu\text{L}$)	95.2 ± 37.0	86.7 ± 24.1	95.7 ± 26.9	104.9 ± 21.5
Differential leukocyte ratio (%)				
Neutrophil	18.2 ± 6.5	17.6 ± 3.1	20.5 ± 5.5	20.2 ± 6.3
Eosinophil	1.2 ± 0.6	1.0 ± 0.4	1.5 ± 0.7	1.0 ± 0.3
Basophil	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1
Monocyte	3.6 ± 1.0	3.5 ± 1.0	3.6 ± 1.4	3.1 ± 1.1
Lymphocyte	77.1 ± 7.3	78.0 ± 3.8	74.4 ± 6.4	75.7 ± 6.8
Reticulocyte ratio (%)	2.64 ± 0.30	2.50 ± 0.30	2.59 ± 0.39	2.93 ± 0.41

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 25-2. Hematological findings of male rats at the end of the recovery period

Group Number of males	Corn oil (control)	2,4-DTAP (50 mg/kg)
	5	5
RBC ($\times 10^4/\mu\text{L}$)	877 ± 34	875 ± 19
Hemoglobin (g/dL)	15.1 ± 0.5	14.9 ± 0.6
Hematocrit (%)	44.3 ± 1.7	43.9 ± 2.0
MCV (fL)	50.5 ± 0.4	50.2 ± 1.3
MCH (pg)	17.2 ± 0.2	17.1 ± 0.4
MCHC (g/dL)	34.0 ± 0.2	34.0 ± 0.3
Platelet ($\times 10^4/\mu\text{L}$)	113.2 ± 6.8	111.9 ± 13.5
PT (sec)	20.3 ± 3.4	18.2 ± 6.7
APTT (sec)	25.7 ± 2.1	23.7 ± 4.8
WBC ($\times 10^2/\mu\text{L}$)	58.7 ± 10.9	57.9 ± 14.3
Differential leukocyte ratio (%)		
Neutrophil	28.9 ± 6.8	26.7 ± 7.0
Eosinophil	2.3 ± 0.7	1.3 ± 0.3 *
Basophil	0.0 ± 0.0	0.0 ± 0.1
Monocyte	3.7 ± 0.8	3.7 ± 1.1
Lymphocyte	65.1 ± 6.2	68.3 ± 8.1
Reticulocyte ratio (%)	2.92 ± 0.43	3.11 ± 0.59

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 26-1. Hematological findings of female rats at the end of the dosing period

Group Number of females	Corn oil (control)	2,4-DTAP (10 mg/kg)	2,4-DTAP (50 mg/kg)
	5	5	5
RBC ($\times 10^4/\mu\text{L}$)	661 ± 64	695 ± 57	635 ± 35
Hemoglobin (g/dL)	12.6 ± 1.1	12.6 ± 0.9	12.1 ± 0.6
Hematocrit (%)	36.2 ± 1.8	37.6 ± 2.5	37.1 ± 1.7
MCV (fL)	55.1 ± 4.8	54.2 ± 2.4	58.5 ± 2.6
MCH (pg)	19.1 ± 0.6	18.2 ± 0.7	19.0 ± 0.5
MCHC (g/dL)	34.9 ± 2.5	33.5 ± 0.4	32.5 ± 0.6 *
Platelet ($\times 10^4/\mu\text{L}$)	99.8 ± 28.6	122.8 ± 24.9	108.6 ± 11.3
PT (sec)	11.3 ± 0.5	11.9 ± 0.5	11.3 ± 0.5
APTT (sec)	17.1 ± 1.0	16.8 ± 0.9	17.8 ± 1.6
WBC ($\times 10^2/\mu\text{L}$)	94.0 ± 18.7	94.9 ± 28.2	103.7 ± 22.4
Differential leukocyte ratio (%)			
Neutrophil	35.5 ± 8.0	28.1 ± 8.5	32.0 ± 7.5
Eosinophil	0.5 ± 0.2	0.7 ± 0.5	0.4 ± 0.3
Basophil	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1
Monocyte	3.3 ± 2.6	3.4 ± 1.7	2.9 ± 0.9
Lymphocyte	60.6 ± 10.1	67.8 ± 7.8	64.7 ± 6.6
Reticulocyte ratio (%)	4.74 ± 2.57	5.94 ± 2.02	9.27 ± 1.56 **

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 26-2. Hematological findings of female rats at the end of the dosing period, satellite group

Group	Corn oil (control)		2,4-DTAP (100 mg/kg)	
		5		5
Number of females				
RBC ($\times 10^4/\mu\text{L}$)	789	\pm 53	724	\pm 31 *
Hemoglobin (g/dL)	14.7	\pm 0.6	13.2	\pm 0.4 **
Hematocrit (%)	43.4	\pm 0.9	39.1	\pm 1.1 **
MCV (fL)	55.2	\pm 2.7	54.0	\pm 1.4
MCH (pg)	18.7	\pm 0.6	18.2	\pm 0.4
MCHC (g/dL)	33.9	\pm 0.8	33.8	\pm 0.3
Platelet ($\times 10^4/\mu\text{L}$)	100.3	\pm 3.6	114.5	\pm 9.5 *
PT (sec)	10.9	\pm 0.2	11.1	\pm 0.4
APTT (sec)	18.6	\pm 1.7	17.7	\pm 1.6
WBC ($\times 10^2/\mu\text{L}$)	52.3	\pm 12.8	67.2	\pm 20.7
Differential leukocyte ratio (%)				
Neutrophil	9.0	\pm 3.4	10.1	\pm 2.4
Eosinophil	1.3	\pm 0.3	1.3	\pm 0.5
Basophil	0.0	\pm 0.0	0.0	\pm 0.0
Monocyte	2.8	\pm 0.8	2.7	\pm 0.5
Lymphocyte	86.9	\pm 3.7	86.0	\pm 3.1
Reticulocyte ratio (%)	3.31	\pm 0.69	2.91	\pm 0.56

Each value shows mean \pm S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 26-3. Hematological findings of female rats at the end of the recovery period

Group Number of males	Corn oil (control)		2,4-DTAP (100 mg/kg)	
	5	5	5	5
RBC ($\times 10^4/\mu\text{L}$)	824 ± 34		798 ± 27	
Hemoglobin (g/dL)	14.5 ± 0.7		14.5 ± 0.6	
Hematocrit (%)	42.9 ± 2.1		43.5 ± 1.0	
MCV (fL)	52.2 ± 1.8		54.5 ± 1.5	
MCH (pg)	17.7 ± 0.6		18.1 ± 0.2	
MCHC (g/dL)	33.9 ± 0.2		33.3 ± 0.9	
Platelet ($\times 10^4/\mu\text{L}$)	104.9 ± 11.8		100.5 ± 2.8	
PT (sec)	11.2 ± 0.5		11.2 ± 0.4	
APTT (sec)	18.1 ± 1.3		17.8 ± 1.5	
WBC ($\times 10^2/\mu\text{L}$)	52.0 ± 9.3		68.7 ± 31.1	
Differential leukocyte ratio (%)				
Neutrophil	10.2 ± 2.9		11.1 ± 4.3	
Eosinophil	2.3 ± 1.0		1.9 ± 0.9	
Basophil	0.0 ± 0.0		0.0 ± 0.0	
Monocyte	3.0 ± 0.6		3.2 ± 0.9	
Lymphocyte	84.5 ± 3.8		83.8 ± 5.5	
Reticulocyte ratio (%)	2.60 ± 0.30		2.77 ± 0.38	

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 27-1. Biochemical findings of male rats at the end of the dosing period

Group Number of males	Corn oil (control)		2,4-DTAP (10 mg/kg)	2,4-DTAP (50 mg/kg)	2,4-DTAP (100 mg/kg)
	5	5	5	4	
Total protein (g/dL)	5.4 ± 0.4		5.3 ± 0.2	5.1 ± 0.2	5.2 ± 0.1
Albumin (g/dL)	3.5 ± 0.2		3.5 ± 0.1	3.5 ± 0.2	3.4 ± 0.1
A/G	1.89 ± 0.18		1.91 ± 0.14	2.06 ± 0.16	1.88 ± 0.20
Glucose (mg/dL)	137 ± 12		136 ± 10	137 ± 8	139 ± 8
Total cholesterol (mg/dL)	53 ± 12		48 ± 9	58 ± 11	53 ± 7
Triglyceride (mg/dL)	48 ± 24		63 ± 36	52 ± 14	38 ± 16
Phospholipid (mg/dL)	86 ± 17		81 ± 14	83 ± 11	77 ± 11
AST (U/L)	60 ± 14		59 ± 8	55 ± 6	58 ± 2
ALT (U/L)	30 ± 11		28 ± 8	26 ± 7	26 ± 3
γ-GTP (U/L)	0 ± 0		0 ± 0	0 ± 0	0 ± 0
LDH (U/L)	131 ± 84		96 ± 41	98 ± 54	110 ± 54
Bile acid (μmol/L)	12.0 ± 12.5		6.7 ± 3.3	3.4 ± 1.3	3.0 ± 0.8
Blood urea nitrogen (mg/dL)	12 ± 1		11 ± 2	12 ± 1	13 ± 3
Creatinine (mg/dL)	0.4 ± 0.1		0.4 ± 0.1	0.4 ± 0.0	0.4 ± 0.1
Total bilirubin (mg/dL)	0.05 ± 0.01		0.05 ± 0.01	0.05 ± 0.01	0.06 ± 0.01
ALP (U/L)	361 ± 54		402 ± 84	467 ± 118	701 ± 364
Inorganic phosphorus (mg/dL)	6.1 ± 0.8		5.8 ± 0.4	6.2 ± 0.4	6.9 ± 0.6
Ca (mg/dL)	9.2 ± 0.4		9.2 ± 0.1	9.4 ± 0.3	9.2 ± 0.3
Na (mEq/L)	144.3 ± 1.0		144.8 ± 0.7	143.9 ± 1.1	144.0 ± 1.2
K (mEq/L)	3.92 ± 0.12		3.77 ± 0.29	3.80 ± 0.17	3.96 ± 0.11
Cl (mEq/L)	107.9 ± 1.4		108.1 ± 0.6	108.0 ± 2.1	108.2 ± 1.0

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 27-2. Biochemical findings of male rats at the end of the recovery period

Group Number of females	Corn oil (control)		2,4-DTAP (50 mg/kg)	
	5	5	5	5
Total protein (g/dL)	5.8 ± 0.3		5.6 ± 0.3	
Albumin (g/dL)	3.6 ± 0.1		3.6 ± 0.2	
A/G	1.67 ± 0.12		1.81 ± 0.05 *	
Glucose (mg/dL)	138 ± 9		138 ± 9	
Total cholesterol (mg/dL)	62 ± 12		56 ± 8	
Triglyceride (mg/dL)	24 ± 5		37 ± 18	
Phospholipid (mg/dL)	85 ± 13		82 ± 8	
AST (U/L)	84 ± 19		85 ± 15	
ALT (U/L)	27 ± 3		32 ± 6	
γ-GTP (U/L)	0 ± 0		0 ± 0	
LDH (U/L)	144 ± 117		131 ± 30	
Bile acid (μmol/L)	7.2 ± 1.9		14.9 ± 11.4	
Blood urea nitrogen (mg/dL)	15 ± 2		16 ± 1	
Creatinine (mg/dL)	0.5 ± 0.1		0.4 ± 0.1	
Total bilirubin (mg/dL)	0.04 ± 0.01		0.05 ± 0.01	
ALP (U/L)	273 ± 36		322 ± 43	
Inorganic phosphorus (mg/dL)	5.1 ± 0.6		5.5 ± 0.2	
Ca (mg/dL)	9.3 ± 0.1		9.4 ± 0.2	
Na (mEq/L)	144.8 ± 0.8		144.8 ± 0.9	
K (mEq/L)	3.66 ± 0.12		3.67 ± 0.26	
Cl (mEq/L)	108.1 ± 1.9		107.9 ± 1.8	

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 28-1. Biochemical findings of female rats at the end of the dosing period

Group Number of females	Corn oil (control)		2,4-DTAP (10 mg/kg)		2,4-DTAP (50 mg/kg)	
	5	5	5	5	5	5
Total protein (g/dL)	5.2 ± 0.3		5.5 ± 0.5		5.8 ± 0.4	
Albumin (g/dL)	3.6 ± 0.2		3.8 ± 0.3		3.9 ± 0.3	
A/G	2.23 ± 0.14		2.35 ± 0.54		2.07 ± 0.12	
Glucose (mg/dL)	106 ± 17		136 ± 19 *		129 ± 7	
Total cholesterol (mg/dL)	66 ± 9		63 ± 11		75 ± 9	
Triglyceride (mg/dL)	29 ± 8		43 ± 15		53 ± 23	
Phospholipid (mg/dL)	102 ± 12		104 ± 22		121 ± 10	
AST (U/L)	125 ± 48		74 ± 24 *		71 ± 12	
ALT (U/L)	84 ± 37		38 ± 10 *		41 ± 11	
γ-GTP (U/L)	0 ± 0		0 ± 0		0 ± 0	
LDH (U/L)	93 ± 64		95 ± 59		130 ± 86	
Bile acid (μmol/L)	14.6 ± 5.8		16.8 ± 8.4		6.6 ± 1.1	
Blood urea nitrogen (mg/dL)	10 ± 4		12 ± 4		10 ± 3	
Creatinine (mg/dL)	0.5 ± 0.1		0.5 ± 0.1		0.5 ± 0.0	
Total bilirubin (mg/dL)	0.06 ± 0.01		0.06 ± 0.02		0.05 ± 0.01	
ALP (U/L)	205 ± 64		217 ± 105		248 ± 44	
Inorganic phosphorus (mg/dL)	7.2 ± 0.9		6.7 ± 0.5		6.0 ± 0.3 *	
Ca (mg/dL)	9.5 ± 0.7		10.1 ± 0.4		9.8 ± 0.4	
Na (mEq/L)	141.8 ± 4.2		143.2 ± 1.5		143.1 ± 1.4	
K (mEq/L)	3.30 ± 0.66		3.41 ± 0.10		3.50 ± 0.16	
Cl (mEq/L)	101.9 ± 9.2		105.9 ± 3.3		108.0 ± 1.1	

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01)

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 28-2. Biochemical findings of female rats at the end of the dosing period, satellite group

Group Number of females	Corn oil (control)		2,4-DTAP (100 mg/kg)	
	5	5	5	5
Total protein (g/dL)	6.1 ± 0.2		6.2 ± 0.3	
Albumin (g/dL)	4.4 ± 0.3		4.3 ± 0.3	
A/G	2.62 ± 0.43		2.28 ± 0.20	
Glucose (mg/dL)	138 ± 14		133 ± 21	
Total cholesterol (mg/dL)	71 ± 14		88 ± 13	
Triglyceride (mg/dL)	26 ± 16		17 ± 8	
Phospholipid (mg/dL)	119 ± 15		137 ± 23	
AST (U/L)	62 ± 15		51 ± 5	
ALT (U/L)	23 ± 5		17 ± 2	
γ-GTP (U/L)	0 ± 0		1 ± 1	
LDH (U/L)	95 ± 36		104 ± 80	
Bile acid (μmol/L)	9.9 ± 3.1		7.1 ± 2.0	
Blood urea nitrogen (mg/dL)	15 ± 4		15 ± 3	
Creatinine (mg/dL)	0.6 ± 0.1		0.7 ± 0.1	
Total bilirubin (mg/dL)	0.05 ± 0.00		0.07 ± 0.01	
ALP (U/L)	219 ± 45		249 ± 70	
Inorganic phosphorus (mg/dL)	4.9 ± 0.5		5.6 ± 0.5	
Ca (mg/dL)	9.7 ± 0.2		9.9 ± 0.2	
Na (mEq/L)	143.5 ± 0.6		143.5 ± 1.0	
K (mEq/L)	3.80 ± 0.17		3.96 ± 0.19	
Cl (mEq/L)	108.2 ± 0.5		106.5 ± 1.6	

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 28-3. Biochemical findings of female rats at the end of the recovery period

Group Number of females	Corn oil (control)		2,4-DTAP (100 mg/kg)	
	5	5	5	5
Total protein (g/dL)	6.1 ± 0.2		6.2 ± 0.4	
Albumin (g/dL)	4.2 ± 0.2		4.2 ± 0.4	
A/G	2.30 ± 0.41		2.12 ± 0.16	
Glucose (mg/dL)	128 ± 10		131 ± 10	
Total cholesterol (mg/dL)	70 ± 8		83 ± 15	
Triglyceride (mg/dL)	33 ± 22		40 ± 33	
Phospholipid (mg/dL)	114 ± 16		132 ± 25	
AST (U/L)	63 ± 25		64 ± 11	
ALT (U/L)	25 ± 15		23 ± 10	
γ-GTP (U/L)	0 ± 1		0 ± 0	
LDH (U/L)	62 ± 28		57 ± 26	
Bile acid (μmol/L)	11.9 ± 5.8		11.6 ± 5.5	
Blood urea nitrogen (mg/dL)	15 ± 3		14 ± 2	
Creatinine (mg/dL)	0.6 ± 0.1		0.5 ± 0.1	
Total bilirubin (mg/dL)	0.07 ± 0.02		0.07 ± 0.02	
ALP (U/L)	118 ± 25		108 ± 27	
Inorganic phosphorus (mg/dL)	4.5 ± 0.6		4.8 ± 0.9	
Ca (mg/dL)	9.7 ± 0.3		9.9 ± 0.4	
Na (mEq/L)	143.6 ± 0.7		143.5 ± 1.1	
K (mEq/L)	3.43 ± 0.19		3.53 ± 0.17	
Cl (mEq/L)	108.4 ± 0.9		108.2 ± 2.1	

Each value shows mean±S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 29-1. Organ weights of male rats at the end of the dosing period

Group Number of males	Corn oil (control)		2,4-DTAP 10 mg/kg		2,4-DTAP 50 mg/kg		2,4-DTAP 100 mg/kg	
	8	13	8	13	8	4	8	23.1
Body weight (g)	479.1 ± 27.7		472.8 ± 37.6		456.4 ± 27.6		458.8 ± 23.1	
Brain (mg)	2022.5 ± 62.3		2007.5 ± 75.1		2022.3 ± 55.6		2045.8 ± 36.8	
	(mg/g)	4.238 ± 0.346		4.273 ± 0.396		4.444 ± 0.264		4.466 ± 0.208
Thymus (mg)	307.5 ± 85.2		272.5 ± 59.1		280.7 ± 77.8		242.7 ± 40.4	
	(mg/g)	0.643 ± 0.185		0.579 ± 0.137		0.617 ± 0.167		0.530 ± 0.095
Heart (mg)	1420.8 ± 93.6		1344.7 ± 125.4		1290.2 ± 97.3		1285.5 ± 64.0	
	(mg/g)	2.969 ± 0.166		2.849 ± 0.215		2.830 ± 0.192		2.802 ± 0.041
Liver (mg)	12956.5 ± 1265.3		13364.9 ± 1935.8		14157.5 ± 1237.1		16419.6 ± 2820.8 **	
	(mg/g)	27.005 ± 1.565		28.177 ± 2.454		31.002 ± 1.605 **		35.647 ± 4.367 **
Kidney (R) (mg)	1483.3 ± 141.9		1500.5 ± 171.1		1440.6 ± 52.9		1592.1 ± 81.3	
	(mg/g)	3.092 ± 0.172		3.180 ± 0.323		3.167 ± 0.221		3.474 ± 0.182
Kidney (L) (mg)	1474.8 ± 132.2		1511.0 ± 182.8		1422.8 ± 74.9		1533.8 ± 16.4	
	(mg/g)	3.076 ± 0.170		3.199 ± 0.316		3.127 ± 0.240		3.350 ± 0.193
Kidneys (mg)	2958.0 ± 272.2		3011.4 ± 351.3		2863.5 ± 115.0		3125.8 ± 87.5	
	(mg/g)	6.169 ± 0.336		6.379 ± 0.634		6.294 ± 0.442		6.824 ± 0.336
Spleen (mg)	795.4 ± 97.1		757.7 ± 123.8		745.1 ± 119.3		862.3 ± 191.8	
	(mg/g)	1.658 ± 0.159		1.602 ± 0.222		1.625 ± 0.163		1.882 ± 0.418
Testis (R) (mg)	1656.6 ± 107.8		1672.3 ± 136.8		1664.5 ± 174.9		1591.9 ± 26.2	
	(mg/g)	3.466 ± 0.277		3.555 ± 0.362		3.649 ± 0.349		3.477 ± 0.191
Testis (L) (mg)	1640.4 ± 114.3		1680.2 ± 102.3		1647.4 ± 173.7		1613.6 ± 45.2	
	(mg/g)	3.435 ± 0.329		3.573 ± 0.335		3.613 ± 0.361		3.525 ± 0.231
Testes (mg)	3297.0 ± 218.8		3352.5 ± 236.7		3311.8 ± 348.2		3205.5 ± 36.3	
	(mg/g)	6.902 ± 0.603		7.128 ± 0.690		7.262 ± 0.710		7.002 ± 0.401
Epididymis (R) (mg)	627.7 ± 28.2		667.3 ± 53.4		633.3 ± 72.8		635.0 ± 24.7	
	(mg/g)	1.313 ± 0.082		1.417 ± 0.125		1.392 ± 0.182		1.386 ± 0.066
Epididymis (L) (mg)	613.9 ± 33.7		650.8 ± 42.4		614.4 ± 57.3		621.4 ± 38.1	
	(mg/g)	1.283 ± 0.059		1.381 ± 0.100		1.351 ± 0.151		1.356 ± 0.072
Epididymides (mg)	1241.6 ± 55.4		1318.1 ± 90.5		1247.7 ± 128.4		1256.5 ± 60.6	
	(mg/g)	2.596 ± 0.130		2.798 ± 0.216		2.743 ± 0.329		2.741 ± 0.129
Prostate, ventral (mg)	651.9 ± 167.8		662.1 ± 135.5		632.9 ± 196.4		726.9 ± 105.4	
	(mg/g)	1.371 ± 0.381		1.399 ± 0.256		1.408 ± 0.496		1.586 ± 0.236
Seminal vesicles (mg)	1675.4 ± 275.5		1868.2 ± 188.1		1636.3 ± 341.1		1787.8 ± 274.8	
	(mg/g)	3.510 ± 0.661		3.973 ± 0.498		3.593 ± 0.769		3.907 ± 0.660

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 29-1 (continued). Organ weights of male rats at the end of the dosing period

Group Number of males	Corn oil (control)		2,4-DTAP 10 mg/kg		2,4-DTAP 50 mg/kg		2,4-DTAP 100 mg/kg	
	8	13	8	13	8	4		
Body weight	(g)	479.1 ± 27.7		472.8 ± 37.6		456.4 ± 27.6		458.8 ± 23.1
Thyroid gland	(mg)	21.7 ± 3.4		22.1 ± 4.7		23.8 ± 3.9		22.4 ± 5.1
	(mg/g)	0.046 ± 0.009		0.047 ± 0.010		0.052 ± 0.007		0.049 ± 0.010
Adrenal gland (R)	(mg)	25.4 ± 2.3		25.8 ± 3.2		24.0 ± 3.1		27.4 ± 1.8
	(mg/g)	0.053 ± 0.004		0.055 ± 0.007		0.053 ± 0.008		0.060 ± 0.005
Adrenal gland (L)	(mg)	27.7 ± 3.3		26.9 ± 4.2		25.7 ± 4.5		27.8 ± 2.0
	(mg/g)	0.058 ± 0.006		0.057 ± 0.009		0.057 ± 0.011		0.061 ± 0.003
Adrenal glands	(mg)	53.1 ± 5.3		52.7 ± 7.1		49.7 ± 7.0		55.2 ± 3.1
	(mg/g)	0.111 ± 0.009		0.112 ± 0.015		0.109 ± 0.018		0.121 ± 0.007

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 29-2. Organ weights of male rats at the end of the recovery period

Group Number of males	Corn oil (control)			2,4-DTAP 50 mg/kg		
		5	5		5	5
Body weight	(g)	510.5	± 27.3	473.6	± 36.1	
Brain	(mg)	2077.9	± 70.1	2028.8	± 49.5	
	(mg/g)	4.083	± 0.319	4.303	± 0.333	
Thymus	(mg)	223.3	± 53.3	257.2	± 75.8	
	(mg/g)	0.437	± 0.101	0.541	± 0.148	
Heart	(mg)	1374.3	± 55.3	1409.6	± 152.0	
	(mg/g)	2.696	± 0.126	2.978	± 0.258	
Liver	(mg)	13684.0	± 1162.1	12520.2	± 1899.3	
	(mg/g)	26.778	± 1.234	26.337	± 2.409	
Kidney (R)	(mg)	1578.4	± 195.3	1453.8	± 75.9	
	(mg/g)	3.090	± 0.332	3.077	± 0.163	
Kidney (L)	(mg)	1543.6	± 181.1	1450.1	± 79.9	
	(mg/g)	3.024	± 0.327	3.071	± 0.210	
Kidneys	(mg)	3122.0	± 375.5	2903.9	± 141.2	
	(mg/g)	6.114	± 0.656	6.148	± 0.351	
Spleen	(mg)	843.5	± 134.1	749.2	± 90.1	
	(mg/g)	1.656	± 0.280	1.586	± 0.198	
Testis (R)	(mg)	1680.6	± 130.8	1660.4	± 61.4	
	(mg/g)	3.293	± 0.215	3.528	± 0.380	
Testis (L)	(mg)	1656.0	± 83.1	1649.2	± 66.7	
	(mg/g)	3.245	± 0.087	3.503	± 0.373	
Testes	(mg)	3336.5	± 206.0	3309.6	± 123.7	
	(mg/g)	6.538	± 0.293	7.031	± 0.750	
Epididymis (R)	(mg)	659.5	± 68.2	631.5	± 28.8	
	(mg/g)	1.294	± 0.139	1.341	± 0.143	
Epididymis (L)	(mg)	647.2	± 45.5	653.1	± 32.7	
	(mg/g)	1.271	± 0.109	1.387	± 0.147	
Epididymides	(mg)	1306.7	± 111.1	1284.7	± 36.4	
	(mg/g)	2.564	± 0.242	2.728	± 0.272	
Prostate, ventral	(mg)	695.4	± 167.8	641.8	± 93.7	
	(mg/g)	1.359	± 0.310	1.361	± 0.231	
Seminal vesicles	(mg)	1796.2	± 142.1	1622.2	± 129.0	
	(mg/g)	3.531	± 0.379	3.437	± 0.332	

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 29-2 (continued). Organ weights of male rats at the end of the recovery period

Group Number of males	Corn oil (control)			2,4-DTAP 50 mg/kg		
		5		5		5
Body weight	(g)	510.5 ± 27.3		473.6 ± 36.1		
Thyroid gland	(mg)	16.5 ± 2.3		17.9 ± 3.0		
	(mg/g)	0.032 ± 0.006		0.038 ± 0.007		
Adrenal gland (R)	(mg)	28.3 ± 3.8		27.0 ± 4.7		
	(mg/g)	0.056 ± 0.006		0.057 ± 0.008		
Adrenal gland (L)	(mg)	29.6 ± 4.5		27.7 ± 3.6		
	(mg/g)	0.058 ± 0.008		0.058 ± 0.007		
Adrenal glands	(mg)	57.9 ± 8.2		54.7 ± 8.1		
	(mg/g)	0.114 ± 0.013		0.116 ± 0.015		

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 30-1. Organ weights of female rats at the end of the dosing period

Group	Corn oil (control)	2,4-DTAP 10 mg/kg		2,4-DTAP 50 mg/kg	
		12	11	11	11
Number of females					
Body weight	(g)	311.7 ± 29.0	317.3 ± 44.1	322.4 ± 27.4	
Brain	(mg)	1908.3 ± 75.8	1894.1 ± 89.7	1896.0 ± 89.2	
	(mg/g)	6.175 ± 0.686	6.082 ± 0.967	5.916 ± 0.524	
Thymus	(mg)	157.5 ± 72.7	154.1 ± 71.5	176.9 ± 71.0	
	(mg/g)	0.493 ± 0.213	0.469 ± 0.193	0.547 ± 0.218	
Heart	(mg)	948.1 ± 71.5	969.0 ± 103.7	975.8 ± 72.6	
	(mg/g)	3.053 ± 0.202	3.069 ± 0.164	3.036 ± 0.229	
Liver	(mg)	9925.6 ± 1145.7	10608.8 ± 1382.5	11454.6 ± 885.2 **	
	(mg/g)	31.857 ± 2.334	33.555 ± 2.380	35.612 ± 2.228 **	
Kidney (R)	(mg)	1017.6 ± 76.7	990.5 ± 101.0	1003.9 ± 64.5	
	(mg/g)	3.299 ± 0.477	3.201 ± 0.748	3.134 ± 0.330	
Kidney (L)	(mg)	1001.6 ± 80.6	966.2 ± 89.4	996.7 ± 59.1	
	(mg/g)	3.248 ± 0.495	3.114 ± 0.654	3.113 ± 0.339	
Kidneys	(mg)	2019.2 ± 155.3	1956.7 ± 187.6	2000.7 ± 120.2	
	(mg/g)	6.547 ± 0.969	6.315 ± 1.400	6.247 ± 0.663	
Spleen	(mg)	651.5 ± 161.1	677.5 ± 138.3	698.7 ± 91.5	
	(mg/g)	2.064 ± 0.401	2.126 ± 0.268	2.177 ± 0.303	
Ovary (R)	(mg)	50.9 ± 8.2	59.0 ± 9.6	54.8 ± 13.8	
	(mg/g)	0.165 ± 0.031	0.189 ± 0.039	0.170 ± 0.038	
Ovary (L)	(mg)	49.2 ± 8.6	53.1 ± 7.5	48.3 ± 8.7	
	(mg/g)	0.159 ± 0.030	0.171 ± 0.036	0.151 ± 0.028	
Ovaries	(mg)	100.1 ± 10.3	112.1 ± 15.4	103.2 ± 17.7	
	(mg/g)	0.324 ± 0.043	0.360 ± 0.071	0.320 ± 0.050	
Uterus	(mg)	570.5 ± 68.5	614.8 ± 77.4	585.4 ± 76.7	
	(mg/g)	1.841 ± 0.258	1.964 ± 0.324	1.832 ± 0.300	
Thyroid gland	(mg)	15.0 ± 5.1	18.6 ± 3.8	18.5 ± 5.5	
	(mg/g)	0.048 ± 0.016	0.060 ± 0.015	0.058 ± 0.018	
Adrenal gland (R)	(mg)	38.4 ± 6.9	39.0 ± 5.9	36.5 ± 5.7	
	(mg/g)	0.124 ± 0.023	0.125 ± 0.025	0.113 ± 0.017	
Adrenal gland (L)	(mg)	40.2 ± 6.2	40.1 ± 5.2	38.4 ± 4.5	
	(mg/g)	0.130 ± 0.022	0.129 ± 0.026	0.120 ± 0.016	
Adrenal glands	(mg)	78.6 ± 11.0	79.1 ± 10.9	74.8 ± 10.1	
	(mg/g)	0.254 ± 0.039	0.254 ± 0.051	0.233 ± 0.033	

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 30-2. Organ weights of female rats at the end of the dosing period, satellite group

Group	Number of females	Corn oil (control)		2,4-DTAP 100 mg/kg	
			5		6
Body weight	(g)	300.8	± 28.0	283.2	± 18.4
Brain	(mg)	1897.0	± 52.9	1909.7	± 30.7
	(mg/g)	6.349	± 0.602	6.766	± 0.429
Thymus	(mg)	279.4	± 48.7	237.4	± 63.2
	(mg/g)	0.933	± 0.168	0.846	± 0.258
Heart	(mg)	967.3	± 104.0	881.4	± 61.6
	(mg/g)	3.215	± 0.132	3.116	± 0.188
Liver	(mg)	7831.1	± 811.2	9062.5	± 526.0 *
	(mg/g)	26.031	± 1.241	32.027	± 1.162 **
Kidney (R)	(mg)	940.1	± 80.6	935.0	± 48.8
	(mg/g)	3.128	± 0.062	3.311	± 0.240
Kidney (L)	(mg)	939.2	± 115.9	947.4	± 80.3
	(mg/g)	3.119	± 0.160	3.352	± 0.294
Kidneys	(mg)	1879.3	± 189.5	1882.4	± 126.6
	(mg/g)	6.247	± 0.148	6.663	± 0.517
Spleen	(mg)	527.9	± 54.8	584.7	± 51.2
	(mg/g)	1.760	± 0.177	2.075	± 0.264 *
Ovary (R)	(mg)	43.1	± 6.6	45.8	± 7.0
	(mg/g)	0.143	± 0.017	0.163	± 0.029
Ovary (L)	(mg)	46.3	± 8.7	42.6	± 7.3
	(mg/g)	0.154	± 0.024	0.150	± 0.020
Ovaries	(mg)	89.3	± 14.7	88.4	± 12.6
	(mg/g)	0.297	± 0.039	0.313	± 0.043
Uterus	(mg)	669.0	± 248.3	518.1	± 138.9
	(mg/g)	2.185	± 0.657	1.844	± 0.556
Thyroid gland	(mg)	17.2	± 5.5	15.1	± 7.0
	(mg/g)	0.057	± 0.013	0.053	± 0.024
Adrenal gland (R)	(mg)	30.9	± 4.7	34.1	± 3.1
	(mg/g)	0.103	± 0.015	0.121	± 0.013
Adrenal gland (L)	(mg)	34.7	± 3.9	36.2	± 4.8
	(mg/g)	0.115	± 0.015	0.128	± 0.016
Adrenal glands	(mg)	65.6	± 8.5	70.3	± 7.9
	(mg/g)	0.219	± 0.030	0.249	± 0.028

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 30-3. Organ weights of female rats at the end of the recovery period

Group Number of females	Corn oil (control)			2,4-DTAP 100 mg/kg		
		5	5		5	5
Body weight	(g)	310.1 ± 26.0		317.1 ± 20.1		
Brain	(mg)	1929.4 ± 44.8		1914.7 ± 146.7		
	(mg/g)	6.258 ± 0.570		6.068 ± 0.706		
Thymus	(mg)	264.2 ± 58.8		342.1 ± 75.9		
	(mg/g)	0.858 ± 0.205		1.072 ± 0.187		
Heart	(mg)	947.5 ± 50.2		978.6 ± 53.0		
	(mg/g)	3.063 ± 0.130		3.094 ± 0.220		
Liver	(mg)	7754.1 ± 764.9		8360.9 ± 757.1		
	(mg/g)	24.983 ± 0.795		26.350 ± 1.295		
Kidney (R)	(mg)	924.2 ± 82.9		996.9 ± 98.3		
	(mg/g)	2.981 ± 0.126		3.139 ± 0.127		
Kidney (L)	(mg)	914.3 ± 102.2		963.9 ± 115.2		
	(mg/g)	2.945 ± 0.162		3.034 ± 0.200		
Kidneys	(mg)	1838.5 ± 180.3		1960.9 ± 210.7		
	(mg/g)	5.926 ± 0.247		6.172 ± 0.313		
Spleen	(mg)	533.8 ± 65.1		665.0 ± 86.4 *		
	(mg/g)	1.732 ± 0.256		2.097 ± 0.222 *		
Ovary (R)	(mg)	52.5 ± 14.1		49.5 ± 11.3		
	(mg/g)	0.172 ± 0.054		0.157 ± 0.041		
Ovary (L)	(mg)	49.2 ± 8.2		46.2 ± 12.2		
	(mg/g)	0.160 ± 0.031		0.148 ± 0.047		
Ovaries	(mg)	101.7 ± 20.5		95.7 ± 22.0		
	(mg/g)	0.332 ± 0.080		0.305 ± 0.083		
Uterus	(mg)	491.7 ± 71.0		603.8 ± 225.7		
	(mg/g)	1.597 ± 0.287		1.878 ± 0.592		
Thyroid gland	(mg)	14.5 ± 1.9		17.0 ± 3.1		
	(mg/g)	0.047 ± 0.005		0.054 ± 0.011		
Adrenal gland (R)	(mg)	31.5 ± 3.0		29.8 ± 5.8		
	(mg/g)	0.102 ± 0.009		0.094 ± 0.018		
Adrenal gland (L)	(mg)	34.3 ± 2.9		34.8 ± 5.0		
	(mg/g)	0.111 ± 0.005		0.110 ± 0.015		
Adrenal glands	(mg)	65.8 ± 5.2		64.6 ± 10.6		
	(mg/g)	0.212 ± 0.013		0.204 ± 0.032		

Each value shows mean ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 31-1-1. Macroscopic findings of male rats at the end of the dosing period

Findings	Dose Grade	Corn oil (control)		2,4-DTAP (10 mg/kg)		2,4-DTAP (50 mg/kg)		2,4-DTAP (100 mg/kg)	
		-	P	-	P	-	P	-	P
Kidney									
Enlargement		8	0	13	0	8	0	2	2
Liver									
Accentuated lobular pattern		8	0	12	1	8	0	4	0
Enlargement		8	0	13	0	6	2	2	2
Lung									
Dark reddish area		8	0	13	0	8	0	3	1
Spleen									
Accessory spleen		8	0	12	1	8	0	4	0
Enlargement		8	0	13	0	8	0	3	1
Thymus									
Small		8	0	12	1	5	3	4	0

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 31-1-2. Macroscopic findings of female rats at the end of the dosing period

Findings	Dose Grade	Corn oil (control)		2,4-DTAP (10 mg/kg)		2,4-DTAP (50 mg/kg)	
		-	P	-	P	-	P
Cecum							
Retention, black content		12	0	10	1	11	0
Ileum							
Diverticulum		11	1	11	0	11	0
Kidney							
Discoloration, pale colored		11	1	10	1	11	0
Liver							
Discoloration, pale colored		11	1	11	0	11	0
Lung							
Dark reddish area, scattered		12	0	11	0	10	1
Spleen							
Discoloration, pale colored		11	1	11	0	11	0
Stomach							
Dark colored spot, mucosa, glandular stomach		11	1	9	2	11	0
Thickening, mucosa, forestomach		12	0	10	1	10	1
Thymus							
Small		10	2	9	2	9	2

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 31-2-1. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Grade	Corn oil (control)		2,4-DTAP (100 mg/kg)	
		-	P	-	P
Liver					
Enlargement		5	0	5	1

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 32-1. Macroscopic findings of male rats at the end of the recovery period

Findings	Dose(mg/kg)	Corn oil (control)		2,4-DTAP (50 mg/kg)	
	Grade	-	P	-	P
All organs and tissues		5		5	

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 32-2. Macroscopic findings of female rats at the end of the recovery period

Findings	Dose(mg/kg)	Corn oil (control)		2,4-DTAP (100 mg/kg)	
	Grade	-	P	-	P
All organs and tissues		5		5	

- : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 33-1-1. Histopathological findings of male rats at the end of the dosing period [H.E. staining]

Findings	Dose Grade	Corn oil (control)						2,4-DTAP (10 mg/kg)						2,4-DTAP (50 mg/kg)						2,4-DTAP (100 mg/kg)									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5														5								4					
Spinal cord		5														5								4					
Pituitary gland		5														5								4					
Submandibular gland		5														5								4					
Sublingual gland		5														5								4					
Lymph node, submandibular		5														5								4					
Thyroid gland		5														5								4					
Parathyroid gland		4							1							5								4					
Thymus		5								1						5								4					
Heart																													
Degeneration/fibrosis, myocardial, focal		3	2	0	0	0										5	0	0	0	0	0			4	0	0	0	0	0
Trachea		5														5								4					
Lung																													
Accumulation, foam cell, alveolus		5	0	0	0	0										5	0	0	0	0	0			3	1	0	0	0	0
Mineralization, focal, arterial wall		5	0	0	0	0										4	1	0	0	0	0			4	0	0	0	0	0
Bronchus		5														5								4					
Liver																													
Fatty change, hepatocyte, periportal		0	4	1	0	0										0	0	1	0	0	0			0	0	3	1	0	0
Microgranuloma		2	3	0	0	0										1	0	0	0	0	0			0	4	0	0	0	0
Pancreas																													
Atrophy, acinar cell, focal, with ductal proliferation		4	1	0	0	0										5	0	0	0	0	0			4	0	0	0	0	0
Cellular infiltration, lymphocyte, around artery		4	1	0	0	0										5	0	0	0	0	0			4	0	0	0	0	0
Stomach		5														5								4					
Duodenum		5														5								4					
Jejunum		5														5								4					
Ileum		5														5								4					

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 33-1-1 (continued). Histopathological findings of male rats at the end of the dosing period [H.E. staining]

Findings	Dose Grade	Corn oil (control)						2,4-DTAP (10 mg/kg)						2,4-DTAP (50 mg/kg)						2,4-DTAP (100 mg/kg)									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Cecum		5														5								4					
Colon		5														5								4					
Rectum		5														5								4					
Lymph node, mesenteric		5														5								4					
Spleen																													
Deposit, pigment, brown		0	5	0	0	0										0	5	0	0	0				0	2	2	0	0	
Hematopoiesis, extramedullary		0	0	5	0	0										0	2	3	0	0				0	1	3	0	0	
Kidney																													
Basophilic tubule, cortex/medulla		5	0	0	0	0										5	0	0	0	0				0	0	4	0	0	**,##
Basophilic tubule, cortex		3	2	0	0	0										3	2	0	0	0				4	0	0	0	0	
Cast, hyalin, cortex/medulla		5	0	0	0	0										5	0	0	0	0				1	3	0	0	0	#
Cyst, cortico-medullary junction		4				1										5				0				3				1	
Urinary bladder		5														5								4					
Adrenal gland		5														5								4					
Testis		5														5								4					
Epididymis		5														5								4					
Prostate																													
Cellular infiltration, lymphocyte, interstitial		2	3	0	0	0										3	2	0	0	0				2	0	2	0	0	
Seminal vesicle		5														5								4					
Coagulating gland		5														5								4					
Eyeball		5														5								4					
Harderian gland		5														5								4					
Sciatic nerve		5														5								4					
Skeletal muscle		5														5								4					
Femur		5														5								4					
Marrow, femur		5														5								4					

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

** P<0.01 : Significantly different from control. (Two-tailed Mann -Whitney U test)

P<0.05, ## P<0.01 : Significantly different from control. (One-tailed Fisher exact test)

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 33-1-2. Histopathological findings of female rats at the end of the dosing period [H.E. staining]

Findings	Dose Grade	Corn oil (control)						2,4-DTAP (10 mg/kg)						2,4-DTAP (50 mg/kg)										
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE		
Brain		5													5									
Spinal cord		5													5									
Pituitary gland		5													5									
Submandibular gland		5													5									
Sublingual gland		5													5									
Lymph node, submandibular Atrophy, follicle		3	2	0	0	0									5	0	0	0	0	0				
Thyroid gland		5													5									
Parathyroid gland		5													5									
Thymus Atrophy		2	0	1	2	0				0	0	0	1	1		3	1	1	0	0				
Heart Degeneration/fibrosis, myocardial, focal		4	1	0	0	0									5	0	0	0	0	0				
Trachea		5													5									
Lung Accumulation, foam cell, alveolus		5	0	0	0	0									4	2	0	0	0	0				
Bronchus		5													5									
Liver Fatty change, hepatocyte, periportal		5	0	0	0	0									3	2	0	0	0	0				
Microgranuloma		4	1	0	0	0									2	3	0	0	0	0				
Vacuolation, hepatocyte, midzonal		2	1	0	2	0									5	0	0	0	0	0				
Pancreas		5													5									
Stomach Edema, submucosa, forestomach		5	0	0	0	0				1	0	1	0	0		4	0	1	0	0				
Erosion, mucosa, glandular stomach		4	1	0	0	0				1	1	0	0	0		5	0	0	0	0				
Hyperplasia, squamous cell, mucosa, forestomach		5	0	0	0	0				1	0	1	0	0		4	1	0	0	0				
Ulcer, mucosa, forestomach		5	0	0	0	0				1	1	0	0	0		5	0	0	0	0				
Duodenum		5													5									

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 33-1-2 (continued). Histopathological findings of female rats at the end of the dosing period [H.E. staining]

Findings	Dose Grade	Corn oil (control)						2,4-DTAP (10 mg/kg)						2,4-DTAP (50 mg/kg)										
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE		
Jejunum		5														5								
Ileum																								
Diverticulum		5							1							5						0		
Cecum		5														5								
Colon		5														5								
Rectum		5														5								
Lymph node, mesenteric																								
Atrophy, follicle		4	1	0	0	0										5	0	0	0	0	0			
Spleen																								
Decrease, red pulp		4	0	1	0	0										5	0	0	0	0	0			
Deposit, pigment, brown		0	0	4	1	0										0	1	4	0	0	0			
Hematopoiesis, extramedullary		0	1	3	1	0										0	0	1	4	0				
Kidney																								
Basophilic tubule, cortex		0	4	1	0	0										0	0	1	0	0	0			
Cast, hyalin, cortex/medulla		4	0	1	0	0										1	0	0	0	0	0			
Degeneration/necrosis, proximal tubular epithelium, cortex		2	1	2	0	0										0	0	1	0	0	0			
Urinary bladder		5														5								
Adrenal gland		5														5								
Ovary		5														5								
Uterus		5														5								
Vagina		5														5								
Eyeball		5														5								
Harderian gland		5														5								
Sciatic nerve		5														5								
Skeletal muscle		5														5								
Femur		5														5								
Marrow, femur		5														5								

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 33-2. Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Findings	Dose Grade	Corn oil (control)						2,4-DTAP (100 mg/kg)							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain															
Cellular infiltration, lymphocyte, choroid plexus, ventricle		5	0	0	0	0			5	1	0	0	0		
Spinal cord		5							6						
Pituitary gland		5							6						
Submandibular gland		5							6						
Sublingual gland		5							6						
Lymph node, submandibular		5							6						
Thyroid gland															
Ectopic thymus		5				0			5				1		
Parathyroid gland		4					1		5				1		
Thymus		5							6						
Heart		5							6						
Trachea		5							6						
Lung															
Accumulation, foam cell, alveolus		3	2	0	0	0			6	0	0	0	0		
Mineralization, focal, arterial wall		4	1	0	0	0			6	0	0	0	0		
Bronchus		5							6						
Liver															
Fatty change, hepatocyte, periportal		4	1	0	0	0			5	1	0	0	0		
Microgranuloma		3	2	0	0	0			4	2	0	0	0		
Pancreas															
Atrophy, acinar cell, focal, with ductal proliferation		5	0	0	0	0			5	1	0	0	0		
Stomach		5							6						
Duodenum		5							6						
Jejunum		5							6						

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 33-2 (continued). Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Findings	Dose Grade	Corn oil (control)						2,4-DTAP (100 mg/kg)						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Ileum		5							6					
Cecum		5							6					
Colon		5							6					
Rectum		5							6					
Lymph node, mesenteric		5							6					
Spleen														
Deposit, pigment, brown		0	0	5	0	0			0	0	5	1	0	
Hematopoiesis, extramedullary		0	1	4	0	0			0	2	4	0	0	
Kidney														
Basophilic tubule, cortex		2	3	0	0	0			0	1	5	0	0	
Calculus, pelvis		4	1	0	0	0			6	0	0	0	0	
Cyst, cortico-medullary junction		5					0		5				1	
Hyperplasia, transitional cell, pelvis		4	0	1	0	0			6	0	0	0	0	
Mineralization, cortex/medulla		5	0	0	0	0			5	1	0	0	0	
Urinary bladder		5							6					
Adrenal gland		5							6					
Ovary		5							6					
Uterus		5							6					
Vagina		5							6					
Eyeball		5							6					
Harderian gland		5							6					
Sciatic nerve		5							6					
Skeletal muscle		5							6					
Femur		5							6					
Marrow, femur		5							6					

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

* P<0.05 : Significantly different from control. (Two-tailed Mann -Whitney U test)

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 34. Histopathological findings of female rats at the end of the recovery period [H.E. staining]

Findings	Dose Grade	Corn oil (control)						2,4-DTAP (100 mg/kg)						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Brain							5							
Spinal cord							5							
Pituitary gland							5							
Submandibular gland							5							
Sublingual gland							5							
Lymph node, submandibular							5							
Thyroid gland							5							
Parathyroid gland							5							
Thymus							5							
Heart							5							
Trachea							5							
Lung														
Metaplasia, osseous, focal							4	1	0	0	0			
Bronchus							5							
Liver														
Fatty change, hepatocyte, periportal							3	2	0	0	0			
Microgranuloma							2	3	0	0	0			
Necrosis, focal, subserosa							4	1	0	0	0			
Pancreas														
Atrophy, acinar cell, focal, with ductal proliferation							3	2	0	0	0			
Stomach							5							
Duodenum							5							
Jejunum							5							

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 34 (continued). Histopathological findings of female rats at the end of the recovery period [H.E. staining]

Findings	Dose Grade	Corn oil (control)						2,4-DTAP (100 mg/kg)						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Ileum								5						
Cecum								5						
Colon								5						
Rectum								5						
Lymph node, mesenteric								5						
Spleen														
Deposit, pigment, brown								0	0	1	4	0		
Hematopoiesis, extramedullary								0	1	4	0	0		
Kidney														
Basophilic tubule, cortex	4	1	0	0	0			1	4	0	0	0		
Cast, hyalin, cortex/medulla	5	0	0	0	0			4	1	0	0	0		
Mineralization, cortico-medullary junction	5	0	0	0	0			4	1	0	0	0		
Urinary bladder								5						
Adrenal gland								5						
Ovary								5						
Uterus								5						
Vagina								5						
Eyeball								5						
Harderian gland								5						
Sciatic nerve								5						
Skeletal muscle								5						
Femur								5						
Marrow, femur								5						

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 35. Results of observations about estrous cycle

Dose	Corn oil (vehicle)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg	2,4-DTAP 100 mg/kg
Number of animals examined	13	13	13	13
<u>Pre-treatment period</u>				
Number of animals showing type of cycle				
4-day cycle	8	10	11	11
4 and 5-day cycle	2	1	0	2
5-day cycle	3	2	2	0
Mean length of estrous cycle in days; Mean±S.D. (N)	4.3 ± 0.4 (13)	4.2 ± 0.4 (13)	4.2 ± 0.4 (13)	4.1 ± 0.2 (13)
<u>Treatment period</u>				
Number of animals showing each type of cycle				
4-day cycle	8	10	11	5
4 and 5-day cycle	2	1	2	0
5-day cycle	2	2	0	0
Irregular cycle	1	0	0	0
Mean length of estrous cycle in days; Mean±S.D. (N)	4.2 ± 0.4 (13)	4.2 ± 0.4 (13)	4.1 ± 0.2 (13)	4.0 ± 0.0 (5)
Frequency of animals of which type of estrus cycle was changed after the treatment	3 / 13	0 / 13	2 / 13	2 / 5
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.0 ± 0.0 (13)	1.0 ± 0.0 (13)	1.0 ± 0.0 (13)	

Significantly different from the control group (*: p<0.05, **: p<0.01).

Figures in parentheses indicate the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 36. Results of observations about reproductive performance

Dose	Corn oil (vehicle)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg
Number of mated pares [A]	13	13	13
Number of copulated pares [B]	13	13	13
Copulation index [(B/A)×100, %]	100.0	100.0	100.0
Number of fertile males [C]	13	12	13
Fertility index [(C/B)×100, %]	100.0	92.3	100.0
Paring days until copulation ; Mean±S.D. (N)	2.7 ± 1.4 (13)	2.5 ± 1.1 (13)	2.8 ± 1.1 (13)

Significantly different from the control group (*: p<0.05, **: p<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 37. Observation of offspring (F₁)

Group	Corn oil (control)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg
Number of dams	13	11	12
Gestation length (days)			
Mean ± S.D. per dam	22.5 ± 0.5	22.5 ± 0.5	22.3 ± 0.5
Number of corpora lutea			
Total	202	197	208
Mean ± S.D. per dam	15.5 ± 1.5	16.4 ± 1.4 (12)	16.0 ± 2.0 (13)
Number of implantation scars			
Total	199	193	200
Mean ± S.D. per dam	15.3 ± 1.5	16.1 ± 1.3 (12)	15.4 ± 2.5 (13)
Implantation index (%) ^{a)}	98.6 ± 3.7	98.1 ± 2.9 (12)	96.0 ± 7.4 (13)
Delivery index (dams, %) ^{b)}	100.0	91.7	92.3
Number of offspring at birth			
Total	186	162	175
Mean ± S.D. per dam	14.3 ± 1.5	14.7 ± 1.7	14.6 ± 2.8
Number of live offspring at birth			
Male	88	74	76
Female	98	77	81
Total	186	151	157
Mean ± S.D. per dam	14.3 ± 1.5	13.7 ± 2.3	13.1 ± 3.9
Sex ratio ^{c)}			
Mean ± S.D. per dam	0.48 ± 0.11	0.48 ± 0.12	0.50 ± 0.17
Number of dead offspring			
Total	0	11	18
Mean ± S.D. per dam	0.0 ± 0.0	1.0 ± 1.8	1.5 ± 3.8
Delivery index (offspring) ^{d)}			
Mean% ± S.D. per dam	93.5 ± 4.5	92.0 ± 7.5	93.7 ± 7.0
Birth index ^{e)}			
Mean% ± S.D. per dam	93.5 ± 4.5	85.6 ± 10.7	84.8 ± 21.3
Live birth index ^{f)}			
Mean% ± S.D. per dam	100.0 ± 0.0	93.4 ± 11.9	90.9 ± 22.2
Number of offspring on day 4			
Male	79	69	71
Female	87	71	76
Sex ratio ^{c)}			
Mean ± S.D. per dam	0.48 ± 0.11 (12)	0.48 ± 0.15	0.48 ± 0.16 (11)
Viability index ^{g)}			
Mean% ± S.D. per dam	90.2 ± 27.7	92.1 ± 14.3	88.5 ± 28.5
Number of external abnormalities ^{h)}	0	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

Significantly different from the control group (*: P<0.05, **: P<0.01).

a): (Number of implantation scars/Number of corpora lutea)×100.

b): (Number of dams with live offspring/number of pregnant dams)×100.

c): Number of male offspring/(number of male offspring + number of female offspring).

d): (Number of offspring at birth/Number of implantation scars)×100.

e): (Number of live offspring at birth/number of implantation scars)×100.

f): (Number of live offspring at birth/number of offspring at birth)×100.

g): (Number of live offspring 4 days after birth/number of live offspring at birth)×100.

h): Number of external abnormalities in live offspring at birth.

Figures in parentheses indicate number of dams.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 38. Body weights of offspring (F_1) before weaning

Group	Corn oil (control)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg
Number of dams	13	11	12
Male			
Days after birth			
0	7.0 ± 0.5	6.6 ± 0.7	6.6 ± 0.7
4	9.9 ± 1.7 (12)	10.3 ± 2.5	10.4 ± 1.9 (11)
Number of dams	13	11	12
Female			
Days after birth			
0	6.6 ± 0.6	6.3 ± 0.7	6.1 ± 0.7
4	9.4 ± 1.7 (12)	10.1 ± 2.4	10.0 ± 1.7 (11)

Each value shows mean ± S.D. per dam. (g).

Figures in parentheses indicate number of dams.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 39. General conditions in offspring (F₁) before weaning

Group	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
Corn oil (control)	Number of offspring	186	186	185	183	172
	General appearance, No abnormality	186	185	183	172	166
	General appearance, Death		1	2	11	6
2,4-DTAP 10 mg/kg	Number of offspring	151	151	144	142	140
	General appearance, No abnormality	151	144	142	140	140
	General appearance, Death		7	2	2	
2,4-DTAP 50 mg/kg	Number of offspring	157	153	149	148	148
	General appearance, No abnormality	157	149	148	148	147
	General appearance, Death		4	1		1

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Table 40. Morphological observations of offspring (F₁)

Dose	Corn oil (control)	2,4-DTAP 10 mg/kg	2,4-DTAP 50 mg/kg
Dead offspring			
Number of dead offspring ^{a)}	20	22	24
Number of missing offspring	4	5	5
Number of dead offspring examined	16 (12) ^{b)}	17 (3) ^{b)}	19 (13) ^{b)}
Number of dead offspring with external changes	0	0	0
Number of dead offspring with visceral changes	0	0	0
Live offspring			
Number of live offspring examined (postnatal day 0)	186	151	157
Number of live offspring with external changes	0	0	0
Number of live offspring examined (postnatal day 4)	166	140	147 ^{c)}
Number of live offspring with external changes	0	0	0
Number of live offspring with visceral changes	0	0	0

Significantly different from the control group (*: p<0.05, **: p<0.01).

a) including missing offspring

b) Parenthesis indicates the number of offspring not examined because of their autolysis.

c) Four offspring were autopsied on the postnatal day 0, when their dam was sacrificed for moribundity.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 1-1-1. General conditions of male rats

Corn oil (control)

Male No.	Days of administration																									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

g: Skin, Crust formation, Posterior neck.

Appendix 1-1-1 (continued). General conditions of male rats

Corn oil (control)

Male No.	Days of administration																									
	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	Pre	Post	Pre	Post	Pre	Post	Pre	Post
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01008	g	g	g	g	g	g	g	g	g	g	g	g	g	g	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8
-	12	12	12	12	12	12	12	12	12	12	12	12	13	13	13	13	13	13	13	13	13	13	13	13	13	8
g	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

g: Skin, Crust formation, Posterior neck.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 1-1-2. General conditions of male rats

2,4-DTAP 10 mg/kg

Male No.	Days of administration																										
	1 Pre	2 Post	3 Pre	4 Post	5 Pre	6 Post	7 Pre	8 Post	9 Pre	10 Post	11 Pre	12 Post	13 Pre	14 Post	15 Pre	16 Post	17 Pre	18 Post	19 Pre	20 Post	21 Pre	22 Post	23 Pre	24 Post	25 Pre	Post	
M02001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	-
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	-

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1-1-2 (continued). General conditions of male rats

2,4-DTAP 10 mg/kg

Male No.	Days of administration																									
	26 Pre	27 Post	28 Pre	29 Post	30 Pre	31 Post	32 Pre	33 Post	34 Pre	35 Post	36 Pre	37 Post	38 Pre	39 Post	40 Pre	41 Post	42 Pre	43 Post	Pre	Post	Pre	Post	Pre	Post		
M02001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 1-1-3. General conditions of male rats

2,4-DTAP 50 mg/kg

Male No.	Days of administration																									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
M03001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	c	
M03003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	c	c	
M03011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	12
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Mouth, Salivation.

Appendix 1-1-3 (continued). General conditions of male rats

2,4-DTAP 50 mg/kg

Male No.	Days of administration																										
	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43									
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
M03001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	c	-		
M03003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03010	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-		
M03011	-	o	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-		
M03012	-	-	c	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	8		
-	13	11	13	11	13	11	13	12	13	11	13	11	13	11	13	11	13	10	13	11	13	11	13	11	13	10	
c	0	2	0	2	0	2	0	1	0	2	0	2	0	2	0	2	0	3	0	2	0	2	0	2	0	3	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 1-1-4. General conditions of male rats

2,4-DTAP 100 mg/kg

Male No.	Days of administration																										
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25		
M04001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04003	-	-	-	-	-	d	b	a,d,m	a,b,m	f	-	-	d	b	d,h	b	a,d,h	a,b,c,q	a,d,e,h	a,b,e,k	f	-	-	-	-		
M04004	-	-	-	-	-	-	-	-	-	-	-	-	b	-	-	-	-	-	-	-	-	-	-	-	-		
M04005	-	-	-	-	-	-	b	-	-	-	-	-	b	-	-	s,d,h,k	a,b,e,j,k	f	-	-	-	-	-	-	-	-	
M04006	-	-	-	-	-	-	-	-	i	-	-	b	a,d,j	a,b,j,n,o,p,r	-	-	-	-	-	-	-	-	-	-	-	-	
M04007	-	-	-	-	-	d	a,l	a,b	f	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04008	-	-	-	-	-	-	b	a,d,i	a,b	f	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04011	-	-	-	-	-	-	b	a,d	a,b	a,d,e,n,o,s	-	-	b	a	a,b	a,d,h	a,b	a,b,d,h	a,b,c	f	-	-	-	-	-	-	
M04012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04013	-	i	-	-	-	b	a,l	a,b	f	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	13	13	13	13	13	13	13	13	13	13	12	12	8	8	8	8	8	7	7	6	6	5	5	4	4	4	
-	13	13	12	13	13	13	13	12	10	8	8	7	7	6	4	5	4	4	4	3	4	4	4	3	4	4	4
a	0	0	0	0	0	0	0	0	1	4	4	1	0	1	2	2	3	3	2	1	1	0	0	0	0	0	0
b	0	0	0	0	0	0	0	1	0	5	0	4	0	1	0	4	0	3	0	2	1	1	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0	1
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	2	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
i	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
k	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
l	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
m	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
n	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
o	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
p	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
q	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
r	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
s	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Anorectal region, Soiled perineal region.

b: Behavior, Decrease in locomotor activity.

c: Mouth, Salivation.

d: Excretion, Decrease in amount of feces.

e: General appearance, Emaciation.

f: General appearance, Death.

g: Skin, Crust formation.

h: Excretion, Blackish feces.

i: Excretion, Loose stool.

j: Eye, Eyeball, Bulbi, Globe, Laceration.

k: Excretion, Reddish urine.

l: Excretion, No-feces.

m: Eye, Eyeball, Bulbi, Globe, Reddish tear.

n: General appearance, Moribundity.

o: Body temperature, Hypothermia.

p: Posture, Body position, Lateral position.

q: Fur, Hair, Coat, Pilorection.

r: Breathing, Bradypnea.

s: Behavior, Loss of locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 1-1-4 (continued). General conditions of male rats

2,4-DTAP 100 mg/kg

Male No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post						
M04001	-	-	-	c	-	-	-	c	-	c	-	-	c	-	c	-	c	-	c	-	c	-	c	-	-	-	-	c	-	-	-					
M04004	-	c	-	c	-	c	-	c	-	c	-	-	c	-	c	-	-	c	-	c	-	c	-	c	-	c	-	c	-	c	-					
M04009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
M04010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Number of males	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4					
-	4	3	4	2	4	3	4	2	4	2	4	3	4	3	4	2	4	2	4	3	4	2	4	2	4	3	4	3	4	2	4	3				
c	0	1	0	2	0	1	0	2	0	2	0	1	0	1	0	2	0	2	0	1	0	2	0	2	0	1	0	1	0	2	0	1				

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

c: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 1-2-1. General conditions of male rats at the recovery period

Corn oil (control)

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 1-2-2. General conditions of male rats at the recovery period

2,4-DTAP 50 mg/kg

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M03009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-1-1. General conditions of female rats

Corn oil (control)

Female No.	Days of administration																					
	1		2		3		4		5		6		7		8		9		10		11	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 2-1-1 (continued). General conditions of female rats

Corn oil (control)

Female No.	Days of administration																					
	12		13		14		15		16		17		18		19							
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	13	13	13	13	13	13	13	13	13	13	10	10	6	6	5	5	1	1				
	-	13	13	13	13	13	13	13	13	13	10	10	6	6	5	5	1	1				

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-1-2. General conditions of female rats

2,4-DTAP 10 mg/kg

Female No.	Days of administration											
	1		2		3		4		5		6	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02001	-	-	-	-	-	-	-	-	-	-	-	-
F02002	-	-	-	-	-	-	-	-	-	-	-	-
F02003	-	-	-	-	-	-	-	-	-	-	-	-
F02004	-	-	-	-	-	-	-	-	-	-	-	-
F02005	-	-	-	-	-	-	-	-	-	-	-	-
F02006	-	-	-	-	-	-	-	-	-	-	-	-
F02007	-	-	-	-	-	-	-	-	-	-	-	-
F02008	-	-	-	-	-	-	-	-	-	-	-	-
F02009	-	-	-	-	-	-	-	-	-	-	-	-
F02010	-	-	-	-	-	-	-	-	-	-	-	-
F02011	-	-	-	-	-	-	-	-	-	-	-	-
F02012	-	-	-	-	-	-	-	-	-	-	-	-
F02013	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	13	13	13	13	13	13	13	13	13	13	13	13
	-	13	13	13	13	13	13	13	13	13	13	13

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 2-1-2 (continued). General conditions of female rats

2,4-DTAP 10 mg/kg

Female No.	Days of administration											
	12		13		14		15		16		17	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02001	-	-	-	-	-	-	-	-	-	-	-	-
F02002	-	-	-	-	-	-	-	-	-	-	-	-
F02003	-	-	-	-	-	-	-	-	-	-	-	-
F02004	-	-	-	-	-	-	-	-	-	-	-	-
F02005	-	-	-	-	-	-	-	-	-	-	-	-
F02006	-	-	-	-	-	-	-	-	-	-	-	-
F02007	-	-	-	-	-	-	-	-	-	-	-	-
F02008	-	-	-	-	-	-	-	-	-	-	-	-
F02009	-	-	-	-	-	-	-	-	-	-	-	-
F02010	-	-	-	-	-	-	-	-	-	-	-	-
F02011	-	-	-	-	-	-	-	-	-	-	-	-
F02012	-	-	-	-	-	-	-	-	-	-	-	-
F02013	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	13	13	13	13	13	13	13	10	10	6	6	3
	-	13	13	13	13	13	13	10	10	6	6	3
												0
												0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-1-3. General conditions of female rats

2,4-DTAP 50 mg/kg

Female No.	Days of administration																					
	1		2		3		4		5		6		7		8		9		10		11	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03 001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 2-1-3 (continued). General conditions of female rats

2,4-DTAP 50 mg/kg

Female No.	Days of administration																					
	12		13		14		15		16		17		18		19							
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F03 001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03 013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	13	13	13	13	13	13	13	13	13	11	11	8	8	4	4	0	0	0	0	0	0	0
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-1-4. General conditions of female rats

2,4-DTAP 250 mg/kg

Female No.	Days of administration																					
	1		2		3		4		5		6		7		8		9		10		11	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04002	-	-	g	-	-	-	-	-	-	-	c	-	a,b,c	a,b,d,f	e	-	-	-	-	-	-	-
F04003	-	-	-	-	b,p	-	-	-	-	-	-	-	-	-	a,c	a,b	a,b,c,d,h,j,l	-	-	-	-	-
F04004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04005	-	-	-	-	a	a	a	a	a,m,n	a,b,f,k,m	a,c	a,b,f,m	e	-	-	-	-	-	-	-	-	-
F04006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04007	-	-	-	-	-	-	-	-	a,c	a,b	a,c,i	a,b,i	a,c,i	a,b,d,f,i	e	-	-	-	-	-	-	-
F04008	-	-	-	-	-	-	-	-	a,c	a,b,k	a,c	a,b	e	a,b,d,f,j	-	-	-	-	-	-	-	-
F04009	-	-	-	-	-	-	-	-	a,c	a,b	a,c	a	a,c	a,b,d,f,j	-	-	-	-	-	-	-	-
F04010	-	-	-	-	-	-	-	-	c	b	a,b,d,h,n	a,b,d,h	e	-	-	-	-	-	-	-	-	-
F04011	-	-	-	-	g	-	-	-	b	a,c	a,b	e	-	-	-	-	-	-	-	-	-	-
F04012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	13	13	13	13	13	13	13	13	13	13	13	12	12	9	8	6	6	5	5	5	5	5
-	13	13	11	13	12	11	12	11	7	7	6	7	6	5	5	5	5	5	5	5	5	5
a	0	0	0	0	1	1	1	1	5	5	5	5	3	3	1	1	1	0	0	0	0	0
b	0	0	0	0	0	1	0	1	0	6	1	4	1	3	0	1	1	0	0	0	0	0
c	0	0	0	0	0	0	0	0	5	0	5	0	3	0	1	0	1	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	1	1	0	3	0	0	1	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	1	0	3	0	2	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	1	0	1	0	3	0	0	0	0	0	0	0
g	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
k	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0
l	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
m	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0
n	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0
p	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Anorectal region, Soiled perineal region.

b: Behavior, Decrease in locomotor activity.

c: Excretion, Decrease in amount of feces.

d: Body temperature, Hypothermia.

e: General appearance, Death.

f: Fur, Hair, Coat, Piloerection.

g: Excretion, Loose stool.

h: Eye, Eyeball, Bulbi, Globe, Lacrimation.

i: Excretion, Reddish urine.

j: General appearance, Moribundity.

k: Excretion, Mucous feces.

l: General appearance, Emaciation.

m: Nose, Smudge of perinasal area.

n: Excretion, No-feces.

p: Mouth, Salivation.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-2-1. General conditions of female rats, satellite group

Corn oil (control)

Female No.	Days of administration																					
	1		2		3		4		5		6		7		8		9		10		11	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F05001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 2-2-1 (continued). General conditions of female rats, satellite group

Corn oil (control)

Female No.	Days of administration																										
	12		13		14		15		16		17		18		19		20		21		22		23		24		25
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F05001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-2-1 (continued). General conditions of female rats, satellite group

Female No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post						
F05001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F05002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F05003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F05004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F05005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F05006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F05007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F05008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F05009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F05010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5						
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5							

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-2-2. General conditions of female rats, satellite group

2,4-DTAP 250 mg/kg

Female No.	Days of administration																						
	1		2		3		4		5		6		7		8		9		10		11		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F06001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06002	-	-	-	-	-	-	-	-	-	-	-	-	a	a,b	a,b,c	a,b,d,j,l	-	-	-	-	-	-	-
F06003	-	-	-	-	-	-	-	-	-	-	-	-	a	a,b	a,b,c	a,b,d,j,l,o	-	-	-	-	-	-	-
F06004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06005	-	-	-	-	-	-	-	-	-	-	-	-	q	e	-	-	-	-	-	-	-	-	
F06006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06008	-	-	-	-	-	-	-	-	-	-	k	-	a,c,k	a,b,d	e	-	-	-	-	-	-	-	
F06009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06010	-	g	-	-	-	-	-	-	-	-	g	-	-	-	-	-	-	-	-	-	-	-	
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	9	9	8	6	6	6	6	6	6	6	
-	10	10	9	10	10	10	10	10	10	10	9	8	6	6	6	6	6	6	6	6	6	6	
a	0	0	0	0	0	0	0	0	0	0	0	0	3	3	2	2	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	3	2	2	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	0	0	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
l	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
k	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0
g	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
o	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
q	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Anorectal region, Soiled perineal region.

b: Behavior, Decrease in locomotor activity.

c: Excretion, Decrease in amount of feces.

d: Body temperature, Hypothermia.

e: General appearance, Death.

g: Excretion, Loose stool.

j: General appearance, Moribundity.

k: Excretion, Mucous feces.

l: General appearance, Emaciation.

o: Eye, Eyeball, Bulbi, Globe, Reddish tear.

q: Eye, Eyeball, Bulbi, Globe, Lacrimation.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-2-2 (continued). General conditions of female rats, satellite group

2,4-DTAP 100 mg/kg

Female No.	Days of administration																										
	12		13		14		15		16		17		18		19		20		21		22		23		24		25
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F04001	-	-	-	-	-	-	-	p	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06001	-	-	-	-	-	-	-	-	-	-	-	-	p	-	-	-	p	-	p	-	p	-	p	-	p	-	
F06004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	p	-	p	-	-	-	-	-	-	
F06007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	p	-	-	-	-	-	-	-	-	
F06009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
-	11	11	11	11	11	11	11	10	11	11	10	11	10	11	11	11	11	8	11	9	11	8	11	9	11	10	
p	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	3	0	2	0	3	0	2	0	1		

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

p: Mouth, Salivation.

Appendix 2-2-2 (continued). General conditions of female rats, satellite group

2,4-DTAP 100 mg/kg

Female No.	Days of administration																												
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
F04001	-	-	-	-	-	-	-	-	p	-	p	-	-	p	-	p	-	p	-	p	-	p	-	p	-	p	-		
F04004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04012	-	-	-	-	-	-	-	-	-	-	p	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F06001	-	p	-	p	-	p	-	p	-	p	-	p	-	p	-	p	-	p	-	p	-	p	-	p	-	p	-		
F06004	-	-	-	-	-	-	-	-	-	-	g	-	-	g	-	-	-	-	g	-	-	-	-	-	-	-	-		
F06006	-	-	-	-	-	-	-	-	-	-	-	p	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F06007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	p	-	-	-	-	-			
F06009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F06010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Number of females	11	6	11	6	11	6	11	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			
-	11	5	11	5	11	5	11	5	5	5	5	5	11	4	5	5	11	5	5	5	11	4	11	5	11	5			
p	0	1	0	1	0	1	0	1	0	1	0	2	0	1	0	1	0	1	0	1	0	1	0	1	0	1			
g	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0			

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

p: Mouth, Salivation.

g: Excretion, Loose stool.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-3-1. General conditions of female rats at the recovery period

Corn oil (control)

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F05006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 2-3-2. General conditions of female rats at the recovery period

2,4-DTAP 100 mg/kg

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F04012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 3-1. General conditions in dams during pregnancy

Corn oil (control)

Dam No.	Days of pregnancy													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01013	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 3-1 (continued). General conditions in dams during pregnancy

Corn oil (control)

Dam No.	Days of pregnancy												
	14	15	16	17	18	19	20	21	22	Pre	Post	Pre	Post
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Pre	Post	Pre	Post	Pre
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-
F01013	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	7
-	13	13	13	13	13	13	13	13	13	13	13	13	7

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 3-2. General conditions in dams during pregnancy

2,4-DTAP 10 mg/kg

Dam No.	Days of pregnancy																											
	0		1		2		3		4		5		6		7		8		9		10		11		12		13	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02012	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 3-2 (continued). General conditions in dams during pregnancy

2,4-DTAP 10 mg/kg

Dam No.	Days of pregnancy																											
	14		15		16		17		18		19		20		21		22		23		24		25		26			
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b	-		
F02002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02012	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	->	
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	

>: Excluded from analysis (not pregnant)

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

b: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 3-3. General conditions in dams during pregnancy

2,4-DTAP 50 mg/kg

Dam No.	Days of pregnancy																										
	0		1		2		3		4		5		6		7		8		9		10		11		12		13
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F03001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 3-3 (continued). General conditions in dams during pregnancy

2,4-DTAP 50 mg/kg

Dam No.	Days of pregnancy																										
	14		15		16		17		18		19		20		21		22										
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post										
F03001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F03002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Number of dams	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	5	4						
-	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	4	4					
a	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0					

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

b: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 4-1. General conditions in dams during lactation

Corn oil (control)

Dam No.	Days of lactation									
	0		1		2		3		4	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01001	-	-	-	-	-	-	-	-	-	-
F01002	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	a	a	-
F01005	-	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-
F01009	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-
F01013	-	-	-	-	-	-	-	-	-	-
Number of dams	13	13	13	13	13	13	13	13	12	12
-	13	13	13	13	13	13	13	12	11	12
a	0	0	0	0	0	0	0	1	1	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Anorectal region, Soiled perineal region.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 4-2. General conditions in dams during lactation

2,4-DTAP 10 mg/kg

Dam No.	Days of lactation									
	0		1		2		3		4	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02002	-	-	-	-	-	-	-	-	-	-
F02003	-	-	-	-	-	-	-	-	-	-
F02004	-	-	-	-	-	-	-	-	-	-
F02005	-	-	-	-	-	-	-	-	-	-
F02006	-	-	-	-	-	-	-	-	-	-
F02007	-	-	-	-	-	-	-	-	-	-
F02008	-	-	-	-	-	-	-	-	-	-
F02009	-	-	-	-	-	-	-	-	-	-
F02010	-	-	-	-	-	-	-	-	-	-
F02011	-	-	-	-	-	-	-	-	-	-
F02013	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11
-	11	11	11	11	11	11	11	11	11	11

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 4-3. General conditions in dams during lactation

2,4-DTAP 50 mg/kg

Dam No.	Days of lactation									
	0		1		2		3		4	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03001	-	-	-	-	-	-	-	-	-	-
F03003	-	-	-	-	-	-	-	-	-	-
F03004	-	-	-	-	-	-	-	-	-	-
F03005	-	-	-	-	-	-	-	-	-	-
F03006	-	-	-	-	-	-	-	-	-	-
F03007	-	-	-	-	-	-	-	-	-	-
F03008	-	-	-	-	-	-	-	-	-	-
F03009	-	-	-	-	-	-	-	-	-	-
F03010	-	-	-	-	-	-	-	-	-	-
F03011	a,b,c,d,e,f									
F03012	-	-	-	-	-	-	-	-	-	-
F03013	-	-	-	-	-	-	-	-	-	-
Number of dams	12	11	11	11	11	11	11	11	11	11
-	11	11	11	11	11	11	11	11	11	11
a	1	0	0	0	0	0	0	0	0	0
b	1	0	0	0	0	0	0	0	0	0
c	1	0	0	0	0	0	0	0	0	0
d	1	0	0	0	0	0	0	0	0	0
e	1	0	0	0	0	0	0	0	0	0
f	1	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Anorectal region, Soiled perineal region.

b: General appearance, Emaciation.

c: Body temperature, Hypothermia.

d: Fur, Hair, Coat, Piloerection.

e: Skin, Pale skin.

f: General appearance, Moribundity.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-1. Detailed clinical observations of male rats

Corn oil (control)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, exophthalmos, pupillary size, salivation), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary reflex), c) Open-field observations (posture, exploration, palpebral opening, tremor, convolution, tremor, convulsion, stereotypy, bizarre tail, vocalization, touch response, withdrawal reflex, piloerection reflex).

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2: normal; 1: no resistance; 3: resistance]

Heart beats [3 normal; 1 bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Body temperature [2, normal; 1,
Eur. 1/2, normal; 1 Soiled fur 1.

Skin color / Mucous membranes [2: normal; 1: abnormal]

Lacrimation (Reddish tear) [2, not observed; 3, observed, slight]

Ribcavation [2, normal; 3, slight]

Respiratory rate [2, normal; 3, hypopneic]

Gait [2, normal; 3, tip-toe gait].

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-1 (continued). Detailed clinical observations of male rats

Corn oil (control)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation) and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, strabismus, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

I locomotor in home cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity].

Locomotor in home-cage [2, normal; 1, decrease in locomotor
Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [3 normal; 1 bradycardia]

Body temperature [2: normal; 1: decrease of temperature]

Body temperature [2, normal, 1]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation/Reddish tear) [2 , not observed; 3 , observed slight; 4 , observed severe])

Lachrymation (reddish tear) [2, hot
Piloerection [2, normal; 3, slight]

Piloerection [2, normal; 3, slight]

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Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-1 (continued). Detailed clinical observations of male rats

Corn oil (control)

Male No.	Open-field observations ^{c)}										Defecation							
	Urination								Defecation									
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	R7 ^{f)}	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14
M01001	0	0	0	1	0	0	1			0	0	0	0	0	0	0	0	0
M01002	0	0	0	0	0	1	0			0	0	0	0	0	0	0	0	0
M01003	0	0	0	0	0	1	0			0	0	1	0	0	0	0	0	0
M01004	1	0	0	0	0	0	0			1	0	0	0	0	0	0	0	0
M01005	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	0
M01006	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	0
M01007	1	1	0	1	1	1	0			0	0	0	0	0	0	0	0	0
M01008	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	0
M01009	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
M01010	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01011	1	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0
M01012	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
M01013	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0
Total	4	2	1	3	1	4	2	0	3	1	0	1	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-2. Detailed clinical observations of male rats

2,4-DTAP (10 mg/kg)

Male No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}										Body temperature										Fur								
	Posture in home-cage					Locomotor in home-cage					Handling behavior					Heart beats					Pre T7 T14 T21 T28 T30 T36 T42					Pre T7 T14 T21 T28 T30 T36 T42					Pre T7 T14 T21 T28 T30 T36 T42								
	Pre	T7	T14	T21	T30	T36	T42	Pre	T7	T14	T21	T30	T36	T42	Pre	T7	T14	T21	T28	T30	T36	T42	Pre	T7	T14	T21	T28	T30	T36	T42	Pre	T7	T14	T21	T28	T30	T36	T42	
M02001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, stereotypy, bizarre behavior, strabismus, vocalization, touch response, withdrawal reflex, pinna reflex).

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membrane [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe)]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3, tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-2 (continued). Detailed clinical observations of male rats

2,4-DTAP (10 mg/kg)														
Male No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}			
	Skin color / Mucous membranes					Lacration					Piloerection			
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	Pre	T7	T14	T21	T30	T36	T42
M02001	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02002	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02003	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02004	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02005	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02006	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02007	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02008	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02009	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02010	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02011	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02012	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacration(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe]]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-2 (continued). Detailed clinical observations of male rats

2,4-DTAP (10 mg/kg)

Male No.	Open-field observations ^{c)}							Defecation						
	Urination							Defecation						
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	Pre	T7	T14	T21	T30	T36	T42
M02001	2	1	0	1	1	1	1	0	2	0	1	0	0	0
M02002	0	0	0	0	0	0	0	0	0	0	0	0	0	1
M02003	1	0	1	1	0	0	0	0	0	0	0	0	0	0
M02004	1	0	0	0	1	0	0	0	0	0	0	0	0	0
M02005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02007	0	0	0	0	0	0	1	0	0	0	0	0	0	0
M02008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02009	0	0	1	0	0	0	0	0	0	0	0	0	0	0
M02010	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M02011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02013	0	0	0	0	1	0	1	0	0	0	0	0	0	0
Total score (N)	4 (13)	1 (13)	2 (13)	3 (13)	3 (13)	1 (13)	3 (13)	0 (13)	2 (13)	0 (13)	1 (13)	0 (13)	0 (13)	1 (13)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-3. Detailed clinical observations of male rats

2,4-DTAP (50 mg/kg)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convolution), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation) and c) Open-field observations (posture, exploration, palpebral opening, tremor, convolution, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale

Lacration(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe]

Piloerection [2, normal; 3, slight]

Respiratory rate [2, normal; 3, slight]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-3 (continued). Detailed clinical observations of male rats

2,4-DTAP (50 mg/kg)

Male No.	Removing from cage / Observations made while handling ^{b)}												Open-field observations ^{c)}												Gait																		
	Skin color / Mucous membranes						Lacration						Piloerection						Respiratory rate						Gait																		
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	R7 ^{f)}	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14							
M03001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M03013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	(13)	(13)	(13)	(13)	(13)	(5)	(5)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacration(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe]]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-3 (continued). Detailed clinical observations of male rats

2,4-DTAP (50 mg/kg)

Male No.	Open-field observations ^{c)}																	
	Urination					Defecation												
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	R7 ^{f)}	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14
M03001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03003	0	0	1	1	0	0	0	0	0	0	0	2	0	0	0	0	0	0
M03004	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03005	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03006	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03007	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03008	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03009	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03010	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
M03011	1	1	1	0	1	1	1	0	1	0	0	0	0	0	0	0	0	0
M03012	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0
M03013	0	0	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0
Total score	1	3	4	3	3	2	1	1	3	0	0	2	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(5)	(5)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-4. Detailed clinical observations of male rats

2,4-DTAP (100 mg/kg)														
Male No.	Cage-side observations ^{a)}							Removing from cage / Observations made while handling ^{b)}						
	Posture in home-cage		Locomotor in home-cage					Handling behavior		Heart beats				
	Pre	T7 ^{c)}	T14	T21	T30	T36	T42	Pre	T7	T14	T21	T30	T36	T42
M04001	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04002	2	2			2	1		2	2		2	2		2
M04003	2			2				2			2			2
M04004	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04005	2	2			2	2		2	2		2	2		2
M04006	2	2			2	2		2	2		2	2		2
M04007	2			2				2			2			2
M04008	2			2				2			2			2
M04009	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04010	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04011	2			2				2			2			2
M04012	2	2			2	2		2	2		2	2		2
M04013	2			2				2			2			2
(N)	(13)	(8)	(4)	(4)	(4)	(4)	(4)	(13)	(8)	(4)	(4)	(4)	(4)	(4)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur { 2, normal; 1, Soiled fur }

Skin color / Mucous membranes { 2, normal; 1, abnormal (a, anemic b, pale skin) }

Lacration(Reddish tear) { 2, not observed; 3, observed, slight; 4, observed, severe} }

Piloerection { 2, normal; 3, slight}

Respiratory rate{ 2, normal; 1, hypopnea}

Gait { 2, normal; 3,tip toe gait }

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 5-1-4 (continued). Detailed clinical observations of male rats

2,4-DTAP (100 mg/kg)

Male No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}							Respiratory rate							Gait						
	Skin color / Mucous membranes					Lacration					Piloerection				Pre T7 T14 T21 T30 T36 T42				Pre T7 T14 T21 T30 T36 T42				Pre T7 T14 T21 T30 T36 T42				Pre T7 T14 T21 T30 T36 T42				
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	Pre	T7	T14	T21	T30	T36	T42	Pre	T7	T14	T21	T30	T36	T42	Pre	T7	T14	T21	T30	T36	T42			
M04001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
M04002	2	2						2	2					2	2			2	2				2	2				2	2		
M04003	2							2						2				2					2					2			
M04004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
M04005	2	2						2	2					2	2			2	2				2	2				2	2		
M04006	2	2						2	2					2	2			2	2				2	2				2	2		
M04007	2							2						2				2					2					2			
M04008	2							2						2				2					2					2			
M04009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
M04010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
M04011	2							2						2				2					2					2			
M04012	2	2						2	2					2	2			2	2				2	2				2			
M04013	2							2						2				2					2					2			
(N)	(13)	(8)	(4)	(4)	(4)	(4)	(4)	(13)	(8)	(4)	(4)	(4)	(4)	(13)	(8)	(4)	(4)	(4)	(4)	(4)	(4)	(13)	(8)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacration(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe)]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 5-1-4 (continued). Detailed clinical observations of male rats

2,4-DTAP (100 mg/kg)

Male No.	Open-field observations ^{c)}							Defecation						
	Urination							Defecation						
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	Pre	T7	T14	T21	T30	T36	T42
M04001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04002	1	0						0	0					
M04003	0							0						
M04004	1	1	0	0	1	1	1	0	0	0	0	0	0	0
M04005	0	0						0	0					
M04006	0	0						0	0					
M04007	0							0						
M04008	0							0						
M04009	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M04010	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04011	0							0						
M04012	2	1	0	0	0	0	0	0	0	0	0	0	0	0
M04013	0							0						
Total score	4	2	0	1	1	1	1	0	0	0	0	0	0	0
(N)	(13)	(8)	(5)	(5)	(5)	(5)	(5)	(13)	(8)	(5)	(5)	(5)	(5)	(5)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-1. Detailed clinical observations of female rats

Corn oil (control)

Female No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}										Body temperature										Fur							
	Posture in home-cage					Locomotor in home-cage					Handling behavior					Heart beats					Body temperature					Fur												
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{f)}	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L			
F01001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1
F01005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F01013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)		

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery; ^{d)} lactation period

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe]]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-1 (continued). Detailed clinical observations of female rats

Corn oil (control)

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}										Gait									
	Skin color / Mucous membranes					Lacrimation					Piloerection					Respiratory rate					Gait									
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{f)}	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L		
F01001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F01013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)		

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery; ^{g)} lactation period

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe)]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-1 (continued). Detailed clinical observations of female rats

Corn oil (control)

Female No.	Open-field observations ^{c)}													
	Urination					Defecation								
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{g)}	Pre	T7	T14	T21	T30	T36	L
F01001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01005	0	0	0	0	1	0	0	0	0	0	0	0	0	0
F01006	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01010	1	0	0	0	0	0	0	0	0	0	0	0	0	0
F01011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	1	0	0	0	1	0	0	0	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery; ^{g)} lactation period

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-2. Detailed clinical observations of female rats

2,4-DTAP (10 mg/kg)

Female No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}										Body temperature										Fur							
	Posture in home-cage					Locomotor in home-cage					Handling behavior					Heart beats					Body temperature					Fur												
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{f)}	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L			
F02001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(11)	(13)	(13)	(13)	(13)	(13)	(13)	(11)	(13)	(13)	(13)	(13)	(13)	(13)	(11)	(13)	(13)	(13)	(13)	(13)	(11)	(13)	(13)	(13)	(13)	(13)	(11)					

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery; ^{d)} lactation period

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe]]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-2 (continued). Detailed clinical observations of female rats

2,4-DTAP (10 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}										Respiratory rate										Gait											
	Skin color / Mucous membranes					Lacrimation					Piloerection					Respiratory rate					Gait					Respiratory rate					Gait					Respiratory rate						
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{f)}	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L
F02001	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02002	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02003	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02004	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02005	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02006	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02007	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02008	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02009	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02010	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02011	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02012	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F02013	2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
(N)	(13)	(13)	(13)	(13)	(13)	(13)		(11)	(13)	(13)	(13)	(13)	(13)		(11)	(13)	(13)	(13)	(13)	(13)		(11)	(13)	(13)	(13)	(13)	(13)		(11)	(13)	(13)	(13)	(13)	(13)		(11)	(13)	(13)	(13)	(13)		(11)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, , tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery; ^{d)} lactation period

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe)]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-2 (continued). Detailed clinical observations of female rats

2,4-DTAP (10 mg/kg)

Female No.	Open-field observations ^{c)}													
	Urination					Defecation								
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{g)}	Pre	T7	T14	T21	T30	T36	L
F02001	0	0	0	0	0	0		0	0	0	0	0	0	0
F02002	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02004	1	1	1	0	1	0	0	0	0	0	0	0	0	0
F02005	0	1	0	0	0	0	0	0	0	0	0	0	0	0
F02006	0	1	0	0	0	0	0	0	0	0	0	0	0	0
F02007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02010	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02011	1	0	0	0	0	0	0	1	0	0	0	0	0	0
F02012	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F02013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	2	3	1	0	1	0	0	1	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(11)	(13)	(13)	(13)	(13)	(13)	(13)	(11)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery; ^{g)} lactation period

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-3. Detailed clinical observations of female rats

2,4-DTAP (50 mg/kg)		Cage-side observations ^{a)}																		Removing from cage / Observations made while handling ^{b)}																					
Female No.		Posture in home-cage						Locomotor in home-cage						Handling behavior						Heart beats						Body temperature						Fur									
		Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{f)}	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L					
F03001		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03002		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F03003		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03004		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03005		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03006		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03007		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03008		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03009		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03010		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03011		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03012		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
F03013		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
(N)		(13)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(12)				

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery; ^{d)} lactation period

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe]]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-3 (continued). Detailed clinical observations of female rats

2,4-DTAP (50 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}										Respiratory rate										Gait			
	Skin color / Mucuous membranes					Lacration					Piloerection					Respiratory rate					Gait													
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{f)}	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36
F03001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F03013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(12)	

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery; ^{g)} lactation period

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucuous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacration(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe)]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-3 (continued). Detailed clinical observations of female rats

2,4-DTAP (50 mg/kg)

Female No.	Open-field observations ^{c)}													
	Urination					Defecation								
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{g)}	Pre	T7	T14	T21	T30	T36	L
F03001	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03002	0	0	0	0	0	0		0	0	0	0	0	0	0
F03003	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03005	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03006	0	0	0	0	1	0	0	0	0	0	0	0	0	0
F03007	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03008	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03010	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03011	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F03012	0	1	0	0	1	0	1	0	0	0	0	0	0	0
F03013	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	0	1	0	0	2	0	1	0	0	0	0	0	0	0
(N)	(13)	(13)	(13)	(13)	(13)	(13)	(12)	(13)	(13)	(13)	(13)	(13)	(13)	(12)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery; ^{g)} lactation period

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-4. Detailed clinical observations of female rats

2,4-DTAP (250 mg/kg)

Female No.	Cage-side observations ^{a)}										Removing from cage / Observations made while handling ^{b)}										Body temperature										Fur									
	Posture in home-cage					Locomotor in home-cage					Handling behavior					Heart beats					Body temperature					Fur														
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{f)}	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L					
F04001	2	2						2	2						2	2																			2	2				
F04002	2	1						2	1						2	1																			2	1				
F04003	2	2						2	2						2	2																			2	2				
F04004	2	2						2	2						2	2																			2	2				
F04005	2							2							2																					2				
F04006	2	2						2	2						2	2																			2	2				
F04007	2	1						2	1						2	1																			2	1				
F04008	2							2							2																					2				
F04009	2	1						2	1						2	2																			2	1				
F04010	2							2							2																					2				
F04011	2							2							2																					2				
F04012	2	2						2	2						2	2																			2	2				
F04013	2	2						2	2						2	2																			2	2				
(N)	(13)	(9)						(13)	(9)						(13)	(9)																		(13)	(9)					

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery; ^{d)} lactation period

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe]]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-4 (continued). Detailed clinical observations of female rats

2,4-DTAP (250 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}										Gait						
	Skin color / Mucous membranes					Lacrimation					Piloerection					Respiratory rate					Gait						
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{f)}	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36	L	Pre	T7	T14	T21	T30	T36
F04001	2	2						2	2						2	2						2	2				
F04002	2	1b						2	2						2	1						2	3				
F04003	2	2						2	2						2	2						2	2				
F04004	2	2						2	2						2	2						2	2				
F04005	2							2							2							2					
F04006	2	2						2	2						2	2						2	2				
F04007	2	1a						2	3						2	1						2	3				
F04008	2							2							2							2					
F04009	2	1a						2	4						2	1						2	2				
F04010	2							2							2							2					
F04011	2							2							2							2					
F04012	2	2						2	2						2	2						2	2				
F04013	2	2						2	2						2	2						2	2				
(N)	(13)	(9)						(13)	(9)						(13)	(9)						(13)	(9)				

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery; ^{d)} lactation period

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe)]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-1-4 (continued). Detailed clinical observations of female rats

2,4-DTAP (250 mg/kg)

Female No.	Open-field observations ^{c)}						
	Urination				Defecation		
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	L ^{g)}
F04001	0	0			0	0	
F04002	0	0			0	0	
F04003	0	0			0	0	
F04004	0	0			0	0	
F04005	1				0		
F04006	0	0			0	0	
F04007	0	0			0	0	
F04008	0				0		
F04009	1	0			0	0	
F04010	0				0		
F04011	0				0		
F04012	0	0			0	0	
F04013	0	0			0	0	
Total score	2	0			0	0	
(N)	(13)	(9)			(13)	(9)	

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery; ^{g)} lactation period

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-2-1. Detailed clinical observations of female rats, satellite group

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation) and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 1, observed (a, slight; b, severe)]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hyp-

Gait [2, normal; 3,tip toe gait]

[*Continued from page 3*]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-2-1 (continued). Detailed clinical observations of female rats, satellite group

Corn oil (control)

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}										Gait																							
	Skin color / Mucous membranes					Lacration					Piloerection					Respiratory rate					Gait																							
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	R7 ^{f)}	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14								
F05001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05002	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05003	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05005	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(5)	(5)					

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beats [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacration(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe]]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3,tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-2-1 (continued). Detailed clinical observations of female rats, satellite group

Corn oil (control)

Female No.	Open-field observations ^{c)}																	
	Urination					Defecation												
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	R7 ^{f)}	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14
F05001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05005	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05006	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
F05007	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
F05008	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
F05009	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05010	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score (N)	1 (10)	1 (10)	0 (10)	0 (10)	0 (10)	1 (10)	0 (10)	1 (5)	1 (5)	0 (10)	0 (5)	0 (5)						

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, straub tail, vocalization, touch response, withdrawal reflex, pinna reflex).

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-2-2. Detailed clinical observations of female rats, satellite group

Except the above findings, there were no changes in all animals; a) Cage-side observations (vocalization, tremor, convolution), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c.) Open-field observations (rooting, exhalation, palpation opening, tremor, convolution, stereotypy, bizarre behavior, stupor tail, vocalization, touch response, withdrawal, reflex, biting reflex).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery.

Boutonniere deformity [3, sitting or standing; 1, squatting position].

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Locomotor in home-cage [2, normal; 1, decrease in locomotor
Handling behavior [3, normal; 1, no resistance; 3, resistance]

Heart beats [3, normal; 1, bradycardia]

Body temperature [? normal; 1, decrease of temperature]

Fur (2, normal; 1, Soiled fur)

Skin color / Mucous membrane

SECRETION / Mucous membrane:

Piloerection [2 normal; 3 slight]

Bacillary rate [3 normal]: 1 by

Respiratory rate| 2, normal; 1, hy-

Gait [2, normal; 3, tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-2-2 (continued). Detailed clinical observations of female rats, satellite group

2,4-DATP (100 mg/kg)

Female No.	Removing from cage / Observations made while handling ^{b)}										Open-field observations ^{c)}										Piloerection					Respiratory rate					Gait				
	Skin color / Mucous membranes					Lacrimation					Piloerection					Respiratory rate					Gait					Gait									
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	R7 ^{f)}	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14	Pre	T7	T14	T21	T30	T36	T42	R7
F04001	2	2	2	2	2	2				2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F04002																																			
F04003																																			
F04004	2	2	2	2	2	2				2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F04005																																			
F04006	2	2	2	2	2	2				2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
F04007																																			
F04008																																			
F04009																																			
F04010																																			
F04011																																			
F04012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F04013	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F06001	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F06002	2	2								2	2						2	2																	
F06003	2	2								2	3						2	2																	
F06004	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F06005	2									2							2																		
F06006	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F06007	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F06008	2	1a								2	3						2	1																	
F06009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
F06010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, strabismus, vocalization, touch response, withdrawal reflex, pinna reflex).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

^{a)} pre-treatment; ^{b)} day 7 of treatment; ^{c)} day 7 of recovery

Posture in home-cage [2, sitting or standing; 1, crouching position]

Locomotor in home-cage [2, normal; 1, decrease in locomotor activity; 0, loss of locomotor activity]

Handling behavior [2, normal; 1, no resistance; 3, resistance]

Heart beat [2, normal; 1, bradycardia]

Body temperature [2, normal; 1, decrease of temperature]

Fur [2, normal; 1, Soiled fur]

Skin color / Mucous membranes [2, normal; 1, abnormal (a, anemic b, pale skin)]

Lacrimation(Reddish tear) [2, not observed; 3, observed, slight; 4, observed, severe)]

Piloerection [2, normal; 3, slight]

Respiratory rate[2, normal; 1, hypopnea]

Gait [2, normal; 3, tip toe gait]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 6-2-2 (continued). Detailed clinical observations of female rats, satellite group

2,4-DTAP (100 mg/kg)																		
Female No.	Open-field observations ^{c)}																	
	Urination																	
	Pre ^{d)}	T7 ^{e)}	T14	T21	T30	T36	T42	R7 ^{f)}	R14	Pre	T7	T14	T21	T30	T36	T42	R7	R14
F04001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04002																		
F04003																		
F04004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04005																		
F04006	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F04007																		
F04008																		
F04009																		
F04010																		
F04011																		
F04012	0	0	0	0	0	0	0	1		0	0	0	0	0	0	0	0	0
F04013	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
F06001	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
F06002	0	0								0	0							
F06003	0	1								0	0							
F06004	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
F06005	1									0								
F06006	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
F06007	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
F06008	0	0								0	0							
F06009	0	0	0	1	1	0	0	0		0	0	0	0	0	0	0	0	0
F06010	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Total score (N)	1 (10)	1 (9)	0 (11)	1 (11)	1 (11)	0 (11)	0 (11)	1 (5)	1 (5)	0 (10)	0 (9)	0 (11)	0 (11)	0 (11)	0 (11)	0 (11)	0 (5)	0 (5)

Except the above findings, there were no changes in all animals; a) Cage-side observation (vocalization, tremor, convulsion), b) Observations made while handling (behavior while removing from cage, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, palpebral opening, tremor, convulsion, stereotypy, bizarre behavior, strabismus, vocalization, touch response, withdrawal reflex, pinna reflex).

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

^{d)} pre-treatment; ^{e)} day 7 of treatment; ^{f)} day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 7-1-1. Body weights of male rats

Corn oil (control)

Male No.	Days of administration												
	1	7	10	12	14	17	21	24	28	31	35	38	42
M01001	348.3	367.2	380.6	387.8	395.8	395.9	409.8	423.7	436.2	445.0	462.4	464.2	471.1
M01002	373.5	397.2	399.1	409.8	417.7	418.3	441.2	451.8	463.4	478.8	486.7	493.6	496.8
M01003	377.5	407.5	420.7	428.4	438.4	440.0	458.9	460.5	474.9	473.4	481.5	482.8	490.1
M01004	379.6	403.7	415.4	420.1	431.1	438.8	455.8	467.8	487.0	493.2	507.5	514.5	516.9
M01005	392.6	426.7	437.3	450.1	456.9	459.6	476.2	489.8	498.3	503.5	507.6	507.9	524.1
M01006	368.3	389.2	400.6	409.3	418.1	424.2	440.5	450.0	464.6	484.4	496.0	506.8	517.2
M01007	344.3	376.5	382.9	389.5	399.9	398.7	412.2	414.9	426.5	432.0	440.4	447.2	462.2
M01008	366.9	397.9	414.3	424.4	430.4	439.3	464.3	481.2	493.5	502.2	519.9	530.2	538.9
M01009	387.3	428.4	437.6	447.4	461.9	455.0	464.0	468.8	483.8	493.0	500.0	506.0	518.8
M01010	363.2	390.3	396.2	408.2	415.7	409.8	425.3	437.1	454.7	468.0	479.8	487.0	496.3
M01011	356.5	377.5	385.6	394.8	402.6	408.8	419.3	430.7	447.0	456.9	471.8	478.6	494.3
M01012	375.7	400.2	415.1	427.7	438.2	445.5	462.8	481.5	501.0	507.1	519.1	533.1	550.9
M01013	377.4	402.2	406.4	411.5	416.7	411.7	434.6	452.2	462.2	475.4	491.9	496.6	513.6
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	370.1	397.3	407.1	416.1	424.9	426.6	443.5	454.6	468.7	477.9	489.6	496.0	507.0
S.D.	14.2	17.9	18.7	19.7	20.5	21.1	22.0	23.3	23.7	23.0	22.8	24.5	25.1

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 7-1-2. Body weights of male rats

2,4-DTAP 10 mg/kg

Male No.	Days of administration												
	1	7	10	12	14	17	21	24	28	31	35	38	42
M02001	358.7	370.9	374.4	387.3	394.0	399.5	412.9	419.3	431.6	437.4	453.0	449.0	459.5
M02002	366.8	387.1	391.7	395.4	399.8	404.2	416.6	428.5	438.2	449.8	453.2	455.9	452.2
M02003	397.8	434.3	443.5	454.8	460.2	455.9	479.8	482.9	492.2	503.8	519.3	521.7	529.5
M02004	389.7	423.2	439.2	452.9	460.1	465.4	484.6	499.8	521.0	529.1	543.1	550.7	559.3
M02005	386.4	405.5	416.4	419.0	423.5	427.1	445.1	456.0	469.7	479.4	488.0	498.6	502.0
M02006	357.8	377.2	387.6	400.3	405.0	411.4	424.7	423.8	436.3	438.4	454.8	454.4	466.0
M02007	356.5	385.4	399.0	411.6	413.1	416.8	424.7	438.5	446.0	446.7	452.8	462.7	475.8
M02008	349.7	364.1	371.9	376.8	378.7	378.6	392.5	398.0	407.6	415.7	421.6	428.8	435.3
M02009	373.3	399.3	408.4	415.7	422.7	422.0	437.2	450.6	466.8	475.6	477.4	496.5	504.9
M02010	366.6	390.8	400.6	405.0	406.0	402.6	427.8	434.5	445.3	454.4	455.1	464.0	471.0
M02011	388.1	416.0	431.9	438.8	444.1	455.7	476.5	485.3	493.8	508.6	513.7	522.6	532.2
M02012	378.2	413.1	422.5	431.7	440.5	442.8	453.4	458.0	469.2	472.9	484.4	494.6	509.3
M02013	380.1	412.8	418.0	429.0	438.3	444.3	465.7	479.9	497.1	507.0	522.0	530.0	533.4
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	373.1	398.4	408.1	416.8	422.0	425.1	441.7	450.4	462.7	470.7	479.9	486.9	494.6
S.D.	15.0	21.3	23.2	24.1	25.5	26.2	28.7	30.2	32.2	33.9	35.8	37.2	37.6
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	DU	DU	AN								

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 7-1-3. Body weights of male rats

2,4-DTAP 50 mg/kg

Male No.	Days of administration												
	1	7	10	12	14	17	21	24	28	31	35	38	42
M03001	362.7	389.5	396.5	405.9	403.8	410.7	424.7	429.1	446.7	445.9	449.6	454.1	466.8
M03002	381.5	400.6	401.7	412.0	418.1	412.1	436.5	446.6	466.9	476.2	490.5	495.0	499.0
M03003	390.6	417.3	417.6	432.1	435.1	439.4	458.6	472.8	480.2	487.0	500.8	488.1	502.5
M03004	348.5	371.2	376.5	380.2	385.9	400.9	416.8	421.9	436.7	452.2	455.2	456.7	458.9
M03005	401.3	444.3	456.5	464.7	470.7	477.6	488.2	489.4	506.5	513.8	524.4	525.6	534.0
M03006	368.7	370.4	378.4	383.9	391.9	394.2	406.5	412.4	424.4	433.6	443.9	446.6	457.3
M03007	362.5	379.5	383.6	394.0	397.7	386.2	397.2	408.1	418.7	426.3	438.6	440.8	450.2
M03008	358.8	373.4	378.6	383.7	390.3	401.1	415.5	423.5	443.5	460.3	473.7	485.1	492.4
M03009	358.3	378.6	390.5	397.5	404.1	406.5	429.2	435.0	444.6	453.2	459.6	464.4	477.1
M03010	380.8	406.3	415.2	423.7	434.3	431.3	448.0	457.8	473.2	481.8	491.7	494.0	502.2
M03011	346.1	360.3	369.3	372.6	379.4	382.2	394.1	398.3	407.4	414.3	421.5	429.4	437.3
M03012	375.7	392.5	400.6	408.9	414.9	414.2	440.8	463.6	476.5	485.9	494.7	499.4	517.4
M03013	362.1	384.0	389.5	397.1	406.1	409.7	421.0	430.1	445.0	456.5	462.5	464.5	477.8
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	369.0	389.8	396.5	404.3	410.2	412.8	429.0	437.6	451.6	460.5	469.7	472.6	482.5
S.D.	16.2	22.8	23.2	25.0	24.9	25.1	26.0	27.0	27.9	27.8	29.2	27.6	28.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	DU	DU	AN								

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 7-1-4. Body weights of male rats

2,4-DTAP 100 mg/kg

Male No.	Days of administration												
	1	7	10	12	14	17	21	24	28	31	35	38	42
M04001	377.7	377.6	386.2	383.6	407.2	407.7	423.3	431.9	446.7	456.3	464.2	469.2	475.1
M04002	395.9	361.4	319.9										
M04003	362.5												
M04004	376.1	362.8	368.7	388.0	406.5	418.5	434.7	445.7	458.6	470.9	475.7	481.8	495.8
M04005	392.5	359.2	300.7										
M04006	359.5	348.7											
M04007	357.8												
M04008	371.2												
M04009	392.7	372.2	379.5	385.3	406.1	423.1	443.1	461.2	482.9	496.6	506.8	507.9	512.4
M04010	364.2	361.3	360.5	360.3	385.2	394.0	412.2	421.2	436.8	447.2	446.6	445.6	457.0
M04011	367.2	298.7											
M04012	375.8	370.8	336.0	285.3									
M04013	379.3												
Number of males	13	9	7	5	4	4	4	4	4	4	4	4	4
Mean	374.8	357.0	350.2	360.5	401.3	410.8	428.3	440.0	456.3	467.8	473.3	476.1	485.1
S.D.	12.8	23.4	32.1	43.5	10.7	12.9	13.5	17.3	19.9	21.6	25.3	26.0	24.1
Significance	NS	**	**	**	NS								
Statistical method	AN	DU	DU	DU	AN								

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 7-2-1. Body weights of male rats at the recovery period

Corn oil (control)

Male No.	Days of recovery		
	1	7	14
M01009	517.6	535.6	540.1
M01010	491.6	501.8	514.6
M01011	492.5	507.1	523.0
M01012	552.0	570.6	586.3
M01013	513.6	529.5	542.2
Number of males	5	5	5
Mean	513.5	528.9	541.2
S.D.	24.6	27.4	27.7

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 7-2-2. Body weights of male rats at the recovery period

2,4-DTAP 50 mg/kg

Male No.	Days of recovery		
	1	7	14
M03009	478.9	496.2	510.4
M03010	505.5	512.3	516.9
M03011	430.8	443.4	453.3
M03012	526.7	543.9	556.1
M03013	474.8	484.4	484.4
Number of males	5	5	5
Mean	483.3	496.0	504.2
S.D.	36.1	37.0	38.3
Significance	NS	NS	NS
Statistical method	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 8-1-1. Body weights of female rats

Corn oil (control)

Female No.	Days of administration					
	1	7	10	12	14	17
F01001	256.2	269.3	263.8	279.3	274.2	290.8
F01002	269.3	279.8	290.9	293.2	297.3	
F01003	249.5	251.2	263.8	265.1	266.2	281.4
F01004	260.4	276.7	287.4	280.8	292.0	
F01005	243.6	269.8	278.1	285.7	290.5	
F01006	263.4	282.0	293.5	292.1	299.0	
F01007	265.3	273.9	270.7	283.7	280.2	291.9
F01008	233.8	240.4	235.9	242.8	237.4	
F01009	255.5	270.1	270.8	279.6	281.2	297.5
F01010	278.7	283.4	292.5	297.4	303.6	315.0
F01011	273.1	288.7	293.5	299.3	296.8	304.4
F01012	261.3	279.2	281.0	286.3	292.8	
F01013	243.6	264.7	268.5	274.2	278.0	
Number of females	13	13	13	13	13	6
Mean	258.0	271.5	276.2	281.5	283.8	296.8
S.D.	12.8	13.4	16.5	15.0	17.7	11.7

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 8-1-2. Body weights of female rats

2,4-DTAP 10 mg/kg

Female No.	Days of administration					
	1	7	10	12	14	17
F02001	245.9	250.8	254.5	265.7	260.9	274.2
F02002	254.2	269.6	271.2	273.7	273.8	
F02003	276.3	293.4	301.6	302.0	304.5	
F02004	268.1	285.2	290.5	290.5	296.3	
F02005	269.9	282.8	284.6	293.2	294.7	298.9
F02006	260.6	268.9	277.1	268.6	275.4	
F02007	246.7	264.5	259.0	264.5	264.0	280.5
F02008	260.0	274.8	282.3	285.0	288.4	
F02009	260.8	268.4	283.1	278.5	285.7	294.1
F02010	233.7	254.9	258.2	263.3	266.9	
F02011	264.5	283.6	281.5	295.5	291.6	303.6
F02012	280.6	283.4	301.5	297.7	306.1	311.0
F02013	269.7	294.8	299.5	308.2	312.2	
Number of females	13	13	13	13	13	6
Mean	260.8	275.0	280.4	283.6	286.2	293.7
S.D.	13.1	13.7	16.1	15.5	16.8	14.0
Significance	NS	NS	NS	NS	NS	NS
Statistical method	AN	DT	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 8-1-3. Body weights of female rats

2,4-DTAP 50 mg/kg

Female No.	Days of administration					
	1	7	10	12	14	17
F03001	266.2	269.5	288.0	286.3	293.7	
F03002	237.8	249.2	246.2	257.3	250.2	265.0
F03003	260.4	267.5	277.3	279.8	278.6	
F03004	253.7	260.8	258.3	265.7	262.4	268.7
F03005	273.6	278.9	287.4	290.6	293.0	300.8
F03006	252.9	270.8	269.6	282.2	277.4	293.4
F03007	263.5	263.3	278.1	278.1	278.2	289.5
F03008	276.4	284.3	279.9	291.1	284.2	302.9
F03009	260.8	277.9	273.7	285.2	283.4	294.2
F03010	257.2	275.4	278.1	274.6	280.9	
F03011	267.8	274.7	289.0	287.7	290.1	293.9
F03012	268.6	299.2	302.2	313.3	316.4	
F03013	275.2	290.4	296.2	292.8	305.6	
Number of females	13	13	13	13	13	8
Mean	262.6	274.0	278.8	283.4	284.2	288.6
S.D.	10.7	13.0	15.0	13.7	17.0	14.1
Significance	NS	NS	NS	NS	NS	NS
Statistical method	AN	DT	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 8-1-4. Body weights of female rats

2,4-DTAP 250 mg/kg

Female No.	Days of administration		
	1	7	10
F04001	265.8	258.2	274.2
F04002	246.9	206.9	Died on day 8 of administration.
F04003	278.7	253.8	Sacrificed on day 9 of administration for moribundity.
F04004	243.4	262.4	263.8
F04005	261.6		Died on day 7 of administration.
F04006	268.1	267.4	274.7
F04007	271.8	217.0	Died on day 8 of administration.
F04008	271.3		Died on day 7 of administration.
F04009	271.4	205.5	Sacrificed on day 7 of administration for moribundity.
F04010	243.1		Died on day 7 of administration.
F04011	265.9		Died on day 6 of administration.
F04012	275.0	292.4	299.6
F04013	260.4	267.2	276.0
Number of females	13	9	5
Mean	263.3	247.9	277.7
S.D.	11.9	30.7	13.2
Significance	NS	NS	NS
Statistical method	AN	DT	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 8-2-1. Body weights of female rats, satellite group

Corn oil (control)

Female No.	Days of administration												
	1	7	10	12	14	17	21	24	28	31	35	38	42
F05001	260.8	281.7	287.8	290.3	290.4	289.8	291.8	301.8	304.4	309.2	313.0	314.7	316.5
F05002	279.2	300.3	299.5	314.0	312.9	323.7	337.9	340.2	350.9	350.8	348.0	359.7	357.5
F05003	268.4	271.0	282.4	289.3	286.2	291.4	295.9	294.9	303.7	295.4	302.9	307.7	310.2
F05004	284.2	286.1	293.6	295.3	295.8	303.8	306.2	305.6	311.8	311.7	317.4	318.8	325.7
F05005	252.6	264.0	263.4	265.4	264.4	262.8	264.4	271.0	275.8	273.0	280.4	268.5	276.9
F05006	258.2	259.9	264.3	264.4	267.5	273.4	275.7	273.9	276.9	275.0	277.3	281.3	285.7
F05007	258.3	272.2	276.2	279.7	281.2	285.9	283.5	298.3	301.0	293.9	301.3	315.8	314.1
F05008	281.4	290.6	301.1	303.1	304.3	311.9	319.5	318.7	325.8	328.2	333.4	341.3	344.9
F05009	280.4	286.8	298.1	298.1	303.3	309.1	319.5	317.1	327.3	326.2	336.6	345.8	343.4
F05010	247.6	263.8	266.7	271.1	267.5	279.2	283.5	289.2	293.9	299.3	304.3	304.3	306.6
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	267.1	277.6	283.3	287.1	287.4	293.1	297.8	301.1	307.2	306.3	311.5	315.8	318.2
S.D.	13.4	13.4	14.9	16.6	17.1	18.9	22.8	20.9	23.1	24.3	23.2	28.1	25.7

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 8-2-2. Body weights of female rats, satellite group

2,4-DTAP 100 mg/kg

Female No.	Days of administration												
	1	7	10	12	14	17	21	24	28	31	35	38	42
F04001				276.3	289.2	289.7	295.7	297.3	304.3	302.3	300.6	305.6	313.6
F04002				Died on day 8 of administration.									
F04003				Sacrificed on day 9 of administration for moribundity.									
F04004				261.7	271.9	273.8	273.8	274.3	277.7	283.8	287.2	292.6	292.6
F04005				Died on day 7 of administration.									
F04006				282.5	277.4	279.5	290.0	298.8	300.0	291.7	299.9	284.8	302.8
F04007	See appendix 8-1-4			Died on day 8 of administration.									
F04008				Died on day 7 of administration.									
F04009				Sacrificed on day 7 of administration for moribundity.									
F04010				Died on day 7 of administration.									
F04011				Died on day 6 of administration.									
F04012				290.7	305	309.1	308.4	308.3	307.6	317	323.3	325.1	329.3
F04013				281.4	284.7	291.2	297.1	299.7	307.4	304.4	309.4	314.9	318.6
F06001	253.6	243.3	265.8	272.9	275.3	266.4	274.8	276.5	278.0	279.3	282.5	285.5	288.7
F06002	275.0	227.9		Sacrificed on day 8 of administration for moribundity.									
F06003	257.8	214.7		Sacrificed on day 8 of administration for moribundity.									
F06004	259.5	267.6	276.7	267.5	284.8	273.8	274.4	289.0	284.0	275.4	282.3	288.4	293.5
F06005	258.5			Died on day 7 of administration.									
F06006	270.4	272.3	283.7	298.3	303.8	308.7	318.2	326.4	331.1	329.1	331.7	331.9	334.0
F06007	270.8	287.1	298.8	297.1	308.4	305.1	320.8	331.9	338.7	339.8	351.6	357.9	353.1
F06008	264.0	221.8		Died on day 8 of administration.									
F06009	278.5	274.4	290.2	297.9	301.2	307.3	319.0	325.1	332.7	334.5	337.7	338.2	349.0
F06010	274.0	269.6	289.3	292.3	299.6	297.9	300.1	308.8	316.4	312.0	314.7	310.4	316.4
Number of females	10	9	6	11	11	11	11	11	11	11	11	11	11
Mean	266.2	253.2	284.1	283.5	291.0	291.1	297.5	303.3	307.1	306.3	311.0	312.3	317.4
S.D.	8.6	26.6	11.6	12.8	13.1	15.8	18.0	19.3	21.5	22.4	23.2	24.1	22.2
Significance	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 8-3-1. Body weights of female rats at the recovery period

Corn oil (control)

Female No.	Days of recovery		
	1	7	14
F05006	284.1	293.4	291.8
F05007	313.5	320.4	334.3
F05008	340.8	353.3	361.2
F05009	346.2	350.1	354.6
F05010	311.3	318.6	321.0
Number of females	5	5	5
Mean	319.2	327.2	332.6
S.D.	25.1	24.8	27.9

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 8-3-2. Body weights of female rats at the recovery period

2,4-DTAP 100 mg/kg

Female No.	Days of recovery		
	1	7	14
F04012	321.0	323.8	325.4
F04013	316.3	328.6	331.0
F06007	363.1	375.4	353.7
F06009	350.8	357.8	366.6
F06010	321.4	315.1	308.6
Number of females	5	5	5
Mean	334.5	340.1	337.1
S.D.	21.0	25.4	23.1
Significance	NS	NS	NS
Statistical method	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 9-1. Body weights of dams during pregnancy

Corn oil (control)

Dam No.	Days of pregnancy						
	0	3	7	10	14	17	20
F01001	288.2	305.4	321.0	334.2	352.0	379.1	423.7
F01002	307.4	324.8	344.9	362.4	382.9	419.3	468.0
F01003	289.8	308.7	333.4	346.2	380.2	413.4	477.1
F01004	299.0	315.8	326.0	342.4	367.4	397.4	441.7
F01005	300.8	317.6	331.5	347.9	372.6	407.3	458.2
F01006	313.0	319.6	338.4	359.5	374.3	409.8	470.5
F01007	289.1	314.3	329.2	344.6	362.3	389.7	428.6
F01008	257.6	266.9	287.6	303.0	331.7	363.2	420.1
F01009	297.1	307.5	332.3	345.9	375.4	404.4	450.5
F01010	310.3	334.1	349.9	360.5	386.5	416.5	472.2
F01011	301.2	320.2	333.9	354.5	378.6	414.8	460.7
F01012	293.7	310.5	317.7	331.0	352.5	385.3	429.2
F01013	284.5	296.7	314.2	329.0	344.7	380.1	431.2
Number of dams	13	13	13	13	13	13	13
Mean	294.7	310.9	327.7	343.2	366.2	398.5	448.6
S.D.	14.2	16.2	15.7	16.2	16.6	17.6	20.5

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 9-2. Body weights of dams during pregnancy

2,4-DTAP 10 mg/kg

Dam No.	Days of pregnancy						
	0	3	7	10	14	17	20
F02001	274.0	290.3	301.1	315.6	332.8	368.7	411.4
F02002	279.2	301.5	318.6	331.2	356.8	392.2	450.8
F02003	319.0	335.9	346.7	362.4	377.7	410.2	462.7
F02004	299.2	321.3	340.2	358.8	389.0	433.5	480.3
F02005	302.6	324.9	337.5	353.8	379.6	412.1	451.7
F02006	276.2	293.2	309.1	322.6	343.6	380.5	430.2
F02007	279.0	294.8	304.7	321.1	345.1	378.0	419.7
F02008	304.8	326.1	347.2	378.3	410.3	455.6	511.9
F02009	290.6	304.8	324.8	333.9	355.2	394.2	442.9
F02010	271.2	284.5	302.1	319.0	338.6	376.3	417.6
F02011	305.5	318.6	342.6	355.4	384.7	416.1	464.3
F02012	319.9 >	326.7 >	333.9 >	336.6 >	342.9 >	345.6 >	341.6 >
F02013	306.3	335.2	344.5	366.2	399.2	434.9	486.1
Number of dams	12	12	12	12	12	12	12
Mean	292.3	310.9	326.6	343.2	367.7	404.4	452.5
S.D.	15.9	18.2	18.6	21.6	25.6	27.3	30.5
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 9-3. Body weights of dams during pregnancy

2,4-DTAP 50 mg/kg

Dam No.	Days of pregnancy						
	0	3	7	10	14	17	20
F03 001	289.0	320.2	343.3	359.8	391.3	443.4	503.9
F03 002	267.0	282.2	300.0	315.4	333.4	370.2	413.3
F03 003	283.8	302.9	323.3	334.5	361.5	387.9	416.2
F03 004	275.2	295.0	310.9	321.5	340.9	365.7	393.6
F03 005	308.5	322.1	347.9	364.9	390.3	420.9	465.3
F03 006	296.7	305.3	320.3	330.4	355.5	388.0	433.4
F03 007	293.1	302.8	322.3	331.5	349.1	377.8	429.3
F03 008	305.6	325.9	342.4	359.1	381.8	413.5	463.3
F03 009	292.8	316.0	329.3	342.4	366.3	394.3	439.4
F03 010	284.1	293.0	310.1	319.8	336.5	371.1	413.1
F03 011	295.9	315.5	336.1	359.1	385.0	432.8	471.2
F03 012	327.1	346.6	363.4	378.5	401.6	428.8	471.4
F03 013	306.5	333.5	349.8	368.4	401.0	443.7	493.1
Number of dams	13	13	13	13	13	13	13
Mean	294.3	312.4	330.7	345.0	368.8	402.9	446.7
S.D.	15.6	17.8	18.4	20.9	24.5	28.8	33.9
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 10-1. Body weights of dams during lactation

Corn oil (control)

Dam No.	Days of lactation	
	0	4
F01001	339.7	333.3
F01002	332.6	355.7
F01003	340.8	350.1
F01004	307.1	240.5
F01005	335.0	303.6 Total litter loss.
F01006	330.7	325.2
F01007	315.6	356.9
F01008	298.1	323.0
F01009	344.8	364.0
F01010	353.6	376.7
F01011	361.8	283.5
F01012	297.7	333.8
F01013	343.7	335.5
Number of dams	13	13
Mean	330.9	329.4
S.D.	20.4	36.6

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 10-2. Body weights of dams during lactation

2,4-DTAP 10 mg/kg

Dam No.	Days of lactation	
	0	4
F02002	305.4	259.2
F02003	325.8	354.8
F02004	350.9	362.9
F02005	341.1	364.1
F02006	300.5	317.7
F02007	337.9	340.7
F02008	404.4	409.7
F02009	314.0	250.4
F02010	313.4	334.3
F02011	379.6	398.5
F02013	399.2	383.0
Number of dams	11	11
Mean	342.9	343.2
S.D.	36.9	51.4
Significance	NS	NS
Statistical method	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 10-3. Body weights of dams during lactation

2,4-DTAP 50 mg/kg

Dam No.	Days of lactation	
	0	4
F03 001	363.7	376.5
F03 003	313.9	321.2
F03 004	311.2	335.6
F03 005	360.6	363.4
F03 006	293.8	332.3
F03 007	309.7	351.9
F03 008	360.2	349.4
F03 009	300.9	331.0
F03 010	288.2	323.6
F03 011	294.8	Sacrificed on day 0 of lactation for moribundity.
F03 012	392.1	384.6
F03 013	368.6	384.9
Number of dams	12	11
Mean	329.8	350.4
S.D.	36.3	23.9
Significance	NS	NS
Statistical method	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 11-1-1. Food consumption of male rats

Corn oil (control)

Male No.	Days of administration					
	1	7	14	29	35	41
M01001	18.6	19.1	19.5	19.9	18.0	16.7
M01002	27.1	22.2	17.4	23.2	18.1	18.9
M01003	26.7	22.6	24.2	21.2	21.3	17.9
M01004	19.8	21.4	19.5	24.2	22.6	19.0
M01005	28.1	23.6	22.2	23.2	20.7	21.6
M01006	24.6	23.0	21.7	23.2	25.3	20.1
M01007	22.4	18.5	19.7	20.3	19.1	24.9
M01008	22.5	22.8	23.3	23.4	22.1	20.7
M01009	24.2	22.5	24.3	23.0	20.7	18.8
M01010	20.6	20.1	18.8	23.0	19.2	15.8
M01011	19.9	19.0	19.9	21.2	20.1	21.1
M01012	24.6	24.9	20.3	22.0	22.5	21.6
M01013	27.4	19.6	19.4	24.4	22.6	24.3
Number of males	13	13	13	13	13	13
Mean	23.6	21.5	20.8	22.5	20.9	20.1
S.D.	3.2	2.0	2.2	1.4	2.1	2.7

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 11-1-2. Food consumption of male rats

2,4-DTAP 10 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02001	23.7	17.3	19.3	18.5	20.1	16.9
M02002	21.7	21.7	19.0	20.7	18.1	16.8
M02003	28.6	24.6	21.5	22.6	19.9	21.3
M02004	28.5	23.7	24.2	23.8	22.6	20.3
M02005	27.7	21.9	20.8	23.4	22.5	19.3
M02006	21.3	18.3	20.3	19.7	18.1	17.2
M02007	28.6	21.8	21.2	21.4	18.8	21.6
M02008	21.1	19.2	19.0	19.6	19.7	19.9
M02009	27.6	20.3	21.3	23.9	20.5	18.4
M02010	24.3	22.9	21.6	20.1	21.6	18.1
M02011	22.6	21.4	24.5	21.2	21.9	20.2
M02012	24.5	23.8	24.8	25.2	23.9	26.4
M02013	29.1	25.7	23.1	24.6	25.7	22.3
Number of males	13	13	13	13	13	13
Mean	25.3	21.7	21.6	21.9	21.0	19.9
S.D.	3.1	2.5	2.0	2.2	2.3	2.7
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DT	DU	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 11-1-3. Food consumption of male rats

2,4-DTAP 50 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03001	20.3	18.8	17.6	19.9	17.1	21.3
M03002	26.1	22.1	20.3	23.6	22.1	20.8
M03003	23.7	21.8	24.0	21.3	20.7	22.5
M03004	22.3	17.3	18.0	20.3	17.4	17.9
M03005	24.9	26.9	23.7	21.9	21.9	22.5
M03006	18.9	17.8	19.6	22.7	19.4	20.1
M03007	19.8	18.4	17.2	21.2	20.1	17.5
M03008	20.5	18.1	20.5	23.9	23.2	19.2
M03009	24.7	20.7	22.9	23.0	20.7	19.2
M03010	26.3	23.5	20.4	24.9	20.7	21.2
M03011	20.7	19.2	20.7	18.1	18.9	18.9
M03012	26.1	23.6	21.2	25.2	21.4	18.8
M03013	23.7	20.8	20.1	22.1	18.1	22.7
Number of males	13	13	13	13	13	13
Mean	22.9	20.7	20.5	22.2	20.1	20.2
S.D.	2.6	2.8	2.1	2.0	1.9	1.8
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DU	DT	DU	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 11-1-4. Food consumption of male rats

2,4-DTAP 100 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04001	21.7	19.4	27.5	22.0	22.2	21.0
M04002	22.9	0.0	Died on day 12 of administration.			
M04003	19.8		Died on day 7 of administration.			
M04004	17.6	14.2	24.4	20.9	22.3	24.5
M04005	19.5	5.9	Died on day 11 of administration.			
M04006	14.6	5.2	Sacrificed on day 9 of administration for moribundity.			
M04007	20.6		Died on day 7 of administration.			
M04008	20.9		Died on day 7 of administration.			
M04009	20.8	12.7	23.8	26.6	25.8	20.2
M04010	19.2	16.7	25.9	21.4	20.7	19.6
M04011	21.4		Sacrificed on day 7 of administration for moribundity.			
M04012	21.6	6.5	Died on day 13 of administration.			
M04013	17.2		Died on day 6 of administration.			
Number of males	13	8	4	4	4	4
Mean	19.8	10.1	25.4	22.7	22.8	21.3
S.D.	2.3	6.7	1.7	2.6	2.2	2.2
Significance	**	**	**	NS	NS	NS
Statistical method	DU	DT	DU	AN	AN	AN

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 11-2-1. Food consumption of male rats at the recovery period

Corn oil (control)

Male No.	Days of recovery	
	6	12
M01009	30.0	28.6
M01010	23.1	24.0
M01011	23.7	26.9
M01012	30.3	30.0
M01013	28.9	31.2
Number of males	5	5
Mean	27.2	28.1
S.D.	3.5	2.8

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 11-2-2. Food consumption of male rats at the recovery period

2,4-DTAP 50 mg/kg

Male No.	Days of recovery	
	6	12
M03009	26.9	28.7
M03010	27.7	28.2
M03011	24.7	23.6
M03012	29.8	30.7
M03013	28.7	27.6
Number of males	5	5
Mean	27.6	27.8
S.D.	1.9	2.6
Significance	NS	NS
Statistical method	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 12-1-1. Food consumption of female rats

Corn oil (control)

Female No.	Days of administration		
	1	7	14
F01001	12.2	19.4	11.7
F01002	18.7	15.6	16.9
F01003	16.3	17.6	9.5
F01004	20.8	14.4	21.2
F01005	19.2	20.2	18.5
F01006	15.0	16.8	17.9
F01007	16.7	19.0	13.4
F01008	15.5	11.7	14.6
F01009	18.2	17.2	12.9
F01010	22.3	20.3	17.6
F01011	13.9	17.3	17.6
F01012	16.8	16.7	16.8
F01013	16.7	19.4	19.7
Number of females	13	13	13
Mean	17.1	17.4	16.0
S.D.	2.8	2.5	3.4

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 12-1-2. Food consumption of female rats

2,4-DTAP 10 mg/kg

Female No.	Days of administration		
	1	7	14
F02001	11.3	18.2	16.6
F02002	19.4	18.1	17.3
F02003	19.0	16.6	22.1
F02004	18.6	11.4	19.8
F02005	13.4	19.4	15.2
F02006	19.7	12.0	17.8
F02007	14.1	17.7	16.9
F02008	18.7	17.9	20.9
F02009	18.7	18.3	12.9
F02010	16.9	15.2	17.2
F02011	22.2	20.2	12.8
F02012	20.2	21.1	12.5
F02013	22.5	21.4	21.4
Number of females	13	13	13
Mean	18.1	17.5	17.2
S.D.	3.3	3.1	3.3
Significance	NS	NS	NS
Statistical method	AN	DT	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 12-1-3. Food consumption of female rats

2,4-DTAP 50 mg/kg

Female No.	Days of administration		
	1	7	14
F03001	19.0	20.7	14.0
F03002	9.1	18.5	16.3
F03003	19.7	16.8	20.0
F03004	12.3	16.9	17.8
F03005	18.6	20.2	13.4
F03006	20.5	18.9	16.0
F03007	19.9	16.6	15.3
F03008	13.6	18.8	16.4
F03009	14.7	17.8	19.7
F03010	19.0	15.6	14.6
F03011	19.4	17.9	13.7
F03012	21.1	19.6	20.7
F03013	22.0	15.4	19.4
Number of females	13	13	13
Mean	17.6	18.0	16.7
S.D.	3.9	1.7	2.6
Significance	NS	NS	NS
Statistical method	AN	DT	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 12-1-4. Food consumption of female rats

2,4-DTAP 250 mg/kg

Female No.	Days of administration	
	1	7
F04001	19.7	9.6
F04002	15.2	Died on day 8 of administration.
F04003	18.0	2.8
F04004	19.9	15.2
F04005	10.3	Died on day 7 of administration.
F04006	14.0	14.4
F04007	18.3	Died on day 8 of administration.
F04008	11.4	Died on day 7 of administration.
F04009	16.0	Sacrificed on day 7 of administration for moribundity.
F04010	10.6	Died on day 7 of administration.
F04011	12.8	Died on day 6 of administration.
F04012	21.2	17.3
F04013	17.1	12.4
Number of females	13	6
Mean	15.7	12.0
S.D.	3.7	5.2
Significance	NS	*
Statistical method	AN	DT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 12-2-1. Food consumption of female rats, satellite group

Corn oil (control)

Female No.	Days of administration					
	1	7	14	21	29	35
F05001	19.9	19.6	18.6	20.1	18.9	18.8
F05002	22.7	21.4	17.5	24.8	18.2	17.2
F05003	17.1	17.1	11.2	14.9	17.6	14.1
F05004	20.7	20.3	14.4	17.5	21.0	18.0
F05005	18.6	17.1	18.0	12.7	11.0	17.0
F05006	18.3	15.4	9.4	16.0	16.1	17.7
F05007	18.7	17.3	14.8	15.4	15.1	13.2
F05008	20.6	18.8	15.1	17.9	20.0	18.2
F05009	16.2	18.1	13.1	18.9	20.7	16.2
F05010	17.0	16.3	16.7	18.5	18.7	18.0
Number of females	10	10	10	10	10	10
Mean	19.0	18.1	14.9	17.7	17.7	16.8
S.D.	2.0	1.9	3.0	3.3	3.0	1.8
						1.7

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 12-2-2. Food consumption of female rats, satellite group

2,4-DTAP 100 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F04001			19.0	19.7	17.8	19.9	20.2
F04002			Died on day 8 of administration.				
F04003			Sacrificed on day 9 of administration for moribundity.				
F04004			18.3	20.1	17.9	14.0	14.8
F04005			Died on day 7 of administration.				
F04006			21.0	9.0	13.7	20.3	12.9
F04007	See appendix 12-1-4		Died on day 8 of administration.				
F04008			Died on day 7 of administration.				
F04009			Sacrificed on day 7 of administration for moribundity.				
F04010			Died on day 7 of administration.				
F04011			Died on day 6 of administration.				
F04012			19.4	20.8	20.5	15.1	17.2
F04013			15.0	18.8	17.5	16.3	18.5
F06001	16.1	11.2	18.3	14.8	16.2	18.8	15.8
F06002	16.5	0.3	Sacrificed on day 8 of administration for moribundity.				
F06003	13.7	0.4	Sacrificed on day 8 of administration for moribundity.				
F06004	16.4	16.0	19.8	18.3	13.7	12.3	13.2
F06005	17.1		Died on day 7 of administration.				
F06006	14.0	17.9	24.1	15.9	15.2	20.3	18.3
F06007	16.7	16.7	24.8	18.9	22.5	20.5	16.8
F06008	18.0		Died on day 8 of administration.				
F06009	18.8	16.4	23.3	15.6	18.1	15.7	17.6
F06010	17.3	15.1	22.5	17.2	18.6	16.8	19.8
Number of females	10	8	11	11	11	11	11
Mean	16.5	11.8	20.5	17.2	17.4	17.3	16.8
S.D.	1.6	7.3	3.0	3.3	2.7	2.9	2.4
Significance	**	*	*	NS	NS	NS	NS
Statistical method	AW	TT	TT	TT	TT	TT	TT

The high dose of 2,4-DTAP was changed from 250 mg/kg to 100 mg/kg on the day 12 of administration.

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 12-3-1. Food consumption of female rats at the recovery period

Corn oil (control)

Female No.	Days of recovery	
	6	12
F05006	21.6	15.3
F05007	20.5	18.7
F05008	21.7	19.5
F05009	19.9	19.3
F05010	22.8	19.8
Number of females	5	5
Mean	21.3	18.5
S.D.	1.1	1.8

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 12-3-2. Food consumption of female rats at the recovery period

2,4-DTAP 100 mg/kg

Female No.	Days of recovery	
	6	12
F04012	21.0	24.5
F04013	21.0	17.4
F06007	28.9	28.0
F06009	21.6	22.5
F06010	15.9	26.0
Number of females	5	5
Mean	21.7	23.7
S.D.	4.6	4.0
Significance	NS	*
Statistical method	AW	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 13-1. Food consumption in dams during pregnancy

Corn oil (control)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	18.6	24.8	19.8	14.3
F01002	16.6	19.2	23.5	17.1
F01003	17.7	26.1	21.5	11.0
F01004	20.4	19.4	20.3	16.5
F01005	14.9	21.3	21.9	13.1
F01006	11.6	22.2	22.5	15.2
F01007	15.3	25.9	21.2	13.8
F01008	15.5	20.5	22.8	16.1
F01009	14.3	23.0	23.6	19.8
F01010	16.8	25.2	22.4	20.1
F01011	20.0	23.7	21.3	13.2
F01012	19.6	18.5	18.5	13.3
F01013	16.6	21.9	22.5	20.4
Number of dams	13	13	13	13
Mean	16.8	22.4	21.7	15.7
S.D.	2.5	2.6	1.5	3.0

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 13-2. Food consumption in dams during pregnancy

2,4-DTAP 10 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02001	16.4	21.5	16.9	1.3
F02002	15.1	23.1	23.7	17.3
F02003	19.8	24.7	21.6	19.4
F02004	15.5	23.7	24.0	13.8
F02005	18.4	23.8	20.7	17.3
F02006	16.4	18.9	19.2	8.0
F02007	21.6	20.9	20.8	21.2
F02008	19.5	31.4	34.8	23.9
F02009	15.8	24.7	21.6	3.6
F02010	15.1	20.6	21.4	15.7
F02011	20.2	26.6	24.2	17.8
F02012	18.6 >	15.5 >	20.8 >	14.2 >
F02013	18.5	25.1	28.5	26.0
Number of dams	12	12	12	12
Mean	17.7	23.8	23.1	15.4
S.D.	2.2	3.3	4.7	7.6
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	KW

>: Excluded from analysis (not pregnant).

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 13-3. Food consumption in dams during pregnancy

2,4-DTAP 50 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03 001	14.8	22.3	25.5	19.3
F03 002	17.4	20.0	19.2	10.5
F03 003	17.2	21.5	22.6	5.1
F03 004	18.0	19.6	20.6	21.0
F03 005	18.8	26.9	24.5	15.5
F03 006	14.9	21.4	17.2	12.8
F03 007	17.5	21.8	18.5	17.1
F03 008	21.2	25.4	25.6	16.5
F03 009	19.2	25.0	21.4	7.6
F03 010	14.0	17.6	19.5	16.3
F03 011	13.4	26.2	28.0	5.4
F03 012	18.3	26.1	26.2	20.0
F03 013	19.8	22.4	27.4	18.9
Number of dams	13	13	13	13
Mean	17.3	22.8	22.8	14.3
S.D.	2.4	2.9	3.6	5.5
Significance	NS	NS	NS	NS
Statistical method	AN	AN	KW	KW

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 14-1. Food consumption in dams during lactation

Corn oil (control)

Dam No.	Days of lactation
	3
F01001	28.7
F01002	31.5
F01003	28.3
F01004	0.2
F01005	0.0
F01006	26.5
F01007	44.6
F01008	39.9
F01009	38.8
F01010	41.7
F01011	0.2
F01012	30.1
F01013	25.8
Number of dams	13
Mean	25.9
S.D.	15.9

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 14-2. Food consumption in dams during lactation

2,4-DTAP 10 mg/kg

Dam No.	Days of lactation
	3
F02002	3.2
F02003	40.1
F02004	30.6
F02005	40.9
F02006	23.3
F02007	48.6
F02008	36.1
F02009	0.7
F02010	34.9
F02011	38.5
F02013	29.3
Number of dams	11
Mean	29.7
S.D.	15.2
Significance	NS
Statistical method	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 14-3. Food consumption in dams during lactation

2,4-DTAP 50 mg/kg

Dam No.	Days of lactation
	3
F03 001	40.4
F03 003	35.5
F03 004	39.5
F03 005	32.4
F03 006	49.5
F03 007	39.7
F03 008	29.6
F03 009	36.6
F03 010	42.8
F03 012	31.4
F03 013	38.4
Number of dams	11
Mean	37.8
S.D.	5.7
Significance	NS
Statistical method	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 15-1. Functional findings of male rats and female rats at the end of the dosing period

Com oil (control)

Male, Administration period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M01001	2	2	2	2	+	+	+
M01002	2	2	2	2	+	+	+
M01003	2	2	2	2	+	+	+
M01004	2	2	2	2	+	+	+
M01005	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

Female, dam

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F01002	2	2	2	2	+	+	+
F01004	2	2	2	2	+	+	+
F01005	2	2	2	2	+	+	+
F01006	2	2	2	2	+	+	+
F01008	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 15-2. Functional findings of male rats and female rats at the end of the dosing period

2,4-DTAP (10 mg/kg)

Male, Administration period

Male No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M02001	2	2	2	2	+	+	+
M02002	2	2	2	2	+	+	+
M02003	2	2	2	2	+	+	+
M02004	2	2	2	2	+	+	+
M02005	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+; 5	+; 5	+; 5

Female, dam

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F02002	2	2	2	2	+	+	+
F02003	2	2	2	2	+	+	+
F02004	2	2	2	2	+	+	+
F02006	2	2	2	2	+	+	+
F02007	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+; 5	+; 5	+; 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 15-3. Functional findings of male rats and female rats at the end of the dosing period

2,4-DTAP (50 mg/kg)

Male, Administration period

Male No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M03001	2	2	2	2	+	+	+
M03002	2	2	2	2	+	+	+
M03003	2	2	2	2	+	+	+
M03004	2	2	2	2	+	+	+
M03005	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+; 5	+; 5	+; 5

Female, dam

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F03001	2	2	2	2	+	+	+
F03003	2	2	2	2	+	+	+
F03004	2	2	2	2	+	+	+
F03008	2	2	2	2	+	+	+
F03009	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+; 5	+; 5	+; 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 15-4. Functional findings of male rats and female rats at the end of the dosing period

2,4-DTAP (100 mg/kg)

Male, Administration period

Male No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M04001	2	2	2	2	+	+	+
M04004	2	2	2	2	+	+	+
M04009	2	2	2	2	+	+	+
M04010	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 15-5. Functional findings of male rats and female rats at the end of the dosing period

Com oil (control)

Female, Administration period

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F05001	2	2	2	2	+	+	+
F05002	2	2	2	2	+	+	+
F05003	2	2	2	2	+	+	+
F05004	2	2	2	2	+	+	+
F05005	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+; 5	+; 5	+; 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 15-6. Functional findings of male rats and female rats at the end of the dosing period

2,4-DTAP (100 mg/kg)

Female, Administration period

Female No.	Righting reflex	Visual placing	Papillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F04001	2	2	2	2	+	+	+
F04004	2	2	2	2	+	+	+
F04006	2	2	2	2	+	+	+
F06001	2	2	2	2	+	+	+
F06004	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 16-1. Functional findings of male rats at the end of the recovery period

Com oil (control)

Male, Recovery period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M01009	2	2	2	2	+	+	+
M01010	2	2	2	2	+	+	+
M01011	2	2	2	2	+	+	+
M01012	2	2	2	2	+	+	+
M01013	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 16-2. Functional findings of male rats at the end of the recovery period

2,4-D TAP (50 mg/kg)

Male, Recovery period

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
M03009	2	2	2	2	+	+	+
M03010	2	2	2	2	+	+	+
M03011	2	2	2	2	+	+	+
M03012	2	2	2	2	+	+	+
M03013	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+; 5	+; 5	+; 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 16-3. Functional findings of female rats at the end of the recovery period

Com oil (control)

Female, Recovery period

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F05006	2	2	2	2	+	+	+
F05007	2	2	2	2	+	+	+
F05008	2	2	2	2	+	+	+
F05009	2	2	2	2	+	+	+
F05010	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 16-4. Functional findings of female rats at the end of the recovery period

2,4-DTAP (100 mg/kg)

Female, Recovery period

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Prayer's reaction	Withdrawal reflex	Eyelid reflex
F04012	2	2	2	2	+	+	+
F04013	2	2	2	2	+	+	+
F06007	2	2	2	2	+	+	+
F06009	2	2	2	2	+	+	+
F06010	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+; 5	+; 5	+; 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 17-1. Assessment of grip strength of male rats

Corn oil (control)

Male No.	Administration period		Male No.	Recovery period	
	Forelimb	Hindlimb		Forelimb	Hindlimb
	(kg)	(kg)		(kg)	(kg)
M01001	0.888	0.944	M01009	1.071	0.496
M01002	1.257	0.824	M01010	1.141	0.565
M01003	1.066	0.707	M01011	1.278	0.722
M01004	1.099	0.668	M01012	1.021	0.562
M01005	0.945	0.589	M01013	1.130	0.556
Number of males	5	5	Number of males	5	5
Mean	1.051	0.746	Mean	1.128	0.580
S.D.	0.144	0.139	S.D.	0.097	0.084

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 17-2. Assessment of grip strength of male rats

2,4-DTAP (10 mg/kg)

Male No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
M02001	1.120	0.537
M02002	1.115	0.705
M02003	1.087	0.515
M02004	1.155	0.472
M02005	1.057	0.502
Number of males	5	5
Mean	1.107	0.546 *
S.D.	0.037	0.092

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 17-3. Assessment of grip strength of male rats

2,4-DTAP (50 mg/kg)

Male No.	Administration period		Male No.	Recovery period	
	Forelimb	Hindlimb		Forelimb	Hindlimb
	(kg)	(kg)		(kg)	(kg)
M03001	0.884	0.440	M03009	1.128	0.597
M03002	1.055	0.447	M03010	1.109	0.366
M03003	1.159	0.415	M03011	1.154	0.641
M03004	1.194	0.489	M03012	1.066	0.566
M03005	1.247	0.621	M03013	1.064	0.598
Number of males	5	5	Number of males	5	5
Mean	1.108	0.482 **	Mean	1.104	0.554
S.D.	0.143	0.082	S.D.	0.039	0.108

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 17-4. Assessment of grip strength of male rats

2,4-DTAP (100 mg/kg)

Male No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
M04001	1.178	0.783
M04004	1.137	0.504
M04009	1.116	0.451
M04010	1.116	0.432
Number of males	4	4
Mean	1.137	0.543
S.D.	0.029	0.163

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 18-1. Assessment of grip strength of female rats

Corn oil (control)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F01002	1.131	0.559
F01004	1.066	0.440
F01005	1.150	0.354
F01006	0.997	0.456
F01008	1.131	0.450
Number of females	5	5
Mean	1.095	0.452
S.D.	0.063	0.073

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 18-2. Assessment of grip strength of female rats

2,4-DTAP (10 mg/kg)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F02002	1.112	0.416
F02003	1.022	0.294
F02004	1.048	0.385
F02006	0.911	0.484
F02007	1.076	0.337
Number of females	5	5
Mean	1.034	0.383
S.D.	0.076	0.073

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 18-3. Assessment of grip strength of female rats

2,4-DTAP (50 mg/kg)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F03001	1.114	0.531
F03003	1.069	0.428
F03004	1.007	0.419
F03008	1.225	0.449
F03009	1.031	0.537
Number of females	5	5
Mean	1.089	0.473
S.D.	0.086	0.057

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 19-1. Assessment of grip strength of female rats, satellite group

Corn oil (control)

Female No.	Administration period		Female No.	Recovery period	
	Forelimb	Hindlimb		Forelimb	Hindlimb
	(kg)	(kg)		(kg)	(kg)
F05001	1.014	0.547	F05006	1.050	0.551
F05002	1.134	0.620	F05007	0.986	0.669
F05003	0.992	0.306	F05008	1.140	0.524
F05004	1.230	0.614	F05009	0.988	0.426
F05005	1.255	0.519	F05010	1.226	0.384
Number of females	5	5	Number of females	5	5
Mean	1.125	0.521	Mean	1.078	0.511
S.D.	0.120	0.128	S.D.	0.104	0.112

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 19-2. Assessment of grip strength of female rats, satellite group

2,4-DTAP (100 mg/kg)

Female No.	Administration period		Female No.	Recovery period	
	Forelimb	Hindlimb		Forelimb	Hindlimb
	(kg)	(kg)		(kg)	(kg)
F04001	0.873	0.317	F04012	1.155	0.595
F04004	1.089	0.370	F04013	1.148	0.401
F04006	1.098	0.693	F06007	1.210	0.499
F06001	1.128	0.333	F06009	1.093	0.454
F06004	1.031	0.573	F06010	1.051	0.439
Number of females	5	5	Number of females	5	5
Mean	1.044	0.457	Mean	1.131	0.478
S.D.	0.102	0.167	S.D.	0.061	0.074

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 20-1. Motor activity of male rats

Corn oil (control)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1212	975	905	395	3487	36	22	20	2	80
M01002	1156	1029	1078	582	3845	48	30	24	15	117
M01003	1101	1063	925	869	3958	37	30	28	17	112
M01004	1140	1150	1045	807	4142	33	27	31	7	98
M01005	1261	1240	1170	914	4585	42	49	27	17	135
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1174	1091	1025	713	4003	39	32	26	12	108
S.D.	63	105	110	219	404	6	10	4	7	21
Male No.										
Recovery period										
Male No.	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01009	872	788	762	765	3187	42	35	34	23	134
M01010	1050	986	857	691	3584	36	22	19	13	90
M01011	905	946	689	590	3130	36	25	25	10	96
M01012	1153	1099	1021	780	4053	57	39	34	22	152
M01013	1108	969	741	337	3155	37	32	21	7	97
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1018	958	814	633	3422	42	31	27	15	114
S.D.	124	112	131	182	399	9	7	7	7	28

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 20-2. Motor activity of male rats

2,4-DTAP (10 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02001	972	868	784	647	3271	28	26	13	23	90
M02002	1160	1129	967	978	4234	31	43	23	27	124
M02003	1109	987	744	682	3522	33	22	10	16	81
M02004	1228	1175	1037	521	3961	39	32	19	6	96
M02005	1053	849	620	524	3046	39	20	14	9	82
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1104	1002	830	670	3607	34	29	16	16	95
S.D.	98	148	170	186	488	5	9	5	9	18

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 20-3. Motor activity of male rats

2,4-DTAP (50 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03001	1324	1134	1082	736	4276	49	49	39	21	158
M03002	1123	1094	875	731	3823	43	30	16	11	100
M03003	1175	1047	552	651	3425	34	30	6	11	81
M03004	1271	1167	866	722	4026	41	33	13	10	97
M03005	1872	1658	1308	1499	6337	36	34	14	23	107
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1353	1220	937	868	4377	41	35	18	15	109
S.D.	301	249	281	355	1139	6	8	13	6	29
Recovery period										
Male No.	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
	1086	958	664	731	3439	37	40	17	27	121
M03009	1284	1097	1156	1035	4572	41	32	24	35	132
M03010	1203	914	1233	1045	4395	36	9	36	20	101
M03011	769	843	688	603	2903	32	34	24	25	115
M03012	1385	1419	999	835	4638	49	39	24	17	129
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1145	1046	948	850	3989	39	31	25	25	120
S.D.	237	228	262	192	776	6	13	7	7	12

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 20-4. Motor activity of male rats

2,4-DTAP (100 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04001	1149	910	768	509	3336	31	28	17	8	84
M04004	1171	1044	945	563	3723	41	31	16	10	98
M04009	1197	1083	965	833	4078	33	25	19	14	91
M04010	753	634	651	630	2668	32	28	20	26	106
Number of males	4	4	4	4	4	4	4	4	4	4
Mean	1068	918	832	634	3451	34	28	18	15	95
S.D.	211	203	150	142	604	5	2	2	8	9

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 21-1. Motor activity of female rats

Corn oil (control)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01002	1139	913	880	792	3724	34	4	8	13	59
F01004	960	255	417	2	1634	23	3	7	0	33
F01005	1134	484	645	26	2289	29	13	11	0	53
F01006	1203	732	560	493	2988	63	26	11	10	110
F01008	1208	1005	858	703	3774	31	14	20	10	75
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1129	678	672	403	2882	36	12	11	7	66
S.D.	101	309	198	372	925	16	9	5	6	29

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 21-2. Motor activity of female rats

2,4-DTAP (10 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02002	720	841	443	136	2140	13	21	9	0	43
F02003	1182	914	939	532	4234	37	8	14	3	62
F02004	1027	831	697	523	3522	24	17	13	0	54
F02006	1120	995	883	806	3961	35	20	13	16	84
F02007	1134	910	895	594	3046	34	19	26	3	82
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1037	898	771	518	3381	29	17	15	4	65
S.D.	186	66	206	242	827	10	5	6	7	18

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 21-3. Motor activity of female rats

2,4-DTAP (50 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03001	1266	1126	795	851	4038	55	20	14	8	97
F03003	1024	722	883	615	3244	26	17	22	12	77
F03004	1242	887	843	895	3867	44	18	8	11	81
F03008	843	676	854	607	2980	22	7	5	5	39
F03009	1713	1475	1330	1343	5861	33	23	12	6	74
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1218	977	941	862	3998	36	17	12	8	74
S.D.	326	329	220	299	1129	14	6	6	3	21

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 22-1. Motor activity of female rats, satellite group

Corn oil (control)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05001	1357	1285	1250	1008	4900	47	49	36	31	163
F05002	1307	1195	883	741	4126	39	30	25	24	118
F05003	1248	1160	1194	1057	4659	50	46	41	35	172
F05004	1277	1201	1091	874	4443	43	40	20	14	117
F05005	1433	1052	955	726	4166	75	30	38	18	161
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1324	1179	1075	881	4459	51	39	32	24	146
S.D.	73	84	155	151	328	14	9	9	9	27
Female No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05006	1371	931	786	932	4020	71	25	18	21	135
F05007	1106	957	680	773	3516	46	31	8	12	97
F05008	1111	737	927	651	3426	37	17	25	10	89
F05009	1188	873	926	893	3880	34	20	17	10	81
F05010	1620	1210	1509	844	5183	27	11	36	5	79
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1279	942	966	819	4005	43	21	21	12	96
S.D.	219	172	321	111	703	17	8	10	6	23

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 22-2. Motor activity of female rats, satellite group

2,4-DTAP (100 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04001	912	742	985	907	3546	30	13	20	26	89
F04004	1247	1146	1084	923	4234	38	31	31	22	122
F04006	973	1032	970	787	3522	28	26	22	16	92
F06001	1249	1144	1109	824	3961	40	22	36	15	113
F06004	1271	1082	737	779	3046	57	36	24	20	137
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1130	1029	977	844	3662	39	26	27	20	111
S.D.	173	167	147	67	455	11	9	7	4	20
Female No.	Recovery period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04012	1147	1165	1095	881	4288	42	39	38	20	139
F04013	1132	1119	692	857	3800	35	33	7	16	91
F06007	1358	1320	1189	850	4717	25	31	19	6	81
F06009	816	651	509	613	2589	36	12	8	11	67
F06010	1399	1463	1439	1399	5700	47	38	38	47	170
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1170	1144	985	920	4219	37	31	22	20	110
S.D.	232	307	378	289	1149	8	11	15	16	43

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 23-1-1. Urinalysis in male rats

Com oil (control)

Male No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	-	-
M01002	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	-	-
M01003	Light yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-
M01004	Light yellow	-	7.0	+	-	-	-	-	±	-	-	-	-	-
M01005	Yellow	-	7.0	2+	-	+	-	-	2+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M01001	10.8	1.050	80.4	159.9	79.3	0.87	1.73	0.86
M01002	9.2	1.078	143.0	207.0	191.0	1.32	1.90	1.76
M01003	8.1	1.073	190.0	199.1	196.8	1.54	1.61	1.59
M01004	17.0	1.042	76.4	167.2	95.7	1.30	2.84	1.63
M01005	6.3	1.086	184.0	198.0	214.8	1.16	1.25	1.35
Number of males	5	5	5	5	5	5	5	5
Mean	10.3	1.066	134.8	186.2	155.5	1.24	1.87	1.44
±S.D.	4.1	0.019	54.6	21.2	63.0	0.25	0.59	0.36

Turbidity, -: negative

Protein, +: 30≤ and < 100 mg/dL; 2+: 100≤ and < 300 mg/dL; 3+: 300≤ and < 600 mg/dL

Glucose, -: negative; ±: 30≤ and < 70 mg/dL

Ketone, -: negative; ±: 5≤ and < 10 mg/dL; +: 10≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, -: normal; +: 2.0≤ and < 4.0 mg/dL; 2+: 4.0≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 23-1-2. Urinalysis in male rats

2,4-DTAP (10 mg/kg)

Male No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02001	Yellow	-	6.5	3+	±	+	-	-	+	-	-	-	±	-
M02002	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	±
M02003	Yellow	-	7.5	2+	-	+	-	-	+	-	-	-	±	-
M02004	Light yellow	-	7.5	+	-	+	-	-	±	-	-	-	±	-
M02005	Yellow	-	7.0	2+	-	+	-	-	2+	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M02001	6.1	1.086	178.5	231.8	188.4	1.09	1.41	1.15
M02002	25.0	1.027	56.4	124.3	71.1	1.41	3.11	1.78
M02003	10.5	1.068	118.3	187.8	168.8	1.24	1.97	1.77
M02004	12.3	1.066	169.4	198.7	191.3	2.08	2.44	2.35
M02005	8.6	1.078	111.7	185.2	149.2	0.96	1.59	1.28
Number of males	5	5	5	5	5	5	5	5
Mean	12.5	1.065	126.9	185.6	153.8	1.36	2.10	1.67
±S.D.	7.4	0.023	49.4	39.0	49.2	0.44	0.69	0.48

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, +: 30≤ and < 100 mg/dL; 2+: 100≤ and < 300 mg/dL; 3+: 300≤ and < 600 mg/dL

Glucose, -: negative; ±: 30≤ and < 70 mg/dL

Ketone, -: negative; ±: 5≤ and < 10 mg/dL; +: 10≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0≤ and < 4.0 mg/dL; 2+: 4.0≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 23-1-3. Urinalysis in male rats

2,4-DTAP (50 mg/kg)

Male No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03001	Yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-
M03002	Light yellow	-	6.5	2+	-	+	-	-	±	-	-	-	-	-
M03003	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	-	-
M03004	Light yellow	-	6.5	+	-	+	-	-	±	-	-	-	-	-
M03005	Light yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M03001	8.8	1.067	138.8	173.4	166.3	1.22	1.53	1.46
M03002	14.5	1.059	126.8	195.7	139.3	1.84	2.84	2.02
M03003	31.9	1.019	41.4	91.3	42.9	1.32	2.91	1.37
M03004	10.1	1.061	166.0	210.3	153.3	1.68	2.12	1.55
M03005	11.0	1.059	76.8	196.9	91.9	0.84	2.17	1.01
Number of males	5	5	5	5	5	5	5	5
Mean	15.3	1.053	110.0	173.5	118.7	1.38	2.31	1.48
±S.D.	9.5	0.019	50.1	47.8	50.9	0.39	0.57	0.36

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, +: 30≤ and < 100 mg/dL; 2+: 100≤ and < 300 mg/dL; 3+: 300≤ and < 600 mg/dL

Glucose, -: negative; ±: 30≤ and < 70 mg/dL

Ketone, -: negative; ±: 5≤ and < 10 mg/dL; +: 10≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0≤ and < 4.0 mg/dL; 2+: 4.0≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 23-1-4. Urinalysis in male rats

2,4-DTAP (100 mg/kg)

Male No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04001	Light yellow	-	7.5	+	-	+	-	-	±	-	-	-	±	-
M04004	Light yellow	-	8.0	+	-	-	-	-	±	-	-	-	±	-
M04009	Light yellow	-	8.0	±	-	±	-	-	±	-	-	-	-	-
M04010	Light yellow	-	6.5	±	-	±	-	-	±	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M04001	21.5	1.038	75.3	171.2	97.2	1.62	3.68	2.09
M04004	17.4	1.044	92.9	171.4	115.8	1.62	2.98	2.01
M04009	32.8	1.021	51.6	84.1	41.5	1.69	2.76	1.36
M04010	18.2	1.036	94.1	141.3	110.6	1.71	2.57	2.01
Number of males	4	4	4	4	4	4	4	4
Mean	22.5	1.035	78.5	142.0	91.3	1.66	3.00	1.87
±S.D.	7.1	0.010	19.9	41.1	34.1	0.05	0.48	0.34

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, +: 30≤ and < 100 mg/dL; 2+: 100≤ and < 300 mg/dL; +3: 300≤ and < 600 mg/dL

Glucose, -: negative; ±: 30≤ and < 70 mg/dL

Ketone, -: negative; ±: 5≤ and < 10 mg/dL; +: 10≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0≤ and < 4.0 mg/dL; 2+: 4.0≤ and < 8.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed

Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 23-2-1. Urinalysis in male rats of the recovery period

Com oil (control)

Male No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01009	Light yellow	-	8.5	+	-	-	-	-	±	-	-	-	±	-
M01010	Light yellow	-	7.5	2+	-	+	-	-	+	-	-	-	±	-
M01011	Light yellow	-	8.0	+	-	-	-	-	±	-	-	-	±	-
M01012	Light yellow	-	8.0	+	-	±	-	-	±	-	-	-	±	-
M01013	Light yellow	-	7.5	+	-	+	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M01009	13.0	1.069	141.1	260.2	132.8	1.83	3.38	1.73
M01010	10.6	1.077	133.9	250.1	162.1	1.42	2.65	1.72
M01011	18.8	1.056	110.9	224.4	132.2	2.08	4.22	2.49
M01012	16.2	1.065	128.4	206.6	144.9	2.08	3.35	2.35
M01013	12.2	1.080	153.9	418.5	190.1	1.88	5.11	2.32
Number of males	5	5	5	5	5	5	5	5
Mean	14.2	1.069	133.6	272.0	152.4	1.86	3.74	2.12
±S.D.	3.3	0.010	15.9	84.6	24.3	0.27	0.95	0.37

Turbidity, -: negative

Protein, +: 30≤ and < 100 mg/dL; 2+: 100≤ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5≤ and < 10 mg/dL; +: 10≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative; +: 0.06≤ and < 0.20 mg/dL

Urobilinogen, ±: normal; +: 2.0≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed; +: 10-99/3 visual field

Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 23-2-2. Urinalysis in male rats of the recovery period

2,4-DTAP (50 mg/kg)

Male No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03009	Light yellow	-	8.0	+	-	±	-	-	+	-	-	-	±	-
M03010	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M03011	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M03012	Light yellow	-	8.5	+	-	±	-	-	±	-	-	-	±	-
M03013	Light yellow	-	7.0	+	-	±	-	+	+	+	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M03009	13.5	1.065	84.7	198.1	117.1	1.14	2.67	1.58
M03010	18.3	1.052	98.5	177.2	95.8	1.80	3.24	1.75
M03011	14.3	1.071	161.1	395.4	173.1	2.30	5.65	2.48
M03012	15.6	1.068	132.6	261.5	149.8	2.07	4.08	2.34
M03013	11.0	1.071	132.7	198.9	139.4	1.46	2.19	1.53
Number of males	5	5	5	5	5	5	5	5
Mean	14.5	1.065	121.9	246.2	135.0	1.75	3.57	1.94
±S.D.	2.7	0.008	30.4	89.2	29.8	0.46	1.36	0.44

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, +: 30≤ and <100 mg/dL; 2+: 100≤ and <300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5≤ and < 10 mg/dL; +: 10≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative; +: 0.06≤ and < 0.20 mg/dL

Urobilinogen, ±: normal; +: 2.0≤ and < 4.0 mg/dL

Red blood cells, White blood cells and Casts, -: not observed; +: 10-99/3 visual field

Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 24-1-1. Urinalysis in female rats, satellite group

Corn oil (control)

Male No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05001	Yellow	-	6.5	2+	±	+	-	-	+	-	-	-	-	-
F05002	Light yellow	-	8.0	-	-	-	-	-	±	-	-	-	±	-
F05003	Light yellow	-	7.0	±	-	±	-	-	±	-	-	-	-	-
F05004	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	-	-
F05005	Light yellow	-	6.0	±	-	±	-	-	±	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05001	7.8	1.066	77.1	177.2	153.4	0.60	1.38	1.20
F05002	19.1	1.037	73.9	139.7	90.5	1.41	2.67	1.73
F05003	8.1	1.063	105.1	204.1	138.7	0.85	1.65	1.12
F05004	9.6	1.067	127.9	173.5	149.5	1.23	1.67	1.44
F05005	13.0	1.025	38.3	96.8	28.9	0.50	1.26	0.38
Number of females	5	5	5	5	5	5	5	5
Mean	11.5	1.052	84.5	158.3	112.2	0.92	1.73	1.17
±S.D.	4.7	0.019	33.9	41.3	52.9	0.39	0.56	0.50

Turbidity, -: negative

Protein, -: negative; ±: 10≤ and < 30 mg/dL; +: 30≤ and < 100 mg/dL; 2+: 100≤ and < 300 mg/dL

Glucose, -: negative; ±: 30≤ and < 70 mg/dL

Ketone, -: negative; ±: 5≤ and < 10 mg/dL; +: 10≤ and < 40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0≤ and < 4.0 mg/dL

Red blood cells, White blood cells, Casts and Epithelial cells -: not observed

Crystals, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 24-1-2. Urinalysis in female rats, satellite group

2,4-DTAP (100 mg/kg)

Male No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F04001	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	-	-
F04004	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	-	-
F04006	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	-	-
F06001	Light yellow	-	6.5	±	-	-	-	-	±	-	-	-	-	-
F06004	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	-	±

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F04001	20.6	1.023	41.2	92.3	37.3	0.85	1.90	0.77
F04004	20.0	1.026	45.3	110.3	58.8	0.91	2.21	1.18
F04006	14.4	1.026	65.1	92.7	59.0	0.94	1.33	0.85
F06001	19.7	1.032	75.6	124.4	89.8	1.49	2.45	1.77
F06004	18.2	1.034	71.9	145.3	90.4	1.31	2.64	1.65
Number of females	5	5	5	5	5	5	5	5
Mean	18.6*	1.028	59.8	113.0	67.1	1.10	2.11	1.24
±S.D.	2.5	0.005	15.7	22.5	22.8	0.28	0.51	0.45

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, -: negative; ±: 10≤ and <30 mg/dL; +: 30≤ and <100 mg/dL; 2+: 100≤ and <300 mg/dL

Glucose, -: negative; ±: 30≤ and <70 mg/dL

Ketone, -: negative; ±: 5≤ and <10 mg/dL; +: 10≤ and <40 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0≤ and <4.0 mg/dL

Red blood cells, White blood cells, Casts and Epithelial cells -: not observed

Crystals, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 24-2-1. Urinalysis in female rats of the recovery period

Corn oil (control)

Female No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells ^{a)}	White blood cells ^{a)}	Casts ^{a)}	Crystals ^{b)}	Epithelial cells ^{b)}
F05006	Light yellow	-	6.0	+	-	±	-	-	±	-	-	-	-	-
F05007	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	-
F05008	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	±	-
F05009	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	±	-
F05010	Light yellow	-	7.0	±	-	-	-	-	+	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05006	6.0	1.080	65.0	246.8	124.3	0.39	1.48	0.75
F05007	18.6	1.045	83.0	159.7	107.7	1.54	2.97	2.00
F05008	10.8	1.077	142.2	229.6	172.9	1.54	2.48	1.87
F05009	12.1	1.072	142.6	211.8	173.2	1.73	2.56	2.10
F05010	9.7	1.064	117.5	202.7	145.0	1.14	1.97	1.41
Number of females	5	5	5	5	5	5	5	5
Mean	11.4	1.068	110.1	210.1	144.6	1.27	2.29	1.63
±S.D.	4.6	0.014	35.0	32.9	29.1	0.54	0.58	0.56

Turbidity, -: negative

Protein, -: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL

Red blood cells, White blood cells, Casts and Epithelial cells -: not observed

Crystals, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 24-2-2. Urinalysis in female rats of the recovery period

2,4-DTAP (100 mg/kg)

Female No.	Quality								Urinary sediments					
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells ^{a)}	White blood cells ^{a)}	Casts ^{a)}	Crystals ^{b)}	Epithelial cells ^{b)}
F04012	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F04013	Light yellow	-	6.5	+	-	-	-	-	+	-	-	-	±	-
F06007	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	±	-
F06009	Light yellow	-	7.0	+	-	-	-	-	+	-	-	-	±	-
F06010	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F04012	17.5	1.048	115.7	184.0	98.7	2.02	3.22	1.73
F04013	8.2	1.080	146.6	240.6	185.9	1.20	1.97	1.52
F06007	25.2	1.023	43.3	104.6	22.3	1.09	2.64	0.56
F06009	15.7	1.066	128.3	207.8	161.1	2.01	3.26	2.53
F06010	9.1	1.053	76.2	143.6	45.5	0.69	1.31	0.41
Number of females	5	5	5	5	5	5	5	5
Mean	15.1	1.054	102.0	176.1	102.7	1.40	2.48	1.35
±S.D.	6.9	0.021	41.8	53.4	70.9	0.59	0.84	0.88

Significantly different from the control group (*: P<0.05, **: P<0.01).

Turbidity, -: negative

Protein, -: negative; ±: 10≤and<30 mg/dL; +: 30≤and<100 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: 5≤and<10 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

Urobilinogen, ±: normal; +: 2.0≤and<4.0 mg/dL

Red blood cells, White blood cells, Casts and Epithelial cells -: not observed

Crystals, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 25-1-1. Hematological findings of male rats at the end of the dosing period

Corn oil (control)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M01001	944	15.3	44.0	46.6	16.2	34.8	121.0	14.1	23.4
M01002	907	15.5	44.3	48.8	17.1	35.0	120.8	17.9	27.8
M01003	863	15.6	46.6	54.0	18.1	33.5	106.6	26.1	28.8
M01004	811	15.3	45.7	56.4	18.9	33.5	102.5	20.3	26.7
M01005	820	15.1	44.0	53.7	18.4	34.3	114.9	21.7	28.1
Number of males	5	5	5	5	5	5	5	5	5
Mean	869	15.4	44.9	51.9	17.7	34.2	113.2	20.0	27.0
S.D.	57	0.2	1.2	4.0	1.1	0.7	8.4	4.5	2.1

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M01001	113.1	9.9	0.4	0.0	2.1	87.6	2.42
M01002	151.8	12.4	1.3	0.1	4.5	81.7	2.69
M01003	73.4	21.1	1.9	0.0	4.1	72.9	2.61
M01004	62.5	23.5	1.3	0.0	3.0	72.2	3.12
M01005	75.2	23.9	0.9	0.0	4.3	70.9	2.38
Number of males	5	5	5	5	5	5	5
Mean	95.2	18.2	1.2	0.0	3.6	77.1	2.64
S.D.	37.0	6.5	0.6	0.0	1.0	7.3	0.30

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 25-1-2. Hematological findings of male rats at the end of the dosing period

2,4-DTAP (10 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M02001	878	15.0	43.8	49.9	17.1	34.2	115.1	21.2	25.4
M02002	875	14.9	43.1	49.3	17.0	34.6	119.0	14.8	25.0
M02003	907	15.3	44.7	49.3	16.9	34.2	135.9	30.4	42.1
M02004	890	15.4	43.5	48.9	17.3	35.4	132.1	13.0	22.8
M02005	879	15.0	42.9	48.8	17.1	35.0	146.3	38.8	42.1
Number of males	5	5	5	5	5	5	5	5	5
Mean	886	15.1	43.6	49.2	17.1	34.7	129.7	23.6	31.5
S.D.	13	0.2	0.7	0.4	0.1	0.5	12.7	10.9	9.7

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M02001	80.1	17.0	0.5	0.0	4.6	77.9	3.04
M02002	56.5	23.0	1.1	0.0	4.2	71.7	2.29
M02003	116.0	15.2	0.8	0.0	2.1	81.9	2.35
M02004	74.9	15.6	1.5	0.0	3.2	79.7	2.41
M02005	106.1	17.1	1.0	0.0	3.2	78.7	2.43
Number of males	5	5	5	5	5	5	5
Mean	86.7	17.6	1.0	0.0	3.5	78.0	2.50
S.D.	24.1	3.1	0.4	0.0	1.0	3.8	0.30

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 25-1-3. Hematological findings of male rats at the end of the dosing period

2,4-DTAP (50 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M03001	867	15.1	44.5	51.3	17.4	33.9	117.3	17.1	32.2
M03002	830	14.6	43.6	52.5	17.6	33.5	115.6	22.8	27.6
M03003	851	14.7	42.7	50.2	17.3	34.4	137.2	29.5	32.5
M03004	867	15.1	43.4	50.1	17.4	34.8	104.8	38.7	38.5
M03005	834	15.1	43.9	52.6	18.1	34.4	98.9	23.7	29.4
Number of males	5	5	5	5	5	5	5	5	5
Mean	850	14.9	43.6	51.3	17.6	34.2	114.8	26.4	32.0
S.D.	18	0.2	0.7	1.2	0.3	0.5	14.7	8.2	4.1

Male No.	WBC	NEUT	EOSI	BAZO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M03001	131.9	14.3	0.8	0.0	2.4	82.5	2.59
M03002	101.8	15.8	1.0	0.0	3.4	79.8	2.89
M03003	95.2	23.2	1.3	0.1	4.2	71.2	2.92
M03004	56.4	27.8	2.5	0.0	2.3	67.4	2.63
M03005	93.4	21.2	1.8	0.0	5.8	71.2	1.94
Number of males	5	5	5	5	5	5	5
Mean	95.7	20.5	1.5	0.0	3.6	74.4	2.59
S.D.	26.9	5.5	0.7	0.0	1.4	6.4	0.39

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 25-1-4. Hematological findings of male rats at the end of the dosing period

2,4-DTAP (100 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M04001	870	15.1	44.4	51.0	17.4	34.0	116.0	45.8	41.6
M04004	725	13.3	39.5	54.5	18.3	33.7	126.5	41.3	45.6
M04009	778	13.5	39.4	50.6	17.4	34.3	136.2	32.7	35.5
M04010	824	13.6	40.6	49.3	16.5	33.5	118.0	36.8	43.9
Number of males	4	4	4	4	4	4	4	4	4
Mean	799	13.9 **	41.0 **	51.4	17.4	33.9	124.2	39.2 **	41.7
S.D.	62	0.8	2.3	2.2	0.7	0.4	9.2	5.7	4.4

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M04001	98.4	19.3	0.6	0.0	3.2	76.9	3.17
M04004	136.1	11.9	1.3	0.1	2.5	84.2	3.38
M04009	87.0	26.7	0.8	0.0	4.6	67.9	2.62
M04010	98.1	22.9	1.2	0.0	2.1	73.8	2.54
Number of males	4	4	4	4	4	4	4
Mean	104.9	20.2	1.0	0.0	3.1	75.7	2.93
S.D.	21.5	6.3	0.3	0.1	1.1	6.8	0.41

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 25-2-1. Hematological findings of male rats at the end of the recovery period

Com oil (control)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M01009	854	14.6	43.2	50.6	17.1	33.8	120.5	17.6	24.9
M01010	929	15.9	47.1	50.7	17.1	33.8	112.6	18.3	24.2
M01011	844	14.7	43.0	50.9	17.4	34.2	102.8	18.7	23.7
M01012	892	15.2	44.5	49.9	17.0	34.2	117.9	20.9	27.3
M01013	867	14.9	43.7	50.4	17.2	34.1	112.2	25.9	28.5
Number of males	5	5	5	5	5	5	5	5	5
Mean	877	15.1	44.3	50.5	17.2	34.0	113.2	20.3	25.7
S.D.	34	0.5	1.7	0.4	0.2	0.2	6.8	3.4	2.1

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M01009	52.1	21.9	3.3	0.0	4.2	70.6	2.45
M01010	59.5	26.5	2.2	0.0	4.7	66.6	2.61
M01011	57.9	39.1	2.6	0.0	2.9	55.4	3.55
M01012	47.6	24.8	2.3	0.0	3.2	69.7	2.88
M01013	76.2	32.3	1.3	0.0	3.3	63.1	3.09
Number of males	5	5	5	5	5	5	5
Mean	58.7	28.9	2.3	0.0	3.7	65.1	2.92
S.D.	10.9	6.8	0.7	0.0	0.8	6.2	0.43

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 25-2-2. Hematological findings of male rats at the end of the recovery period

2,4-DTAP (50 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M03009	852	14.2	41.8	49.1	16.7	34.0	115.4	13.6	24.6
M03010	881	15.2	44.6	50.6	17.3	34.1	133.6	11.8	16.6
M03011	875	15.2	44.4	50.7	17.4	34.2	105.6	28.1	29.3
M03012	904	15.7	46.8	51.8	17.4	33.5	106.1	21.8	26.3
M03013	865	14.4	42.1	48.7	16.6	34.2	98.9	15.7	21.7
Number of males	5	5	5	5	5	5	5	5	5
Mean	875	14.9	43.9	50.2	17.1	34.0	111.9	18.2	23.7
S.D.	19	0.6	2.0	1.3	0.4	0.3	13.5	6.7	4.8

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M03009	79.8	33.8	1.8	0.0	4.5	59.9	3.75
M03010	55.8	17.5	1.3	0.2	3.0	78.0	2.87
M03011	60.9	33.5	1.3	0.0	5.1	60.1	3.59
M03012	52.3	25.3	1.1	0.0	3.4	70.2	3.08
M03013	40.7	23.3	1.0	0.0	2.5	73.2	2.27
Number of males	5	5	5	5	5	5	5
Mean	57.9	26.7	1.3 *	0.0	3.7	68.3	3.11
S.D.	14.3	7.0	0.3	0.1	1.1	8.1	0.59

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 26-1-1. Hematological findings of female rats at the end of the dosing period

Corn oil (control)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F01002	602	11.7	35.8	59.5	19.4	32.7	73.2	11.4	16.8
F01004	752	13.7	35.6	47.3	18.2	38.5	83.3	10.8	18.1
F01006	600	11.3	33.8	56.3	18.8	33.4	83.9	11.3	16.5
F01008	664	12.8	38.5	58.0	19.3	33.2	116.9	10.8	18.2
F01011	688	13.6	37.3	54.2	19.8	36.5	141.6	12.1	16.1
Number of females	5	5	5	5	5	5	5	5	5
Mean	661	12.6	36.2	55.1	19.1	34.9	99.8	11.3	17.1
S.D.	64	1.1	1.8	4.8	0.6	2.5	28.6	0.5	1.0
Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET		
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)		
F01002	75.7	31.7	0.8	0.0	0.8	66.7	7.16		
F01004	84.9	42.9	0.7	0.0	6.5	49.9	2.60		
F01006	94.2	32.9	0.3	0.0	1.1	65.7	6.08		
F01008	125.0	25.6	0.6	0.0	2.6	71.2	6.47		
F01011	90.2	44.6	0.3	0.0	5.4	49.7	1.39		
Number of females	5	5	5	5	5	5	5		
Mean	94.0	35.5	0.5	0.0	3.3	60.6	4.74		
S.D.	18.7	8.0	0.2	0.0	2.6	10.1	2.57		

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 26-1-2. Hematological findings of female rats at the end of the dosing period

2,4-DTAP (10 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F02002	754	12.9	38.2	50.7	17.1	33.8	134.6	11.8	16.4
F02003	641	11.6	34.2	53.4	18.1	33.9	111.1	11.4	17.4
F02004	704	12.7	38.4	54.5	18.0	33.1	158.3	12.1	17.0
F02006	631	12.0	36.2	57.4	19.0	33.1	92.4	12.6	15.5
F02007	743	13.8	40.9	55.0	18.6	33.7	117.4	11.5	17.7
Number of females	5	5	5	5	5	5	5	5	5
Mean	695	12.6	37.6	54.2	18.2	33.5	122.8	11.9	16.8
S.D.	57	0.9	2.5	2.4	0.7	0.4	24.9	0.5	0.9

Female No.	WBC	NEUT	EOSI	BAZO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F02002	124.7	41.7	0.3	0.0	3.7	54.3	2.86
F02003	84.6	29.7	0.4	0.0	0.6	69.3	6.70
F02004	82.7	19.1	1.5	0.0	5.3	74.1	5.53
F02006	59.5	23.7	0.5	0.0	3.7	72.1	8.40
F02007	123.1	26.4	0.6	0.0	3.7	69.3	6.19
Number of females	5	5	5	5	5	5	5
Mean	94.9	28.1	0.7	0.0	3.4	67.8	5.94
S.D.	28.2	8.5	0.5	0.0	1.7	7.8	2.02

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 26-1-3. Hematological findings of female rats at the end of the dosing period

2,4-DTAP (50 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F03001	679	13.1	40.0	58.9	19.3	32.8	105.5	11.6	15.9
F03003	641	11.9	35.9	56.0	18.6	33.1	110.9	11.8	17.4
F03004	643	12.0	36.5	56.8	18.7	32.9	115.0	11.4	16.9
F03008	583	11.5	36.5	62.6	19.7	31.5	120.5	11.1	19.7
F03009	627	11.8	36.5	58.2	18.8	32.3	91.0	10.5	19.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	635	12.1	37.1	58.5	19.0	32.5 *	108.6	11.3	17.8
S.D.	35	0.6	1.7	2.6	0.5	0.6	11.3	0.5	1.6

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F03001	128.3	23.2	0.8	0.0	4.1	71.9	8.20
F03003	81.2	32.7	0.1	0.0	2.8	64.4	7.38
F03004	110.0	25.7	0.8	0.0	2.9	70.6	9.98
F03008	119.8	40.6	0.2	0.1	1.7	57.4	11.38
F03009	79.3	37.6	0.3	0.1	3.0	59.0	9.42
Number of females	5	5	5	5	5	5	5
Mean	103.7	32.0	0.4	0.0	2.9	64.7	9.27 **
S.D.	22.4	7.5	0.3	0.1	0.9	6.6	1.56

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 26-2-1. Hematological findings of female rats at the end of the dosing period, satellite group

Corn oil (control)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F05001	754	14.6	43.2	57.3	19.4	33.8	101.8	10.8	19.1
F05002	780	14.9	44.2	56.7	19.1	33.7	104.3	10.6	18.9
F05003	770	14.4	43.1	56.0	18.7	33.4	95.6	11.0	20.6
F05004	758	14.0	42.2	55.7	18.5	33.2	97.5	11.0	18.6
F05005	882	15.7	44.5	50.5	17.8	35.3	102.3	11.0	16.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	789	14.7	43.4	55.2	18.7	33.9	100.3	10.9	18.6
S.D.	53	0.6	0.9	2.7	0.6	0.8	3.6	0.2	1.7

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F05001	74.0	14.4	1.1	0.0	3.0	81.5	2.83
F05002	50.6	8.8	0.8	0.0	3.0	87.4	4.08
F05003	47.3	5.0	1.5	0.0	1.5	92.0	3.11
F05004	49.6	8.7	1.4	0.0	2.8	87.1	3.97
F05005	40.1	8.3	1.5	0.0	3.7	86.5	2.54
Number of females	5	5	5	5	5	5	5
Mean	52.3	9.0	1.3	0.0	2.8	86.9	3.31
S.D.	12.8	3.4	0.3	0.0	0.8	3.7	0.69

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 26-2-2. Hematological findings of female rats at the end of the dosing period, satellite group

2,4-DTAP (100 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F04001	761	13.4	39.2	51.5	17.6	34.2	113.1	11.6	19.7
F04004	702	13.1	38.5	54.8	18.7	34.0	118.1	10.6	18.5
F04006	752	13.7	40.8	54.3	18.2	33.6	118.4	11.2	17.8
F06001	693	12.7	37.9	54.7	18.3	33.5	124.0	11.1	15.6
F06004	711	13.1	38.9	54.7	18.4	33.7	99.1	11.1	16.9
Number of females	5	5	5	5	5	5	5	5	5
Mean	724 *	13.2 **	39.1 **	54.0	18.2	33.8	114.5 *	11.1	17.7
S.D.	31	0.4	1.1	1.4	0.4	0.3	9.5	0.4	1.6

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F04001	103.8	7.8	0.8	0.0	3.0	88.4	3.00
F04004	62.2	7.7	1.0	0.0	1.9	89.4	3.10
F04006	53.3	13.5	2.1	0.0	3.0	81.4	3.71
F06001	59.4	10.1	1.5	0.0	2.9	85.5	2.40
F06004	57.1	11.2	0.9	0.0	2.6	85.3	2.35
Number of females	5	5	5	5	5	5	5
Mean	67.2	10.1	1.3	0.0	2.7	86.0	2.91
S.D.	20.7	2.4	0.5	0.0	0.5	3.1	0.56

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 26-3-1. Hematological findings of female rats at the end of the recovery period

Corn oil (control)

Female No.	RBC ($\times 10^4/\mu\text{L}$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($\times 10^4/\mu\text{L}$)	PT (sec)	APTT (sec)
F05006	831	14.2	42.3	50.9	17.1	33.6	97.0	10.8	18.1
F05007	877	15.7	46.0	52.5	17.9	34.1	103.0	11.4	19.6
F05008	807	13.7	40.2	49.8	17.0	34.1	98.9	11.2	16.0
F05009	788	14.4	42.7	54.2	18.3	33.7	125.6	12.0	18.8
F05010	815	14.7	43.5	53.4	18.0	33.8	99.9	10.8	18.1
Number of females	5	5	5	5	5	5	5	5	5
Mean	824	14.5	42.9	52.2	17.7	33.9	104.9	11.2	18.1
S.D.	34	0.7	2.1	1.8	0.6	0.2	11.8	0.5	1.3
Female No.	WBC ($\times 10^2/\mu\text{L}$)	NEUT (%)	EOSI (%)	BASO (%)	MONO (%)	LYMPH (%)	RET (%)		
F05006	67.4	6.2	1.0	0.0	2.4	90.4	2.23		
F05007	45.2	9.3	1.8	0.0	3.1	85.8	3.01		
F05008	53.8	9.2	3.2	0.0	4.1	83.5	2.56		
F05009	45.5	13.4	3.3	0.0	2.9	80.4	2.76		
F05010	48.1	12.7	2.1	0.0	2.7	82.5	2.44		
Number of females	5	5	5	5	5	5	5		
Mean	52.0	10.2	2.3	0.0	3.0	84.5	2.60		
S.D.	9.3	2.9	1.0	0.0	0.6	3.8	0.30		

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 26-3-2. Hematological findings of female rats at the end of the recovery period

2,4-D TAP (100 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F04012	846	15.4	44.4	52.5	18.2	34.7	103.6	11.1	16.9
F04013	777	13.9	42.1	54.2	17.9	33.0	100.3	11.1	17.2
F06007	789	14.3	43.6	55.3	18.1	32.8	96.0	11.5	16.8
F06009	786	14.4	44.4	56.5	18.3	32.4	100.9	10.8	20.4
F06010	792	14.4	42.8	54.0	18.2	33.6	101.7	11.7	17.7
Number of females	5	5	5	5	5	5	5	5	5
Mean	798	14.5	43.5	54.5	18.1	33.3	100.5	11.2	17.8
S.D.	27	0.6	1.0	1.5	0.2	0.9	2.8	0.4	1.5

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F04012	75.3	11.2	0.9	0.1	3.9	83.9	2.44
F04013	120.3	3.8	1.2	0.0	1.7	93.3	2.81
F06007	44.8	14.2	1.8	0.0	3.6	80.4	2.56
F06009	52.1	12.2	2.9	0.0	3.5	81.4	3.41
F06010	50.9	14.3	2.6	0.0	3.1	80.0	2.62
Number of females	5	5	5	5	5	5	5
Mean	68.7	11.1	1.9	0.0	3.2	83.8	2.77
S.D.	31.1	4.3	0.9	0.0	0.9	5.5	0.38

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 27-1-1. Biochemical findings of male rats at the end of the dosing period

Corn oil (control)

Male No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Tri-glyceride	Phospholipid	AST	ALT	γ -GTP	LDH	Bile acid
	(g/dL)	(g/dL)		(mg/dL)	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(U/L)	(U/L)	(U/L)	(μ mol/L)
M01001	5.4	3.7	2.18	153	69	36	98	55	27	0	82	33.9
M01002	5.6	3.6	1.80	119	53	79	91	86	49	0	76	8.2
M01003	4.7	3.1	1.94	136	38	24	61	51	25	0	64	4.1
M01004	5.4	3.5	1.84	143	45	34	75	55	21	0	260	3.8
M01005	5.7	3.6	1.71	135	61	69	103	55	27	0	175	9.8
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.5	1.89	137	53	48	86	60	30	0	131	12.0
S.D.	0.4	0.2	0.18	12	12	24	17	14	11	0	84	12.5
Male No.	Blood urea nitrogen	Creatinine	Total bilirubin	ALP	Inorganic phosphorus	Ca	Na	K	Cl			
	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(mg/dL)	(mg/dL)	(mEq/L)	(mEq/L)	(mEq/L)			
M01001	13	0.5	0.07	408	5.8	9.0	143.3	4.08	107.1			
M01002	11	0.5	0.05	378	4.8	9.3	143.0	3.80	106.8			
M01003	11	0.4	0.03	301	6.5	8.7	145.0	3.97	110.1			
M01004	13	0.4	0.04	308	6.7	9.2	145.0	3.81	108.5			
M01005	12	0.4	0.05	412	6.7	9.8	145.1	3.95	106.8			
Number of males	5	5	5	5	5	5	5	5	5			
Mean	12	0.4	0.05	361	6.1	9.2	144.3	3.92	107.9			
S.D.	1	0.1	0.01	54	0.8	0.4	1.0	0.12	1.4			

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 27-1-2. Biochemical findings of male rats at the end of the dosing period

2,4-DTAP (10 mg/kg)

Male No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Tri-glyceride	Phospholipid	AST	ALT	γ -GTP	LDH	Bile acid
	(g/dL)	(g/dL)		(mg/dL)	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(U/L)	(U/L)	(U/L)	(μ mol/L)
M02001	5.4	3.5	1.84	132	35	46	61	69	26	0	163	5.0
M02002	5.2	3.5	2.06	129	56	38	80	58	25	0	89	4.6
M02003	5.4	3.5	1.84	142	55	126	99	48	22	0	58	3.4
M02004	5.5	3.5	1.75	151	49	54	88	55	25	0	71	10.7
M02005	4.9	3.3	2.06	127	43	50	78	66	43	0	98	9.9
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.3	3.5	1.91	136	48	63	81	59	28	0	96	6.7
S.D.	0.2	0.1	0.14	10	9	36	14	8	8	0	41	3.3

Male No.	Blood urea nitrogen	Creatinine	Total bilirubin	ALP	Inorganic phosphorus	Ca	Na	K	Cl
	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(mg/dL)	(mg/dL)	(mEq/L)	(mEq/L)	(mEq/L)
M02001	9	0.5	0.05	540	5.5	9.1	143.9	3.84	108.7
M02002	13	0.4	0.05	338	5.3	9.2	145.0	3.58	108.4
M02003	12	0.4	0.04	411	6.3	9.4	144.9	4.00	107.5
M02004	12	0.4	0.05	335	5.7	9.2	145.7	3.37	108.3
M02005	11	0.3	0.04	387	6.2	9.3	144.3	4.06	107.4
Number of males	5	5	5	5	5	5	5	5	5
Mean	11	0.4	0.05	402	5.8	9.2	144.8	3.77	108.1
S.D.	2	0.1	0.01	84	0.4	0.1	0.7	0.29	0.6

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 27-1-3. Biochemical findings of male rats at the end of the dosing period

2,4-DTAP (50 mg/kg)

Male No.	Total protein	Albumin	A/G	Glucose	Total cholesterol	Tri-glyceride	Phospholipid	AST	ALT	γ -GTP	LDH	Bile acid
	(g/dL)	(g/dL)		(mg/dL)	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(U/L)	(U/L)	(U/L)	(μ mol/L)
M03001	5.2	3.5	2.06	142	63	69	96	52	34	0	78	5.8
M03002	5.1	3.5	2.19	146	64	43	86	52	19	0	191	2.4
M03003	5.2	3.6	2.25	138	68	47	86	54	19	0	93	2.9
M03004	4.9	3.2	1.88	124	41	36	65	52	27	0	52	3.0
M03005	5.3	3.5	1.94	137	55	65	84	65	31	0	75	3.1
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.1	3.5	2.06	137	58	52	83	55	26	0	98	3.4
S.D.	0.2	0.2	0.16	8	11	14	11	6	7	0	54	1.3

Male No.	Blood urea nitrogen	Creatinine	Total bilirubin	ALP	Inorganic phosphorus	Ca	Na	K	Cl
	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(mg/dL)	(mg/dL)	(mEq/L)	(mEq/L)	(mEq/L)
M03001	13	0.4	0.07	637	5.6	9.4	142.8	3.85	106.0
M03002	11	0.4	0.05	514	6.2	9.1	143.5	3.73	109.4
M03003	13	0.4	0.04	457	6.8	9.4	144.9	4.06	108.3
M03004	11	0.3	0.04	326	6.1	9.1	145.2	3.76	110.5
M03005	11	0.4	0.05	399	6.3	9.9	143.1	3.62	105.8
Number of males	5	5	5	5	5	5	5	5	5
Mean	12	0.4	0.05	467	6.2	9.4	143.9	3.80	108.0
S.D.	1	0.0	0.01	118	0.4	0.3	1.1	0.17	2.1

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 27-1-4. Biochemical findings of male rats at the end of the dosing period

2,4-DTAP (100 mg/kg)

Male No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ -GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
M04001	5.3	3.3	1.65	131	53	35	78	56	23	0	66	3.6
M04004	5.0	3.4	2.13	140	49	20	67	56	24	0	61	2.5
M04009	5.2	3.4	1.89	149	63	59	92	59	29	0	166	3.8
M04010	5.1	3.3	1.83	135	47	39	71	61	29	0	145	2.2
Number of males	4	4	4	4	4	4	4	4	4	4	4	4
Mean	5.2	3.4	1.88	139	53	38	77	58	26	0	110	3.0
S.D.	0.1	0.1	0.20	8	7	16	11	2	3	0	54	0.8

Male No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
M04001	10	0.4	0.07	429	6.1	8.9	144.1	3.96	108.3
M04004	17	0.5	0.06	1224	6.9	9.3	142.8	4.12	107.2
M04009	13	0.4	0.05	669	7.3	9.5	145.6	3.89	109.5
M04010	13	0.4	0.05	480	7.3	9.2	143.6	3.88	107.6
Number of males	4	4	4	4	4	4	4	4	4
Mean	13	0.4	0.06	701	6.9	9.2	144.0	3.96	108.2
S.D.	3	0.1	0.01	364	0.6	0.3	1.2	0.11	1.0

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 27-2-1. Biochemical findings of male rats at the end of the recovery period

Corn oil (control)

Male No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ -GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
M01009	6.1	3.8	1.65	149	79	26	104	114	31	0	104	9.5
M01010	5.8	3.6	1.64	132	54	17	72	69	27	0	54	6.9
M01011	5.7	3.6	1.71	127	69	20	91	68	23	0	349	4.8
M01012	5.8	3.5	1.52	142	61	30	83	86	26	0	92	6.3
M01013	5.4	3.5	1.84	141	49	28	75	83	28	0	121	8.6
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.6	1.67	138	62	24	85	84	27	0	144	7.2
S.D.	0.3	0.1	0.12	9	12	5	13	19	3	0	117	1.9

Male No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
M01009	13	0.5	0.04	230	4.6	9.4	144.1	3.79	106.7
M01010	17	0.5	0.04	283	5.5	9.2	145.2	3.76	107.6
M01011	16	0.5	0.03	242	4.6	9.1	145.9	3.61	110.9
M01012	15	0.4	0.03	311	5.0	9.4	144.0	3.65	106.4
M01013	14	0.4	0.05	301	5.9	9.2	144.6	3.49	109.0
Number of males	5	5	5	5	5	5	5	5	5
Mean	15	0.5	0.04	273	5.1	9.3	144.8	3.66	108.1
S.D.	2	0.1	0.01	36	0.6	0.1	0.8	0.12	1.9

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 27-2-2. Biochemical findings of male rats at the end of the recovery period

2,4-DTAP (50 mg/kg)

Male No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ-GTP (U/L)	LDH (U/L)	Bile acid (μmol/L)
M03009	6.1	3.9	1.77	138	54	27	77	93	42	0	136	29.3
M03010	5.4	3.5	1.84	151	66	51	92	70	29	0	152	3.8
M03011	5.8	3.7	1.76	125	45	56	81	72	29	0	81	9.0
M03012	5.2	3.4	1.89	139	62	36	87	87	27	0	131	7.5
M03013	5.6	3.6	1.80	137	51	13	73	105	32	0	155	24.7
Number of males	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.6	1.81 *	138	56	37	82	85	32	0	131	14.9
S.D.	0.3	0.2	0.05	9	8	18	8	15	6	0	30	11.4

Male No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mEq/L)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
M03009	18	0.5	0.05	370	5.5	9.7	143.5	4.00	104.9
M03010	15	0.4	0.04	258	5.1	9.3	144.9	3.60	108.4
M03011	15	0.4	0.05	332	5.7	9.3	145.3	3.53	108.1
M03012	17	0.4	0.04	347	5.5	9.4	144.7	3.36	108.3
M03013	16	0.5	0.05	304	5.7	9.5	145.8	3.88	109.6
Number of males	5	5	5	5	5	5	5	5	5
Mean	16	0.4	0.05	322	5.5	9.4	144.8	3.67	107.9
S.D.	1	0.1	0.01	43	0.2	0.2	0.9	0.26	1.8

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 28-1-1. Biochemical findings of female rats at the end of the dosing period

Com oil (control)

female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ -GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
F01002	5.7	3.8	2.00	110	74	37	120	191	125	0	51	19.7
F01004	4.8	3.3	2.20	99	57	22	88	154	89	0	89	5.4
F01006	5.3	3.7	2.31	127	75	35	102	118	112	1	48	13.4
F01008	5.3	3.7	2.31	114	58	30	100	78	43	0	204	19.5
F01011	5.0	3.5	2.33	82	68	19	99	84	49	0	72	15.0
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.2	3.6	2.23	106	66	29	102	125	84	0	93	14.6
S.D.	0.3	0.2	0.14	17	9	8	12	48	37	0	64	5.8

female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F01002	7	0.4	0.05	172	6.7	9.9	143.5	3.80	107.2
F01004	15	0.6	0.06	258	7.9	8.7	134.4	2.59	91.6
F01006	6	0.5	0.06	287	7.6	10.4	144.6	3.80	108.6
F01008	13	0.5	0.06	165	6.0	9.3	144.0	3.74	110.1
F01011	10	0.6	0.05	142	8.0	9.0	142.4	2.56	92.2
Number of females	5	5	5	5	5	5	5	5	5
Mean	10	0.5	0.06	205	7.2	9.5	141.8	3.30	101.9
S.D.	4	0.1	0.01	64	0.9	0.7	4.2	0.66	9.2

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 28-1-2. Biochemical findings of female rats at the end of the dosing period

2,4-DTAP (10 mg/kg)

female No.	Total	Albumin	A/G	Glucose	Total	Tri-	Phospholipid	AST	ALT	γ -GTP	LDH	Bile acid
	protein (g/dL)	(g/dL)		(mg/dL)	cholesterol (mg/dL)	glyceride (mg/dL)	(mg/dL)	(U/L)	(U/L)	(U/L)	(U/L)	(μ mol/L)
F02002	4.6	3.5	3.18	166	65	63	109	61	42	0	58	29.5
F02003	5.7	3.8	2.00	118	81	32	136	116	53	0	47	20.0
F02004	5.8	4.2	2.63	139	54	53	92	64	27	0	118	15.6
F02006	5.4	3.6	2.00	122	53	27	77	73	30	0	187	8.5
F02007	5.9	3.9	1.95	133	64	41	108	56	39	0	63	10.5
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.8	2.35	136 *	63	43	104	74 *	38 *	0	95	16.8
S.D.	0.5	0.3	0.54	19	11	15	22	24	10	0	59	8.4

female No.	Blood urea	Creatinine	Total	ALP	Inorganic	Ca	Na	K	Cl
	nitrogen (mg/dL)	(mg/dL)	bilirubin (mg/dL)	(U/L)	phosphorus (mg/dL)	(mg/dL)	(mEq/L)	(mEq/L)	(mEq/L)
F02002	6	0.6	0.08	382	7.0	9.5	141.2	3.44	100.4
F02003	13	0.5	0.06	168	6.5	10.4	143.3	3.52	107.3
F02004	14	0.5	0.07	167	6.4	10.6	142.4	3.43	105.5
F02006	10	0.5	0.05	254	7.4	10.1	145.1	3.40	108.5
F02007	16	0.6	0.03	115	6.1	10.1	144.2	3.24	108.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	12	0.5	0.06	217	6.7	10.1	143.2	3.41	105.9
S.D.	4	0.1	0.02	105	0.5	0.4	1.5	0.10	3.3

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 28-1-3. Biochemical findings of female rats at the end of the dosing period

2,4-DTAP (50 mg/kg)

female No.	Total	Albumin	A/G	Glucose	Total	Tri-	Phospholipid	AST	ALT	γ -GTP	LDH	Bile acid
	protein				cholesterol	glyceride						
	(g/dL)	(g/dL)		(mg/dL)	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(U/L)	(U/L)	(U/L)	(μ mol/L)
F03001	6.2	4.2	2.10	121	66	70	119	76	45	0	195	6.4
F03003	5.8	4.0	2.22	130	89	79	137	61	32	0	71	6.0
F03004	5.6	3.8	2.11	132	67	42	111	57	30	0	49	8.4
F03008	5.2	3.4	1.89	137	75	53	123	85	57	0	88	5.7
F03009	6.1	4.1	2.05	123	77	22	114	78	43	0	245	6.3
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.9	2.07	129	75	53	121	71	41	0	130	6.6
S.D.	0.4	0.3	0.12	7	9	23	10	12	11	0	86	1.1
female No.	Blood urea	Creatinine	Total	ALP	Inorganic	Ca	Na	K	Cl			
	nitrogen		bilirubin		phosphorus							
	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(mg/dL)	(mg/dL)	(mEq/L)	(mEq/L)	(mEq/L)			
F03001	11	0.5	0.06	258	5.8	10.1	142.3	3.62	107.6			
F03003	9	0.5	0.06	227	6.1	9.9	143.9	3.49	109.6			
F03004	15	0.5	0.05	202	6.3	9.4	141.9	3.69	107.2			
F03008	7	0.4	0.03	319	5.5	9.5	142.4	3.40	107.0			
F03009	9	0.5	0.04	234	6.2	10.2	145.2	3.29	108.4			
Number of females	5	5	5	5	5	5	5	5	5			
Mean	10	0.5	0.05	248	6.0 *	9.8	143.1	3.50	108.0			
S.D.	3	0.0	0.01	44	0.3	0.4	1.4	0.16	1.1			

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 28-2-1. Biochemical findings of female rats at the end of the dosing period, satellite group

Corn oil (control)

female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ -GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
F05001	6.0	4.6	3.29	133	67	22	118	61	30	0	61	8.4
F05002	6.5	4.7	2.61	142	73	51	124	52	18	0	142	9.0
F05003	5.9	4.3	2.69	149	93	31	142	49	19	0	64	14.8
F05004	5.9	4.1	2.28	150	58	12	104	86	26	0	85	6.5
F05005	6.1	4.2	2.21	115	63	13	106	63	20	0	122	10.8
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	4.4	2.62	138	71	26	119	62	23	0	95	9.9
S.D.	0.2	0.3	0.43	14	14	16	15	15	5	0	36	3.1

female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mEq/L)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
F05001	14	0.6	0.05	194	5.0	9.8	142.8	3.58	108.3
F05002	13	0.7	0.05	185	4.0	10.1	143.8	3.68	107.9
F05003	12	0.6	0.05	193	5.0	9.5	143.3	3.83	108.1
F05004	15	0.6	0.05	232	5.4	9.5	143.1	3.86	107.7
F05005	21	0.7	0.05	293	5.2	9.7	144.4	4.03	109.1
Number of females	5	5	5	5	5	5	5	5	5
Mean	15	0.6	0.05	219	4.9	9.7	143.5	3.80	108.2
S.D.	4	0.1	0.00	45	0.5	0.2	0.6	0.17	0.5

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 28-2-2. Biochemical findings of female rats at the end of the dosing period, satellite group

2,4-DTAP (100 mg/kg)

female No.	Total	Albumin	A/G	Glucose	Total	Tri-	Phospholipid	AST	ALT	γ -GTP	LDH	Bile acid
	protein				cholesterol	glyceride						
	(g/dL)	(g/dL)		(mg/dL)	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(U/L)	(U/L)	(U/L)	(μ mol/L)
F04001	6.5	4.6	2.42	165	103	27	167	46	15	0	57	8.9
F04004	6.2	4.2	2.10	124	81	9	120	48	18	3	91	7.9
F04006	5.8	4.0	2.22	107	70	10	110	56	19	0	79	6.2
F06001	5.9	4.0	2.11	139	96	22	149	49	17	0	49	4.1
F06004	6.4	4.6	2.56	128	89	17	138	58	15	0	243	8.4
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.2	4.3	2.28	133	88	17	137	51	17	1	104	7.1
S.D.	0.3	0.3	0.20	21	13	8	23	5	2	1	80	2.0

female No.	Blood urea	Creatinine	Total	ALP	Inorganic	Ca	Na	K	Cl
	nitrogen		bilirubin		phosphorus				
	(mg/dL)	(mg/dL)	(mg/dL)	(U/L)	(mg/dL)	(mg/dL)	(mEq/L)	(mEq/L)	(mEq/L)
F04001	11	0.6	0.08	255	5.9	10.0	142.4	3.80	104.2
F04004	18	0.7	0.07	242	5.7	10.0	145.0	4.14	108.4
F04006	17	0.7	0.06	205	4.9	9.6	143.7	3.82	105.9
F06001	14	0.6	0.06	181	6.1	9.8	143.2	4.20	107.4
F06004	14	0.7	0.08	362	5.4	10.1	143.2	3.84	106.4
Number of females	5	5	5	5	5	5	5	5	5
Mean	15	0.7	0.07	249	5.6	9.9	143.5	3.96	106.5
S.D.	3	0.1	0.01	70	0.5	0.2	1.0	0.19	1.6

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 28-3-1. Biochemical findings of female rats at the end of the recovery period

Com oil (control)

female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ -GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
F05006	5.9	4.0	2.11	114	75	11	94	107	51	2	71	19.2
F05007	6.3	4.2	2.00	134	68	21	110	56	19	0	42	8.5
F05008	6.0	4.2	2.33	122	82	60	136	50	19	0	97	5.5
F05009	6.0	4.5	3.00	138	63	52	120	42	15	0	26	16.6
F05010	6.1	4.1	2.05	133	63	21	108	61	21	0	74	9.7
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.1	4.2	2.30	128	70	33	114	63	25	0	62	11.9
S.D.	0.2	0.2	0.41	10	8	22	16	25	15	1	28	5.8
female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)			
F05006	13	0.5	0.06	142	5.2	9.5	142.6	3.64	108.0			
F05007	11	0.5	0.08	134	4.8	9.7	143.6	3.48	107.7			
F05008	14	0.6	0.10	85	4.3	10.1	143.8	3.44	107.8			
F05009	17	0.6	0.06	99	3.7	9.3	144.6	3.13	109.9			
F05010	19	0.6	0.05	130	4.3	9.7	143.3	3.47	108.8			
Number of females	5	5	5	5	5	5	5	5	5			
Mean	15	0.6	0.07	118	4.5	9.7	143.6	3.43	108.4			
S.D.	3	0.1	0.02	25	0.6	0.3	0.7	0.19	0.9			

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 28-3-2. Biochemical findings of female rats at the end of the recovery period

2,4-DTAP (100 mg/kg)

female No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	Phospholipid (mg/dL)	AST (U/L)	ALT (U/L)	γ -GTP (U/L)	LDH (U/L)	Bile acid (μ mol/L)
F04012	6.4	4.5	2.37	128	100	29	149	65	22	0	46	15.6
F04013	6.1	4.1	2.05	114	69	26	119	74	41	0	65	13.8
F06007	5.6	3.7	1.95	134	82	31	121	53	18	0	44	3.6
F06009	6.7	4.6	2.19	137	97	97	167	52	18	0	31	16.8
F06010	6.1	4.1	2.05	140	68	15	105	75	18	0	97	8.4
Number of females	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.2	4.2	2.12	131	83	40	132	64	23	0	57	11.6
S.D.	0.4	0.4	0.16	10	15	33	25	11	10	0	26	5.5
female No.	Blood urea nitrogen (mg/dL)	Creatinine (mg/dL)	Total bilirubin (mg/dL)	ALP (U/L)	Inorganic phosphorus (mg/dL)	Ca (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)			
F04012	13	0.6	0.10	98	5.6	10.3	142.0	3.66	105.1			
F04013	18	0.5	0.06	151	5.7	9.7	143.3	3.74	106.9			
F06007	13	0.6	0.08	81	5.0	9.3	143.1	3.50	109.8			
F06009	14	0.4	0.05	96	3.7	10.3	144.8	3.36	109.5			
F06010	14	0.6	0.06	113	4.0	10.0	144.3	3.39	109.6			
Number of females	5	5	5	5	5	5	5	5	5			
Mean	14	0.5	0.07	108	4.8	9.9	143.5	3.53	108.2			
S.D.	2	0.1	0.02	27	0.9	0.4	1.1	0.17	2.1			

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-1-1. Organ weights of male rats at the end of the dosing period

Corn oil (control)

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	450.2	2129.9	4.731	451.1	1.002	1421.2	3.157	11715.3	26.022	1331.1	2.957	1333.8	2.963	2664.9	5.919	760.4	1.689
M01002	472.6	1995.8	4.223	317.5	0.672	1362.6	2.883	13215.7	27.964	1480.8	3.133	1502.3	3.179	2983.1	6.312	826.7	1.749
M01003	465.3	2095.3	4.503	194.8	0.419	1338.8	2.877	12639.4	27.164	1435.5	3.085	1411.2	3.033	2846.7	6.118	780.6	1.678
M01004	496.5	1960.9	3.949	340.9	0.687	1582.8	3.188	13931.1	28.059	1507.5	3.036	1508.6	3.038	3016.1	6.075	972.2	1.958
M01005	504.4	2033.2	4.031	384.8	0.763	1427.9	2.831	13120.0	26.011	1735.3	3.440	1673.7	3.318	3409.0	6.759	774.8	1.536
M01006	492.5	1969.8	4.000	297.0	0.603	1524.6	3.096	14572.1	29.588	1408.3	2.859	1358.6	2.759	2766.9	5.618	815.1	1.655
M01007	436.0	2026.7	4.648	225.5	0.517	1302.8	2.988	10671.4	24.476	1332.5	3.056	1360.7	3.121	2693.2	6.177	618.8	1.419
M01008	515.3	1968.7	3.820	248.3	0.482	1406.0	2.729	13786.9	26.755	1635.2	3.173	1649.1	3.200	3284.3	6.374	814.3	1.580
Number of males	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	479.1	2022.5	4.238	307.5	0.643	1420.8	2.969	12956.5	27.005	1483.3	3.092	1474.8	3.076	2958.0	6.169	795.4	1.658
S.D.	27.7	62.3	0.346	85.2	0.185	93.6	0.166	1265.3	1.565	141.9	0.172	132.2	0.170	272.2	0.336	97.1	0.159

Appendix 29-1-1 (continued). Organ weights of male rats at the end of the dosing period

Corn oil (vehicle)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	1677.7	3.727	1705.3	3.788	3383.0	7.514	584.3	1.298	570.2	1.267	1154.5	2.564	667.9	1.484	1243.6	2.762
M01002	1695.3	3.587	1689.5	3.575	3384.8	7.162	649.0	1.373	650.1	1.376	1299.1	2.749	758.6	1.605	1551.6	3.283
M01003	1559.6	3.352	1544.8	3.320	3104.4	6.672	654.3	1.406	625.4	1.344	1279.7	2.750	734.4	1.578	1899.7	4.083
M01004	1729.8	3.484	1687.0	3.398	3416.8	6.882	615.1	1.239	590.5	1.189	1205.6	2.428	554.2	1.116	1616.8	3.256
M01005	1677.8	3.326	1688.4	3.347	3366.2	6.674	647.4	1.284	647.0	1.283	1294.4	2.566	839.1	1.664	1635.1	3.242
M01006	1445.2	2.934	1391.9	2.826	2837.1	5.761	592.4	1.203	629.8	1.279	1222.2	2.482	311.4	0.632	1456.9	2.958
M01007	1672.2	3.835	1697.9	3.894	3370.1	7.730	625.0	1.433	565.3	1.297	1190.3	2.730	766.9	1.759	2089.3	4.792
M01008	1795.3	3.484	1718.4	3.335	3513.7	6.819	654.2	1.270	632.8	1.228	1287.0	2.498	582.5	1.130	1909.8	3.706
Number of males	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	1656.6	3.466	1640.4	3.435	3297.0	6.902	627.7	1.313	613.9	1.283	1241.6	2.596	651.9	1.371	1675.4	3.510
S.D.	107.8	0.277	114.3	0.329	218.8	0.603	28.2	0.082	33.7	0.059	55.4	0.130	167.8	0.381	275.5	0.661

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-1-1 (continued). Organ weights of male rats at the end of the dosing period

Corn oil (control)								
Male No.	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	25.8	0.057	25.7	0.057	25.2	0.056	50.9	0.113
M01002	25.5	0.054	27.5	0.058	27.6	0.058	55.1	0.117
M01003	20.8	0.045	25.3	0.054	30.8	0.066	56.1	0.121
M01004	18.7	0.038	22.2	0.045	22.4	0.045	44.6	0.090
M01005	24.5	0.049	26.8	0.053	30.3	0.060	57.1	0.113
M01006	16.8	0.034	25.2	0.051	30.4	0.062	55.6	0.113
M01007	22.5	0.052	22.0	0.050	24.2	0.056	46.2	0.106
M01008	19.1	0.037	28.5	0.055	30.5	0.059	59.0	0.114
Number of males	8	8	8	8	8	8	8	8
Mean	21.7	0.046	25.4	0.053	27.7	0.058	53.1	0.111
S.D.	3.4	0.009	2.3	0.004	3.3	0.006	5.3	0.009

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-1-2. Organ weights of male rats at the end of the dosing period

2,4-DTAP 10 mg/kg

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02001	437.1	2005.9	4.589	248.9	0.569	1330.6	3.044	11393.7	26.067	1446.3	3.309	1425.9	3.262	2872.2	6.571	535.0	1.224
M02002	433.8	2217.0	5.111	202.9	0.468	1324.2	3.053	11171.9	25.754	1315.7	3.033	1309.1	3.018	2624.8	6.051	614.7	1.417
M02003	510.0	2042.6	4.005	338.8	0.664	1562.8	3.064	16125.0	31.618	1590.7	3.119	1698.6	3.331	3289.3	6.450	892.0	1.749
M02004	533.0	2015.1	3.781	285.1	0.535	1414.5	2.654	15963.6	29.950	1572.4	2.950	1554.9	2.917	3127.3	5.867	790.0	1.482
M02005	479.6	1991.7	4.153	352.4	0.735	1439.2	3.001	13764.1	28.699	1845.2	3.847	1867.9	3.895	3713.1	7.742	810.8	1.691
M02006	449.0	2004.0	4.463	301.8	0.672	1321.3	2.943	12552.4	27.956	1378.6	3.070	1398.5	3.115	2777.1	6.185	817.2	1.820
M02007	451.4	1969.0	4.362	208.0	0.461	1141.8	2.529	11806.7	26.156	1319.8	2.924	1336.4	2.961	2656.2	5.884	741.2	1.642
M02008	411.0	1976.7	4.809	368.6	0.897	1246.7	3.033	10870.0	26.448	1455.2	3.541	1442.2	3.509	2897.4	7.050	647.8	1.576
M02009	484.2	1997.9	4.126	300.9	0.621	1175.9	2.429	12788.0	26.411	1309.3	2.704	1307.4	2.700	2616.7	5.404	861.3	1.779
M02010	446.9	1895.4	4.241	219.6	0.491	1224.9	2.741	12422.1	27.796	1468.0	3.285	1416.0	3.168	2884.0	6.453	819.6	1.834
M02011	516.0	2006.6	3.889	273.3	0.530	1394.6	2.703	13643.5	26.441	1434.2	2.779	1519.0	2.944	2953.2	5.723	957.1	1.855
M02012	481.6	2044.7	4.246	186.5	0.387	1392.9	2.892	16309.2	33.865	1580.7	3.282	1559.4	3.238	3140.1	6.520	753.2	1.564
M02013	512.4	1931.5	3.770	255.3	0.498	1511.6	2.950	14933.4	29.144	1790.2	3.494	1807.2	3.527	3597.4	7.021	609.9	1.190
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	472.8	2007.5	4.273	272.5	0.579	1344.7	2.849	13364.9	28.177	1500.5	3.180	1511.0	3.199	3011.4	6.379	757.7	1.602
S.D.	37.6	75.1	0.396	59.1	0.137	125.4	0.215	1935.8	2.454	171.1	0.323	182.8	0.316	351.3	0.634	123.8	0.222
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	DU	DU	KW	AN	KW	AN	KW	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-1-2 (continued). Organ weights of male rats at the end of the dosing period

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02001	1782.5	4.078	1767.7	4.044	3550.2	8.122	694.1	1.588	627.0	1.434	1321.1	3.022	665.5	1.523	1539.6	3.522
M02002	1610.1	3.712	1703.6	3.927	3313.7	7.639	628.2	1.448	651.6	1.502	1279.8	2.950	773.7	1.784	1738.5	4.008
M02003	1672.2	3.279	1685.3	3.305	3357.5	6.583	764.8	1.500	727.6	1.427	1492.4	2.926	910.4	1.785	2156.0	4.227
M02004	1633.5	3.065	1652.7	3.101	3286.2	6.165	680.1	1.276	664.0	1.246	1344.1	2.522	761.2	1.428	1843.1	3.458
M02005	1568.2	3.270	1605.6	3.348	3173.8	6.618	724.1	1.510	690.2	1.439	1414.3	2.949	692.2	1.443	1927.7	4.019
M02006	1635.3	3.642	1638.4	3.649	3273.7	7.291	591.2	1.317	595.8	1.327	1187.0	2.644	644.5	1.435	2237.0	4.982
M02007	1607.2	3.560	1651.2	3.658	3258.4	7.218	642.2	1.423	645.7	1.430	1287.9	2.853	574.3	1.272	1957.9	4.337
M02008	1708.1	4.156	1688.1	4.107	3396.2	8.263	650.7	1.583	637.6	1.551	1288.3	3.135	472.1	1.149	1857.8	4.520
M02009	1653.9	3.416	1620.2	3.346	3274.1	6.762	612.4	1.265	573.5	1.184	1185.9	2.449	539.6	1.114	1690.0	3.490
M02010	1594.4	3.568	1632.4	3.653	3226.8	7.220	679.9	1.521	621.8	1.391	1301.7	2.913	667.5	1.494	1981.5	4.434
M02011	2085.5	4.042	1980.6	3.838	4066.1	7.880	746.9	1.447	705.9	1.368	1452.8	2.816	703.0	1.362	1829.0	3.545
M02012	1589.8	3.301	1576.7	3.274	3166.5	6.575	638.1	1.325	652.1	1.354	1290.2	2.679	418.3	0.869	1746.3	3.626
M02013	1599.1	3.121	1640.4	3.201	3239.5	6.322	621.7	1.213	668.2	1.304	1289.9	2.517	785.2	1.532	1782.0	3.478
Number of males	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	1672.3	3.555	1680.2	3.573	3352.5	7.128	667.3	1.417	650.8	1.381	1318.1	2.798	662.1	1.399	1868.2	3.973
S.D.	136.8	0.362	102.3	0.335	236.7	0.690	53.4	0.125	42.4	0.100	90.5	0.216	135.5	0.256	188.1	0.498
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	KW	AN	AN	AN	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-1-2 (continued). Organ weights of male rats at the end of the dosing period

2,4-DTAP 10 mg/kg

Male No.	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02001	20.7	0.047	27.1	0.062	30.5	0.070	57.6	0.132
M02002	20.6	0.047	28.6	0.066	29.3	0.068	57.9	0.133
M02003	29.5	0.058	25.6	0.050	27.9	0.055	53.5	0.105
M02004	19.7	0.037	27.6	0.052	23.2	0.044	50.8	0.095
M02005	20.6	0.043	23.0	0.048	24.0	0.050	47.0	0.098
M02006	16.5	0.037	23.4	0.052	24.2	0.054	47.6	0.106
M02007	18.9	0.042	19.4	0.043	20.7	0.046	40.1	0.089
M02008	26.0	0.063	24.9	0.061	22.8	0.055	47.7	0.116
M02009	21.3	0.044	22.0	0.045	23.6	0.049	45.6	0.094
M02010	23.6	0.053	26.8	0.060	28.0	0.063	54.8	0.123
M02011	19.1	0.037	30.9	0.060	35.4	0.069	66.3	0.128
M02012	18.1	0.038	28.8	0.060	31.2	0.065	60.0	0.125
M02013	32.8	0.064	26.7	0.052	28.9	0.056	55.6	0.109
Number of males	13		13		13		13	
Mean	22.1	0.047	25.8	0.055	26.9	0.057	52.7	0.112
S.D.	4.7	0.010	3.2	0.007	4.2	0.009	7.1	0.015
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-1-3. Organ weights of male rats at the end of the dosing period

2,4-DTAP 50 mg/kg																	
Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)		
M03001	438.9	2024.0	4.612	328.8	0.749	1212.7	2.763	13033.6	29.696	1430.8	3.260	1439.1	3.279	2869.9	6.539	678.0	1.545
M03002	472.3	1977.8	4.188	401.3	0.850	1216.5	2.576	14399.5	30.488	1420.3	3.007	1314.7	2.784	2735.0	5.791	778.4	1.648
M03003	471.2	2115.3	4.489	311.3	0.661	1481.3	3.144	15868.8	33.677	1518.5	3.223	1576.8	3.346	3095.3	6.569	813.2	1.726
M03004	437.0	2079.3	4.758	187.2	0.428	1190.7	2.725	12482.1	28.563	1518.8	3.476	1439.6	3.294	2958.4	6.770	626.0	1.432
M03005	506.3	2036.1	4.022	172.0	0.340	1357.5	2.681	15936.8	31.477	1386.5	2.738	1421.5	2.808	2808.0	5.546	992.1	1.960
M03006	432.7	2020.0	4.668	255.8	0.591	1238.5	2.862	13563.0	31.345	1417.3	3.275	1425.2	3.294	2842.5	6.569	702.0	1.622
M03007	424.8	1946.6	4.582	255.6	0.602	1302.3	3.066	13788.5	32.459	1382.9	3.255	1389.5	3.271	2772.4	6.526	634.2	1.493
M03008	468.1	1979.4	4.229	333.4	0.712	1322.0	2.824	14187.4	30.308	1450.0	3.098	1376.3	2.940	2826.3	6.038	736.6	1.574
Number of males	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
Mean	456.4	2022.3	4.444	280.7	0.617	1290.2	2.830	14157.5	31.002	1440.6	3.167	1422.8	3.127	2863.5	6.294	745.1	1.625
S.D.	27.6	55.6	0.264	77.8	0.167	97.3	0.192	1237.1	1.605	52.9	0.221	74.9	0.240	115.0	0.442	119.3	0.163
Significance	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	NS	NS	NS	NS	NS	NS	
Statistical method	AN	AN	AN	AN	AN	AN	DU	KW	AN	KW	AN	KW	AN	AN	AN	AN	

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

2,4-DTAP 50 mg/kg																
Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03001	1836.2	4.184	1846.6	4.207	3682.8	8.391	726.4	1.655	659.3	1.502	1385.7	3.157	874.7	1.993	1804.6	4.112
M03002	1668.9	3.534	1652.3	3.498	3321.2	7.032	679.9	1.440	655.5	1.388	1335.4	2.827	504.6	1.068	1836.7	3.889
M03003	1746.5	3.706	1738.5	3.690	3485.0	7.396	636.2	1.350	605.7	1.285	1241.9	2.636	553.8	1.175	1673.6	3.552
M03004	1612.4	3.690	1589.5	3.637	3201.9	7.327	643.2	1.472	628.2	1.438	1271.4	2.909	825.8	1.890	1992.7	4.560
M03005	1910.5	3.773	1861.6	3.677	3772.1	7.450	666.5	1.316	652.6	1.289	1319.1	2.605	448.4	0.886	1794.1	3.544
M03006	1376.3	3.181	1365.4	3.156	2741.7	6.336	618.4	1.429	590.3	1.364	1208.7	2.793	843.0	1.948	1777.6	4.108
M03007	1677.8	3.950	1662.6	3.914	3340.4	7.863	619.5	1.458	637.0	1.500	1256.5	2.958	650.1	1.530	1172.0	2.759
M03008	1487.0	3.177	1462.6	3.125	2949.6	6.301	476.3	1.018	486.2	1.039	962.5	2.056	362.4	0.774	1038.8	2.219
Number of males	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
Mean	1664.5	3.649	1647.4	3.613	3311.8	7.262	633.3	1.392	614.4	1.351	1247.7	2.743	632.9	1.408	1636.3	3.593
S.D.	174.9	0.349	173.7	0.361	348.2	0.710	72.8	0.182	57.3	0.151	128.4	0.329	196.4	0.496	341.1	0.769
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
Statistical method	KW	AN	AN	AN	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-1-3 (continued). Organ weights of male rats at the end of the dosing period

Male No.	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03001	27.3	0.062	23.5	0.054	26.0	0.059	49.5	0.113
M03002	25.6	0.054	21.8	0.046	24.1	0.051	45.9	0.097
M03003	19.6	0.042	25.3	0.054	28.3	0.060	53.6	0.114
M03004	25.1	0.057	24.9	0.057	27.2	0.062	52.1	0.119
M03005	30.3	0.060	27.1	0.054	26.3	0.052	53.4	0.105
M03006	20.5	0.047	28.4	0.066	28.7	0.066	57.1	0.132
M03007	21.4	0.050	22.2	0.052	29.4	0.069	51.6	0.121
M03008	20.5	0.044	18.7	0.040	15.5	0.033	34.2	0.073
Number of males	8	8	8	8	8	8	8	8
Mean	23.8	0.052	24.0	0.053	25.7	0.057	49.7	0.109
S.D.	3.9	0.007	3.1	0.008	4.5	0.011	7.0	0.018
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-1-4. Organ weights of male rats at the end of the dosing period

2,4-DTAP 100 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M04001	448.7	2089.8	4.657	191.9	0.428	1281.5	2.856	15022.6	33.480	1670.0	3.722	1554.8	3.465	3224.8	7.187	934.9	2.084
M04004	464.5	2040.9	4.394	282.7	0.609	1305.7	2.811	15612.2	33.611	1532.2	3.299	1521.3	3.275	3053.5	6.574	1100.2	2.369
M04009	488.0	2052.1	4.205	230.0	0.471	1354.1	2.775	20590.8	42.194	1653.8	3.389	1520.3	3.115	3174.1	6.504	719.2	1.474
M04010	434.0	2000.5	4.609	266.1	0.613	1200.8	2.767	14452.9	33.302	1512.3	3.485	1538.6	3.545	3050.9	7.030	695.0	1.601
Number of males	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	458.8	2045.8	4.466	242.7	0.530	1285.5	2.802	16419.6	35.647	1592.1	3.474	1533.8	3.350	3125.8	6.824	862.3	1.882
S.D.	23.1	36.8	0.208	40.4	0.095	64.0	0.041	2820.8	4.367	81.3	0.182	16.4	0.193	87.5	0.336	191.8	0.418
Significance	NS	NS	NS	NS	NS	NS	**	**	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	DU	DU	KW	AN	KW	AN	KW	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 29-1-4 (continued). Organ weights of male rats at the end of the dosing period

2,4-DTAP 100 mg/kg

Male No.	Testis (R) (mg)	Testis (R) (mg/g)	Testis (L) (mg)	Testis (L) (mg/g)	Testes (mg)	Testes (mg/g)	Epididymis (R) (mg)	Epididymis (R) (mg/g)	Epididymis (L) (mg)	Epididymis (L) (mg/g)	Epididymides (mg)	Epididymides (mg/g)	Prostate, ventral (mg)	Prostate, ventral (mg/g)	Seminal vesicles (mg)	Seminal vesicles (mg/g)
M04001	1622.8	3.617	1612.4	3.593	3235.2	7.210	660.0	1.471	654.9	1.460	1314.9	2.930	826.0	1.841	2148.4	4.788
M04004	1559.2	3.357	1668.1	3.591	3227.3	6.948	617.7	1.330	624.2	1.344	1241.9	2.674	590.0	1.270	1489.7	3.207
M04009	1597.2	3.273	1557.4	3.191	3154.6	6.464	652.1	1.336	639.1	1.310	1291.2	2.646	790.8	1.620	1809.4	3.708
M04010	1588.3	3.660	1616.5	3.725	3204.8	7.384	610.3	1.406	567.5	1.308	1177.8	2.714	700.6	1.614	1703.5	3.925
Number of males	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	1591.9	3.477	1613.6	3.525	3205.5	7.002	635.0	1.386	621.4	1.356	1256.5	2.741	726.9	1.586	1787.8	3.907
S.D.	26.2	0.191	45.2	0.231	36.3	0.401	24.7	0.066	38.1	0.072	60.6	0.129	105.4	0.236	274.8	0.660
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	KW	AN	AN	AN	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-1-4 (continued). Organ weights of male rats at the end of the dosing period

2,4-DTAP 100 mg/kg

Male No.	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04001	15.5	0.035	27.6	0.062	25.7	0.057	53.3	0.119
M04004	26.1	0.056	29.8	0.064	29.9	0.064	59.7	0.129
M04009	26.5	0.054	25.5	0.052	29.0	0.059	54.5	0.112
M04010	21.5	0.050	26.6	0.061	26.7	0.062	53.3	0.123
Number of males	4	4	4	4	4	4	4	4
Mean	22.4	0.049	27.4	0.060	27.8	0.061	55.2	0.121
S.D.	5.1	0.010	1.8	0.005	2.0	0.003	3.1	0.007
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-2-1. Organ weights of male rats at the end of the recovery period

Corn oil (control)																	
Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01009	515.6	1977.6	3.836	139.0	0.270	1462.3	2.836	14741.9	28.592	1667.0	3.233	1641.8	3.184	3308.8	6.417	701.6	1.361
M01010	477.7	2175.0	4.553	202.3	0.423	1340.1	2.805	12202.0	25.543	1529.7	3.202	1528.5	3.200	3058.2	6.402	737.4	1.544
M01011	498.8	2087.1	4.184	252.1	0.505	1327.2	2.661	12829.0	25.720	1257.6	2.521	1234.7	2.475	2492.3	4.997	981.4	1.968
M01012	552.3	2068.1	3.745	257.1	0.466	1394.4	2.525	14841.9	26.873	1720.7	3.116	1643.5	2.976	3364.2	6.091	810.5	1.467
M01013	508.3	2081.5	4.095	266.0	0.523	1347.6	2.651	13805.2	27.160	1716.9	3.378	1669.6	3.285	3386.5	6.662	986.6	1.941
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	510.5	2077.9	4.083	223.3	0.437	1374.3	2.696	13684.0	26.778	1578.4	3.090	1543.6	3.024	3122.0	6.114	843.5	1.656
S.D.	27.3	70.1	0.319	53.3	0.101	55.3	0.126	1162.1	1.234	195.3	0.332	181.1	0.327	375.5	0.656	134.1	0.280

Appendix 29-2-1 (continued). Organ weights of male rats at the end of the recovery period

Corn oil (control)																
Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01009	1647.8	3.196	1669.4	3.238	3317.2	6.434	567.3	1.100	569.5	1.105	1136.8	2.205	841.7	1.632	1974.5	3.830
M01010	1592.7	3.334	1542.8	3.230	3135.5	6.564	667.4	1.397	654.7	1.371	1322.1	2.768	659.0	1.380	1813.3	3.796
M01011	1795.4	3.599	1692.4	3.393	3487.8	6.992	719.8	1.443	679.7	1.363	1399.5	2.806	420.3	0.843	1885.3	3.780
M01012	1835.9	3.324	1762.8	3.192	3598.7	6.516	726.7	1.316	680.5	1.232	1407.2	2.548	760.6	1.377	1667.8	3.020
M01013	1531.0	3.012	1612.5	3.172	3143.5	6.184	616.3	1.212	651.5	1.282	1267.8	2.494	795.3	1.565	1640.3	3.227
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	1680.6	3.293	1656.0	3.245	3336.5	6.538	659.5	1.294	647.2	1.271	1306.7	2.564	695.4	1.359	1796.2	3.531
S.D.	130.8	0.215	83.1	0.087	206.0	0.293	68.2	0.139	45.5	0.109	111.1	0.242	167.8	0.310	142.1	0.379

Appendix 29-2-1 (continued). Organ weights of male rats at the end of the recovery period

Corn oil (control)								
Male No.	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01009	17.4	0.034	27.1	0.053	29.4	0.057	56.5	0.110
M01010	20.0	0.042	26.7	0.056	27.6	0.058	54.3	0.114
M01011	13.9	0.028	30.4	0.061	32.3	0.065	62.7	0.126
M01012	15.5	0.028	33.7	0.061	35.1	0.064	68.8	0.125
M01013	15.5	0.030	23.8	0.047	23.4	0.046	47.2	0.093
Number of males	5	5	5	5	5	5	5	5
Mean	16.5	0.032	28.3	0.056	29.6	0.058	57.9	0.114
S.D.	2.3	0.006	3.8	0.006	4.5	0.008	8.2	0.013

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-2-2. Organ weights of male rats at the end of the recovery period

2,4-DTAP 50 mg/kg

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03009	477.2	2113.3	4.429	378.1	0.792	1605.8	3.365	12884.0	26.999	1405.6	2.946	1335.2	2.798	2740.8	5.744	764.2	1.601
M03010	488.4	2031.8	4.160	202.4	0.414	1290.5	2.642	14254.0	29.185	1423.9	2.915	1520.0	3.112	2943.9	6.028	845.1	1.730
M03011	423.5	1998.8	4.720	205.4	0.485	1273.2	3.006	10524.8	24.852	1386.6	3.274	1409.2	3.328	2795.8	6.602	764.8	1.806
M03012	520.9	1993.0	3.826	286.0	0.549	1537.7	2.952	14380.1	27.606	1575.3	3.024	1525.3	2.928	3100.6	5.952	771.9	1.482
M03013	458.2	2006.9	4.380	213.9	0.467	1340.7	2.926	10558.2	23.043	1477.8	3.225	1460.6	3.188	2938.4	6.413	599.9	1.309
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	473.6	2028.8	4.303	257.2	0.541	1409.6	2.978	12520.2	26.337	1453.8	3.077	1450.1	3.071	2903.9	6.148	749.2	1.586
S.D.	36.1	49.5	0.333	75.8	0.148	152.0	0.258	1899.3	2.409	75.9	0.163	79.9	0.210	141.2	0.351	90.1	0.198
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 29-2-2 (continued). Organ weights of male rats at the end of the recovery period

2,4-DTAP 50 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03009	1672.5	3.505	1677.2	3.515	3349.7	7.019	638.7	1.338	672.4	1.409	1311.1	2.747	561.6	1.177	1678.1	3.517
M03010	1576.6	3.228	1596.1	3.268	3172.7	6.496	582.7	1.193	682.1	1.397	1264.8	2.590	673.4	1.379	1449.0	2.967
M03011	1748.5	4.129	1745.8	4.122	3494.3	8.251	659.2	1.557	676.1	1.596	1335.3	3.153	730.1	1.724	1648.9	3.894
M03012	1656.1	3.179	1647.3	3.162	3303.4	6.342	642.1	1.233	617.4	1.185	1259.5	2.418	719.8	1.382	1787.2	3.431
M03013	1648.2	3.597	1579.6	3.447	3227.8	7.045	635.0	1.386	617.7	1.348	1252.7	2.734	524.3	1.144	1548.0	3.378
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1660.4	3.528	1649.2	3.503	3309.6	7.031	631.5	1.341	653.1	1.387	1284.7	2.728	641.8	1.361	1622.2	3.437
S.D.	61.4	0.380	66.7	0.373	123.7	0.750	28.8	0.143	32.7	0.147	36.4	0.272	93.7	0.231	129.0	0.332
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 29-2-2 (continued). Organ weights of male rats at the end of the recovery period

2,4-DTAP 50 mg/kg								
Male No.	Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03009	22.8	0.048	25.7	0.054	26.4	0.055	52.1	0.109
M03010	18.2	0.037	22.2	0.045	23.6	0.048	45.8	0.094
M03011	17.5	0.041	24.2	0.057	25.6	0.060	49.8	0.118
M03012	16.0	0.031	34.3	0.066	31.7	0.061	66.0	0.127
M03013	15.1	0.033	28.5	0.062	31.3	0.068	59.8	0.131
Number of males	5	5	5	5	5	5	5	5
Mean	17.9	0.038	27.0	0.057	27.7	0.058	54.7	0.116
S.D.	3.0	0.007	4.7	0.008	3.6	0.007	8.1	0.015
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 30-1-1. Organ weights of female rats at the end of the dosing period

Corn oil (control)																	
Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)		
F01001	312.8	1850.6	5.916	160.5	0.513	892.6	2.854	9032.9	28.878	892.8	2.854	892.8	2.854	1785.6	5.708	588.2	1.880
F01002	327.3	1990.0	6.080	107.6	0.329	873.4	2.668	11699.5	35.745	1021.1	3.120	1024.1	3.129	2045.2	6.249	764.4	2.335
F01003	335.2	1871.3	5.583	237.6	0.709	973.0	2.903	10429.5	31.114	937.4	2.797	913.2	2.724	1850.6	5.521	731.6	2.183
F01004	245.4	1976.7	8.055	33.2	0.135	801.4	3.266	8319.6	33.902	1099.1	4.479	1108.8	4.518	2207.9	8.997	296.1	1.207
F01005	300.6 ^{a)}	1987.2 ^{a)}	6.611 ^{a)}	27.1 ^{a)}	0.090 ^{a)}	1018.9 ^{a)}	3.390 ^{a)}	9515.6 ^{a)}	31.655 ^{a)}	1400.1 ^{a)}	4.658 ^{a)}	1426.9 ^{a)}	4.747 ^{a)}	2827.0 ^{a)}	9.405 ^{a)}	642.9 ^{a)}	2.139 ^{a)}
F01006	304.0	1855.9	6.105	85.6	0.282	935.8	3.078	10154.7	33.404	948.3	3.119	931.3	3.063	1879.6	6.183	630.7	2.075
F01007	314.5	1860.7	5.916	190.7	0.606	1045.3	3.324	10188.6	32.396	957.7	3.045	963.6	3.064	1921.3	6.109	783.6	2.492
F01008	304.2	1743.5	5.731	239.5	0.787	935.4	3.075	9543.8	31.373	1074.6	3.533	997.8	3.280	2072.4	6.813	758.9	2.495
F01009	338.8	1972.1	5.821	240.0	0.708	1004.6	2.965	10405.5	30.713	996.5	2.941	972.6	2.871	1969.1	5.812	699.3	2.064
F01010	353.4	2004.4	5.672	191.9	0.543	1053.2	2.980	11403.7	32.269	1124.8	3.183	1109.6	3.140	2234.4	6.323	831.3	2.352
F01011	275.6	1904.2	6.909	68.8	0.250	925.0	3.356	7913.5	28.714	1021.4	3.706	996.9	3.617	2018.3	7.323	385.4	1.398
F01012	307.1	1925.0	6.268	118.5	0.386	972.1	3.165	10685.3	34.794	1129.0	3.676	1141.8	3.718	2270.8	7.394	665.9	2.168
F01013	322.0	1944.8	6.040	216.0	0.671	965.6	2.999	9330.6	28.977	1008.6	3.132	966.8	3.002	1975.4	6.135	682.0	2.118
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
Mean	311.7	1908.3	6.175	157.5	0.493	948.1	3.053	9925.6	31.857	1017.6	3.299	1001.6	3.248	2019.2	6.547	651.5	2.064
S.D.	29.0	75.8	0.686	72.7	0.213	71.5	0.202	1145.7	2.334	76.7	0.477	80.6	0.495	155.3	0.969	161.1	0.401

a) Excluded from data analysis (total litter loss).

Appendix 30-1-1 (continued). Organ weights of female rats at the end of the dosing period

Corn oil (vehicle)																
Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	57.8	0.185	49.8	0.159	107.6	0.344	572.6	1.831	23.5	0.075	53.6	0.171	34.7	0.111	88.3	0.282
F01002	57.9	0.177	50.8	0.155	108.7	0.332	620.8	1.897	11.0	0.034	35.4	0.108	36.8	0.112	72.2	0.221
F01003	49.5	0.148	42.4	0.126	91.9	0.274	566.5	1.690	15.8	0.047	39.4	0.118	39.4	0.118	78.8	0.235
F01004	43.8	0.178	50.7	0.207	94.5	0.385	422.3	1.721	8.9	0.036	38.7	0.158	42.3	0.172	81.0	0.330
F01005	51.3 ^{a)}	0.171 ^{a)}	56.5 ^{a)}	0.188 ^{a)}	107.8 ^{a)}	0.359 ^{a)}	757.8 ^{a)}	2.521 ^{a)}	15.1 ^{a)}	0.050 ^{a)}	47.6 ^{a)}	0.158 ^{a)}	50.7 ^{a)}	0.169 ^{a)}	98.3 ^{a)}	0.327 ^{a)}
F01006	51.2	0.168	65.7	0.216	116.9	0.385	573.1	1.885	11.7	0.038	33.4	0.110	37.1	0.122	70.5	0.232
F01007	48.9	0.155	53.4	0.170	102.3	0.325	511.3	1.626	12.9	0.041	31.5	0.100	35.5	0.113	67.0	0.213
F01008	48.5	0.159	46.0	0.151	94.5	0.311	632.0	2.078	22.7	0.075	38.7	0.127	40.0	0.131	78.7	0.259
F01009	45.8	0.135	57.1	0.169	102.9	0.304	590.8	1.744	16.3	0.048	30.4	0.090	34.7	0.102	65.1	0.192
F01010	44.4	0.126	58.0	0.164	102.4	0.290	496.3	1.404	14.2	0.040	49.8	0.141	57.0	0.161	106.8	0.302
F01011	54.2	0.197	39.3	0.143	93.5	0.339	677.9	2.460	10.5	0.038	34.9	0.127	41.4	0.150	76.3	0.277
F01012	69.8	0.227	38.5	0.125	108.3	0.353	563.4	1.835	21.8	0.071	37.7	0.123	38.3	0.125	76.0	0.247
F01013	39.1	0.121	38.5	0.120	77.6	0.241	618.7	1.921	11.2	0.035	37.3	0.116	44.7	0.139	82.0	0.255
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
Mean	50.9	0.165	49.2	0.159	100.1	0.324	570.5	1.841	15.0	0.048	38.4	0.124	40.2	0.130	78.6	0.254
S.D.	8.2	0.031	8.6	0.030	10.3	0.043	68.5	0.258	5.1	0.016	6.9	0.023	6.2	0.022	11.0	0.039

a) Excluded from data analysis (total litter loss).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 30-1-2. Organ weights of female rats at the end of the dosing period

2,4-DTAP 10 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02002	256.5	1849.7	7.211	22.9	0.089	840.2	3.276	9757.6	38.041	1046.5	4.080	985.0	3.840	2031.5	7.920	383.9	1.497
F02003	332.2	1895.4	5.706	167.2	0.503	1011.5	3.045	11293.2	33.995	909.6	2.738	941.2	2.833	1850.8	5.571	657.1	1.978
F02004	340.2	1730.7	5.087	166.1	0.488	1073.4	3.155	11289.1	33.184	1010.5	2.970	1019.2	2.996	2029.7	5.966	670.4	1.971
F02005	334.9	2013.9	6.013	265.7	0.793	1025.6	3.062	11598.0	34.631	1031.7	3.081	1022.8	3.054	2054.5	6.135	736.7	2.200
F02006	299.2	1902.1	6.357	119.4	0.399	874.3	2.922	9054.5	30.262	945.4	3.160	880.2	2.942	1825.6	6.102	690.9	2.309
F02007	296.0	1750.8	5.915	155.4	0.525	896.6	3.029	9907.4	33.471	904.8	3.057	909.8	3.074	1814.6	6.130	689.4	2.329
F02008	378.2	1898.2	5.019	245.7	0.650	1070.8	2.831	11820.6	31.255	979.8	2.591	947.5	2.505	1927.3	5.096	931.4	2.463
F02009	238.7	1971.7	8.260	49.3	0.207	813.6	3.408	8597.5	36.018	1218.3	5.104	1138.7	4.770	2357.0	9.874	521.9	2.186
F02010	296.2	1913.5	6.460	172.3	0.582	904.3	3.053	9135.2	30.841	837.5	2.827	813.7	2.747	1651.2	5.575	695.5	2.348
F02011	365.8	1994.5	5.452	168.2	0.460	1067.6	2.919	12930.5	35.349	956.1	2.614	920.6	2.517	1876.7	5.130	785.8	2.148
F02012	354.1 b)	1871.5 b)	5.285 b)	214.3 b)	0.605 b)	934.7 b)	2.640	11012.3 b)	31.099 b)	991.8 b)	2.801 b)	1042.8 b)	2.945 b)	2034.6 b)	5.746 b)	484.5 b)	1.368 b)
F02013	352.9	1914.6	5.425	163.0	0.462	1080.8	3.063	11313.5	32.059	1055.7	2.991	1049.1	2.973	2104.8	5.964	690.0	1.955
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	317.3	1894.1	6.082	154.1	0.469	969.0	3.069	10608.8	33.555	990.5	3.201	966.2	3.114	1956.7	6.315	677.5	2.126
S.D.	44.1	89.7	0.967	71.5	0.193	103.7	0.164	1382.5	2.380	101.0	0.748	89.4	0.654	187.6	1.400	138.3	0.268
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	DU	DU	AN	KW	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

b) Excluded from data analysis (not pregnant).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 30-1-2 (continued). Organ weights of female rats at the end of the dosing period

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02002	49.2	0.192	53.6	0.209	102.8	0.401	623.1	2.429	13.9	0.054	37.0	0.144	35.7	0.139	72.7	0.283
F02003	56.2	0.169	55.7	0.168	111.9	0.337	643.7	1.938	23.5	0.071	37.8	0.114	40.7	0.123	78.5	0.236
F02004	63.2	0.186	58.2	0.171	121.4	0.357	661.1	1.943	23.7	0.070	36.1	0.106	34.9	0.103	71.0	0.209
F02005	65.1	0.194	53.3	0.159	118.4	0.354	615.0	1.836	14.0	0.042	50.7	0.151	49.0	0.146	99.7	0.298
F02006	49.2	0.164	47.8	0.160	97.0	0.324	535.2	1.789	22.1	0.074	38.6	0.129	43.6	0.146	82.2	0.275
F02007	46.6	0.157	48.0	0.162	94.6	0.320	716.0	2.419	17.8	0.060	35.1	0.119	38.7	0.131	73.8	0.249
F02008	51.5	0.136	41.2	0.109	92.7	0.245	675.5	1.786	13.6	0.036	40.7	0.108	40.9	0.108	81.6	0.216
F02009	67.8	0.284	60.0	0.251	127.8	0.535	575.2	2.410	20.6	0.086	43.5	0.182	45.2	0.189	88.7	0.372
F02010	60.9	0.206	42.1	0.142	103.0	0.348	445.0	1.502	15.7	0.053	27.9	0.094	30.8	0.104	58.7	0.198
F02011	78.0	0.213	62.4	0.171	140.4	0.384	585.2	1.600	20.3	0.055	44.5	0.122	43.7	0.119	88.2	0.241
F02012	41.7 b)	0.118 b)	44.4 b)	0.125 b)	86.1 b)	0.243 b)	575.9 b)	1.626 b)	8.5 b)	0.024 b)	36.2 b)	0.102 b)	36.8 b)	0.104 b)	73.0 b)	0.206 b)
F02013	61.6	0.175	62.0	0.176	123.6	0.350	687.3	1.948	19.7	0.056	37.2	0.105	38.0	0.108	75.2	0.213
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	59.0	0.189	53.1	0.171	112.1	0.360	614.8	1.964	18.6	0.060	39.0	0.125	40.1	0.129	79.1	0.254
S.D.	9.6	0.039	7.5	0.036	15.4	0.071	77.4	0.324	3.8	0.015	5.9	0.025	5.2	0.026	10.9	0.051
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

b) Excluded from data analysis (not pregnant).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 30-1-3. Organ weights of female rats at the end of the dosing period

2,4-DTAP 50 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03001	355.4	1879.8	5.289	242.7	0.683	1042.8	2.934	12808.8	36.041	1071.0	3.014	1001.6	2.818	2072.6	5.832	781.3	2.198
F03003	297.0	1834.9	6.178	181.9	0.612	1000.6	3.369	11498.1	38.714	906.3	3.052	897.3	3.021	1803.6	6.073	572.7	1.928
F03004	302.2	1836.6	6.077	298.8	0.989	880.6	2.914	10578.9	35.006	920.1	3.045	933.5	3.089	1853.6	6.134	677.6	2.242
F03005	338.9	2124.5	6.269	209.5	0.618	1032.4	3.046	10738.3	31.686	986.7	2.911	1032.2	3.046	2018.9	5.957	797.5	2.353
F03006	300.1	1946.0	6.485	143.9	0.480	896.4	2.987	11282.1	37.594	1059.9	3.532	1043.6	3.478	2103.5	7.009	656.5	2.188
F03007	305.0	1881.1	6.168	180.2	0.591	1065.5	3.493	11452.3	37.549	1109.0	3.636	1104.1	3.620	2213.1	7.256	674.3	2.211
F03008	337.4	1829.0	5.421	71.3	0.211	968.4	2.870	12383.8	36.704	1017.7	3.016	996.1	2.952	2013.8	5.969	839.2	2.487
F03009	294.7	1824.7	6.192	58.9	0.200	845.2	2.868	10205.6	34.630	993.4	3.371	993.8	3.372	1987.2	6.743	652.9	2.215
F03010	298.6	1950.8	6.533	138.8	0.465	966.8	3.238	10946.5	36.659	1047.6	3.508	1048.9	3.513	2096.5	7.021	808.0	2.706
F03011	294.9 ^{a)}	1958.8 ^{a)}	6.642 ^{a)}	60.1 ^{a)}	0.204 ^{a)}	842.3 ^{a)}	2.856 ^{a)}	12373.1 ^{a)}	41.957 ^{a)}	1078.5 ^{a)}	3.657 ^{a)}	1081.9 ^{a)}	3.669 ^{a)}	2160.4 ^{a)}	7.326 ^{a)}	266.8 ^{a)}	0.905 ^{a)}
F03012	351.3	1916.1	5.454	196.7	0.560	1004.6	2.860	11249.8	32.023	943.9	2.687	957.7	2.726	1901.6	5.413	612.3	1.743
F03013	366.0	1832.1	5.006	222.7	0.608	1030.6	2.816	12856.8	35.128	987.7	2.699	955.2	2.610	1942.9	5.308	613.5	1.676
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	322.4	1896.0	5.916	176.9	0.547	975.8	3.036	11454.6	35.612	1003.9	3.134	996.7	3.113	2000.7	6.247	698.7	2.177
S.D.	27.4	89.2	0.524	71.0	0.218	72.6	0.229	885.2	2.228	64.5	0.330	59.1	0.339	120.2	0.663	91.5	0.303
Significance	NS	NS	NS	NS	NS	NS	NS	**	**	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	DU	DU	AN	KW	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

c) Excluded from data analysis (moribund).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 30-1-3 (continued). Organ weights of female rats at the end of the dosing period

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03001	77.7	0.219	65.7	0.185	143.4	0.403	645.3	1.816	20.6	0.058	42.4	0.119	43.1	0.121	85.5	0.241
F03003	61.6	0.207	44.3	0.149	105.9	0.357	591.3	1.991	28.6	0.096	31.5	0.106	34.5	0.116	66.0	0.222
F03004	46.1	0.153	42.0	0.139	88.1	0.292	623.1	2.062	23.5	0.078	34.0	0.113	36.9	0.122	70.9	0.235
F03005	52.2	0.154	47.7	0.141	99.9	0.295	570.4	1.683	13.2	0.039	40.5	0.120	40.2	0.119	80.7	0.238
F03006	53.1	0.177	62.0	0.207	115.1	0.384	551.2	1.837	19.5	0.065	32.3	0.108	34.5	0.115	66.8	0.223
F03007	36.1	0.118	40.3	0.132	76.4	0.250	599.3	1.965	15.3	0.050	39.4	0.129	42.6	0.140	82.0	0.269
F03008	59.0	0.175	44.2	0.131	103.2	0.306	471.9	1.399	16.5	0.049	44.7	0.132	45.0	0.133	89.7	0.266
F03009	61.4	0.208	46.0	0.156	107.4	0.364	673.0	2.284	13.2	0.045	41.7	0.141	43.1	0.146	84.8	0.288
F03010	40.4	0.135	51.1	0.171	91.5	0.306	563.3	1.886	14.7	0.049	28.7	0.096	33.4	0.112	62.1	0.208
F03011	38.3 ^{c)}	0.130 ^{c)}	51.6 ^{c)}	0.175 ^{c)}	89.9 ^{c)}	0.305 ^{c)}	10999.5 ^{c)}	37.299 ^{c)}	12.2 ^{c)}	0.041 ^{c)}	64.5 ^{c)}	0.219 ^{c)}	78.4 ^{c)}	0.266 ^{c)}	142.9 ^{c)}	0.485 ^{c)}
F03012	40.4	0.115	50.5	0.144	90.9	0.259	699.8	1.992	12.6	0.036	28.8	0.082	32.9	0.094	61.7	0.176
F03013	75.3	0.206	37.7	0.103	113.0	0.309	451.0	1.232	25.6	0.070	37.0	0.101	35.9	0.098	72.9	0.199
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	54.8	0.170	48.3	0.151	103.2	0.320	585.4	1.832	18.5	0.058	36.5	0.113	38.4	0.120	74.8	0.233
S.D.	13.8	0.038	8.7	0.028	17.7	0.050	76.7	0.300	5.5	0.018	5.7	0.017	4.5	0.016	10.1	0.033
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

c) Excluded from data analysis (moribund).

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 30-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Corn oil (control)															
Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05001	299.7	1816.2	6.060	201.1	0.671	923.5	3.081	8393.5	28.006	915.5	3.055	903.0	3.013	1818.5	6.068
F05002	339.2	1931.4	5.694	334.3	0.986	1126.5	3.321	8500.2	25.060	1042.4	3.073	1138.2	3.356	2180.6	6.429
F05003	291.1	1872.0	6.431	282.8	0.971	892.5	3.066	7475.2	25.679	913.4	3.138	906.9	3.115	1820.3	6.253
F05004	311.2	1945.2	6.251	281.2	0.904	1016.3	3.266	8217.5	26.406	994.9	3.197	914.3	2.938	1909.2	6.135
F05005	262.7	1920.2	7.309	297.5	1.132	877.9	3.342	6569.2	25.006	834.3	3.176	833.4	3.172	1667.7	6.348
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
Mean	300.8	1897.0	6.349	279.4	0.933	967.3	3.215	7831.1	26.031	940.1	3.128	939.2	3.119	1879.3	6.247
S.D.	28.0	52.9	0.602	48.7	0.168	104.0	0.132	811.2	1.241	80.6	0.062	115.9	0.160	189.5	0.148

Appendix 30-2-1 (continued). Organ weights of female rats at the end of the dosing period, satellite group

Corn oil (control)																
Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05001	40.9	0.136	46.0	0.153	86.9	0.290	604.6	2.017	14.6	0.049	34.5	0.115	36.0	0.120	70.5	0.235
F05002	50.7	0.149	49.7	0.147	100.4	0.296	1020.3	3.008	26.9	0.079	33.6	0.099	36.4	0.107	70.0	0.206
F05003	33.9	0.116	35.0	0.120	68.9	0.237	766.0	2.631	13.6	0.047	22.9	0.079	27.8	0.095	50.7	0.174
F05004	47.9	0.154	58.5	0.188	106.4	0.342	610.9	1.963	16.0	0.051	32.9	0.106	37.8	0.121	70.7	0.227
F05005	41.9	0.159	42.1	0.160	84.0	0.320	343.0	1.306	14.9	0.057	30.6	0.116	35.3	0.134	65.9	0.251
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5		
Mean	43.1	0.143	46.3	0.154	89.3	0.297	669.0	2.185	17.2	0.057	30.9	0.103	34.7	0.115	65.6	0.219
S.D.	6.6	0.017	8.7	0.024	14.7	0.039	248.3	0.657	5.5	0.013	4.7	0.015	3.9	0.015	8.5	0.030

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 30-2-2. Organ weights of female rats at the end of the dosing period, satellite group

2,4-DTAP 100 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04001	284.6	1955.6	6.871	241.4	0.848	942.8	3.313	9541.2	33.525	1012.1	3.556	1099.3	3.863	2111.4	7.419	554.6	1.949
F04004	268.5	1897.4	7.067	243.5	0.907	824.8	3.072	8437.2	31.423	906.1	3.375	885.3	3.297	1791.4	6.672	537.5	2.002
F04006	284.8	1934.4	6.792	181.5	0.637	868.1	3.048	8855.8	31.095	865.7	3.040	885.9	3.111	1751.6	6.150	584.2	2.051
F06001	268.3	1910.9	7.122	355.8	1.326	906.3	3.378	8603.4	32.066	944.3	3.520	929.0	3.463	1873.3	6.982	678.5	2.529
F06004	275.3	1874.0	6.807	192.6	0.700	798.9	2.902	9169.2	33.306	931.4	3.383	918.1	3.335	1849.5	6.718	599.2	2.177
F06006	317.7	1885.8	5.936	209.6	0.660	947.6	2.983	9768.4	30.747	950.3	2.991	966.6	3.042	1916.9	6.034	554.0	1.744
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	283.2	1909.7	6.766	237.4	0.846	881.4	3.116	9062.5	32.027	935.0	3.311	947.4	3.352	1882.4	6.663	584.7	2.075
S.D.	18.4	30.7	0.429	63.2	0.258	61.6	0.188	526.0	1.162	48.8	0.240	80.3	0.294	126.6	0.517	51.2	0.264
Significance	NS	NS	NS	NS	NS	NS	NS	*	**	NS	NS	NS	NS	NS	NS	NS	*
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	AW	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 30-2-2 (continued). Organ weights of female rats at the end of the dosing period, satellite group

2,4-DTAP 100 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04001	36.6	0.129	35.9	0.126	72.5	0.255	534.2	1.877	19.1	0.067	31.7	0.111	32.6	0.115	64.3	0.226
F04004	52.2	0.194	40.9	0.152	93.1	0.347	776.1	2.891	6.0	0.022	32.3	0.120	31.9	0.119	64.2	0.239
F04006	44.1	0.155	41.8	0.147	85.9	0.302	454.0	1.594	24.1	0.085	30.0	0.105	31.4	0.110	61.4	0.216
F06001	40.6	0.151	35.1	0.131	75.7	0.282	372.9	1.390	17.8	0.066	37.3	0.139	40.2	0.150	77.5	0.289
F06004	55.3	0.201	47.4	0.172	102.7	0.373	520.0	1.889	7.6	0.028	36.6	0.133	38.8	0.141	75.4	0.274
F06006	46.0	0.145	54.5	0.172	100.5	0.316	451.6	1.421	15.7	0.049	36.7	0.116	42.5	0.134	79.2	0.249
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	45.8	0.163	42.6	0.150	88.4	0.313	518.1	1.844	15.1	0.053	34.1	0.121	36.2	0.128	70.3	0.249
S.D.	7.0	0.029	7.3	0.020	12.6	0.043	138.9	0.556	7.0	0.024	3.1	0.013	4.8	0.016	7.9	0.028
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 30-3-1. Organ weights of female rats at the end of the recovery period

Corn oil (control)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05006	271.5	1949.2	7.179	222.6	0.820	878.1	3.234	6511.4	23.983	845.3	3.113	798.2	2.940	1643.5	6.053	502.4	1.850
F05007	310.8	1920.5	6.179	278.5	0.896	981.8	3.159	8056.4	25.921	913.2	2.938	972.8	3.130	1886.0	6.068	633.1	2.037
F05008	335.1	1889.5	5.639	194.9	0.582	978.5	2.920	8164.9	24.366	985.2	2.940	1001.5	2.989	1986.7	5.929	533.1	1.591
F05009	332.4	1996.6	6.007	277.7	0.835	989.0	2.975	8463.6	25.462	1030.9	3.101	991.3	2.982	2022.2	6.084	456.2	1.372
F05010	300.8	1891.1	6.287	347.3	1.155	909.9	3.025	7574.3	25.181	846.3	2.813	807.6	2.685	1653.9	5.498	544.1	1.809
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	310.1	1929.4	6.258	264.2	0.858	947.5	3.063	7754.1	24.983	924.2	2.981	914.3	2.945	1838.5	5.926	533.8	1.732
S.D.	26.0	44.8	0.570	58.8	0.205	50.2	0.130	764.9	0.795	82.9	0.126	102.2	0.162	180.3	0.247	65.1	0.256

Appendix 30-3-1 (continued). Organ weights of female rats at the end of the recovery period

Corn oil (control)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05006	58.8	0.217	45.5	0.168	104.3	0.384	545.7	2.010	13.1	0.048	29.3	0.108	30.7	0.113	60.0	0.221
F05007	72.2	0.232	57.2	0.184	129.4	0.416	494.7	1.592	17.1	0.055	33.4	0.107	36.7	0.118	70.1	0.226
F05008	40.3	0.120	50.4	0.150	90.7	0.271	445.4	1.329	15.8	0.047	28.8	0.086	36.6	0.109	65.4	0.195
F05009	37.7	0.113	37.0	0.111	74.7	0.225	573.2	1.724	14.0	0.042	35.8	0.108	36.0	0.108	71.8	0.216
F05010	53.4	0.178	55.8	0.186	109.2	0.363	399.7	1.329	12.6	0.042	30.0	0.100	31.5	0.105	61.5	0.204
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	52.5	0.172	49.2	0.160	101.7	0.332	491.7	1.597	14.5	0.047	31.5	0.102	34.3	0.111	65.8	0.212
S.D.	14.1	0.054	8.2	0.031	20.5	0.080	71.0	0.287	1.9	0.005	3.0	0.009	2.9	0.005	5.2	0.013

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 30-3-2. Organ weights of female rats at the end of the recovery period

2,4-DTAP 100 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	
F04012	304.6	1914.5	6.285	308.8	1.014	1025.0	3.365	8425.7	27.662	922.2	3.028	914.9	3.004	1837.1	6.031	660.1	2.167
F04013	312.7	2045.7	6.542	374.6	1.198	894.5	2.861	7773.1	24.858	960.5	3.072	862.9	2.760	1823.4	5.831	633.1	2.025
F06007	338.2	1983.8	5.866	429.6	1.270	995.9	2.945	8774.7	25.945	1133.7	3.352	1115.9	3.300	2249.6	6.652	814.7	2.409
F06009	337.2	1666.2	4.941	367.6	1.090	1016.2	3.014	9355.1	27.743	1063.7	3.155	1056.1	3.132	2119.8	6.286	606.7	1.799
F06010	292.7	1963.5	6.708	230.1	0.786	961.6	3.285	7475.9	25.541	904.5	3.090	869.9	2.972	1774.4	6.062	610.4	2.085
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	317.1	1914.7	6.068	342.1	1.072	978.6	3.094	8360.9	26.350	996.9	3.139	963.9	3.034	1960.9	6.172	665.0	2.097
S.D.	20.1	146.7	0.706	75.9	0.187	53.0	0.220	757.1	1.295	98.3	0.127	115.2	0.200	210.7	0.313	86.4	0.222
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	*
Statistical method	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT							

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Appendix 30-3-2 (continued). Organ weights of female rats at the end of the recovery period

2,4-DTAP 100 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04012	68.4	0.225	60.2	0.198	128.6	0.422	466.8	1.533	20.2	0.066	35.5	0.117	37.4	0.123	72.9	0.239
F04013	40.6	0.130	35.9	0.115	76.5	0.245	466.7	1.492	12.4	0.040	22.4	0.072	26.7	0.085	49.1	0.157
F06007	41.3	0.122	34.9	0.103	76.2	0.225	715.8	2.116	18.9	0.056	36.0	0.106	40.0	0.118	76.0	0.225
F06009	50.0	0.148	41.8	0.124	91.8	0.272	949.8	2.817	15.3	0.045	27.3	0.081	35.9	0.106	63.2	0.187
F06010	47.2	0.161	58.3	0.199	105.5	0.360	419.8	1.434	18.3	0.063	27.7	0.095	34.0	0.116	61.7	0.211
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	49.5	0.157	46.2	0.148	95.7	0.305	603.8	1.878	17.0	0.054	29.8	0.094	34.8	0.110	64.6	0.204
S.D.	11.3	0.041	12.2	0.047	22.0	0.083	225.7	0.592	3.1	0.011	5.8	0.018	5.0	0.015	10.6	0.032
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	AW	AW

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 31-1-1. Macroscopic findings of male rats at the end of the dosing period

Findings	Dose(mg/kg) Group Animal No.	Corn oil (control)								2,4-DTAP (10 mg/kg)								2,4-DTAP (50 mg/kg)								2,4-DTAP (100 mg/kg)							
		M01-								M02-								M03-								M04-							
		001	002	003	004	005	006	007	008	001	002	003	004	005	006	007	008	001	002	003	004	005	006	007	008	001	002	003	004	005	006	007	008
Kidney		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	-	-	-	-	-	-	
Liver		-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	-	-	P	P	-	-	
Lung		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	
Spleen		-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	
Thymus		-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	-	-	-	-	-	-
Small		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
Appendix 31-1-2. Macroscopic findings of female rats at the end of the dosing period

- : No abnormal changes P : Non-graded change

Fate : blanks, Subjected to autopsy on day 5 lactation; TL, Total litter loss during lactation; DP, Died during pregnancy; DD, Died during delivery; SL, Sacrificed in the moribund condition during lactation; NP, Non-pregnant.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 31-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Dose(mg/kg)	Corn oil (control)					2,4-DTAP (100 mg/kg)					
		F05-					F04-			F06-		
	Group	Animal No.	001	002	003	004	005	001	004	006	001	004
Liver												
Enlargement		-	-	-	-	-	-	P	-	-	-	-

- : No abnormal changes P : Non-graded change

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 31-3-1. Macroscopic findings of male rats (dead and moribund animals)

Findings	Dose(mg/kg) Group Animal No. Fate	2,4-DTAP (250 mg/kg) M04-									
		002 003 005 006 007 008 011 012 013									
		D	D	D	S	D	D	S	D	D	D
Abdominal cavity		-	-	P	-	-	-	-	-	-	-
Ascites, dark reddish		-	-	P	-	-	-	-	-	-	-
Adrenal gland		P	P	-	-	-	P	P	-	-	P
Discoloration, dark reddish		P	-	-	-	P	P	P	-	-	P
Enlargement		-	-	-	-	-	-	-	-	-	-
Cecum		-	P	P	-	-	P	P	-	-	-
Discoloration, dark reddish, mucosa		-	P	P	-	-	P	P	-	-	-
Retention, black content		-	-	-	-	-	-	P	-	-	-
Epididymis		-	P	-	-	P	-	-	P	-	-
Dark reddish area, head/cauda, uni-/bilateral		-	P	-	-	P	-	-	P	-	-
Hair		P	P	P	P	P	P	P	P	P	P
Soiled fur *		P	P	P	P	P	P	P	P	P	P
Ileum		-	-	P	-	-	-	-	-	-	-
Invagination		-	-	P	-	-	-	-	-	-	-
Kidney		P	-	P	P	-	-	-	P	-	-
Enlargement		P	-	-	P	-	-	-	-	-	-
Rough surface		P	-	P	P	-	-	-	P	-	-
Whitish area, scattered, mottled		P	-	P	P	-	-	-	P	-	-
Liver		P	P	-	-	-	-	P	-	-	-
Discoloration, dark reddish		P	P	-	P	-	-	P	-	-	-
Enlargement		P	-	P	P	-	-	P	-	-	-
Lung		-	P	-	-	P	P	-	P	-	-
Dark reddish area		-	P	-	P	P	P	-	P	-	-
Discoloration, reddish		-	-	-	P	P	P	-	P	-	-
Spleen		P	-	-	P	P	P	-	P	P	P
Discoloration, pale colored		P	-	P	P	P	P	-	P	P	P
Small		P	-	P	P	P	P	-	P	P	P
Stomach		-	-	-	P	-	-	-	P	-	-
Attachment, black content, mucosa, forestomach		-	-	-	P	-	-	-	P	-	-
Dark colored spot, mucosa, glandular stomach		-	P	P	-	P	-	-	P	-	-
Discoloration, dark reddish, mucosa, glandular stomach		-	P	P	-	P	-	-	P	-	-
Thinning, mucosa, forestomach		P	P	P	P	P	P	-	P	P	P
Testis		P	-	-	-	-	-	-	-	-	-
Discoloration, dark reddish, left side		P	-	-	-	-	-	-	-	-	-
Enlargement, left side		P	-	-	-	-	-	-	-	-	-
Thymus		-	-	-	P	-	P	-	P	-	P
Discoloration, dark reddish		-	-	-	P	-	P	-	P	-	P
Small		-	-	P	P	-	P	-	P	-	P

- : No abnormal changes P : Non-graded change

* : Soiled fur was observed in abdomen/periorcular/perioral/perinasal area/perineal region

Fate D : Died during the observation period. S : Sacrificed in the moribund condition during the observation period.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 31-3-2. Macroscopic findings of female rats (dead and moribund animals)

Findings	Dose(mg/kg) Group Animal No. Fate	2,4-DTAP (250 mg/kg)										F06-			
		F04-								F06-					
		002 D	003 S	005 D	007 D	008 D	009 S	010 D	011 D	002 S	003 S	005 D	008 D		
Adrenal gland															
Discoloration, dark reddish	-	-	P	P	-	-	P	-	-	-	P	-	P	-	P
Enlargement	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
Cecum															
Retention, black content	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-
Hair															
Soiled fur *	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
Kidney															
Discoloration, dark reddish	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-
Enlargement	-	P	-	P	-	-	-	-	-	-	P	-	P	-	P
Rough surface	-	P	-	P	-	-	-	-	-	-	P	-	P	-	P
Whitish area, scattered, mottled	-	P	-	P	-	P	-	-	-	P	P	-	P	-	P
Liver															
Discoloration, dark reddish	-	-	P	P	-	-	P	-	-	-	P	-	P	-	P
Enlargement	-	-	P	-	-	-	P	-	-	-	P	-	P	-	P
Whitish area, scattered	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-
Lung															
Dark reddish area, scattered	-	-	P	-	-	-	P	-	-	-	-	-	-	-	-
Discoloration, dark reddish	P	-	-	P	P	-	-	P	-	-	-	-	P	-	-
Small intestine															
Retention, black content	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-
Spleen															
Small	P	P	P	-	P	-	P	P	P	P	P	P	P	P	P
Stomach															
Discoloration, dark reddish, mucosa, glandular stomach	-	-	-	P	-	-	P	P	-	-	P	-	P	-	P
Thinning, mucosa, forestomach	P	P	P	P	P	P	P	P	P	-	P	-	P	-	P
Thymus															
Discoloration, dark reddish	-	-	-	-	P	-	P	-	P	-	-	-	-	-	-
Small	P	-	-	P	P	P	-	P	P	-	-	-	-	-	-
Urinary bladder															
Retention, reddish urine	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

* : Soiled fur was observed in thorax/abdomen/periocular/perioral/perinasal area/perineal region

Fate D : Died during the observation period. S : Sacrificed in the moribund condition during the observation period.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 32-1. Macroscopic findings of male rats at the end of the recovery period

Findings	Dose(mg/kg)	Corn oil (control)					2,4-DTAP (50 mg/kg)					
	Group	M01-					M03-					
		Animal No.	009	010	011	012	013	009	010	011	012	013
All organs		-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes P : Non-graded change

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 32-2. Macroscopic findings of female rats at the end of the recovery period

Findings	Dose(mg/kg)	Corn oil (control)					2,4-DTAP (100 mg/kg)				
	Group	F05-					F04-		F06-		
		Animal No.	006	007	008	009	010	012	013	007	009

All organs

- : No abnormal changes P : Non-graded change

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 33-1-1. Histopathological findings of male rats at the end of the dosing period [H.E. staining]

Findings	Dose Group Animal No.	Corn oil (control)												2,4-DTAP (10 mg/kg)		2,4-DTAP (50 mg/kg)												2,4-DTAP (100 mg/kg)						
		001	002	003	004	005	006	007	008	009	010	011	012	013	M01-	M02-	002	001	002	003	004	005	006	007	008	009	010	011	012	013	M03-	001	004	009
Brain		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Spinal cord		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Pituitary gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Submandibular gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Sublingual gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Thyroid gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Parathyroid gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Thymus		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Heart		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Degeneration/fibrosis, myocardial, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Trachea		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Lung		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Accumulation, foam cell, alveolus		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Mineralization, focal, arterial wall		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Bronchus		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Liver		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatty change, hepatocyte, periportal		±	±	±	+	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Microgranuloma		-	±	±	±	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Pancreas		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Atrophy, acinar cell, focal, with ductal proliferation		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cellular infiltration, lymphocyte, around artery		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stomach		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duodenum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Jejunum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ileum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 33-1-1 (continued). Histopathological findings of male rats at the end of the dosing period [H.E. staining]

Findings	Dose Group Animal No.	Corn oil (control)												2,4-DTAP (10 mg/kg)				2,4-DTAP (50 mg/kg)							2,4-DTAP (100 mg/kg)																		
		001	002	003	004	005	006	007	008	009	010	011	012	013	M01-	M02-	001	002	003	004	005	006	007	008	009	010	011	012	013	M03-	M04-	001	004	009	010								
Cecum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-											
Colon		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-											
Rectum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-											
Lymph node, mesenteric		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-											
Spleen																																											
Deposit, pigment, brown		±	±	±	±	±											±	±	±	±	±										±	±	+	+									
Hematopoiesis, extramedullary		+	+	+	+	+											+	+	+	+	+										+	+	+	±									
Kidney																																											
Basophilic tubule, cortex/medulla		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
Basophilic tubule, cortex		±	±	-	-	-	-	-	-	-	-	-	-	-	-	-	±	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
Cast, hyalin, cortex/medulla		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-								
Cyst, cortico-medullary junction		-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Urinary bladder		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Adrenal gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Testis		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Epididymis		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Prostate																																											
Cellular infiltration, lymphocyte, interstitial		-	±	±	±	-	-	-	-	-	-	-	-	-	-	-	-	±	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Seminal vesicle		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Coagulating gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Eyeball		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Harderian gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Sciatic nerve		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Skeletal muscle		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Femur		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
<u>Marrow, femur</u>		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 33-1-2. Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Findings	Dose Group Animal No. Fate	Corn oil (control)												2,4-DTAP (10 mg/kg)			2,4-DTAP (50 mg/kg)														
		F01-												F02-			F03-														
		001	002	003	004	005	006	007	008	009	010	011	012	013	DP	001	002	009	001	002	003	004	005	006	007	008	009	010	011	012	013
Brain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Spinal cord	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pituitary gland	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Submandibular gland	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sublingual gland	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Atrophy, follicle	-	±	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Thyroid gland	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parathyroid gland	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Hyperplasia, chief cell	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Thymus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Atrophy	-	2+	2+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2+	-
Heart	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Degeneration/fibrosis, myocardial, focal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Trachea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lung	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Accumulation, foam cell, alveolus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bronchus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatty change, hepatocyte, periportal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Microgranuloma	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vacuolation, hepatocyte, midzonal	-	2+	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Pancreas	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stomach	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Edema, submucosa, forestomach	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Erosion, mucosa, glandular stomach	-	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperplasia, squamous cell, mucosa, forestomach	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ulcer, mucosa, forestomach	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duodenum	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Jejunum	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blanks, Subjected to autopsy on day 5 lactation; TL, Total litter loss during lactation; DP, Died during pregnancy; DD, Died during delivery; SL, Sacrificed in the moribund condition during lactation.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 33-1-2 (continued). Histopathological findings of female rats at the end of the dosing period [H.E. staining]

Findings	Dose Group Animal No. Fate	Corn oil (control)												2,4-DTAP (10 mg/kg)			2,4-DTAP (50 mg/kg)														
		F01-						F02-			F03-						F01-						F02-			F03-					
		001	002	003	004	005	006	007	008	009	010	011	012	013	DP	001	002	009	001	002	003	004	005	006	007	008	009	010	011	012	013
		TL						P						DP						DD						SL					
Ileum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Diverticulum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Cecum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Colon		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Rectum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Lymph node, mesenteric		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Atrophy, follicle		-	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Spleen		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Decrease, red pulp		-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Decrease, white pulp		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Deposit, pigment, brown		+	+	+	+	+	+	+	2+	-	-	-	-	-	-	-	±	2+	+	+	+	+	+	+	+	+	+	2+	-	-	
Hematopoiesis, extramedullary		2+	±	+	+	+	+	+	-	-	-	-	-	-	-	-	+	+	2+	2+	2+	2+	2+	2+	2+	2+	2+	2+	+	-	
Kidney		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Basophilic tubule, cortex		±	+	+	±	±	±	±	±	±	±	±	±	±	±	±	+	+	±	+	+	±	+	±	±	2+	-	-	-	-	
Cast, hyalin, cortex/medulla		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Degeneration/necrosis,		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
proximal tubular epithelium, cortex		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Embolus, capillary, glomerulus, cortex		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Urinary bladder		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Adrenal gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Hypertrophy, zona fasciculata, cortex		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Necrosis, focal, cortex		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Ovary		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Uterus		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3+	-	-		
Hemorrhage, endometrium		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Necrosis, endometrium		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3+	-	-		
Vagina		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Eyeball		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Harderian gland		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Sciatic nerve		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Skeletal muscle		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Femur		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Marrow, femur		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate : blanks, Subjected to autopsy on day 5 lactation; TL, Total litter loss during lactation; DP, Died during pregnancy; DD, Died during delivery; SL, Sacrificed in the moribund condition during lactation.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 33-2. Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Findings	Dose Group Animal No.	Corn oil (control)					2,4-DTAP (100 mg/kg)					
		F05-					F04-			F06-		
		001	002	003	004	005	001	004	006	001	004	006
Brain												
Cellular infiltration, lymphocyte, choroid plexus, ventricle		-	-	-	-	-	-	-	-	±	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-	-
Thyroid gland												
Ectopic thymus		-	-	-	-	-	-	-	-	-	-	P
Parathyroid gland		-	-	-	-	M	-	M	-	-	-	-
Thymus		-	-	-	-	-	-	-	-	-	-	-
Heart		-	-	-	-	-	-	-	-	-	-	-
Trachea		-	-	-	-	-	-	-	-	-	-	-
Lung												
Accumulation, foam cell, alveolus		-	±	-	-	±	-	-	-	-	-	-
Mineralization, focal, arterial wall		-	±	-	-	-	-	-	-	-	-	-
Bronchus		-	-	-	-	-	-	-	-	-	-	-
Liver												
Fatty change, hepatocyte, periportal		-	-	-	±	-	±	-	-	-	-	-
Microgranuloma		-	-	-	±	±	±	-	-	-	±	-
Pancreas												
Atrophy, acinar cell, focal, with ductal proliferation		-	-	-	-	-	-	-	-	-	-	±
Stomach		-	-	-	-	-	-	-	-	-	-	-
Duodenum		-	-	-	-	-	-	-	-	-	-	-
Jejunum		-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 33-2 (continued). Histopathological findings of female rats at the end of the dosing period, satellite group [H.E. staining]

Findings	Dose Group Animal No.	Corn oil (control)					2,4-DTAP (100 mg/kg)					
		F05-					F04-			F06-		
		001	002	003	004	005	001	004	006	001	004	006
Ileum		-	-	-	-	-	-	-	-	-	-	-
Cecum		-	-	-	-	-	-	-	-	-	-	-
Colon		-	-	-	-	-	-	-	-	-	-	-
Rectum		-	-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric		-	-	-	-	-	-	-	-	-	-	-
Spleen												
Deposit, pigment, brown		+	+	+	+	+	+	+	+	2+	+	
Hematopoiesis, extramedullary		+	+	±	+	+	±	+	+	+	±	
Kidney												
Basophilic tubule, cortex		-	±	-	±	±	+	+	+	+	+	±
Calculus, pelvis		-	±	-	-	-	-	-	-	-	-	-
Cyst, cortico-medullary junction		-	-	-	-	-	P	-	-	-	-	-
Hyperplasia, transitional cell, pelvis		-	+	-	-	-	-	-	-	-	-	-
Mineralization, cortex/medulla		-	-	-	-	-	-	-	-	±	-	-
Urinary bladder		-	-	-	-	-	-	-	-	-	-	-
Adrenal gland		-	-	-	-	-	-	-	-	-	-	-
Ovary		-	-	-	-	-	-	-	-	-	-	-
Uterus		-	-	-	-	-	-	-	-	-	-	-
Vagina		-	-	-	-	-	-	-	-	-	-	-
Eyeball		-	-	-	-	-	-	-	-	-	-	-
Harderian gland		-	-	-	-	-	-	-	-	-	-	-
Sciatic nerve		-	-	-	-	-	-	-	-	-	-	-
Skeletal muscle		-	-	-	-	-	-	-	-	-	-	-
Femur		-	-	-	-	-	-	-	-	-	-	-
Marrow, femur		-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
 P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 33-3-1. Histopathological findings of male rats (dead and moribund animals) [H.E. staining]

Findings	Dose Group Animal No. Fate	2,4-DTAP (250 mg/kg)									
		M04-									
		002	003	005	006	007	008	011	012	013	
Brain		-	-	-	-	-	-	-	-	-	
Spinal cord		-	-	-	-	-	-	-	-	-	
Pituitary gland		-	-	-	-	-	-	-	-	-	
Submandibular gland		-	-	-	-	-	-	-	-	-	
Sublingual gland		-	-	-	-	-	-	-	-	-	
Lymph node, submandibular Atrophy, follicle		2+	2+	2+	+	2+	2+	2+	2+	2+	
Thyroid gland		-	-	-	-	-	-	-	-	-	
Parathyroid gland Hyperplasia, chief cell		P	P	P	P	P	P	P	P	P	
Thymus Atrophy		3+	3+	2+	+	2+	3+	3+	3+	3+	
Heart Mineralization, myocardium, focal, around artery		-	-	±	-	-	-	-	±	-	
Trachea		-	-	-	-	-	-	-	-	-	
Lung Accumulation, foam cell, alveolus		±	-	-	-	-	-	-	-	-	
Bronchus		-	-	-	-	-	-	-	-	-	
Liver Fatty change, hepatocyte, periportal Vacuolation, hepatocyte, midzonal		-	-	-	-	-	-	±	-	-	
Pancreas		-	-	-	-	-	-	-	-	-	
Stomach Erosion, mucosa, glandular stomach		-	-	-	-	-	-	±	-	±	
Duodenum		-	-	-	-	-	-	-	-	-	
Jejunum		-	-	-	-	-	-	-	-	-	
Ileum Stenosis, focal, lumen, in invagination		-	-	P	-	-	-	-	-	-	
Cecum		-	-	-	-	-	-	-	-	-	

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate D : Died during the observation period. S : Sacrificed in the moribund condition during the observation period.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 33-3-1 (continued). Histopathological findings of male rats (dead and moribund animals) [H.E. staining]

Findings	Dose Group Animal No. Fate	2,4-DTAP (250 mg/kg)									
		M04-									
		002	003	005	006	007	008	011	012	013	
Colon		-	-	-	-	-	-	-	-	-	
Rectum		-	-	-	-	-	-	-	-	-	
Lymph node, mesenteric Atrophy, follicle		2+	2+	+	+	2+	2+	2+	2+	2+	
Spleen											
Decrease, red pulp		2+	+	2+	2+	2+	2+	+	2+	2+	
Decrease, white pulp		2+	+	2+	2+	2+	2+	2+	3+	2+	
Deposit, pigment, brown		-	±	±	-	-	±	+	+	±	
Hematopoiesis, extramedullary		-	±	-	-	-	±	-	±		
Kidney											
Basophilic tubule, cortex/medulla		2+	2+	3+	2+	+	+	2+	3+	2+	
Cast, hyalin, cortex/medulla		+	+	+	+	2+	±	2+	2+	+	
Cell debris, lumen, cortex/medulla		2+	+	2+	±	+	±	+	2+	2+	
Cellular infiltration, neutrophil, interstitial, papilla		-	-	+	±	+	±	±	±	2+	
Degeneration/necrosis, tubular epithelium, cortex/medulla		3+	+	+	+	3+	2+	+	+	+	2+
Hyperplasia, transitional cell, pelvis		+	+	+	+	+	+	+	+	+	
Mineralization, cortex/medulla		-	-	-	-	-	-	+	-	±	
Urinary bladder		-	-	-	-	-	-	-	-	-	
Adrenal gland											
Hypertrophy, zona fasciculata, cortex		+	+	+	+	+	+	+	+	+	
Testis											
Decrease, germ cell layer, seminiferous tubule, unilateral		-	-	+	-	-	-	-	-	-	
Epididymis											
Decrease, sperm, lumen, unilateral		-	-	+	-	-	-	-	-	-	
Prostate		-	-	-	-	-	-	-	-	-	
Seminal vesicle		-	-	-	-	-	-	-	-	-	
Coagulating gland		-	-	-	-	-	-	-	-	-	
Eyeball		-	-	-	-	-	-	-	-	-	
Harderian gland		-	-	-	-	-	-	-	-	-	
Sciatic nerve		-	-	-	-	-	-	-	-	-	
Skeletal muscle		-	-	-	-	-	-	-	-	-	
Femur		-	-	-	-	-	-	-	-	-	
Marrow, femur		-	-	-	-	-	-	-	-	-	

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate D : Died during the observation period. S : Sacrificed in the moribund condition during the observation period.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 33-3-2. Histopathological findings of female rats (dead and moribund animals) [H.E. staining]

Findings	Dose Group Animal No. Fate	2,4-DTAP (250 mg/kg)										
		F04-							F06-			
		002 D	003 S	005 D	007 D	008 D	009 S	010 D	011 D	002 S	003 S	005 D
Brain	-	-	-	-	-	-	-	-	-	-	-	-
Spinal cord	-	-	-	-	-	-	-	-	-	-	-	-
Pituitary gland	-	-	-	-	-	-	-	-	-	-	-	-
Submandibular gland	-	-	-	-	-	-	-	-	-	-	-	-
Sublingual gland	-	-	-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular Atrophy, follicle	2+	+	2+	+	2+	+	2+	+	+	+	+	+
Thyroid gland	-	-	-	-	-	-	-	-	-	-	-	-
Parathyroid gland Hyperplasia, chief cell	P	P	M	P	P	P	P	P	P	P	P	P
Thymus Atrophy	3+	3+	2+	2+	3+	2+	3+	3+	2+	3+	3+	3+
Heart Mineralization, myocardium, focal, around artery	-	-	-	-	-	-	±	-	-	-	±	-
Trachea	-	-	-	-	-	-	-	-	-	-	-	-
Lung Metaplasia, osseous, focal	-	±	-	-	-	-	-	-	-	-	-	-
Bronchus	-	-	-	-	-	-	-	-	-	-	-	-
Liver Microgranuloma Vacuolation, hepatocyte, midzonal	-	-	-	-	-	-	-	-	±	±	+	±
Pancreas	-	-	-	-	-	-	-	-	-	-	-	-
Stomach	-	-	-	-	-	-	-	-	-	-	-	-
Duodenum	-	-	-	-	-	-	-	-	-	-	-	-
Jejunum	-	-	-	-	-	-	-	-	-	-	-	-
Ileum	-	-	-	-	-	-	-	-	-	-	-	-
Cecum	-	-	-	-	-	-	-	-	-	-	-	-

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate D : Died during the observation period. S : Sacrificed in the moribund condition during the observation period.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 33-3-2 (continued). Histopathological findings of female rats (dead and moribund animals) [H.E. staining]

Findings	Dose Group Animal No. Fate	2,4-DTAP (250 mg/kg)									
		F04-					F06-				
		002	003	005	007	008	009	010	011	002	003
Colon		-	-	-	-	-	-	-	-	-	-
Rectum		-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric											
Atrophy, follicle		2+	+	2+	+	2+	+	2+	3+	+	2+
Spleen											
Decrease, red pulp		2+	+	2+	+	+	+	2+	+	2+	3+
Decrease, white pulp		3+	2+	3+	+	2+	2+	2+	+	2+	3+
Deposit, pigment, brown		+	+	-	+	±	+	-	+	+	-
Hematopoiesis, extramedullary		-	-	-	±	±	±	-	-	-	±
Kidney											
Basophilic tubule, cortex/medulla		2+	2+	2+	3+	2+	2+	+	2+	2+	3+
Cast, hyalin, cortex/medulla		2+	±	+	2+	2+	2+	±	±	+	2+
Cell debris, lumen, cortex/medulla		+	±	2+	2+	±	2+	±	±	+	2+
Cellular infiltration, neutrophil, interstitial, papilla		+	±	+	2+	-	2+	-	±	2+	2+
Cyst, cortico-medullary junction		-	-	-	-	P	-	-	-	-	-
Degeneration/necrosis, tubular epithelium, cortex/medulla		+	±	2+	+	2+	+	2+	2+	+	+
Hyperplasia, transitional cell, pelvis		+	±	+	+	+	+	+	+	+	+
Mineralization, cortico-medullary junction		-	-	-	-	±	-	-	-	-	-
Necrosis, papilla		+	-	-	+	-	-	-	-	±	+
Urinary bladder		-	-	-	-	-	-	-	-	-	-
Adrenal gland											
Hypertrophy, zona fasciculata, cortex		+	+	+	+	+	+	+	+	+	+
Ovary		-	-	-	-	-	-	-	-	-	-
Uterus		-	-	-	-	-	-	-	-	-	-
Vagina		-	-	-	-	-	-	-	-	-	-
Eyeball		-	-	-	-	-	-	-	-	-	-
Harderian gland		-	-	-	-	-	-	-	-	-	-
Sciatic nerve		-	-	-	-	-	-	-	-	-	-
Skeletal muscle		-	-	-	-	-	-	-	-	-	-
Femur		-	-	-	-	-	-	-	-	-	-
Marrow, femur		-	-	-	-	-	-	-	-	-	-

: No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate D : Died during the observation period. S : Sacrificed in the moribund condition during the observation period.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 34. Histopathological findings of female rats at the end of the recovery period [H.E. staining]

Findings	Dose Group Animal No.	Corn oil (control)					2,4-DTAP (100 mg/kg)				
		F05-					F04-				
		006	007	008	009	010	012	013	007	009	010
Brain		-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular		-	-	-	-	-	-	-	-	-	-
Thyroid gland		-	-	-	-	-	-	-	-	-	-
Parathyroid gland		-	-	-	-	-	-	-	-	-	-
Thymus		-	-	-	-	-	-	-	-	-	-
Heart		-	-	-	-	-	-	-	-	-	-
Trachea		-	-	-	-	-	-	-	-	-	-
Lung		-	-	-	-	-	±	-	-	-	-
Metaplasia, osseous, focal		-	-	-	-	-	±	-	-	-	-
Bronchus		-	-	-	-	-	-	-	-	-	-
Liver		-	-	-	-	-	±	-	±	-	-
Fatty change, hepatocyte, periportal		-	-	-	-	-	±	-	±	-	-
Microgranuloma		-	-	-	-	-	±	±	±	-	-
Necrosis, focal, subserosa		-	-	-	-	-	±	-	-	-	-
Pancreas		-	-	-	-	-	±	±	-	-	-
Atrophy, acinar cell, focal, with ductal proliferation		-	-	-	-	-	±	±	-	-	-
Stomach		-	-	-	-	-	-	-	-	-	-
Duodenum		-	-	-	-	-	-	-	-	-	-
Jejunum		-	-	-	-	-	-	-	-	-	-

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats
 Appendix 34 (continued). Histopathological findings of female rats at the end of the recovery period [H.E. staining]

Findings	Dose Group Animal No.	Corn oil (control)					2,4-DTAP (100 mg/kg)				
		F05-					F04- F06-				
		006	007	008	009	010	012	013	007	009	010
Ileum		-	-	-	-	-	-	-	-	-	-
Cecum		-	-	-	-	-	-	-	-	-	-
Colon		-	-	-	-	-	-	-	-	-	-
Rectum		-	-	-	-	-	-	-	-	-	-
Lymph node, mesenteric		-	-	-	-	-	-	-	-	-	-
Spleen											
Deposit, pigment, brown							2+	2+	+	2+	2+
Hematopoiesis, extramedullary							±	+	+	+	+
Kidney											
Basophilic tubule, cortex		-	-	-	±	-	±	-	±	±	±
Cast, hyalin, cortex/medulla		-	-	-	-	-	-	-	±	-	-
Mineralization, cortico-medullary junction		-	-	-	-	-	-	-	-	±	-
Urinary bladder		-	-	-	-	-	-	-	-	-	-
Adrenal gland		-	-	-	-	-	-	-	-	-	-
Ovary		-	-	-	-	-	-	-	-	-	-
Uterus		-	-	-	-	-	-	-	-	-	-
Vagina		-	-	-	-	-	-	-	-	-	-
Eyeball		-	-	-	-	-	-	-	-	-	-
Harderian gland		-	-	-	-	-	-	-	-	-	-
Sciatic nerve		-	-	-	-	-	-	-	-	-	-
Skeletal muscle		-	-	-	-	-	-	-	-	-	-
Femur		-	-	-	-	-	-	-	-	-	-
Marrow, femur		-	-	-	-	-	-	-	-	-	-

- : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
 P : Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 35-1. Results of observations about estrous cycle

Corn oil (vehicle)

Animal no.	Pre-mating period						Mating period		
	Pre-treatment period			Treatment period			Stage	Mean length (days)	Times of vaginal estrus obseved
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F01001	E D D D P E D D D P E D D	5-days	5.0	P E D D P E D D P E D D D P E	4/5-days	4.3	D D D P PL		1
F01002	D D E D D D P E D D P E D	4/5-days	4.5	D P E D D D E D D D P E D D P	4/5-days	4.5	PL		1
F01003	D D P E D D P E D D P E D	4-days	4.0	D P E D D D E D D P E D D P E	4-days	4.0	D D P PL		1
F01004	D D D E D D D P E D D P E	4/5-days	4.5	D D P E D D P E D D P E D D P	4-days	4.0	PL		1
F01005	P E D D P E D D P E D D P	4-days	4.0	E D D P E D D P E D D P E D D	4-days	4.0	P PL		1
F01006	D D D P E D D D P E D D D	5-days	5.0	P E D D D P E D D D P E D D D	5-days	5.0	P PL		1
F01007	D D E D D P E D D P E D D	4-days	4.0	D E D D E D D P P E D D P E D	Irregular	4.0	D D P PL		1
F01008	P E D D P E D D P E D D P	4-days	4.0	E D D P E D D P E D D P E D D	4-days	4.0	P PL		1
F01009	D P E D D D P E D D D P E	5-days	5.0	D D D P E D D D P E D D D E E	5-days	5.0	D D D PL		1
F01010	D D P E D D D E D D P E D	4-days	4.0	D P E D D D E D D P E D D P E	4-days	4.0	D D P PL		1
F01011	D P E D D P E D D P E D D	4-days	4.0	P E D D P E D D P E D D P E D	4-days	4.0	D P PL		1
F01012	E D D P E D D P E D D P E	4-days	4.0	D D P E D D P E D D P E D D P	4-days	4.0	PL		1
F01013	P E D D P E D D D E D D D	4-days	4.0	E D D P E D D D E D D P E D D	4-days	4.0	P PL		1
Mean			4.3			4.2			1.0
S.D.			0.4			0.4			0.0
(N)			(13)			(13)			(13)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 35-2. Results of observations about estrous cycle

2,4-DTAP 10 mg/kg

Animal no.	Pre-mating period						Mating period		
	Pre-treatment period			Treatment period			Stage	Times of vaginal estrus obseved	
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F02001	D P E D D P E D D P E D D	4-days	4.0	P E D D P E D D P E D D P E D	4-days	4.0	D P PL	1	
F02002	D E D D D E D D D E D D D	4-days	4.0	E D D D E D D D E D D P E D D	4-days	4.0	P PL	1	
F02003	D D D E D D D P E D D D E	4/5-days	4.5	D D P E D D P E D D D P E D D	4/5-days	4.5	D PL	1	
F02004	E D D P E D D P E D D P E	4-days	4.0	D D P E D D P E D D P E D D P	4-days	4.0	PL	1	
F02005	D D E D D P E D D P E D D	4-days	4.0	P E D D P E D D P E D D P E D	4-days	4.0	D P PL	1	
F02006	E D D P E D D P E D D P E	4-days	4.0	D D P E D D P E D D P E D D D	4-days	4.0	PL	1	
F02007	D P E D D P E D D P E D D	4-days	4.0	P E D D P E D D P E D D P E D	4-days	4.0	D P PL	1	
F02008	D E D D D E D D D E D D P	4-days	4.0	E D D D E D D P E D D P E D D	4-days	4.0	P PL	1	
F02009	D D P E D D P E D D P E D	4-days	4.0	D P E D D D E D D P E D D P E	4-days	4.0	D D P PL	1	
F02010	P E D D D E D D P E D D D	4-days	4.0	E D D P E D D D E D D D E D D	4-days	4.0	P PL	1	
F02011	D D E D D D P E D D D D E	5-days	5.0	D D D P E D D D P E D D D P E	5-days	5.0	D D P PL	1	
F02012	D D P E D D P E D D P E D	4-days	4.0	D P E D D P E D D P E D D P E	4-days	4.0	D D P SP	1	
F02013	D D P E D D D P E D D D P	5-days	5.0	E D D D P E D D D P E D D D P	5-days	5.0	PL	1	
Mean			4.2			4.2		1.0	
S.D.			0.4			0.4		0.0	
(N)			(13)			(13)		(13)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 35-3. Results of observations about estrous cycle

2,4-DTAP 50 mg/kg

Animal no.	Pre-mating period						Mating period		
	Pre-treatment period			Treatment period			Stage	Times of vaginal estrus obseved	
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F03001	D D P E D D P E D D P E D	4-days	4.0	D P E D D P E D D P E D D P E	4-days	4.0	PL	1	
F03002	D P E D D P E D D P E D D	4-days	4.0	P E D D P E D D P E D D P E D	4-days	4.0	D P PL	1	
F03003	P E D D D D E D D D P E D	5-days	5.0	D D P E D D D E D D D P E D D	4/5-days	4.5	P PL	1	
F03004	D D E D D P E D D P E D D	4-days	4.0	P E D D P E D D P E D D P E D	4-days	4.0	D P PL	1	
F03005	D D D E D D D E D D D E D	4-days	4.0	D P E D D P E D D P E D D P E	4-days	4.0	D D P PL	1	
F03006	D D E D D D P E D D P E E	5-days	5.0	D D P P E D D D P E D D P E D	4/5-days	4.5	D D P PL	1	
F03007	D D P E D D P E D D P E D	4-days	4.0	D P E D D P E D D P E D D P E	4-days	4.0	D D D PL	1	
F03008	D P E D D P E D D P E D D	4-days	4.0	P E D D P E D D P E D D P E D	4-days	4.0	D P PL	1	
F03009	D P E D D P E D D P E D D	4-days	4.0	P E D D P E D D P E D D P E D	4-days	4.0	D P PL	1	
F03010	P E D D P E D D P E D D P	4-days	4.0	E D D P E D D P E D D P E D D	4-days	4.0	P PL	1	
F03011	D D D E D D D E D D P E D	4-days	4.0	D P E D D P E D D P E D D P E	4-days	4.0	D D D PL	1	
F03012	D E D D P E D D P E D D D	4-days	4.0	E D D P E D D P E D D D E D D	4-days	4.0	D PL	1	
F03013	E D D D E D D D E D D D E	4-days	4.0	D D D E D D D E D D D E D D D	4-days	4.0	PL	1	
Mean			4.2			4.1		1.0	
S.D.			0.4			0.2		0.0	
(N)			(13)			(13)		(13)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 35-4. Results of observations about estrous cycle

2,4-DTAP 100 mg/kg

Animal no.	Pre-mating period					
	Pre-treatment period			Treatment period		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)
F04001	D D P E D D D E D D D E D	4-days	4.0	D D E D D P E D D D E D D P E	4-days	4.0
F04002	P E D D D E D D P E D D P	4-days	4.0	E D D D E D D		Died on day 8 of administration.
F04003	D D P E D D D P E D D P E D	4-days	4.0	D P E D D D E D D		Sacrificed on day 9 of administration for moribundity.
F04004	D D D E D D D P E D D D E	4/5-days	4.5	D D P E D D P E D D D P E D D D	4-days	4.0
F04005	D P E D D D P E D D P E D D	4-days	4.0	P E D D D D		Died on day 7 of administration.
F04006	D D E D D P E D D P E D D	4-days	4.0	P E D D D E D D D E D D D E D	4-days	4.0
F04007	E D D P E D D P E D D P E	4-days	4.0	D D P E D D D		Died on day 8 of administration.
F04008	D E D D P E D D P E D D D	4-days	4.0	P E D D P P		Died on day 7 of administration.
F04009	E D D P E D D P E D D P E	4-days	4.0	D D P E D D D		Sacrificed on day 7 of administration for moribundity.
F04010	D P E D D P E D D P E D D	4-days	4.0	P E D D D E		Died on day 7 of administration.
F04011	D D E D D D E D D D E D D	4-days	4.0	D E D D D		Died on day 6 of administration.
F04012	E D D P E D D P E D D P E	4-days	4.0	D D P E D D P E D D P E D D D	4-days	4.0
F04013	D D E D D D E D D D P E D	4/5-days	4.5	D D E D D D E D D P E D D P E	4-days	4.0
Mean			4.1			4.0
S.D.			0.2			0.0
(N)			(13)			(5)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 36-1. Results of observations about reproductive performance

Corn oil (vehicle)

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M01001	F01001	+	+	5
M01002	F01002	+	+	1
M01003	F01003	+	+	4
M01004	F01004	+	+	1
M01005	F01005	+	+	2
M01006	F01006	+	+	2
M01007	F01007	+	+	4
M01008	F01008	+	+	2
M01009	F01009	+	+	4
M01010	F01010	+	+	4
M01011	F01011	+	+	3
M01012	F01012	+	+	1
M01013	F01013	+	+	2
Total		+ : 13, -: 0	+ : 13, -: 0	
Mean				2.7
S.D.				1.4
(N)				(13)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 36-2. Results of observations about reproductive performance

2,4-DTAP 10 mg/kg

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M02001	F02001	+	+	3
M02002	F02002	+	+	2
M02003	F02003	+	+	2
M02004	F02004	+	+	1
M02005	F02005	+	+	3
M02006	F02006	+	+	1
M02007	F02007	+	+	3
M02008	F02008	+	+	2
M02009	F02009	+	+	4
M02010	F02010	+	+	2
M02011	F02011	+	+	4
M02012	F02012	+	-	4
M02013	F02013	+	+	1
Total		+: 13, -: 0	+: 12, -: 1	
Mean				2.5
S.D.				1.1
(N)				(13)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 36-3. Results of observations about reproductive performance

2,4-DTAP 50 mg/kg

Male no.	Female no.	Copulation	Conception	Paring days until copulation
M03001	F03001	+	+	1
M03002	F03002	+	+	3
M03003	F03003	+	+	2
M03004	F03004	+	+	3
M03005	F03005	+	+	4
M03006	F03006	+	+	4
M03007	F03007	+	+	4
M03008	F03008	+	+	3
M03009	F03009	+	+	3
M03010	F03010	+	+	2
M03011	F03011	+	+	4
M03012	F03012	+	+	2
M03013	F03013	+	+	1
Total		+ : 13, -: 0	+ : 13, -: 0	
Mean				2.8
S.D.				1.1
(N)				(13)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 37-1. Observation of offspring (F₁)

Corn oil (control)																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (%)	Number of offspring at birth						Delivery index (%)	Birth index (%)	Live birth index (%)	Number of live offspring			External abnormalities ^{b)}		
						Number of offspring	Sex ratio			Dead offspring (offspring %)	Male (%)	Female (%)	4 days Sex ratio			Viability index (%)	(Number)	External abnormalities (%)		
							Male	Female	Total											
F01001	22	13	13	100.0	+	13	7	6	13	0.54	0	100.0	100.0	100.0	7	6	0.54	100.0	0	0.0
F01002	23	17	17	100.0	+	15	6	9	15	0.40	0	88.2	88.2	100.0	6	9	0.40	100.0	0	0.0
F01003	22	18	18	100.0	+	17	7	10	17	0.41	0	94.4	94.4	100.0	7	10	0.41	100.0	0	0.0
F01004	23	15	15	100.0	+	13	6	7	13	0.46	0	86.7	86.7	100.0	5	7	0.42	92.3	0	0.0
F01005	22	16	16	100.0	+	16	6	10	16	0.38	0	100.0	100.0	100.0	0	0	0	0.0	0	0.0
F01006	23	16	16	100.0	+	15	8	7	15	0.53	0	93.8	93.8	100.0	6	6	0.50	80.0	0	0.0
F01007	23	15	15	100.0	+	14	7	7	14	0.50	0	93.3	93.3	100.0	7	7	0.50	100.0	0	0.0
F01008	22	16	16	100.0	+	16	6	10	16	0.38	0	100.0	100.0	100.0	6	10	0.38	100.0	0	0.0
F01009	23	16	14	87.5	+	13	7	6	13	0.54	0	92.9	92.9	100.0	7	6	0.54	100.0	0	0.0
F01010	23	16	16	100.0	+	15	8	7	15	0.53	0	93.8	93.8	100.0	8	7	0.53	100.0	0	0.0
F01011	22	14	14	100.0	+	13	9	4	13	0.69	0	92.9	92.9	100.0	9	4	0.69	100.0	0	0.0
F01012	23	17	16	94.1	+	14	8	6	14	0.57	0	87.5	87.5	100.0	8	6	0.57	100.0	0	0.0
F01013	22	13	13	100.0	+	12	3	9	12	0.25	0	92.3	92.3	100.0	3	9	0.25	100.0	0	0.0
Number of dams		13	13	13	13	13 ^{a)}	13	13	13	13	13	13	13	13	12	13	13	13	13	
Total		202	199			186	88	98	186	0				79	87			0		
Mean		22.5	15.5	15.3		98.6	14.3	6.8	7.5	14.3	0.48	0.0	93.5	93.5	100.0	6.1	6.7	0.48	90.2	0.0
S.D.		0.5	1.5	1.5		3.7	1.5	1.5	1.9	1.5	0.11	0.0	4.5	4.5	0.0	2.4	2.7	0.11	27.7	0.0
%						100.0														

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

b): Number of external abnormalities in live offspring at birth.

c): Total litter loss on the lactational day 4.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 37-2. Observation of offspring (F₁)

2,4-DTAP 10 mg/kg																				
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams)	Number of offspring at birth						Delivery index (offspring)	Birth index	Live birth index	Number of live offspring			External abnormalities ^{b)} (Number) (%)		
						Number of offspring	Sex ratio			Dead offspring (%)	Male (%)	Female (%)	4 days Sex ratio							
							Live	Male	Female											
F02001	18	17	94.4	-		Dam died on the gestational day 23.														
F02002	23	16	15	93.8	+	15	5	6	11	0.45	4	100.0	73.3	73.3	5	4	0.56	81.8	0	0.0
F02003	23	17	16	94.1	+	16	10	6	16	0.63	0	100.0	100.0	100.0	10	6	0.63	100.0	0	0.0
F02004	22	18	17	94.4	+	16	7	9	16	0.44	0	94.1	94.1	100.0	7	9	0.44	100.0	0	0.0
F02005	23	16	16	100.0	+	13	5	8	13	0.38	0	81.3	81.3	100.0	5	8	0.38	100.0	0	0.0
F02006	22	16	16	100.0	+	16	4	7	11	0.36	5	100.0	68.8	68.8	1	5	0.17	54.5	0	0.0
F02007	22	15	15	100.0	+	13	8	5	13	0.62	0	86.7	86.7	100.0	8	5	0.62	100.0	0	0.0
F02008	22	16	16	100.0	+	14	7	5	12	0.58	2	87.5	75.0	85.7	7	5	0.58	100.0	0	0.0
F02009	22	19	19	100.0	+	18	11	7	18	0.61	0	94.7	94.7	100.0	10	5	0.67	83.3	0	0.0
F02010	23	15	15	100.0	+	15	8	7	15	0.53	0	100.0	100.0	100.0	7	7	0.50	93.3	0	0.0
F02011	23	14	14	100.0	+	12	4	8	12	0.33	0	85.7	85.7	100.0	4	8	0.33	100.0	0	0.0
F02012	Not pregnant																			
F02013	22	17	17	100.0	+	14	5	9	14	0.36	0	82.4	82.4	100.0	5	9	0.36	100.0	0	0.0
Number of dams	11	12	12	12	11 ^{a)}	11	11	11	11	11	11	11	11	11	11	11	11	11	11	
Total	197	193				162	74	77	151		11				69	71		0		
Mean	22.5	16.4	16.1	98.1		14.7	6.7	7.0	13.7	0.48	1.0	92.0	85.6	93.4	6.3	6.5	0.48	92.1	0.0	
S.D.	0.5	1.4	1.3	2.9		1.7	2.4	1.4	2.3	0.12	1.8	7.5	10.7	11.9	2.6	1.8	0.15	14.3	0.0	
%				91.7																
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
Statistical method	AN	AN	AN	KW	AN	AN	AN	KW	KW	AN	KW	AN	KW	AN	AN	AN	AN	AN		

Significantly different from the control group (*: P<0.05, **: P<0.01).

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

b): Number of external abnormalities in live offspring at birth.

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 37-3. Observation of offspring (F₁)

2,4-DTAP 50 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (%)	Number of offspring at birth			Delivery index (offspring)	Birth index	Live birth index	Number of live offspring			External abnormalities ^{b)}								
						Number of offspring	Sex ratio					Male	Female	Total	Male	Female	Sex ratio	Viability index (%)	(Number)	(%)			
							Live	Total															
F03001	22	19	19	100.0	+	18	5	11	16	0.31	2	94.7	84.2	88.9	5	10	0.33	93.8	0	0.0			
F03002	15	14		93.3	-	Dam died on the gestational day 22.																	
F03003	22	19	19	100.0	+	17	12	5	17	0.71	0	89.5	89.5	100.0	11	5	0.69	94.1	0	0.0			
F03004	22	12	12	100.0	+	9	5	4	9	0.56	0	75.0	75.0	100.0	5	4	0.56	100.0	0	0.0			
F03005	22	14	14	100.0	+	13	3	10	13	0.23	0	92.9	92.9	100.0	3	10	0.23	100.0	0	0.0			
F03006	23	18	18	100.0	+	17	6	11	17	0.35	0	94.4	94.4	100.0	6	11	0.35	100.0	0	0.0			
F03007	22	15	15	100.0	+	15	5	10	15	0.33	0	100.0	100.0	100.0	5	10	0.33	100.0	0	0.0			
F03008	22	16	15	93.8	+	14	5	6	11	0.45	3	93.3	73.3	78.6	5	6	0.45	100.0	0	0.0			
F03009	22	16	16	100.0	+	15	7	8	15	0.47	0	93.8	93.8	100.0	6	6	0.50	80.0	0	0.0			
F03010	23	15	14	93.3	+	14	9	5	14	0.64	0	100.0	100.0	100.0	9	5	0.64	100.0	0	0.0			
F03011	23	18	17	94.4	+	17	3	1	4	0.75	13	100.0	23.5	23.5	0	0	0	0.0	0	0.0			
F03012	23	15	11	73.3	+	10	5	5	10	0.50	0	90.9	90.9	100.0	5	5	0.50	100.0	0	0.0			
F03013	22	16	16	100.0	+	16	11	5	16	0.69	0	100.0	100.0	100.0	11	4	0.73	93.8	0	0.0			
Number of dams	12	13	13	13	12 ^{a)}	12	12	12	12	12	12	12	12	12	11	12	12	12	12				
Total		208	200			175	76	81	157		18				71	76			0				
Mean	22.3	16.0	15.4		96.0	14.6	6.3	6.8	13.1	0.50	1.5	93.7	84.8	90.9	5.9	6.3	0.48	88.5	0.0				
S.D.	0.5	2.0	2.5		7.4	2.8	2.9	3.2	3.9	0.17	3.8	7.0	21.3	22.2	3.1	3.3	0.16	28.5	0.0				
%					92.3																		
Significance Statistical method	NS AN	NS AN	NS AN	NS KW	NS AN	NS AN	NS KW	NS KW	NS AN	NS KW	NS AN	NS KW	NS AN	NS AN	NS AN	NS AN	NS AN	NS AN					

Significantly different from the control group (*: P<0.05, **: P<0.01).

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

b): Number of external abnormalities in live offspring at birth.

c): Sacrificed on day 0 of lactation for moribundity.

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 38-1. Body weights of offspring (F₁) before weaning

Corn oil (control)

Dam No.	Days after birth			
	Male body weight		Female body weight	
	0	4	0	4
F01001	6.8 (7)	10.6 (7)	6.1 (6)	9.6 (6)
F01002	7.2 (6)	10.2 (6)	6.5 (9)	9.3 (9)
F01003	6.1 (7)	9.1 (7)	5.7 (10)	8.4 (10)
F01004	7.9 (6)	7.6 (5)	7.6 (7)	7.3 (7)
F01005	6.7 (6)	Total litter loss	6.5 (10)	Total litter loss
F01006	6.4 (8)	8.0 (6)	6.1 (7)	7.5 (6)
F01007	7.4 (7)	11.3 (7)	6.9 (7)	11.0 (7)
F01008	6.7 (6)	10.3 (6)	6.0 (10)	9.5 (10)
F01009	7.7 (7)	12.5 (7)	7.3 (6)	12.0 (6)
F01010	7.3 (8)	11.6 (8)	6.8 (7)	11.3 (7)
F01011	6.6 (9)	7.0 (9)	6.0 (4)	6.4 (4)
F01012	7.3 (8)	9.9 (8)	6.9 (6)	9.3 (6)
F01013	7.0 (3)	10.9 (3)	7.0 (9)	10.7 (9)
Number of dams	13	12	13	12
Mean	7.0	9.9	6.6	9.4
S.D.	0.5	1.7	0.6	1.7

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 38-2. Body weights of offspring (F_1) before weaning

2,4-DTAP 10 mg/kg

Dam No.	Days after birth					
	Male body weight		Female body weight		0	4
	0	4	0	4		
F02001	Dam died on the gestational day 23.					
F02002	6.9 (5)	6.8 (5)	6.4 (6)	6.9 (4)		
F02003	6.9 (10)	10.0 (10)	6.6 (6)	9.7 (6)		
F02004	6.7 (7)	10.3 (7)	6.2 (9)	10.3 (9)		
F02005	7.8 (5)	13.7 (5)	7.4 (8)	13.2 (8)		
F02006	6.0 (4)	10.3 (1)	5.8 (7)	10.4 (5)		
F02007	6.7 (8)	11.6 (8)	6.3 (5)	10.9 (5)		
F02008	6.3 (7)	11.1 (7)	5.7 (5)	10.7 (5)		
F02009	5.3 (11)	5.1 (10)	5.1 (7)	4.9 (5)		
F02010	6.2 (8)	9.8 (7)	6.1 (7)	9.8 (7)		
F02011	7.8 (4)	13.6 (4)	7.6 (8)	13.2 (8)		
F02013	6.5 (5)	10.6 (5)	6.1 (9)	10.7 (9)		
Number of dams	11	11	11	11		
Mean	6.6	10.3	6.3	10.1		
S.D.	0.7	2.5	0.7	2.4		
Significance	NS	NS	NS	NS		
Statistical method	AN	AN	AN	AN		

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 38-3. Body weights of offspring (F_1) before weaning

2,4-DTAP 50 mg/kg

Dam No.	Days after birth					
	Male body weight		Female body weight		0	4
	0	4	0	4		
F03001	6.6 (5)	11.9 (5)			6.0 (11)	10.5 (10)
F03002	Dam died on the gestational day 22.					
F03003	5.2 (12)	8.0 (11)			5.1 (5)	8.1 (5)
F03004	7.4 (5)	12.8 (5)			7.0 (4)	12.3 (4)
F03005	7.1 (3)	10.4 (3)			6.4 (10)	9.6 (10)
F03006	6.5 (6)	9.2 (6)			5.9 (11)	8.5 (11)
F03007	6.6 (5)	9.6 (5)			6.0 (10)	9.2 (10)
F03008	6.0 (5)	8.1 (5)			5.4 (6)	8.6 (6)
F03009	6.3 (7)	9.4 (6)			6.3 (8)	8.7 (6)
F03010	7.1 (9)	11.0 (9)			6.6 (5)	10.6 (5)
F03011	6.2 (3)	Sacrificed on day 0 of lactation for moribundity.			5.1 (1)	
F03012	7.9 (5)	14.1 (5)			7.5 (5)	13.4 (5)
F03013	6.4 (11)	10.1 (11)			6.2 (5)	10.5 (4)
Number of dams	12	11			12	11
Mean	6.6	10.4			6.1	10.0
S.D.	0.7	1.9			0.7	1.7
Significance	NS	NS			NS	NS
Statistical method	AN	AN			AN	AN

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

UA: Unable to be analyzed because the value in the treated group was the same as the value in the control group.

NA: Not analyzed.

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 39-1. General conditions in offspring (F₁) before weaning

Corn oil (control)		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
F01001	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01002	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01003	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F01004	Number of offspring	13	13	12	12	12
	General appearance, No abnormality	13	12	12	12	12
	General appearance, Death	0	1	0	0	0
F01005	Number of offspring	16	16	16	15	4
	General appearance, No abnormality	16	16	15	4	0
	General appearance, Death	0	0	1	11	4
F01006	Number of offspring	15	15	15	14	14
	General appearance, No abnormality	15	15	14	14	12
	General appearance, Death	0	0	1	0	2
F01007	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01008	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01009	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01010	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01011	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F01012	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01013	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
		186	186	185	183	172
		186	185	183	172	166
			1	2	11	6

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 39-2. General conditions in offspring (F₁) before weaning

2,4-DTAP 10 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
F02001	Dam died on the gestational day 23.					
F02002	Number of offspring	11	11	9	9	9
	General appearance, No abnormality	11	9	9	9	9
	General appearance, Death	0	2	0	0	0
F02003	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02004	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02005	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F02006	Number of offspring	11	11	7	6	6
	General appearance, No abnormality	11	7	6	6	6
	General appearance, Death	0	4	1	0	0
F02007	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F02008	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02009	Number of offspring	18	18	18	17	15
	General appearance, No abnormality	18	18	17	15	15
	General appearance, Death	0	0	1	2	0
F02010	Number of offspring	15	15	14	14	14
	General appearance, No abnormality	15	14	14	14	14
	General appearance, Death	0	1	0	0	0
F02011	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02013	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
	Number of offspring	151	151	144	142	140
	General appearance, No abnormality	151	144	142	140	140
	General appearance, Death	7	2	2		

Combined repeat dose and reproductive/developmental toxicity screening test of Phenol, 2,4-bis (1,1-dimethylpropyl) by oral administration in rats

Appendix 39-3. General conditions in offspring (F₁) before weaning

2,4-DTAP 50 mg/kg		Days after birth				
Dam No.	Number of offspring and general conditions	0	1	2	3	4
F03 001	Number of offspring	16	16	15	15	15
	General appearance, No abnormality	16	15	15	15	15
	General appearance, Death	0	1	0	0	0
F03 002	Dam died on the gestational day 22.					
F03 003	Number of offspring	17	17	16	16	16
	General appearance, No abnormality	17	16	16	16	16
	General appearance, Death	0	1	0	0	0
F03 004	Number of offspring	9	9	9	9	9
	General appearance, No abnormality	9	9	9	9	9
F03 005	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03 006	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F03 007	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03 008	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F03 009	Number of offspring	15	15	13	12	12
	General appearance, No abnormality	15	13	12	12	12
	General appearance, Death	0	2	1	0	0
F03 010	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03 011	Number of offspring	4	0	0	0	0
	General appearance, No abnormality	4	0	0	0	0
F03 012	Number of offspring	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10
F03 013	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	15
	General appearance, Death	0	0	0	0	1
Number of offspring		157	153	149	148	148
General appearance, No abnormality		157	149	148	148	147
General appearance, Death			4	1		1